

3-23-82
Vol. 47 No. 56
Pages 12327-12604

Tuesday
March 23, 1982

Federal Register



FEDERAL REGISTER Published daily, Monday through Friday, (not published on Saturdays, Sundays, or on official holidays), by the Office of the Federal Register, National Archives and Records Service, General Services Administration, Washington, D.C. 20408, under the Federal Register Act (49 Stat. 500, as amended; 44 U.S.C. Ch. 15) and the regulations of the Administrative Committee of the Federal Register (1 CFR Ch. I). Distribution is made only by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

The **Federal Register** provides a uniform system for making available to the public regulations and legal notices issued by Federal agencies. These include Presidential proclamations and Executive Orders and Federal agency documents having general applicability and legal effect, documents required to be published by Act of Congress and other Federal agency documents of public interest. Documents are on file for public inspection in the Office of the Federal Register the day before they are published, unless earlier filing is requested by the issuing agency.

The **Federal Register** will be furnished by mail to subscribers, free of postage, for \$75.00 per year, or \$45.00 for six months, payable in advance. The charge for individual copies is \$1.00 for each issue, or \$1.00 for each group of pages as actually bound. Remit check or money order, made payable to the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

There are no restrictions on the republication of material appearing in the **Federal Register**.

Questions and requests for specific information may be directed to the telephone numbers listed under INFORMATION AND ASSISTANCE in the READER AIDS section of this issue.

Contents

Federal Register

Vol. 47, No. 56

Tuesday, March 23, 1982

Agricultural Marketing Service

RULES

- 12327 Livestock grading and certification services; fees, increase; final rule

Agriculture Department

See also Agricultural Marketing Service; Animal and Plant Health Inspection Service; Federal Grain Inspection Service.

RULES

- 12327 Conduct standards

Air Force Department

NOTICES

Meetings:

- 12377 Scientific Advisory Board

Animal and Plant Health Inspection Service

RULES

- 12328 Plant quarantine, domestic;
Golden nematode; interim

Civil Aeronautics Board

NOTICES

- 12369 Airport slot allocations; recommendation to Federal Aviation Administration; request for comments
12421 Meetings; Sunshine Act

Commerce Department

See also International Trade Administration; National Bureau of Standards; National Oceanic and Atmospheric Administration.

NOTICES

Committees; establishment, renewals, terminations, etc.:

- 12376 Mid-Atlantic, New England and Western Pacific Fishery Management Councils, Advisory Panels

Commodity Futures Trading Commission

PROPOSED RULES

- 12353 Futures commission merchants; minimum financial and reporting requirements; adjusted net capital requirement

Consumer Product Safety Commission

PROPOSED RULES

- 12353 Urea-formaldehyde foam insulation; proposed ban; extension of time

Defense Department

See also Air Force Department.

PROPOSED RULES

- 12363 Veterans vocational rehabilitation and education; Post-Vietnam era veterans' educational assistance fund; advance payment of allowance

Economic Regulatory Administration

NOTICES

Natural gas; fuel oil displacement certification applications:

- 12378 Jones & Laughlin Steel Corp.
12378 Long Island Lighting Co.

Education Department

NOTICES

Meetings:

- 12377 Postsecondary Education Improvement Fund, National Board

Employment and Training Administration

NOTICES

Adjustment assistance:

- 12402 Carnivale Bag Co. et al.

Energy Department

See also Economic Regulatory Administration; Federal Energy Regulatory Commission; Hearings and Appeals Office, Energy Department.

NOTICES

Meetings:

- 12379 Energy Research Advisory Board

Environmental Protection Agency

RULES

Hazardous waste programs; interim authorizations; various States:

- 12347 Texas

PROPOSED RULES

Air pollution control; new motor vehicles and engines:

- 12366 Gaseous emissions; 1984 and later model year light-duty trucks and heavy-duty engines; extension of time

Air quality implementation plans; approval and promulgation; various States, etc.:

- 12364 Minnesota

Federal Energy Regulatory Commission

NOTICES

Hearings, etc.:

- 12379 Alabama Power Co.
12381 Arkansas-Louisiana Gas Co.
12381 Central Telephone & Utilities Corp.
12381 Duke Power Co.
12381 Mid Louisiana Gas Co.
12382 Ohio Power Co.
12383 Texas Gas Transmission Corp.
12383 Texas Gas Transmission Corp, et al.
12382 Union Electric Co.
12421 Meetings; Sunshine Act
Natural Gas Policy Act:
12383 Jurisdictional agency determinations; well category withdrawals, etc.; Ashland Exploration, Inc.

Federal Grain Inspection Service

NOTICES

Meetings:

- 12369 Advisory Committee

Federal Maritime Commission

PROPOSED RULES

- 12367 Military rates level; removal of CFR Part

NOTICES

- 12385 Agreements filed, etc.

- Complaints filed:
 12386 Kerr Steamship Co., Inc.
 Tariff cancellations:
 12385 Alexander & Associates et al.
- Federal Mine Safety and Health Review Commission**
 NOTICES
 12421 Meetings; Sunshine Act
- Federal Reserve System**
 NOTICES
 Applications, etc.:
 12386 Alden Bancshares, Inc.
 12386 American Bancshares of Arkansas
 12386 Bancshares, Inc.
 12387 Caneyville Bancshares, Inc.
 12387 Carbondale Bancshares, Inc.
 12387 Citiba Financial Corp.
 12387 Citicorp
 12388 Consolidated Holding Co.
 12388 De Kalb County Bancshares, Inc.
 12388 Delhi Bancshares, Inc.
 12388 Financial Services of Lowry, Inc.
 12388 First National Bancorp
 12388 First Selmer Bancshares, Inc.
 12389 Mercantile Texas Corp.
 12389 Mid-Nebraska Bancshares, Inc.
 12389 MPS Bancorp, Inc.
 12389 Mt. Vernon Bancorp, Inc.
 12390 NBE Bancshares, Inc.
 12390 Rocky Financial Corp.
 12390 Salem Financial Corp.
 12390 Security National Corp.
 12390 Southern Bancorporation, Inc.
 12391 State Bancshares, Inc.
 12421 Meetings; Sunshine Act (3 documents)
- Fiscal Service**
 NOTICES
 Surety companies acceptable on Federal bonds:
 12419 National Mutual Insurance Co.
- Food and Drug Administration**
 RULES
 Animal drugs, feeds, and related products:
 12338 Hygromycin B premixes; correction
 PROPOSED RULES
 Biological products:
 12358 Blood derivative, source plasma, and whole blood regulations review; meetings
 Human drugs:
 12430 Acne drug products, topical (OTC); monography establishment; advance notice
 12480 Antifungal drug products, topical (OTC); monographic; establishment; advance notice
 NOTICES
 Meetings:
 12391 Consumer information exchange
- Foreign Assets Control Office**
 RULES
 12338 Czechoslovak assets control regulations; unblocking
 12339 Iranian assets control regulations
- General Services Administration**
 NOTICES
 Authority delegations:
 12391 Energy Department Secretary (2 documents)
- Health and Human Services Department**
See Food and Drug Administration; Health Care Financing Administration; National Institutes of Health.
- Health Care Financing Administration**
 PROPOSED RULES
 Medicare:
 12574 Ambulatory surgical services
 NOTICES
 Medicare:
 12592 Ambulatory surgical services; list of covered surgical procedures
- Hearings and Appeals Office, Energy Department**
 NOTICES
 Applications for exception:
 12384 Decisions and orders (2 documents)
- Interior Department**
See also Land Management Bureau; Surface Mining Reclamation and Enforcement Office.
 NOTICES
 12393 Alaska Land Use Council; call for work program items
- Internal Revenue Service**
 PROPOSED RULES
 Income taxes:
 12361 Travel expenses of Members of Congress; hearing
- International Communication Agency**
 NOTICES
 Art objects, importation for exhibitions:
 12393 Mauritshuis; Dutch painting of the Golden Age from the Royal Picture Gallery, The Hague
- International Trade Administration**
 NOTICES
 12375 Commercial News USA; publication fee for participating firms
 Scientific articles; duty free entry:
 12373 Pennsylvania State University
 12373 State University of New York
 12373 University of Minnesota
 12374 Yale University
- Interstate Commerce Commission**
 RULES
 Accounts, uniform system:
 12349 Income taxes, deferred; financial statement classification
 Motor carriers:
 12349 Gateway elimination rules; removal
 NOTICES
 Motor carriers:
 12394 Finance applications (2 documents)
 12396 Permanent authority applications (3 documents)
 12397 Petitions, applications, finance matters (including temporary authorities), alternate route deviations, intrastate applications, gateways, and pack and crate
 Rail carriers:
 12394 Boston & Maine Corp.; contract tariff exemption

- 12394 Railroad services abandonment:
Illinois Central Gulf Railroad Co.

Labor Department

See Employment and Training Administration;
Mine Safety and Health Administration.

Land Management Bureau

RULES

Rights-of-way:

- 12570 Oil and natural gas pipelines; applications for
rights-of-way grants; use of consolidated form
12568 Principles and procedures; application content,
use of consolidated form

NOTICES

Opening of public lands:

- 12392, California (2 documents)
12393

Mine Safety and Health Administration

NOTICES

Petitions for mandatory safety standard
modifications:

- 12402 Alabama By-Products Corp.
12403 Coal Valley Mining Co.
12403 Consolidation Coal Co.

National Bureau of Standards

NOTICES

Information processing standards, Federal:

- 12375 Data encryption standard; inquiry
12375 I/O channel level interface standards; technical
verification guidance

National Institutes of Health

NOTICES

Meetings:

- 12392 Cancer Biology and Diagnosis; Scientific
Counselors Board
12392 Resources, Centers, and Community Activities;
Scientific Counselors Board

National Oceanic and Atmospheric Administration

PROPOSED RULES

Tuna, Atlantic fisheries:

- 12367 Bluefin tuna; environmental impact statement
intent to prepare

NOTICES

Meetings:

- 12376 Mid-Atlantic Fishery Management Council

Nuclear Regulatory Commission

NOTICES

Applications, etc.:

- 12404 Baltimore Gas & Electric Co.
12403 Exxon Nuclear
12404 Florida Power & Light Co.
12405 Northern States Power Co.
12421 Meetings; Sunshine Act

Reports; availability, etc.:

- 12405 Suppression pool temperature limits for BWR
containments

Personnel Management Office

NOTICES

Excepted service:

- 12405 Schedules A, B, and C; positions placed or
revoked, update

Securities and Exchange Commission

NOTICES

Hearings, etc.:

- 12410 Alex. Brown Cash Reserve Fund, Inc.
12411 American Federation of Labor and Congress of
Industrial Organizations Pooled Investment Trust
Cash Assets Fund
12415 Dreyfus Institutional Money Market Fund, Inc.
12417 Gradison U.S. Government Trust

Small Business Administration

RULES

- 12332 Conduct standards

NOTICES

Disaster loan areas:

- 12419 Oregon
12419 Interest rates; direct business loans, immediate
participation loans

State Department

PROPOSED RULES

Visas:

- 12359 Nonimmigrant classification of students

Surface Mining Reclamation and Enforcement Office

PROPOSED RULES

Permanent and interim regulatory programs:

- 12591 Revegetation requirements
Permanent program submission; various States:
12361 New Mexico; hearing, etc.

NOTICES

Environmental statements; availability, etc.:

- 12393 Heal Property, Centerville, and Klein Mine,
Roundup, Mont.; abandoned mine land
reclamation projects

Textile Agreements Implementation Committee

NOTICES

Cotton, wool, or man-made textiles:

- 12377 India

Treasury Department

See Fiscal Service; Foreign Assets Control Office;
Internal Revenue Service.

Veterans Administration

RULES

- 12340 Appeals from decisions of contracting officers

Loan guaranty:

- 12346 Mobile home loans; maximum term increase

PROPOSED RULES

Adjudication; pensions, compensation, dependency,
etc.:

- 12362 Marriage and birth documentary evidence
submission by claimants

Vocational rehabilitation and education:

- 12363 Post-Vietnam era veterans' educational
assistance fund; advance payment of allowance

NOTICES

Meetings:

- 12419 Educational Allowances Station Committee

CFR PARTS AFFECTED IN THIS ISSUE

A cumulative list of the parts affected this month can be found in the Reader Aids section at the end of this issue.

7 CFR

0.....	12327
53.....	12327
301.....	12328

13 CFR

105.....	12332
----------	-------

16 CFR**Proposed Rules:**

1306.....	12353
-----------	-------

17 CFR**Proposed Rules:**

1.....	12353
--------	-------

21 CFR

558.....	12338
----------	-------

Proposed Rules:

Subch. F.....	12358
333 (2 documents).....	12430,
	12480

22 CFR**Proposed Rules:**

41.....	12359
---------	-------

26 CFR**Proposed Rules:**

1.....	12361
--------	-------

30 CFR**Proposed Rules:**

816.....	12596
817.....	12596
931.....	12361

31 CFR

520.....	12338
535.....	12339

38 CFR

1.....	12340
36.....	12346

Proposed Rules:

3.....	12362
21.....	12363

40 CFR

123.....	12347
----------	-------

Proposed Rules:

52.....	12364
86.....	12366

42 CFR**Proposed Rules:**

405.....	12574
416.....	12574

43 CFR

2800.....	12568
2880.....	12570

46 CFR**Proposed Rules:**

549.....	12367
----------	-------

49 CFR

1065.....	12349
1201.....	12349
1206.....	12349
1207.....	12349

50 CFR**Proposed Rules:**

285.....	12367
----------	-------

Rules and Regulations

Federal Register

Vol. 47, No. 56

Tuesday, March 23, 1982

This section of the FEDERAL REGISTER contains regulatory documents having general applicability and legal effect, most of which are keyed to and codified in the Code of Federal Regulations, which is published under 50 titles pursuant to 44 U.S.C. 1510.

The Code of Federal Regulations is sold by the Superintendent of Documents. Prices of new books are listed in the first FEDERAL REGISTER issue of each month.

DEPARTMENT OF AGRICULTURE

Office of the Secretary

7 CFR Part 0

Employee Responsibilities and Conduct

AGENCY: Department of Agriculture.

ACTION: Final rule.

SUMMARY: The Department of Agriculture is amending its conduct regulations to increase the minimal value of acceptable foreign gifts from \$100 to \$140. On October 20, 1982, the General Services Administration published an amendment of this minimal value for acceptable gifts in the Federal Register (page 51388) which increased it to \$140. This amendment will revise the Department of Agriculture's regulations to reflect this change.

EFFECTIVE DATE: March 23, 1982.

FOR FURTHER INFORMATION CONTACT:

Peter C. Sleight, Employee Relations Specialist, Office of Personnel, Department of Agriculture, Washington, D.C. 20250, (202) 447-7654.

SUPPLEMENTARY INFORMATION: Section 515 of Pub. L. 95-105, 91 Stat. 862 governing the receipt and disposition of gifts from foreign governments to Federal employees contains a section which calls for the redefinition of minimal value as reflected by changes in the consumer price index for the preceding 3 year period. On October 20, 1981, the General Services Administration published an amendment of this minimal value for acceptable gifts in the Federal Register (page 51388) which increased it to \$140. This amendment will revise the Department of Agriculture's regulations to reflect this change.

Since this rule relates solely to internal agency management, it has

been found pursuant to 5 U.S.C. 553 that notice and prior publication for comment is unnecessary, and good cause is found for making this rule effective less than 30 days after publication in the Federal Register. In addition, this regulation has been reviewed under Executive Order 12291, and has been determined to be exempt from those requirements. John W. Fossum, Director of Personnel made this determination because this rule concerns matters related to agency management.

PART 0—EMPLOYEE RESPONSIBILITIES AND CONDUCT

Accordingly, 7 CFR 0.735-12 is amended by changing the dollar value in paragraphs (e)(2), (e)(3), and (e)(4) from \$100 to \$140.

Dated: March 17, 1982.

John R. Block,

Secretary of Agriculture.

[FR Doc. 82-7784 Filed 3-22-82; 6:45 am]

BILLING CODE 3410-01-M

Agricultural Marketing Service

7 CFR Part 53

Livestock and Grain Market News; Increase in Fees for Federal Livestock Grading and Certification Services

AGENCY: Agricultural Marketing Service, USDA.

ACTION: Final rule.

SUMMARY: The Agricultural Marketing Service is adopting without change as a final rule, the interim final rule published in the November 5, 1981, Federal Register (46 FR 54919), in which § 53.18 of the regulations was revised to increase fees for Federal livestock grading and certification services so as to reflect increased program costs.

FOR FURTHER INFORMATION CONTACT:

James A. Ray, Chief, Livestock and Grain Market News Branch; Livestock, Meat, Grain, and Seed Division; Agricultural Marketing Service; U.S. Department of Agriculture; Room 2623, South Agriculture Building; Washington, D.C. 20250. (Telephone: 202-447-6231.)

SUPPLEMENTARY INFORMATION:

Executive Order 12291

This action has been reviewed under Executive Order 12291 and USDA

Secretary's Memorandum 1512-1 implementing Executive Order 12291, and it has been determined that this is not a major rule. Although this rule will directly affect users of Federal livestock grading and certification services, it will not result in an annual effect on the economy of \$100 million or more. There will be no major increase in production costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions. Additionally, this rule will not have significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets. Accordingly, a regulatory impact analysis is not required.

Regulatory Flexibility Act

William T. Manley, Deputy Administrator, Marketing Program Operations, has determined that this action will not have a significant economic impact on a substantial number of small entities, because the fees merely reflect a minimal increase in the cost-per-unit graded and/or certified currently borne by those entities utilizing the services. Additionally, the increased fees will not affect normal competition in the marketplace.

Comments

On November 5, 1981, the Agricultural Marketing Service published in the Federal Register (46 FR 54919) an interim final rule increasing the fees for Federal livestock grading and certification services, effective November 29, 1981. Comments on this amendment were requested by December 31, 1981. No comments were received.

As indicated in the November 5, 1981, publication, since the last fee increase on October 8, 1978, program costs have continued to rise. Federal employees have received pay increases in conformity with the Federal Pay Comparability Act of 1970. In addition, the grade level or pay scale of graders currently performing service has shifted to a higher level due to longevity and progressive promotion to the journeyman market reporter level. Similarly, there have been significant increases in other costs such as supervisory travel, rent, and other

associated overhead and administrative costs.

PART 53—LIVESTOCK (GRADING, CERTIFICATION, AND STANDARDS)

Accordingly, under the authority contained in sections 203 and 205 of the Agricultural Marketing Act of 1946, as amended (7 U.S.C. 1622, 1624), § 53.18 of the regulations published as an interim final rule at 46 FR 54919 is adopted without change as a final rule.

(Agricultural Marketing Act of 1946, as amended; secs. 203 and 205, 60 Stat. 1087, 1090 (7 U.S.C. 1622, 1624))

Done at Washington, D.C., March 17, 1982.

William T. Manley,

Deputy Administrator, Marketing Program Operations.

[FR Doc. 82-7707 Filed 3-22-82; 8:45 am]

BILLING CODE 3410-02-M

Animal and Plant Health Inspection Service

7 CFR Part 301

Golden Nematode Quarantine

AGENCY: Animal and Plant Health Inspection Service, USDA.

ACTION: Interim rule.

SUMMARY: This document amends the golden nematode quarantine and regulations, on an emergency basis, to redefine the term "moved," to add areas in Steuben County, New York, to the list of generally infested areas, and to amend the list of regulated articles by revising the listing for Irish potatoes. The quarantine and regulations restrict the interstate movement of regulated articles from suppressive areas and generally infested areas in New York. The amendments are necessary to conform the regulated activities in the quarantine and regulations to the statutory authority, and to prevent the artificial spread of the golden nematode into noninfested areas of the United States.

DATES: Effective date of the interim rule, March 23, 1982. Written comments concerning this interim rule must be received on or before May 24, 1982.

ADDRESSES: Written comments should be submitted to T. J. Lanier, Chief Staff Officer, Regulatory Support Staff, Plant Protection and Quarantine, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, Room 635 Federal Building, 6505 Belcrest Road, Hyattsville, MD 20782. Written comments received may be inspected at Room 635 of the Federal Building,

between 8 a.m. and 4:30 p.m., Monday through Friday, except holidays.

FOR FURTHER INFORMATION CONTACT:

P. F. Sand, Staff Officer, Pest Program Development Staff, Plant Protection and Quarantine, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, Room 630 Federal Building, 6505 Belcrest Road, Hyattsville, MD 20782, 301-436-8745.

SUPPLEMENTARY INFORMATION:

Executive Order 12291 and Emergency Action

This interim rule is issued in conformance with Executive Order 12291 and Secretary's Memorandum No. 1512-1, and has been determined to be not a "major rule". Based on information compiled by the Department, it has been determined that this interim rule will have an annual effect on the economy of less than \$100,000; will not cause a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; and will not cause significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

Harvey L. Ford, Deputy Administrator of the Animal and Plant Health Inspection Service for Plant Protection and Quarantine, has determined that an emergency situation exists which warrants publication without opportunity for a public comment period on this interim rule. Due to the possibility that the golden nematode could be spread artificially to noninfested areas of the United States, a situation exists requiring immediate action to better control the spread of this pest.

Further, pursuant to the administrative procedure provisions in 5 U.S.C. 553, it is found upon good cause that notice and other public procedure with respect to this interim rule action are impracticable and contrary to the public interest; and good cause is found for making this interim rule action effective less than 30 days after publication of this document in the Federal Register. Comments have been solicited for 60 days after publication of this document, and a final document discussing comments received and any amendments required will be published in the Federal Register as soon as possible.

In addition, because of the need for immediate action, it is impracticable for

the Department to follow the procedures established by Executive Order 12291.

Certification under the Regulatory Flexibility Act

Dr. H. C. Mussman, Administrator of the Animal and Plant Health Inspection Service, has determined that this action will not have a significant economic impact on a substantial number of small entities. This action affects the interstate movement of certain articles from regulated areas in New York. Based on information compiled by the U.S. Department of Agriculture and information submitted by the New York Department of Agriculture and Markets, it has been determined that there are thousands of small entities that move such articles interstate from New York and many more thousands of small entities that move such articles interstate from other States. However, based on such information, it has been determined that fewer than 400 entities move such articles interstate from regulated areas in New York. Further, the overall economic impact from this action is estimated to be less than \$100,000.

Background

The golden nematode is a plant pest which is highly destructive to potatoes and other solanaceous plants. It is undoubtedly the most serious pest threatening the American potato industry. Potatoes cannot be grown economically on land containing large numbers of the nematode.

The golden nematode has been determined to occur in the United States only in parts of New York. The golden nematode quarantine and regulations (7 CFR 301.85 through 301.85-10) were designed to restrict the interstate movement of regulated articles from regulated areas (regulated areas are divided into suppressive areas and generally infested areas) in New York and thereby prevent the artificial spread of the golden nematode.

Pursuant to section 105 and 106 of the Federal Plant Pest Act (7 U.S.C. 150dd, 150ee), this document amends the quarantine and regulations on an emergency basis to redefine the term "moved," to add areas in Steuben County, New York, to the list of generally infested areas, and to amend the list of regulated articles by revising the listing for Irish potatoes.

Definition of "Moved"

The golden nematode quarantine and regulations cite the Plant Quarantine Act (7 U.S.C. 151 *et seq.*) and the Federal Plant Pest Act (7 U.S.C. 150aa *et seq.*) as

authority for the quarantine and regulations. Based on an analysis of this authority, it is necessary to amend the definition of the term "moved."

Prior to the effective date of this document, the quarantine and regulations defined the term "moved" as follows:

"Moved (movement, move). Shipped, offered for shipment to a common carrier, received for transportation or transported by a common carrier, or carried, transported, moved, or allowed to be moved by all means. 'Movement' and 'move' shall be construed accordingly."

This definition is based on language in section 8 of the Plant Quarantine Act (7 U.S.C. 161). However, it has been determined that the term "moved" should be revised to reflect pertinent language in the Federal Plant Pest Act. The Plant Quarantine Act does not contain authority to impose restrictions on the movement of articles to prevent the spread of nematodes, but the Federal Plant Pest Act contains specific authority for this purpose and is the authority for the golden nematode quarantine and regulations. Section 102(g) of the Federal Plant Pest Act (7 U.S.C. 150aa(g)) defines the term "move" in relevant part, as follows:

"Move" means ship, deposit for transmission in the mail, otherwise offer for shipment * * * receive for transportation, carry, or otherwise transport, or move, or allow to be moved, by mail or otherwise.

Accordingly, since the Federal Plant Pest Act provides the authority for the quarantine and regulations, the term "moved" is revised to reflect the definition in the Federal Plant Pest Act. This is necessary as an emergency measure in order to conform the regulated activities in the quarantine and regulations to the statutory authority.

Additions to List of Generally Infested Areas

It is further necessary to amend the list of regulated areas by adding certain areas in Steuben County in New York to the list of generally infested areas.

Regulated areas are those areas in which the golden nematode has been found or in which there is reason to believe that the golden nematode is present or which it is deemed necessary to regulate because of their proximity to infestation or their inseparability for quarantine enforcement purposes from infested localities. As noted above, regulated areas are divided into suppressive areas and generally infested areas. Suppressive areas are regulated areas where eradication of the golden nematode is undertaken as an objective.

Generally infested areas are regulated areas not designated as suppressive areas. The quarantine and regulations were designed to impose restrictions on the interstate movements of regulated articles from generally infested areas and suppressive areas in order to prevent the artificial movement of golden nematode to noninfested areas and to prevent the reinfestation of suppressive areas found free of the golden nematode.

Prior to the effective date of this document, the towns of Prattsburg and Wheeler were the only areas in Steuben County, New York, that were designated as regulated areas. These areas were designated as generally infested areas. However, based on soil sample surveys conducted by inspectors of the United States Department of Agriculture and the New York Department of Agriculture and Markets, it has been determined that the golden nematode has spread to the farm of Dale Werth, known as the "Werthwhile Farm," located in the town of Cohocton in Steuben County, on the north side of County Road 5 (known as Brown Hill Road), and 0.2 mile west of the Junction of County Road 5 with County Road 58 (known as Wager Road), and has spread to the following area in the town of Dansville in Steuben County: That area known as "Arkport Muck" and bounded by a line beginning at a point where the Conrail right-of-way (Erie Lackawanna Rail Road) intersects County Road 52 (known as Burns Road), then north and northeast along County Road 52 to its junction with New York Route 36, then south and southeast along New York Route 36 to its intersection with the Dansville Town line, then west along the Dansville Town line to its intersection with the Conrail right-of-way (Erie Lackawanna Rail Road), then north and northwest along the Conrail right-of-way to the point of beginning. Eradication of the golden nematode is not an objective in any of these areas. Therefore, in order to prevent the further spread of the golden nematode, it is necessary as an emergency measure to add these areas in the towns of Cohocton and Dansville to the list of generally infested areas.

Irish Potatoes

It is also necessary to amend the list of regulated articles by revising the listing for Irish potatoes. Prior to the effective date of this document, the list of regulated articles included Irish potatoes for seed, and included Irish potatoes for other than seed unless graded at an approved grader or washed free of soil and unless packaged in approved containers. Under the revised listing, Irish potatoes are regulated

articles if they are included in any one or more of categories (i), (ii), or (iii) below:

- (i) Irish potatoes for seed,
- (ii) Irish potatoes unless * * *

(A) each is at least 1½ inches in diameter based on measurement by a sizing screen or sizing chain, each is substantially free of soil as a result of grading (a method of removing soil mechanically by chain or perforated belt) under a compliance agreement in accordance with § 301.85-5(b), and they are moved in an approved container; or

(B) each is substantially free of soil as a result of washing or fluming under a compliance agreement in accordance with § 301.85-5(b), and they are moved in an approved container; or

(iii) Irish potatoes harvested from a field tested and found by an inspector to contain an identifiable population of viable golden nematodes, unless such field had been subsequently treated in accordance with provisions in (A), (B), or (C) set forth below, under the supervision of an inspector and in accordance with any additional conditions found necessary by the inspector to assure effective application of the pesticide used; and unless headlands and farm roads are treated in accordance with provisions in (D) set forth below:

(A) Applications of 140.3 liters of Vorlex (1,3 dichloropropene; 1,2 dichloropropene, and other related compounds, 80 percent; plus methyl isothiocyanate, 20 percent active ingredients) per hectare (15 gallons per acre); two applications 5 to 10 days apart with a third application 5 to 10 days after the second application to areas in which the inspector finds upon microscopic examination of soil samples that viable golden nematodes may still exist; soil to be from 3° C to 29° C (38° F to 84° F).

(B) Applications of 280.6 liters of D-D (1,3 dichloropropene; 1,2 dichloropropene, and other related compounds, 100 percent active ingredients) per hectare (30 gallons per acre); two applications 5 to 10 days apart with a third application 5 to 10 days after the second application to areas in which the inspector finds upon microscopic examination of soil samples that viable golden nematodes may still exist (consult product label for heavier dosage in muck or peat soils); soil to be from 4.5° C to 29° C (40° F to 84° F).

(C) Applications of 168.4 liters of Telone II (1,3 dichloropropene, 92 percent active ingredients) per hectare (18 gallons per acre); two applications 5 to 10 days apart with a third application 5 to 10 days after the second application

to areas in which the inspector finds upon microscopic examination of soil samples that viable golden nematodes may still exist (consult product label for heavier dosage in muck or peat soils); soil to be from 4.5° C to 32° C (40° F to 90° F).

(d) Application of Vapam (sodium-N-methyl dithiocarbamate, 32.7 percent active ingredient) mixed with water at the rate of 1 part Vapam to 80 parts water and applied as a drench at the rate of 14.96 cubic meters per hectare (1,600 gallons per acre); soil to be from 4.5° C to 32° C (40° F to 90° F).

The golden nematode is carried by soil and can be carried by even small pieces of soil. Irish potatoes from regulated areas could spread infestations of the golden nematode if adhering soil containing the golden nematode were carried by the potatoes to croplands where potatoes are grown. It is necessary to designate Irish potatoes as regulated articles and thereby subject them to restrictions under the quarantine and regulations in those instances where they present a significant risk of the spread of infestations of the golden nematode.

The criteria in category (i) are designed to designate Irish potatoes from regulated areas as regulated articles if they are intended to be used as seed potatoes. The criteria in category (ii) are designed to designate Irish potatoes as regulated articles if they are not substantially free of soil and moved in containers free of soil. The criteria in category (iii) are designed to designate Irish potatoes as regulated articles if they are from fields with soil containing identifiable populations of the golden nematode.

The risk of spreading infestations of the golden nematode by the movement of Irish potatoes would be virtually eliminated if the potatoes were not used for seed, if all of the soil were removed from the potatoes, or if all of the golden nematodes were destroyed by treatment. Currently soil is being removed from the potatoes by grading, washing, or fluming. Also, all of the fields that grow crops or have grown crops that are hosts to the golden nematode have been tested for the golden nematode, and all of the fields found to be infested with the golden nematode and used for potato production as well as the adjacent headlands and roadways have been or are being treated in accordance with the procedures specified above in category (iii). Due to the different composition of headlands and roadways from fields, different chemical treatments are required to treat headlands and roadways from fields.

Although it does not appear that the movement of Irish potatoes would be likely to spread infestations of the golden nematode if excluded from regulated articles status based on any one of the categories of criteria set forth above, it has been determined that meeting only one or two of the criteria is not sufficient to exclude the potatoes from regulated article status. It is possible that the potatoes could be diverted to such croplands and be used for seed. Also, although almost all soil can be removed by grading, washing, or fluming, there are no commercial methods for assuring that absolutely all of the soil would be removed. Further, although the treatments may be effective in destroying all of the golden nematode in a given field, the treatment or a negative finding would not be sufficient to assure that the field is totally free of the golden nematode. This is because current detection methods would not necessarily establish the presence of the golden nematode if it were present in very low populations, and because climatic or physiological conditions may cause treatments to be less than 100% effective.

However, based on departmental expertise, it has been determined that Irish potatoes not within any of the three categories would not present a significant risk of spreading infestations of the golden nematode. Under these circumstances it has been determined that Irish potatoes not within any of the categories should be excluded from regulated article status. Further, it has been determined that this should be done on an emergency basis in order to delete unnecessary restrictions on the movement of the potatoes.

As noted above in category (ii), exclusion of Irish potatoes from regulated article status based, among other things, on the removal of soil by grading is limited to potatoes 1½ inches or more in diameter. Based on research and field experience it appears that mechanical grading devices are effective for removing soil from those potatoes at least 1½ inches in diameter, and that such devices do not adequately remove soil from smaller potatoes. Also, only potatoes actually measured by a sizing screen or sizing chain are eligible for such exclusion from regulated article status. This is because this procedure is the only feasible method for assuring that the potatoes would be at least 1½ inches in diameter.

Also, as noted above, the previous regulations excluded Irish potatoes from regulated article status, based, among other things, on washing the potatoes free of soil. There are various methods for washing potatoes. One of the most

effective methods is fluming. This is a process of washing potatoes by moving them through running water. The term "washing" in the previous regulations was intended to include fluming, and fluming has been premitted as a method of washing. However, because of trade terminology, the term "fluming" often is not thought to be included by the term "washing." Therefore, in order to avoid confusion, the regulations are clarified on an emergency basis to specify in category (ii) that fluming can be used as a method of cleaning potatoes free of soil.

The regulations are also amended on an emergency basis to provide in category (ii) that in order to exclude potatoes from regulated article status based on grading, washing, or fluming, the procedures must be conducted pursuant to a compliance agreement between the person conducting such operations and Plant Protection and Quarantine wherein such person agrees to conduct such operations in a manner which, in the judgment of the inspector supervising enforcement of the quarantine and regulations will substantially remove the soil from the potatoes. It is necessary to include the compliance agreement procedures to assure that persons performing the grading, washing, or fluming are knowledgeable with respect to the requirements and that they have agreed to comply with them. Also, it should be noted that it is not feasible to set forth more specific criteria concerning the grading, washing, or fluming of potatoes since such operations vary widely. However, if general criteria are developed, amendment of the rule to include such criteria will be considered.

In addition, as noted above under category (ii), Irish potatoes must also be moved in approved containers in order to be excluded from regulated article status. This requirement was designed to prevent the potatoes from becoming contaminated with infested soil. Prior to the effective date of this document, the quarantine and regulations provided that the following categories of containers were approved containers: (1) new paper bags; and consumer packages of any material except cloth or burlap, (2) crates, pallet boxes, trucks, and boxcars, if free of soil, and (3) new burlap bags for shipment of Irish potatoes to Puerto Rico. It is extremely difficult to inspect new or used bags to assure that the bags have not come in contact with soil and that they are free of soil. Such new or used bags used in an infested field could carry the golden nematode. The threat of spreading the golden nematode by such bags could be

a significant problem where Irish potatoes are grown commercially, since bags are often reused in commercial fields where Irish potatoes are harvested. New burlap bags were allowed to be used as containers for the movement of Irish potatoes to Puerto Rico because Irish potatoes were not grown commercially in Puerto Rico. Therefore it had been determined that the bags were unlikely to be reused in commercial fields where Irish potatoes are grown. However, Irish potatoes are now being grown commercially in Puerto Rico. Accordingly, in order to prevent the artificial spread of the golden nematode it is necessary on an emergency basis to delete such new burlap bags from the list of approved containers.

PART 301—DOMESTIC QUARANTINE NOTICES

Under the circumstances referred to above, the golden nematode quarantine and regulations in 7 CFR Part 301 are amended as follows: 1. Subparagraphs (6) through (14) in § 301.85(b) of the quarantine and regulations (7 CFR 301.85(b) (6) through (14)) are redesignated as (b) (6)–(15) and are revised to read as follows:

§ 301.85 Quarantine; restriction on interstate movement of specified regulated areas.

(b) * * *

(6) Irish potatoes included within any one or more of the following subdivisions (i), (ii), or (iii) of this subparagraph:

(i) Irish potatoes for seed; and
(ii) Irish potatoes unless—
(A) Each is at least 1½ inches in diameter based on measurement by a sizing screen or sizing chain, each is substantially free of soil as a result of grading (a method of removing soil mechanically) under a compliance agreement in accordance with § 301.85–5(b), and they are moved in an approved container; or

(B) Each is substantially free of soil as a result of washing or fluming under a compliance agreement in accordance with § 301.85–5(b), and they are moved in an approved container; or

(iii) Irish potatoes harvested from a field tested and found by an inspector to contain an identifiable population of viable golden nematodes, unless such field had been subsequently treated in accordance with paragraph (b)(6)(ii) (A), (B), or (C) of this section under the supervision of an inspector and in accordance with any additional conditions found necessary by the inspector to assure effective application

of the pesticide used; and unless headlands and farm roads are treated in accordance with paragraph (b)(6)(iii)(D) of this section:

(A) Applications of 140.3 liters of Vorlex (1,3 dichloropropene; 1,2 dichloropropane, and other related compounds, 80 percent; plus methyl isothiocyanate, 20 percent active ingredients) per hectare (15 gallons per acre); two applications 5 to 10 days apart with a third application 5 to 10 days after the second application to areas in which the inspector finds upon microscopic examination of soil samples that viable golden nematodes may still exist; soil to be from 3° C to 29° C (38° F to 84° F).

(B) Applications of 280.6 liters of D-D (1,3 dichloropropene; 1,2 dichloropropane, and other related compounds, 100 percent active ingredients) per hectare (30 gallons per acre); two applications 5 to 10 days apart with a third application 5 to 10 days after the second application to areas in which the inspector finds upon microscopic examination of soil samples that viable golden nematodes may still exist (consult product label for heavier dosage in muck or peat soils); soil to be from 4.5° C to 29° C (40° F to 84° F).

(C) Applications of 168.4 liters of Telone II (1,3 dichloropropene, 92 percent active ingredient) per hectare (18 gallons per acre); two applications 5 to 10 days apart with a third application 5 to 10 days after the second application to areas in which the inspector finds upon microscopic examination of soil samples that viable golden nematodes may still exist (consult product label for heavier dosage in muck or peat soils); soil to be from 4.5° C to 32° C (40° F to 90° F).

(D) Application of Vapam (sodium-N-methyl dithiocarbamate, 32.7 percent active ingredient) mixed with water at the rate of 1 part Vapam to 60 parts water and applied as a drench at the rate of 14.96 cubic meters per hectare (1600 gallons per acre); soil to be from 4.5° C to 32° C (40° F to 90° F).

(7) Root crops other than Irish potatoes.

(8) Small grains and soybeans.

(9) Hay, straw, fodder, and plant litter, of any kind.

(10) Ear corn, except shucked ear corn.

(11) Used crates, boxes, and burlap bags, and other used farm products containers.

(12) Used farm tools.

(13) Used mechanized cultivating equipment and used harvesting equipment.

(14) Used mechanized soil-moving equipment.

(15) Any other products, articles, or means of conveyance of any character whatsoever, not covered by paragraphs (b) (1) through (14) of this section, when it is determined by an inspector that they present a hazard of spread of golden nematode, and the person in possession thereof has been so notified.

2. The definition of "Moved (movement, move)" in § 301.85–1(m) of the quarantine and regulations (7 CFR 301.85–1(m)) is revised to read as follows:

§ 301.85–1 Definitions.

(m) *Moved (movement, move).* Shipped, deposited for transmission in the mail, otherwise offered for shipment, received for transportation; carried, or otherwise transported, or moved, or allowed to be moved, by mail or otherwise. "Movement" and "move" shall be construed in accordance with this definition.

3. Section 301.85–2a of the quarantine and regulations (7 CFR 301.85–2a) is amended by revising subparagraph (I), which list regulated areas in New York, to read as follows:

§ 301.85–2a Regulated areas; suppressive and generally infested areas.

(I) *Generally infested area:*
Cayuga County. The town of Montezuma.
Genesee County. The towns of Elba and Byron.

Nassau County. The entire county.
Orleans County. The towns of Barre and Clarendon.

Seneca County. The town of Tyre.
Steuben County. The towns of Prattsburg and Wheeler; that area known as "Arkport Muck" located in the town of Dansville and bounded by a line beginning at a point where the Conrail right-of-way (Erie Lackawanna Rail Road) intersects County Road 52 (known as Burns Road), then north and northeast along County Road 52 to its junction with New York Route 36, then south and southeast along New York Route 36 to its intersection with the Dansville Town line, then west along the Dansville Town line to its intersection with the Conrail right-of-way (Erie Lackawanna Rail Road), then north and northwest along the Conrail right-of-way to the point of beginning; and the Werth, Dale, farm, known as the "Werthwhile Farm," located in the town of Cohocton on the north side of County Road 5 (known as Brown Hill Road), and 0.2 mile west of the junction of County Road 5 with County Road 58 (known as Wager Road).

Suffolk County. The entire county.
Wayne County. The town of Savannah.

§ 301.85–2b [Amended]

4. The provisions in § 301.85–2b(b) of the quarantine and regulations (7 CFR 301.85–2b(b)) are amended by removing subparagraph (1) and by redesignating

subparagraphs (2) and (3) as subparagraphs (1) and (2), respectively.

5. Section 301.85-5 of the quarantine and regulations (7 CFR 301.85-5) is amended by redesignating paragraph (b) as paragraph (c) and by adding a new paragraph (b) to read as follows:

§ 301.85-5 Compliance agreement and cancellation thereof.

(b) Any person engaged in the business of removing soil from Irish potatoes by the process of grading, washing, or fluming may enter into a compliance agreement concerning such operations. The compliance agreement shall be a written agreement between the person conducting such operations and Plant Protection and Quarantine wherein such person agrees to conduct such operations in a manner which, in the judgment of the inspector supervising enforcement of the quarantine and regulations, will substantially remove the soil from the potatoes.

(Secs. 105 and 106, 71 Stat. 32, 33; 7 U.S.C. 150dd, 150ee; 37 FR 28464, 28477, as amended; 45 FR 8564, 8565)

Done at Washington, D.C., this 17th day of March 1982.

William F. Helms,

Acting Deputy Administrator, Plant Protection and Quarantine, Animal and Plant Health Inspection Service.

[FR Doc. 82-7641 Filed 3-22-82; 8:45 am]

BILLING CODE 3410-34-M

SMALL BUSINESS ADMINISTRATION

13 CFR Part 105

Standards of Conduct

AGENCY: Small Business Administration.

ACTION: Final rule.

SUMMARY: This final rule provides amendments to Part 105 of SBA's Standards of Conduct Regulations. These amendments constitute an extensive revision of this regulation. There are five general purposes for these amendments:

First, they reflect the experience of SBA in the general field of employee ethical conduct since the last major revision of these regulations in 1976 (41 FR 29656, July 19, 1976; correction, 41 FR 33547, August 10, 1976). Second, changes in language are made in order to clarify meaning. Many of the interpretative problems that arose since 1976 essentially reflected unanticipated ambiguities in language. Third, changes in position titles are made in accordance with various SBA organizational

changes. Fourth, significant new amendments are included in order to reflect major statutory provisions in the Ethics in Government Act of 1978 (Pub. L. 95-521, October 26, 1978; amended by Pub. L. 96-19 and Pub. L. 96-28). Fifth, interpretations of Agency regulations by the Agency Standards of Conduct Committee (13 CFR 105.801 in both the prior regulations and these amendments) have been incorporated into the body of these regulations. This will provide additional guidance to Agency employees and management officials in the standards of conduct area. This should also diminish the number of requests to the Standards of Conduct Committee from agency employees, former employees, management officials and other interested parties requesting guidance in applying the regulations to specific situations.

EFFECTIVE DATE: March 23, 1982.

FOR FURTHER INFORMATION CONTACT:

Donald W. Farrell, Associate General Counsel, (202) 653-6660 or Robert Peterson, (202) 653-6477.

SUPPLEMENTARY INFORMATION: These regulations were published for public comment in the June 22, 1981, *Federal Register* (46 FR 32259). The sole response received, from the SBA Council of Locals, basically referred to negotiability and procedural issues under the SBA—Union labor agreement, which are being handled under the terms of that agreement. They also requested additional background information on the regulations, which was provided.

Executive Order 12291, effective February 17, 1981, does not apply to these amendments. (See Section 1(a)(3) of the Executive Order.) In addition, it is hereby certified that, for the purposes of the applicability of the requirements of sections 603 and 604 of the Regulatory Flexibility Act (Pub. L. 96-354, September 19, 1980, 5 U.S.C. 603 and 604), these amendments will not have a significant economic impact on a substantial number of small entities. These rules primarily affect the standards of conduct for SBA employees and former SBA employees.

Particular areas covered in the proposed amendments include:

1. Section 105.101, the general purpose clause of the Standards of Conduct Regulations, is amended by adding clarifying language.

2. Section 105.201, "Definitions," is amended in subsection (i) by adding new language making it clear that eligibility determinations under SBA's Section 8(a) Program constitute "SBA Assistance" for the purpose of the

Standards of Conduct Regulations; and by adding a new subsection (1) defining "Senior Employee" for the purposes of other amendments in Part 105 derived from the Ethics in Government Act of 1978.

3. Section 105.401, dealing with former SBA employees appearing in a representational capacity in connection with an SBA matter, is amended by adding general clarifying language and by increasing the proscribed time period under the regulation from one year to two years in order to bring the regulation into conformity with the comparable statutory provision amended by the Ethics in Government Act of 1978.

4. Section 105.402, also generally dealing with former employees acting in a representational capacity in connection with an SBA matter, is amended by adding clarifying language.

5. Section 105.403, dealing with employment of former SBA personnel by recipients of SBA assistance, is amended by deleting a provision in the current regulation that extends the proscription of the regulation to persons providing significant legal, accounting and similar services to the SBA aid recipient. As amended, the regulatory proscription would apply only to the SBA aid recipient itself. SBA's experience has been that this extended limitation in the current regulation is unnecessary and difficult to apply equitably and uniformly to all situations.

6. Section 105.404, dealing with SBA assistance to a concern employing a former SBA employee, is amended to correct minor typographical errors in the current regulation.

7. The current § 105.405 is redesignated as § 105.408 and a new § 105.405, dealing with personal appearances in an SBA matter by a former SBA "Senior Employee," is substituted therefor. This new regulatory provision, though somewhat broader in scope, basically tracks the provisions of 18 U.S.C. 207(b)(ii), enacted as part of the Ethics in Government Act of 1978.

8. Section 105.406, dealing with the involvement by a former SBA "Senior Employee" in SBA decisional matters, is a new regulation which generally tracks the companion statutory provision in 18 U.S.C. 207(c) which was enacted as part of the Ethics in Government Act of 1978.

9. Section 105.407, dealing with debarment of persons in appearances before SBA for violations of the post employment restrictions of 18 U.S.C. 207, as amended, is a new regulation in accord with the directive of 18 U.S.C. 207(j), adopted as part of the Ethics in

Government Act of 1978. This provision sets forth detailed procedures for these debarment proceedings.

10. Section 105.408, dealing with statutory cross references, is the repositioning, without substantive change, of § 105.405 in the current regulation.

11. Section 105.505, dealing with situations creating an "appearance" of a conflict of interest, is significantly expanded by adding new language to clarify the application of this "appearance" rule and to emphasize its importance as part of the employee's official Standards of Conduct.

12. Section 105.510, dealing with outside employment and activities, is amended by adding clarifying language and by redesignating the respective responsibilities of SBA's field offices and Central office in considering applications for outside employment activity approval.

13. Sections 105.511 and 105.512 deal with financial disclosure statements required from SBA employees. Section 105.511, dealing with financial disclosure statements required under E.O. 11222 basically adds clarifying language and language distinguishing between required filings under E.O. 11222 and filings under the Ethics in Government Act of 1978. Section 105.512 is a new provision dealing with financial disclosure statements required under the Ethics in Government Act of 1978 from designated SBA employees and the procedures for effecting these required filings.

14. Current §§ 105.512, 105.513, 105.514, 105.515, 105.516, 105.517, 105.518, 105.519, are respectively redesignated as §§ 105.513, 105.514, 105.515, 105.516, 105.517, 105.518, 105.519, and 105.520.

15. Section 105.513 (currently § 105.512), dealing with political activity of employees, adds the position of Chief Counsel for Advocacy to those SBA positions excepted from the restrictions of subsection (c) against active participation in political management or political campaigning.

16. Section 105.516 (currently § 105.515), dealing with the duty of SBA employees to report official irregularities, changes the SBA official to whom such reports must be made from the "Director, Investigations and Security Division" to the "SBA Inspector General."

17. Section 105.520 (currently § 105.519), dealing with employee recommendations of private persons, is amended to clarify that the regulation would not prohibit assisting small concerns by providing, without official recommendation, lists of available private financial institutions or others

participating with SBA in its various programs.

18. Section 105.601, dealing with assistance to employees of Government organizations, is amended by adding the new subsection (b) that would emphasize the general rule of Government procurement that, except in special circumstances, SBA will not enter into a contract with a Government employee or a concern significantly connected with a Government employee. The former subsection (b) is redesignated as subsection (c) to accommodate this new provision.

19. Section 105.801, dealing with the composition and functions of the Standards of Conduct Committee is amended to clarify that the Committee will provide guidance in connection with a request from any agency management official and to change membership and position titles in order to reflect Agency reorganizations.

20. Section 105.802, dealing with the designation of Standards of Conduct Counselors and their functions, is amended by changing position titles therein to reflect SBA reorganizations and to clarify the responsibilities of Standards of Conduct Counselors in administering the program.

21. Section 105.803, dealing with SBA Designated Ethics Officials and their functions, is a new provision implementing that section of the Ethics in Government Act of 1978, requiring the designation of agency officials to administer that Act.

22. Section 105.901, which cites relevant statutory and regulatory provisions in the Standards of Conduct area, is revised and updated to reflect changes in the law.

Dated: March 8, 1982.

Donald R. Templeman,
Acting Administrator.

Therefore, pursuant to the authority of Section 5(b)(6) of the Small Business Act (15 U.S.C. 634), the Small Business Administration hereby amends Part 105 of its Regulations (13 CFR Part 105), as follows:

The table of contents at the beginning of Part 105 is revised to read as follows:

PART 105—STANDARDS OF CONDUCT

Sec.

- 105.101 Purpose and scope.
- 105.201 Definitions.
- 105.301 General requirements.

Restrictions Relating to Former SBA Employees

- 105.401 Acting as representative in matter previously under the official responsibility of former employee.

Sec.

- 105.402 Acting as representative in matter in which former employee personally participated.
- 105.403 Employment of former employee by person previously the recipient of SBA assistance.
- 105.404 SBA assistance to person employing former SBA employee.
- 105.405 Personal appearance by former Senior Employee in matter in which he personally participated.
- 105.406 Involvement by former Senior Employee in SBA decisional matters.
- 105.407 Proceedings for debarment from appearances before SBA for violations of post employment restrictions contained in 18 U.S.C. 207 (a), (b) and (c).
- 105.408 Cross references.

Restrictions Relating to Present SBA Employees

- 105.501 Involvement in matters in which Government has substantial interest.
- 105.502 Compensation relating to official duties from nongovernment source.
- 105.503 Gratuities from persons dealing with SBA.
- 105.504 Other gifts and gratuities.
- 105.505 Situations creating a conflict of interest or the appearance thereof.
- 105.506 Personal interests in firms or matters having SBA involvement.
- 105.507 Use of Government property and supplies.
- 105.508 Conversion of public and other property.
- 105.509 Distortion of records; false statements.
- 105.510 Outside employment and activities.
- 105.511 Financial disclosure statements under Executive Order 11222.
- 105.512 Financial disclosure statements under the Ethics in Government Act of 1978.
- 105.513 Political activity of employees.
- 105.514 Striking against Government.
- 105.515 Disclosure of official information.
- 105.516 Duty to report irregularities.
- 105.517 Applicable rules and directions.
- 105.518 Gambling.
- 105.519 Payment of financial obligations.
- 105.520 Recommendations of private person.

Restrictions Relating to Officers or Employees of Other Government or Quasi-Government Organizations

- 105.601 Assistance to officers or employees of other Government organizations.
- 105.602 Assistance to employees or members of quasi-Government organizations.

Administrative Provisions

- 105.701 Penalties.
- 105.801 Standards of Conduct Committee.
- 105.802 Standards of Conduct Counselors.
- 105.803 Designated Agency Ethics Officials.
- 105.901 Statutory and other regulatory provisions.

Authority: Sec. 5, 72 Stat. 385 (15 U.S.C. 634); E.O. 11222, 3 CFR 1964-65; Comp. 5 CFR 735.104, unless otherwise noted.

1. Section 105.101, dealing with the purpose and scope of the regulation, is revised to read as follows:

§ 105.101 Purpose and scope.

(a) This part prescribes standards of conduct for current SBA employees and former SBA employees, relating to possible conflicts between their official duties or the public interest and their private interests.

(b) Except as otherwise noted, this part deals with SBA administrative standards and does not purport to be interpretative of requirements imposed by analogous criminal statutes or regulations or directions of other proper authorities. For example, interpretations with respect to criminal statutes normally should be obtained from the Department of Justice.

§ 105.201 [Amended]

2. Section 105.201, Definitions, is amended as follows:

a. Paragraph (i) is revised to read as follows:

(i) "SBA Assistance" means financial, contractual, grant, managerial or other aid, including size, Section 8(a) or other eligibility determinations granted by SBA under applicable law. For the purposes of this part, this term shall also include an express decision to compromise or defer possible litigation or other adverse action.

* * *

b. A new paragraph (l) is added to read as follows:

* * *

(l) "Senior Employee" means an SBA employee paid at the Executive Level pursuant to subchapter 11 of Chapter 53 of Title 5, U.S.C. and any other employee, GS-17 or above or a member of the Senior Executive Service who has significant decisionmaking or policy responsibilities and is so designated by the Director, Office of Government Ethics pursuant to 18 U.S.C. 207(d).

3. Section 105.401, dealing with representational activities of former employees before SBA, is revised to read as follows:

§ 105.401 Acting as representative in matter previously under official responsibility of former employee.

No former employee may, within two years after his employment with SBA has ceased, appear before SBA or in any proceeding conducted by or on behalf of SBA, or in which SBA has an interest, as agent, attorney or representative, or make any oral or written communications to SBA with intent to influence, in connection with any claim, determination or other specific matter which was under his official responsibility within one year prior to the termination of his employment.

4. Section 105.402, also dealing with representational activities of former employees before SBA is revised to read as follows:

§ 105.402 Acting as representative in matter in which former employee personally participated.

No former employee may ever, after his employment with SBA has ceased, appear as agent, attorney or representative before SBA or in any proceeding conducted by or on behalf of SBA, or in which SBA has an interest, or make any oral or written communication to SBA with intent to influence, in connection with any claim, determination or other specific matter in which he participated personally and substantially while an employee through decision, approval, disapproval, recommendation, the rendering of advice, investigation or otherwise.

§ 105.403 [Amended]

5. Section 105.403, dealing with employment of former SBA personnel by recipients of SBA assistance, is amended by deleting from the introductory paragraph the words "or with a person who provides significant legal, accounting or other services to the concern," and also deleting the comma prior to this clause.

§ 105.404 [Amended]

6. Section 105.404, dealing with SBA assistance to concerns employing a former SBA employee, is amended by substituting the word "or" for the word "of" following the word "creditor" in paragraph (a) of this provision.

§ 105.405 [Redesignated as § 105.408]

7. Section 105.405, dealing with cross references to statutory provisions, is renumbered as § 105.408.

8. A new § 105.405, dealing with appearances before the Agency by a former SBA Senior Employee, reads as follows:

§ 105.405 Personal appearance by former Senior Employee in matter in which he personally participated.

No former SBA Senior Employee may, within two years after his employment has ceased, assist by personal presence, another person in representations in any formal or informal appearance before SBA or in any formal or informal proceeding conducted by or on behalf of SBA, or in which SBA has an interest, in connection with any claim, determination or other specific matter in which he participated personally and substantially while an SBA Senior Employee through decision, approval, disapproval, recommendation, the rendering of advice or otherwise.

9. A new § 105.406, dealing with involvement in SBA decisional matters by a former SBA Senior Employee, reads as follows:

§ 105.406 Involvement by former Senior Employee in SBA decisional matters.

No former SBA Senior Employee may, within one year after his employment has ceased, make any formal or informal appearance before SBA or in any proceeding conducted by or on behalf of SBA as agent, attorney or representative or make any oral or written communication to SBA with intent to influence, in connection with any matter, whether or not dealing with a particular person or particular persons, which involves a decision, ruling, approval, disapproval, investigation, rulemaking or similar determination by SBA.

10. A new § 105.407, setting forth the detailed procedures for debarment proceedings for violations of 18 U.S.C. 207, reads as follows:

§ 105.407 Proceedings for debarment from appearances before SBA for violations of post employment restrictions contained in 18 U.S.C. 207 (a), (b) and (c).

(a) SBA may, in accordance with section 207(j) of 18 U.S.C. (included in the Ethics in Government Act of 1978, Pub. L. 95-521, as amended), as an administrative penalty for violation of 18 U.S.C. 207 (a), (b) or (c), prohibit a former SBA employee from making, on behalf of any other person, any informal or formal appearance before or, with intent to influence, any oral or written communication to SBA on a pending matter for a period not to exceed five years, or take other appropriate disciplinary action.

(b) The Standards of Conduct Committee (established pursuant to § 105.801) after reviewing all available information, may determine that there is reasonable cause to believe that a former employee (referred to in this section as Respondent) has violated 18 U.S.C. 207 (a), (b), or (c). This determination shall be set forth in a Report (Report) containing the relevant facts and inferences therefrom, and a recommendation for sanctions and/or disciplinary action, within the limitations of paragraph (a) of this section.

(c)(1) A copy of this Report and any appropriate comments will be provided to the Director of the Office of Government Ethics and, in coordination with the SBA Inspector General, to the Criminal Division of the Department of Justice. SBA administrative proceedings will be coordinated with the Department of Justice unless the Department advises SBA that it does not intend to initiate criminal prosecution.

(2) Copies of this Report and all other notices, pleadings, motions and other

official documents relative to a proceeding under this section shall be provided by the Standards of Conduct Committee, by the SBA General Counsel, by the Respondent and by any other parties to the SBA Office of Hearings and Appeals. This office will serve as the Docket Office for these proceedings and the documents filed with it will constitute the official files for the proceedings.

(d)(1) *Service upon respondent.* Notice of Intent to Impose Administrative Sanctions (Notice) on Respondent for violation of post-employment restrictions, signed by the Chairman of the Standards of Conduct Committee, and subsequent papers for such proceeding shall be served upon the Respondent in the following manner:

(i) By delivering it to the Respondent personally; or

(ii) By registered mail; or

(iii) If a Respondent has signed and filed with the Director of the SBA Office of Hearings and Appeals written consent to be served in some other practicable manner, by that other manner. Where service is by registered mail, evidence of such mailing by SBA shall affirm proper service.

(2) *Service upon SBA.* Papers shall be served upon SBA as follows:

(i) By delivering them to the General Counsel of SBA; or

(ii) By registered mail addressed to the General Counsel of the Small Business Administration, Washington, D.C. 20416. See paragraph (c)(2) of this section

regarding the delivery of copies of all documents in a proceedings to the SBA Office of Hearings and Appeals.

(e) The Notice of Intent to Impose Administrative Sanctions shall contain:

(1) A copy of the Report of the Standards of Conduct Committee, referenced in paragraph (b) herein. The basis for the proposed administrative action shall be the facts and charges set forth in this Report.

(2) A copy of this § 105.407.

(f)(1) In the event a Respondent, who has been served a Notice, fails to file an Answer within the time limits set forth in this section, SBA may base its decision solely on information contained in the Standards of Conduct Committee Report.

(2) A recommended decision, based solely on the Notice and Report, shall be made by an attorney-examiner authorized by the Director of SBA's Office of Hearings and Appeals. No person, who has significantly participated in other aspects of a proceeding or who is directly under the organizational jurisdiction of the

General Counsel, may serve as an examiner in that proceeding.

(g) Within thirty (30) days of service of the Notice, the Respondent may file a written Answer to the allegations contained in said Notice. Answers should be filed in accordance with paragraph (d)(2) of this section and copies provided in accordance with paragraph (c)(2) of this section. This Answer shall include

Respondent's determination whether the allegations set forth in the Notice should be decided solely on the basis of the Notice and the Answer, or only after a Hearing, as described in paragraph (h) of this section. Upon the failure of such a determination by Respondent in the Answer, the matter will be decided solely on the basis of the Notice and Answer.

A recommended decision made solely on the Notice and Answer shall be made by an attorney-examiner authorized as set forth in paragraph (f)(2) of this section.

(h) A Hearing, if requested, shall be informal and held before an attorney-examiner duly authorized as set forth in paragraph (f)(2) of this section. The attorney-examiner shall determine the time, place, and manner for the Hearing and the form in which evidence shall be received; he may establish the format for prehearing conferences and the narrowing of issues, and rules of evidence, including rules and determinations concerning relevancy and repetition, as required for the orderly disposition of the case. A transcript of the Hearing will be made. Respondent shall have the right of self-representation, the right to counsel, the right to introduce and examine witnesses, the right to confront and cross-examine adverse witnesses, the right to submit physical evidence, and the right to present oral argument. Except as noted herein, Respondent shall have sole responsibility for obtaining witnesses and evidence for his case and for the cost thereof.

Respondent may request the examiner to provide SBA employees as witnesses. The examiner may direct the presence of SBA employees as witnesses, whose appearance shall thereupon constitute the performance of an official function. A recommended decision will be made, based upon the full record, including the Hearing, by the attorney-examiner.

(i) The attorney-examiner shall base his determinations exclusively on matters of record in the proceedings, either limited to the Notice, or to the Notice and Answer, or to the Notice, Answer and record of the Hearing, including ancillary evidentiary material

produced as part of the Hearing (depending upon the type of proceeding used); and he shall make a written recommended decision setting forth all findings of fact and conclusions of law, relevant to the matters at issue. In the event the attorney-examiner determines that Respondent has violated any of the post-employment provisions of 18 U.S.C. 207 (a) (b), or (c), this decision shall also include a recommended penalty, within the limits set forth in paragraph (a) of this section. A copy of the attorney-examiner's recommended decision shall be served on Respondent and SBA as provided in paragraph (d) of this section. In the absence of a timely appeal by either the Respondent or by the SBA General Counsel, on behalf of the Agency, the attorney-examiner's recommended decision will be adopted by the Administrator as the Agency's final decision, including recommendations regarding administrative sanctions or disciplinary actions against Respondent.

(j)(1) Within twenty (20) business days from the date of service of the attorney-examiner's recommended decision, either party may appeal the recommended decision to the Administrator by serving a written appeal on the Administrator, personally or by registered mail. A written copy of the appeal must also be served on the other party in accordance with paragraph (d) of this section. The other party will be allowed ten (10) business days after being served with notice of an appeal to submit any desired response. In evaluating an appeal under this subsection, the Administrator may utilize the advice and assistance of the SBA Office of Hearings and Appeals, provided, that neither the attorney-examiner who made the recommended decision in this case nor any other person who significantly participated in the recommended decision may provide such advice or assistance. Neither designation of an attorney-examiner to a case nor general supervision of the office will preclude the Director of the Office of Hearings and Appeals from providing advice and assistance to the Administrator under this paragraph.

(2) The appeal shall state in detail how the recommended decision of the attorney-examiner is erroneous and/or should be changed or modified.

(3) The Administrator shall base his decision on the complete record of the proceedings, including the appeal and response thereto. The Administrator's decision may adopt, modify or change the recommended decision of the attorney-examiner, including

recommended sanctions or disciplinary actions against Respondent. In such a decision upon appeal, the Administrator is not precluded from changing or modifying any finding of fact or conclusion of law nor from increasing any sanction or disciplinary action against Respondent.

(4) The decision of the Administrator shall be the final administrative determination of the Small Business Administration.

11. Section 105.505, dealing with conflicts situations and the appearances thereof, is amended by adding a new paragraph (b) which reads as follows:

§ 105.505 Situations creating a conflict of interest or the appearance thereof.

(b) Employees should be aware that the appearance of a conflict of interest, even absent the existence of any actual conflict, are matters of significant concern in the administration of employee standards of conduct. "Appearances" problems could arise, for example, where an employee is involved in the consideration of SBA assistance to a personal friend, a former supervisor or a similarly situated person, or where an employee is considering a business or commercial transaction with a known applicant for or recipient of SBA assistance, or where an employee is involved, in a personal capacity, in business negotiations with a known applicant for or recipient of SBA assistance. Special care should be taken by each employee to guard against the occurrence of any "appearance" violation of these regulations. Violations may be the basis for SBA disciplinary action. Where there is any question relating to the application of these rules to a particular situation, the employee is required to disqualify himself from any official action which might create such an "appearance" of a conflict of interest until he has received written approval from the appropriate SBA Standards of Conduct Counselor or from the SBA Standards of Conduct Committee.

§ 105.510 [Amended]

12. Section 105.510, dealing with outside employment and activities, is amended as follows:

a. Paragraph (a) of this section is revised to read as follows:

(a) Except with the written approval of the appropriate agency official as noted in paragraph (b) of this section, no employee shall engage in any outside business, employment, occupation or similar activity. This limitation applies regardless of whether a fee, gift, salary

or other compensation is received for the activity.

b. Existing paragraph (b) is redesignated as (c) and the introductory paragraph thereof will be revised to read as follows:

(c) In reviewing applications for approval under this section, all relevant factors will be considered, including:

c. A new paragraph (b) is added to read as follows:

(b) Requests for approval under this section shall be submitted as follows:

(1) For employees of SBA offices, other than the Central Office, all submittals shall initially be made to the Regional Standards of Conduct Counselors, noted in § 105.802 of this regulation.

(i) Requests by employees below the level of GS-13 and relating to outside activities of a noncontroversial, low visibility nature having no apparent connection with SBA activities, having no significant "appearances" problems, and involving no apparent interference with the performance of official duties or official time shall be resolved by the Regional Standards of Conduct Counselor. Copies of these written decisions will be forwarded to the Agency Standards of Conduct Counselor noted in § 105.802.

(ii) All other SBA field office requests shall be reviewed by the Regional Standards of Conduct Counselor and forwarded with his written recommendations to the Agency Standards of Conduct Counselor for preparation and submittal for decision to the SBA Standards of Conduct Committee pursuant to § 105.801.

(2) For employees of SBA's Central Office, all submittals shall initially be made to the Agency Standards of Conduct Counselor, noted in § 105.802.

(i) Requests by employees below the level of GS-15 and relating to outside activities of a noncontroversial, low visibility nature, having no apparent connection with SBA activities, having no significant "appearances" problems, and involving no apparent interference with the performance of official duties or official time shall be resolved by the Agency Standards of Conduct Counselor.

(ii) All other SBA Central Office requests shall be prepared by the Agency Standards of Conduct Counselor for submittal to and decision by the Standards of Conduct Committee pursuant to § 105.801.

(3) It is contemplated that the Committee will decide all requests for outside activity approval that involve a significant appearances issue (see § 105.505), situations of a controversial nature, situations having a high public visibility, activities that would involve a significant interaction with SBA or other governmental units, activities involving interference with the official functions of the employee and situations involving high-ranking Agency officials who have wide discretionary authority with respect to the granting and administration of SBA assistance.

d. Existing paragraph (c) will be redesignated as (d)

e. Existing paragraph (d)(1) of the current regulation will be removed in its entirety and paragraph (d)(2) will be redesignated (e) and the introductory clause revised to read as follows:

* * * This section does not preclude an employee from:

§ 105.511 [Amended]

13. Section 105.511, dealing with financial disclosure statements required from employees, is amended as follows:

a. The title of this provision is amended to read as follows:

Financial Disclosure Statements Under Executive Order 11222

b. The introductory phrase of paragraph (a) is revised to read as follows:

(a) Financial disclosure statements under Executive Order 11222 (May 8, 1965) are required from the following SBA employees:

c. Paragraph (a)(1) of the current regulations is removed.

d. Paragraph (a)(2) of the current regulations is removed.

e. Paragraph (a)(3) of the current regulations is redesignated (a)(1) and is revised to read as follows:

(a) * * *
(1) All Regional Administrators, District Directors, and Branch Managers, except those who file a Financial Disclosure Report under § 105.512.

f. Paragraph (a)(4) of the current regulations is redesignated (a)(2) and is amended by adding at the end thereof the following new paragraph:

(a) * * *
(2) * * * All employees in the Senior Executive Service and those paid at GS-16 or above level are required to file a Financial Disclosure Report under § 105.512 of these regulations pursuant

to the Ethics in Government Act of 1978. These employees and any others who file under that Act are not required to file under this paragraph (a)(2).

g. Paragraph (d)(1) is amended by substituting reference to "paragraph (a)(2)" for "paragraph (a)(4)" wherever it appears; substituting the title "Regional Administrator" for "Regional Director" wherever it appears; and inserting after the title "Assistant Administrator," a comma and the title "the Inspector General."

h. Paragraph (d)(2) is revised to read as follows:

(d) * * *

(2) Any employee who contends that he is improperly required to file a Financial Disclosure Statement under this section may request a review of his complaint under an SBA grievance procedure. Advice concerning SBA grievance procedures may be obtained from the SBA Office of Personnel.

i. Paragraph (g) is amended by substituting therein the title "Office of Government Ethics" for the title "Civil Service Commission."

§ 105.512 [Redesignated as § 105.513]

14. Existing § 105.512, dealing with political activity of employees is redesignated § 105.513 and is amended by adding in paragraph (c), after the word "Administrator," the words "or the Chief Counsel for Advocacy."

15. A new § 105.512, dealing with Financial Disclosure Statements of employees required under the Ethics in Government Act of 1978, is added to read as follows:

§ 105.512 Financial disclosure statements under the Ethics in Government Act of 1978.

(a) Financial Disclosure Statements under the Ethics in Government Act of 1958 (Pub. L. 95-521 as amended) are required from the following SBA employees. Those who file under this provision are not required to file under § 105.511 of this regulation:

(1) The Administrator, the Inspector General, and the Chief Counsel for Advocacy.

(2) All SBA employees in the Executive Schedule.

(3) All SBA employees paid at the GS-16 or above in the General Schedule or at an equivalent rate for other pay schedules. This will include all members of the Senior Executive Service.

(4) Administrative Law Judges, regardless of grade.

(5) Employees in the excepted service in positions which are of a confidential

or policymaking character, regardless of grade (except that the Director of the Office of Government Ethics may exclude individuals or groups of individuals where the Director determines such exclusion would not adversely affect the integrity of the Government nor the confidence of the public in that integrity).

(b) The Designated Agency Ethics Officials described in § 105.803.

(c) These statements shall be filed on the form prescribed by the Office of Government Ethics. Forms are available from SBA's Designated Agency Ethics Officials.

(d) These statements shall be filed with SBA's Designated Agency Ethics Officials within time frames specified by him.

(e) The general policies, special provisions, requirements for reporting by trusts, procedures and other matters relating to these statements and their filing by SBA employees are set forth in 5 CFR Part 734. These are regulations promulgated by and, from time to time, amended by the Office of Government Ethics. Employees should be cognizant of these regulations in assessing their obligations regarding these Financial Disclosure statements.

§ 105.513 [Redesignated as § 105.514]

16. Existing § 105.513, dealing with strikes against the Government, is redesignated § 105.514.

§ 105.514 [Redesignated as § 105.515]

17. Existing § 105.514, dealing with disclosure of official information, is redesignated § 105.515.

§ 105.515 [Redesignated as § 105.516 and Amended]

18. Existing § 105.515, dealing with the duty of employees to report official irregularities, is redesignated § 105.516 and the reference therein to "Director, Security and Investigations Division" is deleted and substituted therefor is the title "SBA Inspector General."

§ 105.516 [Redesignated as § 105.517]

19. Existing § 105.516, dealing with other rules and directives applicable to SBA employees, is redesignated § 105.517.

§ 105.517 [Redesignated as § 105.518]

20. Existing § 105.517, "Gambling," is redesignated § 105.518.

§ 105.518 [Redesignated as § 105.519]

21. Existing § 105.518, dealing with payment of financial obligations, is redesignated § 105.519.

§ 105.519 [Redesignated as § 105.520 and Amended]

22. Existing § 105.519, is redesignated § 105.520 and is amended by removing at the end thereof the words "or any other Government department" and adding a new paragraph which reads as follows:

This regulation does not preclude an employee from providing a list of nongovernmental entities which participate or evince an interest in participating in SBA assistance programs where the purpose is solely to assist current or potential applicants or recipients of SBA assistance and where it is made clear that no recommendations or certification as to quality of service, ability or other attributes is involved.

§ 105.601 [Amended]

23. Section 105.601 is amended as follows:

a. Paragraph (a) is amended by inserting at the beginning the words "Except as noted in paragraph (b) of this section."

b. Existing paragraph "(b)" is redesignated "(c)" and a new (b) is added to read as follows:

(b) Except in special circumstances approved by the Standards of Conduct Committee, SBA will not enter into a contract with a person when its sole proprietor, partner, officer, director or stockholder with a 10 or more percent interest, or a member of his household, is an employee of a Government agency. In this connection, also see 41 CFR 1-1.302.3.

§ 105.801 [Amended]

24. Section 105.801, "Standards of Conduct Committee," is amended as follows:

a. Paragraph (a)(2) is amended by removing the words "the Director of Personnel and from others" and inserting therefor the words "Agency management officials."

b. Paragraph (b)(2) is amended by substituting the title "Assistant Administrator for Administration" for the title "Associate Deputy Administrator for Support Services," and the title "Director of Labor Relations" for the title "Assistant Administrator for Personnel Management."

c. Paragraph (b)(3) is amended by substituting the title "Director of Field Management" for the title "Associate Deputy Administrator for Programs," and the title "Deputy Director of Field

Management" for the title "Director, Office of Field Management."

§ 105.802 [Amended]

25. Section 105.802, "Standards of Conduct Counselors," is amended as follows:

a. By removing the title "Associate General Counsel for Interagency Affairs," wherever it appears, and substituting therefor the title "Associate General Counsel for General Law;"

b. By revising paragraph (b)(2) to read as follows:

(b) * * *

(2) "Monitor the Standards of Conduct Program within their respective areas and provide required reports thereon; and"

c. By adding a new paragraph (b)(4) to read as follows:

(b) * * *

(4) Provide Outside Employment and Activities decisions pursuant to § 105.510 of this regulation

d. By revising paragraph (d) to read as follows:

(d) Where a specific ruling regarding a particular situation is required, the request should be directed through the Standards of Conduct Counselor to the Standards of Conduct Committee.

26. A new § 105.803, "Designated Agency Ethics Officials," is added to read as follows:

§ 105.803 Designated Agency Ethics Officials.

(a) The Designated Agency Ethics Official, appointed by the Administrator pursuant to the Ethics in Government Act of 1978, shall be the Associate General Counsel for General Law. He shall be assisted by an Alternate Designated Agency Ethics Official, who will be an attorney in the Office of General Law. The Alternate Official will assist the Designated Agency Ethics Official and shall act for him, in his absence, in the performance of his official functions.

(b) The Designated Agency Ethics Officials shall administer the program for Financial Disclosure Statements under § 105.512, receive and evaluate these statements and provide advice and counsel regarding matters relating to the Ethics in Government Act of 1978 and its implementing regulations. The duties and responsibilities of the Designated Agency Ethics Officials are set forth in more detail in 5 CFR Part 738

which is promulgated by and, from time to time, amended by the Office of Government Ethics.

27. Section 105.901, dealing with other statutory and regulatory provisions in the area of Standards of Conduct is amended by adding new paragraphs (r), (s), (t), (u), (v), and (w) as follows:

§ 105.901 Statutory and Other Regulatory Provisions.

(r) The provisions relating to post Government employment restrictions (18 U.S.C. 207).

(s) The prohibition against official acts affecting employees' personal financial interest (18 U.S.C. 208).

(t) The prohibition against the payment of Government employees' salary by other than the United States (18 U.S.C. 209).

(u) The prohibition against Government employees receiving basic pay from more than one Federal Government job for more than 40 hours per week (5 U.S.C. 5533).

(v) The prohibitions against accepting honorariums beyond designated amounts (2 U.S.C. 441(i)).

(w) Code of Ethics for Government Service (Pub. L. 96-303; July 3, 1980).

[FR Doc. 82-7475 Filed 3-19-82; 12:32 pm]

BILLING CODE 8025-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 558

New Animal Drugs for Use in Animal Feeds; Hygromycin B

Correction

In FR Doc. 82-2247 appearing at page 4250 in the issue of Friday, January 29, 1982, make the following changes:

(1) On page 4251, first column, under part heading, "PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS, in the tenth and eleventh lines of the amendatory language, "paragraphs" should read "paragraph".

(2) On page 4251, first column, in the text of § 558.274, in the first line of paragraph (a)(5), "0.048" should read "0.48".

(3) On page 4251, in the table for § 558.274, in the column under "Sponsor", the word "or" which appears twice should be removed.

BILLING CODE 1505-01-M

DEPARTMENT OF THE TREASURY

Office of Foreign Assets Control

31 CFR Part 520

Foreign Funds Control Regulations: Unblocking of Czechoslovak Assets

AGENCY: Office of Foreign Assets Control, Treasury.

ACTION: Final rule.

SUMMARY: The Office of Foreign Assets Control is amending the Foreign Funds Control Regulations for the purpose of removing the remaining World War II controls on blocked Czechoslovak property in the United States. The controls heretofore blocked property of Czechoslovakia and of any individual, partnership, association, corporation, or other organization which on December 7, 1945, was in Czechoslovakia. The controls are being removed in implementation of the U.S.-Czechoslovak Agreement concerning the Settlement of Certain Outstanding Claims and Financial Issues signed on January 29, 1982. The effect of this amendment to the Regulations is to unblock Czechoslovak assets in the United States and delete any reference to Czechoslovakia as a blocked country.

EFFECTIVE DATE: March 19, 1982.

FOR FURTHER INFORMATION CONTACT: Raymond W. Konan, Chief Counsel, Office of Foreign Assets Control, Department of the Treasury, Washington, D.C. 20220, Tel. (202) 376-0236.

SUPPLEMENTARY INFORMATION: Under the provisions of the claims settlement agreement entered into between the United States and the Czechoslovak Socialist Republic, the latter government has paid to the U.S. a lump sum of \$81,500,000 in satisfaction of the claims of U.S. nationals relating to the expropriation of their property. In addition, an initial payment of \$2,869,968 has been made by the Czechoslovak Socialist Republic to the U.S. in partial satisfaction of the Credit Agreement on the Purchase of Surplus Property of the U.S. Army dated May 28, 1946. In return, the U.S. has consented to the delivery to Czechoslovakia of the remainder of its share of Nazi-looted monetary gold which was recovered by the allied forces at the end of World War II and which had been in the custody of the American-British-French Tripartite Gold Commission pending resolution of expropriation claims which arose following the war.

Since the Regulations invoke a foreign affairs function, the provisions of the Administrative Procedure Act, 5 U.S.C. 553, requiring notice of proposed rulemaking, opportunity for public participation and a delay in effective date are inapplicable. Similarly, because the Regulations are issued with respect to a foreign affairs function of the United States, they are not subject to Executive Order 12291 of February 17, 1981, dealing with Federal Regulations.

PART 520—FOREIGN FUNDS CONTROL REGULATIONS

Section 520.101 is amended by the deletion of Czechoslovakia from paragraphs (a) (1) and (2). As revised § 520.101(a) (1) and (2) read as follows:

§ 520.101 General License No. 101.

(a) A general license is hereby granted licensing all property now blocked under the order to be regarded as property in which no blocked country or national thereof has, or has had, any interest: *Provided, however,* That the license granted by this paragraph shall not apply to any property blocked by reason of the interest on or since the effective date of the order of any of the following:

(1) Estonia, Latvia, Lithuania and Germany (except for any interest of Germany now owned by the Federal Republic of Germany, the city of Berlin (Western Sectors) or the Saar);

(2) Any individual, partnership, association, corporation, or other organization which on December 7, 1945, was in Estonia, Latvia, or Lithuania;

Section 520.103 is amended by the insertion of Czechoslovak in the heading and the addition of paragraph (b). As revised § 520.103 reads as follows:

§ 520.103 Unblocking of Hungarian and Czechoslovak Property.

A general license is hereby granted licensing the following property blocked under Executive Order 8389, as amended, to be regarded as property in which no blocked country or national thereof has, or has had, any interest:

(a) All property blocked by reason of the interest on or since March 13, 1941, of Hungary or of any individual, partnership, association, corporation, or other organization which on January 1, 1945, was in Hungary.

(b) All property blocked by reason of the interest on or since June 14, 1941, of Czechoslovakia or of any individual partnership, association, corporation or

other organization which on December 7, 1945, was in Czechoslovakia.

Dennis M. O'Connell,

Director, Office of Foreign Assets Control.

Approved:

John M. Walker, Jr.,

Assistant Secretary, Enforcement and Operations.

[FR Doc. 82-7805 Filed 3-19-82; 1:08 pm]

BILLING CODE 4810-25-M

31 CFR Part 535

Iranian Assets Control Regulations: Time To Establish Blocked Accounts in Lieu of Payments Under Standby Letters of Credit

AGENCY: Office of Foreign Assets Control, Treasury.

ACTION: Final rule.

SUMMARY: The Office of Foreign Assets Control is amending § 535.568 of the Iranian Assets Control Regulations. The purposes of this amendment are: (1) To establish procedures for the establishment of a blocked account by the account party to a standby letter of credit in cases where a demand for payment is outstanding and payment was barred by a court injunction which is removed; (2) to provide that the account party may apply for a specific license providing an extension of time to establish a blocked account where a demand for payment has been made and the account party has filed a petition in an appropriate court for a judicial order barring payment of a standby letter of credit.

EFFECTIVE DATE: March 19, 1982.

FOR FURTHER INFORMATION CONTACT: Raymond W. Konan, Chief Counsel, Office of Foreign Assets Control, Department of the Treasury, Washington, D.C. 20220, Tel. (202) 376-0236.

SUPPLEMENTARY INFORMATION: Since the Regulations involve a foreign affairs function, the provisions of the Administrative Procedure Act, 5 U.S.C. 553, requiring notice of proposed rulemaking, opportunity for public participation and delay in effective date, are inapplicable. Similarly, because the Regulations are issued with respect to a foreign affairs function of the United States, they are not subject to Executive Order 12291 of February 17, 1981, dealing with Federal regulations.

PART 535—IRANIAN ASSETS CONTROL REGULATIONS

Section 535.568 is amended by the addition of a new paragraph (c), the appropriate relettering of subsequent

paragraphs, the addition of appropriate references to new paragraph (c), and the revision of former paragraph (h). As revised § 535.568 reads as follows:

§ 535.568 Certain Standby Letters of Credit and Performance Bonds.

(a) Notwithstanding any other provision of law, payment into a blocked account in a domestic bank by an issuing or confirming bank under a standby letter of credit in favor of an Iranian entity is prohibited by § 535.201 and not authorized, notwithstanding the provisions of § 535.508, if either (1) a specific license has been issued pursuant to the provisions of paragraph (b) of this section or (2) eight business days have not expired after notice to the account party pursuant to paragraph (b) of this section.

(b) Whenever an issuing or confirming bank shall receive such demand for payment under a standby letter of credit, it shall promptly notify the person for whose account the credit was opened. Such person may then apply within five business days for a specific license authorizing the account party to establish a blocked account on its books in the name of the Iranian entity in the amount payable under the credit, in lieu of payment by the issuing or confirming bank into a blocked account and reimbursement therefor by the account party.

(c) Where there is outstanding a demand for payment under a standby letter of credit, and the issuing or confirming bank has been enjoined from making payment, upon removal of the injunction, the person for whose account the credit was opened may apply for a specific license for the same purpose and in the same manner as that set forth in paragraph (b) of this section. The issuing or confirming bank shall not make payment under the standby letter of credit unless (1) eight business days have expired since the bank has received notice of the removal of the injunction and (2) a specific license issued to the account party pursuant to the provisions of this paragraph has not been presented to the bank.

(d) If necessary to assure the availability of the funds blocked, the Secretary may at any time require the payment of the amounts due under any letter of credit described in paragraph (a) of this section into a blocked account in a domestic bank or the supplying of any form of security deemed necessary.

(e) Nothing in this section precludes any person for whose account a standby letter of credit was opened or any other person from at any time contesting the legality of the demand from the Iranian

entity or from raising any other legal defense to payment under the standby letter of credit.

(f) This section does not affect the obligation of the various parties of the instruments covered by this section if the instruments and payment thereunder are subsequently unblocked.

(g) For the purposes of this section, the term "standby letter of credit" shall mean a letter of credit securing performance of, or repayment of, any advance payments of deposits, under a contract with Iran or an Iranian entity, or any similar obligation in the nature of a performance bond.

(h) The regulations do not authorize any person subject to the jurisdiction of the United States to reimburse a non-U.S. bank for payment to Iran or an Iranian entity under a standby letter of credit, except by payment into a blocked account in accordance with § 535.508 or paragraph (b) or (c) of this section.

(i) A person receiving a specific license under paragraph (b) or (c) of this section shall certify to the Office of Foreign Assets Control within five business days after receipt of that license that it has established the blocked account on its books as provided for in those paragraphs. However, in appropriate cases, this time may be extended upon application to the Office of Foreign Assets Control when the account party has filed a petition with an appropriate court seeking a judicial order barring payment by the issuing or confirming bank.

(j) The extension or renewal of a standby letter of credit is authorized.

Dennis M. O'Connell,

Director, Office of Foreign Assets Control.

Approved:

John M. Walker, Jr.,

Assistant Secretary, (Enforcement and Operations)

[FR Doc. 82-7806 Filed 3-19-82; 1:08 pm]

BILLING CODE 4810-25-M

VETERANS ADMINISTRATION

38 CFR Part 1

Appeals From Decisions of Contracting Officers

AGENCY: Veterans Administration.

ACTION: Final regulations.

SUMMARY: These Veterans Administration regulations set forth the jurisdiction and organization of the VA Board of Contract Appeals and the rules which govern procedure before the Board in appeals subject to the Contract Disputes Act of 1978. The regulations are required by the Act. The intended

effect of this action is to inform the public of the new jurisdiction, organization, and Rules of Procedure.

EFFECTIVE DATE: March 5, 1982.

FOR FURTHER INFORMATION CONTACT: Dan R. Anders, (09) (202-275-1750).

SUPPLEMENTARY INFORMATION: On November 1, 1978, the President signed into law the Contract Disputes Act of 1978 (Pub. L. 95-563, 41 U.S.C. 601-613). That Act, among other things, expanded Board jurisdiction and required the promulgation of new Rules of Procedure for use by agency Boards of Contract Appeals. To assure uniformity of language, a suggested text of provisions to implement the Act was published by OFPP (the Office of Federal Procurement Policy) at 44 FR 5219, on January 25, 1979, for public comment. After consideration of comments received, a set of interim final rules was published by OFPP at 44 FR 12519, on March 7, 1979. The interim final rules were made final by notice published by OFPP at 44 FR 34227, on June 14, 1979. At that time, OFPP announced that, to achieve maximum uniformity of Government contract appeal practice agency Boards of Contract Appeals were expected to adopt the uniform rules as published, except for minor variances.

Compliance with 38 CFR 1.12, as to notice of proposed regulatory development and delayed effective date, is unnecessary in this instance and would serve no useful purpose because (1) the provisions regarding organization and jurisdiction of the Board are set forth as contained in and as required by the Contract Disputes Act and (2) the Rules of Procedure, except for minor variances and nonsubstantive editorial changes, track the Uniform Rules published by OFPP after public participation.

Since a proposed notice will not be published, these regulations are not subject to requirements of the Regulatory Flexibility Act, Pub. L. 96-354.

The agency has determined that these regulations are nonmajor in accordance with Executive Order 12291, Federal Regulation. These regulations will not have a large effect on the economy, will not cause an increase of costs or prices, and will not otherwise have any significant adverse economic effects.

Approved: March 5, 1982.

By direction of the Administrator.

Charles T. Hagel,

Deputy Administrator.

PART 1—GENERAL PROVISIONS

Part 1, Title 38, Code of Federal Regulations is amended by adding

§§ 1.780, 1.781, 1.782 and 1.783 as follows:

Appeals From Decisions of Contracting Officers Under the Contract Disputes Act of 1978

Sec.

1.780 Board of Contract Appeals—jurisdiction.

1.781 Organization and address of the Board.

1.782 Policy and procedure.

1.783 Rules of the Board.

Authority: 41 U.S.C. 601-613, 38 U.S.C. 210(c).

Appeals From Decisions of Contracting Officers Under the Contract Disputes Act of 1978

§ 1.780 Board of Contract Appeals—jurisdiction.

The Veterans Administration Board of Contract Appeals (referred to in §§ 1.780 through 1.783 as the "Board") shall consider and determine appeals from decisions of contracting officers pursuant to the Contract Disputes Act of 1978 (Pub. L. 95-563, 41 U.S.C. 601-613) relating to contracts made by (a) the Veterans Administration or (b) any other executive agency when such agency or the Administrator for Federal Procurement Policy has designated the Board to decide the appeal.

§ 1.781 Organization and address of the Board.

(a) The Board consists of a Chair, Vice Chair, and other members, all of whom are attorneys at law duly licensed by any State, commonwealth, territory, or the District of Columbia. In general, the appeals are assigned to a panel of at least 3 members who decide the case by a majority vote. Board Members are designated Administrative Judges.

(b) The Board's mailing address is 810 Vermont Avenue, N.W., Washington, D.C. 20420.

§ 1.782 Policy and procedure.

(a) *Rules of procedure.* Appeals to the Board are processed in accordance with Rules of Procedure adopted by the Board in compliance with the guidelines issued by the Office of Federal Procurement Policy under the provisions of the Contract Disputes Act of 1978 (41 U.S.C. 601, 607(h)). There is no further administrative appeal within the Veterans Administration from final decisions rendered by the Board.

(b) *Application and interpretation of rules.* It is impracticable to articulate a rule to fit every possible circumstance which may be encountered. The rules, therefore, are applied and interpreted to provide, to the fullest extent practicable, informal expeditious, and inexpensive resolution of disputes. For that purpose,

the Board is authorized to require contracting officers and other Veterans Administration officials to furnish the Board with such information, technical data, and other assistance as the Board may require in the performance of its duties.

§ 1.783 Rules of the Board.

(a) *Rule 1: appeals from final decisions and requests for final decisions*—(1) *Notice of appeal.* Notice of an appeal shall be in writing and mailed to or otherwise furnished the Board within 90 days from the date of receipt of a contracting officer's final decision. A copy thereof shall be furnished the contracting officer from whose decision the appeal is taken.

(2) *Failure to issue a final decision.* (i) Where the contractor has submitted a claim of \$50,000 or less to the contracting officer and, in writing, has requested a decision within 60 days from receipt of the request, and the contracting officer has not done so, the contractor may file a notice of appeal as provided in paragraph (a)(1) of this section, citing the failure of the contracting officer to issue a decision.

(ii) Where the contractor has submitted a properly certified claim in excess of \$50,000 to the contracting officer, or pursuant to the Disputes Clause, has requested a decision by the contracting officer which presently involves no monetary amount, and the contracting officer has failed to issue a decision within a reasonable time, taking into account such factors as the size and complexity of the claim, the contractor may file a notice of appeal as provided in paragraph (a)(1) of this section, citing the failure of the contracting officer to issue a decision.

(3) *Stay of proceedings.* Upon the docketing of an appeal filed pursuant to the provisions of paragraph (a)(2) of this section, the Board may, at its option, stay further proceedings pending issuance of a final decision by the contracting officer within such period of time as determined by the Board.

(4) *Request for final decision.* In lieu of filing a notice of appeal under paragraph (a)(2) of this section, the contractor, in the event of undue delay or refusal on the part of the contracting officer, may request that the Board direct the contracting officer to issue a decision in a specified period of time, as determined by the Board.

(b) *Rule 2: notice of appeal, contents of.* A notice of appeal should indicate that an appeal is being taken and should identify the contract by number, the department, agency, or bureau involved in the dispute, the decision from which the appeal is taken, and the amount in

dispute, if known. The notice of appeal should be signed by the appellant (the contractor taking the appeal) or by the appellant's duly authorized representative or attorney. The complaint referred to in paragraph (f) of this section (Rule 6) may be filed with the notice of appeal, or the appellant may designate the notice of appeal as a complaint, if it otherwise fulfills the requirements of a complaint.

(c) *Rule 3: docketing of appeals.* When a notice of appeal in any form has been received by the Board, it shall be docketed promptly. Notice in writing shall be given to the appellant with a copy of §§ 1.780 through 1.783 and to the contracting officer.

(d) *Rule 4: preparation, content, organization, forwarding, and status of appeal file*—(1) *Duties of contracting officer.* Within 30 days of receipt of notice that an appeal has been filed, the contracting officer shall assemble and transmit to the Board through the Office of General Counsel an appeal file consisting of all documents pertinent to the appeal, including:

(i) The decision from which the appeal is taken;

(ii) The contract, including specifications and pertinent amendments, plans, and drawings;

(iii) All correspondence between the parties relevant to the appeal, including the letter or letters of claim in response to which the decision was issued;

(iv) Transcripts of any testimony taken during the course of proceedings, and affidavits or statements of any witnesses on the matter in dispute made prior to the filing of the notice of appeal with the Board; and

(v) Any additional information considered relevant to the appeal. Within the same time above specified, the Office of General Counsel shall furnish the appellant a copy of each document transmitted to the Board, except those in paragraph (d)(1)(ii) of this section. As to the latter, a list furnished appellant indicating specific contractual documents transmitted will suffice.

(2) *Duties of the appellant.* Within 30 days after receipt of a copy of the appeal file assembled by the contracting officer, the appellant shall transmit to the Board any documents not contained therein which are considered to be relevant to the appeal, and shall furnish two copies of such documents to the government trial attorney.

(3) *Organization of appeal file.* Documents in the appeal file may be originals or legible facsimiles or authenticated copies, and shall be arranged in chronological order where

practicable, numbered sequentially, tabbed, and indexed to identify the contents of the file.

(4) *Lengthy documents.* Upon request by either party the Board may waive the requirement to furnish to the other party copies of bulky, lengthy, or out-of-size documents in the appeal file when it would be burdensome to do so. At the time a party files with the Board a document as to which such a waiver has been granted the party shall notify the other party that the document or a copy thereof is available for inspection at the office of the Board or of the party filing same.

(5) *Status of documents in appeal file.* Documents contained in the appeal file are considered, without further action by the parties, as part of the record upon which the Board will render its decision. However, a party may object, for reasons stated, to consideration of a particular document or documents reasonably in advance of hearing or, if there is no hearing, of settling the record. If such objection is made the Board shall remove the document or documents from the appeal file and permit the party offering the document to move its admission as evidence in accordance with paragraphs (m) and (t) of this section (Rules 13 and 20).

(6) *Dispensing with appeal file requirements.* Notwithstanding the provisions of paragraph (d) (1) through (5) of this section, the filing of the documents in paragraph (d) (1) and (2) of this section may be dispensed with by the Board either upon request of the appellant in the notice of appeal or thereafter upon stipulation of the parties.

(e) *Rule 5: dismissal for lack of jurisdiction.* Any motion addressed to the jurisdiction of the Board shall be promptly filed. Hearing on the motion shall be afforded on application of either party. However, the Board may defer its decision on the motion pending hearing on both the merits and the motion. The Board shall have the right at any time and on its own initiative to raise the issue of its jurisdiction to proceed with a particular case, and shall do so by an appropriate order, affording the parties an opportunity to be heard thereon.

(f) *Rule 6: pleadings and motions*—(1) *Appellant.* Within 30 days after receipt of notice of docketing of the appeal, the appellant shall file with the Board an original and two copies of a complaint setting forth simple, concise, and direct statements of each of its claims. Appellant shall also set forth the basis, with appropriate reference to contract provisions, of each claim and the dollar amount claimed, to the extent known.

This pleading shall fulfill the generally recognized requirements of a complaint, although no particular form is required. Upon receipt of the complaint, the Board shall serve a copy of it upon the Government. Should the complaint not be received within 30 days, appellant's claim and appeal may, if in the opinion of the Board the issues before the Board are sufficiently defined, be deemed to set forth its complaint and the Government shall be so notified.

(2) *Government.* Within 30 days from receipt of the complaint, or the aforesaid notice from the Board, the Government shall prepare and file with the Board an original and two copies of an answer thereto. The answer shall set forth simple, concise, and direct statements of the Government's defenses to each claim asserted by appellant, including any affirmative defenses available. Upon receipt of the answer, the Board shall serve a copy upon appellant. Should the answer not be received within 30 days, the Board may, in its discretion, enter a general denial on behalf of the Government, and the appellant shall be so notified.

(3) *Motions.* The Board may entertain and rule upon appropriate motions.

(g) *Rule 7; amendments of pleadings or record—(1) More definite statement and reply.* The Board, upon its own initiative or upon application by a party, may order a party to make a more definite statement of the complaint or answer, or to reply to an answer.

(2) *Amendments.* The Board may, in its discretion, and within the proper scope of the appeal, permit either party to amend its pleadings upon conditions fair to both parties. When issues within the proper scope of the appeal, but not raised by the pleadings, are tried by express or implied consent of the parties, or by permission of the Board, they shall be treated in all respects as if they had been raised therein. In such instances, motions to amend the pleadings to conform to the proof may be entered, but are not required. If evidence is objected to at a hearing on the ground that it is not within the issues raised by the pleadings, it may be admitted within the proper scope of the appeal, provided, however, that the objecting party may be granted a continuance if necessary to enable that party to meet such evidence.

(h) *Rule 8; hearing election.* After filing of the Government's answer or notice from the Board that it has entered a general denial on behalf of the Government, each party shall advise whether it elects a hearing, as prescribed in paragraphs (q) through (y) of this section (Rules 17 through 25), or whether it elects to submit its case on

the record without a hearing, as prescribed in paragraph (k) of this section (Rule 11).

(i) *Rule 9; prehearing briefs.* Based on an examination of the pleadings, and its determination of whether the arguments and authorities addressed to the issues are adequately set forth therein, the Board may, in its discretion, require the parties to submit prehearing briefs in any case in which a hearing has been elected pursuant to paragraph (h) of this section (Rule 8). If the Board does not require prehearing briefs, either party may, upon appropriate and sufficient notice to the other party, furnish a prehearing brief to the Board. In any case where a prehearing brief is submitted, it shall be filed with the Board at least 15 days prior to the date set for hearing, and a copy simultaneously furnished to the other party.

(j) *Rule 10; prehearing or presubmission conference.* (1) Whether the case is to be submitted pursuant to paragraph (k) of this section (Rule 11), or heard pursuant to paragraphs (q) through (y) of this section (Rules 17 through 25), the Board may, upon its own initiative, or upon the application of either party, arrange a telephone conference or require the parties to appear before an Administrative Judge or examiner of the Board for a conference to consider:

- (i) Simplification, clarification, or severance of the issues;
- (ii) The possibility of obtaining stipulations, admissions, agreements, and rulings on admissibility of documents, understandings on matters already of record, or similar agreements that will avoid unnecessary proof;
- (iii) Agreements and rulings to facilitate discovery;
- (iv) Limitation of the number of expert witnesses, or avoidance of similar cumulative evidence;
- (v) The possibility of agreement disposing of any or all of the issues in dispute; and
- (vi) Such other matters as may aid in the disposition of the appeal.

(2) The Administrative Judge or examiner of the Board shall make such rulings and orders as may be appropriate to achieve settlement by agreement of the parties or to aid in the disposition of the appeal. The results of pretrial conferences, including any rulings and orders, shall be reduced to writing by the Administrative Judge or examiner and this writing shall thereafter constitute a part of the record.

(k) *Rule 11; submission without a hearing.* Either party may elect to waive a hearing and submit its case upon the record as settled pursuant to paragraph

(m) of this section (Rule 13). Submission of a case without hearing does not relieve the parties from the necessity of proving the facts supporting their allegations or defenses. In accordance with paragraph (m) of this section (Rule 13), affidavits, depositions, admissions, answers to interrogatories, and stipulations may be employed to supplement other documentary evidence in the record. The Board may permit such submissions to be supplemented by oral argument (transcribed, if requested), and by briefs filed in accordance with paragraph (w) of this section (Rule 23).

(l) *Rule 12; optional small claims (expedited) and accelerated procedures.* These procedures are available solely at the election of the appellant.

(1) 12.1 *Elections to utilize small claims (expedited) and accelerated procedures.*

(i) In appeals where the amount in dispute is \$10,000 or less, the appellant may elect to have the appeal processed under a small claims (expedited) procedure requiring decision of the appeal, whenever possible, within 120 days after the Board receives written notice of the appellant's election. The details of this procedure appear in paragraph (1)(2) of this section (rule 12). An appellant may elect the accelerated procedure set forth in paragraph (1)(3) of this section (Rule 12) in any appeal eligible for small claims (expedited) procedure.

(ii) In appeals where the amount in dispute is \$50,000 or less, the appellant may elect to have the appeal processed under an accelerated procedure requiring decision of the appeal, whenever possible, within 180 days after the Board receives written notice of the appellant's election. The details of this procedure appear in paragraph (1)(3) of this section (Rule 12).

(iii) The appellant's election of either the small claims (expedited) procedure or the accelerated procedure may be made by written notice within 60 days after receipt of notice of docketing the appeal unless such period is extended by the Board for good cause. The election may not be withdrawn except with permission of the Board and for good cause.

(iv) In deciding whether the small claims (expedited) procedure or the accelerated procedure is applicable to a given appeal, the Board shall determine the amount in dispute.

(2) 12.2 *The small claims (expedited) procedure.* (i) In cases proceeding under the small claims (expedited) procedure, the following time periods shall apply:

(A) Within 10 days from the Government's first receipt from either the appellant or the Board of a copy of the appellant's notice of election of the small claims (expedited) procedure, the Government shall send the Board a copy of the contract, the contracting officer's final decision, and the appellant's claim letter or letters, if any; remaining documents required under paragraph (d) of this section (Rule 4) shall be submitted in accordance with times specified in that rule unless the Board otherwise directs;

(B) Within 15 days after the Board has acknowledged receipt of appellant's notice of election, the assigned Administrative Judge shall take the following actions, if feasible, in an informal meeting or a telephone conference with both parties: (1) Identify and simplify the issues; (2) establish a simplified procedure appropriate to the particular appeal involved; (3) determine whether either party wants a hearing and, if so, fix a time and place therefor; (4) require the Government to furnish all the additional documents relevant to the appeal; and (5) establish an expedited schedule for resolution of the appeal.

(ii) Pleadings, discovery, and other prehearing activity will be allowed only as consistent with the requirement to conduct the hearing on the date scheduled or, if no hearing is scheduled, to close the record on a date that will allow decisions within the 120-day limit. The Board, in its discretion, may impose shortened time periods for any actions prescribed or allowed under this section 1.783, as necessary to enable the Board to decide the appeal within the 120-day limit, allowing whatever time, up to 30 days, that the Board considers necessary for the preparation of the decision after closing the record and the filing of briefs, if any.

(iii) Written decisions by the Board in cases processed under the small claims (expedited) procedure will be brief and contain only summary findings of fact and conclusions. Decisions will be rendered for the Board by a single Administrative Judge. If there has been a hearing, the Administrative Judge presiding at the hearing may, in the judge's discretion, at the conclusion of the hearing and after entertaining such oral arguments as deemed appropriate, render on the record oral summary findings of fact, conclusions, and a decision of the appeal. Whenever such an oral decision is rendered, the Board will subsequently furnish the parties a typed copy of such oral decision for record and payment purposes and to establish the starting date for the period for filing a motion for reconsideration

under paragraph (cc) of this section (Rule 29).

(iv) Decisions under this procedure shall have no value as precedent and, in the absence of fraud, shall be final and conclusive and may not be appealed or set aside.

(3) 12.3 The accelerated procedure.

(i) In cases proceeding under the accelerated procedure, the parties are encouraged, to the extent possible consistent with adequate presentation of their factual and legal positions, to waive pleadings, discovery, and briefs. Pleadings, discovery, and other prehearing activity will be allowed only as consistent with the requirement to conduct the hearing on the date scheduled or, if no hearing is scheduled, to close the record on a date that will allow decision within the 180-day limit. The Board, in its discretion, may shorten time periods prescribed or allowed under this § 1.783, as necessary to enable the Board to decide the appeal within 180 days after the Board has received the appellant's notice of election of the accelerated procedure, and may reserve 30 days for preparation of the decision.

(ii) Written decisions by the Board in cases processed under the accelerated procedure will normally be brief and contain only summary findings of fact and conclusions. Decisions will be rendered for the Board by a single Administrative Judge with the concurrence of the Chair, Vice Chair, or other designated Administrative Judge, or by a majority among these two and an additional designated member in case of disagreement. Alternatively, in cases where the amount in dispute is \$10,000 or less as to which the accelerated procedure has been elected and in which there has been a hearing, the single Administrative Judge presiding at the hearing may, with the concurrence of both parties, at the conclusion of the hearing and after entertaining such oral arguments as deemed appropriate, render on the record oral summary findings of fact, conclusions, and a decision of the appeal. Whenever such an oral decision is rendered, the Board will subsequently furnish the parties a typed copy of such oral decision for record and payment purposes, and to establish the starting date for the period for filing a motion for reconsideration under paragraph (cc) of this section (Rule 29).

(4) 12.4 Motions for reconsideration in cases under paragraph (1) of this section (Rule 12). Motions for reconsideration of cases decided under either the small claims (expedited) procedure or the accelerated need not be decided within the original 120-day

or 180-day limits, but all such motions shall be processed and decided rapidly so as to fulfill the intent of paragraph (1) of this section (Rule 12).

(m) Rule 13; settling the record. (1) The record upon which the Board's decision will be rendered consists of the documents furnished under paragraphs (d) and (1) of this section (Rules 4 and 12), to the extent admitted in evidence, and the following items, if any: pleadings prehearing conference memoranda or orders, prehearing briefs, depositions or interrogatories received in evidence, admissions, stipulations, transcripts of conferences and hearings, hearing exhibits, posthearing briefs, and documents which the Board has specifically designated be made a part of the record. The record will, at all reasonable times, be available for inspection by the parties at the office of the Board.

(2) Except as the Board may otherwise order in its discretion, no evidence shall be received after completion of an oral hearing or, in cases submitted on the record, after notification by the Board that the case is ready for decision.

(3) The weight to be attached to any evidence of record will rest within the sound discretion of the Board. The Board may in any case require either party, with appropriate notice to the other party, to submit additional evidence on any matter relevant to the appeal.

(n) Rule 14; discovery—depositions—(1) General policy and protective orders. The parties are encouraged to engage in voluntary discovery procedures. In connection with any deposition or other discovery procedure, the Board may make any order required to protect a party or person from annoyance, embarrassment, or undue burden or expense. Such orders may include limitations on the scope, method, time and place for discovery, and provision for protecting the secrecy of confidential information or documents.

(2) When depositions permitted. After an appeal has been docketed and complaint filed, the parties may agree to, or the Board may order, upon application of either party, the taking of testimony of any person by deposition upon oral examination or written interrogatories before any officer authorized to administer oaths at the place of examination, for use as evidence or for purpose of discovery. The application for order shall specify whether the purpose of the deposition is discovery or for use as evidence.

(3) Orders on depositions. The time, place, and manner of taking depositions shall be as agreed upon by the parties

or, failing such agreement, governed by order of the Board.

(4) *Use as evidence.* No testimony taken by deposition shall be considered as part of the evidence in the hearing of an appeal until such testimony is offered and received in evidence at such hearing. It will not ordinarily be received in evidence if the deponent is present and can testify at the hearing. In such instances, however, the deposition may be used to contradict or impeach the testimony of the deponent given at the hearing. In cases submitted on the record, the Board may, in its discretion, receive depositions to supplement the record.

(5) *Expenses.* Each party shall bear its own expenses associated with the taking of any deposition.

(6) *Subpoenas.* Where appropriate, a party may request the issuance of a subpoena under the provisions of paragraph (u) of this section (Rule 21).

(c) *Rule 15; interrogatories to parties, admissions of fact, and production and inspection of documents.* After an appeal has been docketed and complaint filed with the Board, a party may serve on the other party: (1) Written interrogatories to be answered separately in writing, signed under oath and answered or objected to within 30 days after service; (2) a request for the admission of specified facts and/or the authenticity of any documents, to be answered or objected to within 30 days after service, the factual statements and the authenticity of the documents to be deemed admitted upon failure of a party to respond to the request; and (3) a request for the production, inspection, and copying of any documents or objects, not privileged, which reasonably may lead to the discovery of admissible evidence, to be answered or objected to within 30 days after service. Any discovery engaged in under this rule shall be subject to the provisions of paragraph (n)(1) of this section (Rule 14(A)) with respect to general policy and protective orders, and paragraph (ii) of this section (Rule 35) with respect to sanctions.

(p) *Rule 16; service of papers other than subpoenas.* Papers shall be served personally or by mail, addressed to the party upon whom service is to be made. Copies of complaints, answers, replies, and briefs shall be filed directly with the Board for service. The party filing any other paper with the Board shall send a copy thereof to the opposing party, noting on the paper filed with the Board that a copy has been so furnished. Subpoenas shall be served as provided in paragraph (u) of this section (Rule 21).

(q) *Rule 17; hearings, where and when held.* Hearings will be held at such

places determined by the Board to best serve the interests of the parties and the Board. Hearings will be scheduled at the discretion of the Board with due consideration to the regular order of appeals, requirements of paragraph (1) of this section (Rule 12), and other pertinent factors. On request or motion by either party and for good cause, the Board may, in its discretion, adjust the date of a hearing.

(r) *Rule 18; notice of hearings.* The parties shall be given at least 15 days notice of the time and place set for hearings. In scheduling hearings, the Board will consider the desires of the parties and the requirement for just and inexpensive determination of appeals without unnecessary delay. Notices of hearing shall be promptly acknowledged by the parties.

(s) *Rule 19; unexcused absence of a party.* The unexcused absence of a party at the time and place set for hearing will not be occasion for delay. In the event of such absence, the hearing will proceed and the case will be regarded as submitted by the absent party as provided in paragraph (k) of this section (Rule 11).

(t) *Rule 20; hearings, nature of and examination of witnesses—(1) Nature of hearings.* Hearings shall be as informal as may be reasonable and appropriate under the circumstances. Appellant and respondent may offer such relevant evidence as they deem appropriate and as would be admissible under the Federal Rules of Evidence, subject, however, to the sound discretion of the presiding Administrative Judge or examiner in supervising the extent and manner of presentation of such evidence. In general, admissibility will depend on relevancy and materiality. Evidence which may not be admissible under the Federal Rules of Evidence may be admitted in the discretion of the presiding Administrative Judge or examiner. The weight to be attached to evidence presented in any particular form will be within the discretion of the Board. Stipulations of fact agreed upon by the parties may be regarded and used as evidence at the hearing. The parties may stipulate the testimony that would be given by a witness if the witness were present. The Board may in any case require evidence in addition to that offered by the parties.

(2) *Examination of witnesses.* Witnesses before the Board will be examined orally under oath or affirmation, unless the presiding Administrative Judge or examiner shall otherwise order. If the testimony of a witness is not given under oath, the Board may advise the witness that his or her statements may be subject to the

provisions of 18 U.S.C. 287 and 1001, and any other provision of law imposing penalties for knowingly making false representations in connection with claims against the United States or in any matter within the jurisdiction of any department or agency thereof.

(u) *Rule 21; subpoenas—(1) General.* Upon written request of either party filed with the Board, or on the Board's own initiative, the Administrative Judge to whom a case is assigned or who is otherwise designated by the Chair may issue a subpoena requiring:

(i) Testimony at a deposition—the deposing of a witness in the city or county where the witness resides or is employed or transacts business in person, or at another location convenient for the witness that is specifically determined by the Board;

(ii) Testimony at a hearing—the attendance of a witness for the purpose of taking testimony at a hearing; and

(iii) Production of books and papers—in addition to paragraph (u) (1)(i) or (ii) of this section, the production by the witness at the deposition or hearing of books and papers designated in the subpoena.

(2) *Voluntary cooperation.* Each party is expected (i) to cooperate and make available witnesses and evidence under its control as requested by the other party, without issuance of a subpoena, and (ii) to secure voluntary attendance of desired third-party witnesses and production of desired third-party books, papers, documents, or tangible things whenever possible.

(3) *Requests for subpoenas—(i) A request for a subpoena shall normally be filed at least:*

(A) 15 days before a scheduled deposition where the attendance of a witness at a deposition is sought;

(B) 30 days before a scheduled hearing where the attendance of a witness at a hearing is sought.

In its discretion, the Board may honor requests for subpoenas not made within these time limitations.

(ii) A request for a subpoena shall state the reasonable scope and general relevance to the case of the testimony and of any books and papers sought.

(4) *Requests to quash or modify.* Upon written request by the person subpoenaed or by a party, made within 10 days after service but in any event not later than the time specified in the subpoena for compliance, the Board may (i) quash or modify the subpoena if it is unreasonable and oppressive or for other good cause shown, or (ii) require the person in whose behalf the subpoena was issued to advance the reasonable cost of producing

subpoenaed books and papers. Where circumstances require, the Board may act upon such a request at any time after a copy has been served upon the opposing party.

(5) *Form; issuance*—(i) Every subpoena shall state the name of the Board and the title of the appeal, and shall command each person to whom it is directed to attend and give testimony and, if appropriate, to produce specified books and papers at a time and place therein specified. In issuing a subpoena to a requesting party, the Administrative Judge shall sign the subpoena and may, in his or her discretion, enter the name of the witness and otherwise leave it blank. The party to whom the subpoena is issued shall complete the subpoena before service.

(ii) Where the witness is located in a foreign country, a letter rogatory or subpoena may be issued and served under the circumstances and in the manner provided in 28 U.S.C. 1781-1784.

(6) *Service*. (i) The party requesting issuance of a subpoena shall arrange for service.

(ii) A subpoena requiring the attendance of a witness at a deposition or hearing may be served at any place. A subpoena may be served by a United States marshal or deputy marshal, or by any other person who is not a party and not less than 18 years of age. Service of a subpoena upon a person named therein shall be made by personally delivering a copy to that person and tendering the fees for one day's attendance and the mileage provided by 28 U.S.C. 1821 or other applicable law; however, where the subpoena is issued on behalf of the Government, money payments need not be tendered in advance of attendance.

(iii) The party at whose request a subpoena is issued shall be responsible for the payment of fees and mileage of the witness and of the officer who serves the subpoena. The failure to make payment of such charges on demand may be deemed by the Board as a sufficient ground for striking the testimony of the witness and the books or papers the witness has produced.

(7) *Contumacy or refusal to obey a subpoena*. In case of contumacy or refusal to obey a subpoena by a person who resides, is found, or transacts business within the jurisdiction of a United States District Court, the Board will apply to the Court through the Attorney General of the United States for an order requiring the person to appear before the Board or a member thereof to give testimony or produce evidence or both. Any failure of any such person to obey the order of the

Court may be punished by the Court as a contempt thereof.

(v) *Rule 22; copies of papers*. When books, records, papers, or documents have been received in evidence, true copies thereof, or of such part thereof as may be material or relevant, may be substituted therefor, during the hearing or at the conclusion thereof.

(w) *Rule 23; posthearing briefs*. Posthearing briefs may be submitted upon such terms as may be agreed to by the parties and the presiding Administrative Judge or examiner at the conclusion of the hearing.

(x) *Rule 24; transcript of proceedings*. Testimony and argument at hearings shall be reported verbatim, unless the Board otherwise orders. Waiver of transcript may be especially suitable for hearings under paragraph (1)(2) of this section (Rule 12.2). Transcripts or copies of the proceedings shall be supplied to the parties at the actual cost of duplication.

(y) *Rule 25; withdrawal of exhibits*. After a decision has become final, the Board may, upon request and after notice to the other party, in its discretion, permit the withdrawal of original exhibits, or any part thereof, by the party entitled thereto. The substitution of true copies of exhibits or any part thereof may be required by the Board in its discretion as a condition of granting permission for such withdrawal.

(z) *Rule 26; representation—the appellant*. An individual appellant may appear before the Board in person; a corporation by one of its officers; and a partnership or joint venture by one of its members; or any of these by an attorney at law duly licensed in any State, commonwealth, territory, the District of Columbia, or in a foreign country. An attorney representing an appellant shall file a written notice of appearance with the Board.

(aa) *Rule 27; representation—the government*. Government counsel may, in accordance with their authority, represent the interests of the Government before the Board. They shall file notices of appearance with the Board, and notice thereof will be given appellant or appellant's attorney in the form specified by the Board from time to time.

(bb) *Rule 28; decisions*. Decisions of the Board will be made in writing and authenticated copies of the decision will be forwarded simultaneously to both parties. The rules of the Board and all final orders and decisions (except those required for good cause to be held confidential and not cited as precedents) shall be open for public inspection at the office of the Board in Washington, D.C.

Decisions of the Board will be made solely upon the record, as described in paragraph (m) of this section (Rule 13).

(cc) *Rule 29; motions for reconsideration*. A motion for reconsideration may be filed by either party. It shall set forth specifically the grounds relied upon to support the motion. The motion shall be filed within 30 days from the date of the receipt of a copy of the decision of the Board by the party filing the motion.

(dd) *Rule 30; suspension and dismissal without prejudice*. Whenever appellant and the Government counsel are in agreement as to disposition of the controversy, the Board may suspend or terminate further processing of the appeal. If, thereafter, the Board is advised by either party that the controversy has not been disposed of by agreement, the case shall be restored to the Board's calendar without loss of position. In other cases where the Board is unable to proceed with disposition for reasons not within the control of the Board, an appeal may be placed in a suspense status. Where the suspension has continued, or may continue, for an inordinate length of time, the Board, in its discretion, may dismiss such appeal from its docket without prejudice to restoration when the cause of suspension has been removed. Unless either party or the Board acts within three years to reinstate any appeal dismissed without prejudice, the dismissal shall be deemed to be with prejudice.

(ee) *Rule 31; dismissal or default for failure to prosecute or defend*. Whenever a record discloses the failure of either party to file documents required by these rules, respond to notices or correspondence from the Board, comply with orders of the Board, or otherwise indicates an intention not to continue the prosecution or defense of an appeal, the Board may, in the case of a default by the appellant, issue an order to show cause why the appeal should not be dismissed or, in the case of a default by the Government, issue an order to show cause why the Board should not act thereon pursuant to paragraph (ii) of this section (Rule 35). If good cause is not shown, the Board may take appropriate action.

(ff) *Rule 32; remand from court*. Whenever any court remands a case to the Board for further proceedings, each of the parties shall, within 20 days of such remand, submit a report to the Board recommending procedures to be followed so as to comply with the court's order. The Board shall consider the reports and enter special orders governing the handling of the remanded

case. To the extent the court's directive and time limitations permit, such orders shall conform to these rules.

(gg) *Rule 33; time, computation, and extensions.* (1) Where possible, procedural actions should be taken in less time than the maximum time allowed. Where appropriate and justified, however, extensions of time will be granted. All requests for extensions of time shall be in writing.

(2) In computing any period of time, the day of the event from which the designated period of time begins to run shall not be included, but the last day of the period shall be included unless it is a Saturday, Sunday, or a legal holiday, in which event the period shall run to the end of the next business day.

(hh) *Rule 34; ex parte communications.* No member of the Board or of the Board's staff shall entertain, nor shall any person directly or indirectly involved in an appeal submit to the Board or the Board's staff, off the record, any evidence, explanation, analysis, or advice, whether written or oral, regarding any matter at issue in an appeal. This provision does not apply to consultation among Board members nor to ex parte communications concerning the Board's administrative functions or procedures.

(ii) *Rule 35; sanctions.* If any party fails or refuses to obey an order issued by the Board, the Board may make such order as it considers necessary to the just and expeditious conduct of the appeal.

(jj) *Rule 36; effective date and applicability.* These rules shall apply (1) mandatorily, to all appeals relating to contracts entered into on or after March 1, 1979, and (2) at the contractor's election, to appeals relating to earlier contracts, with respect to claims pending before the contracting officer on March 1, 1979 or initiated thereafter.

[FR Doc. 82-7780 Filed 3-22-82; 8:45 am]

BILLING CODE 8320-01-M

38 CFR Part 36

Loan Guaranty for Mobile Homes; Increase in the Maximum Terms

AGENCY: Veterans Administration.

ACTION: Final regulation.

SUMMARY: The VA (Veterans Administration) is amending its regulations to lengthen the maximum terms allowed for guaranteed loans on mobile home purchases as provided by the Veterans' Disability Compensation, Housing, and Memorial Benefits Amendments of 1981.

EFFECTIVE DATE: October 17, 1981.

FOR FURTHER INFORMATION CONTACT: Mr. George D. Moerman, Loan Guaranty Service (264), Department of Veterans Benefits, Veterans Administration, 810 Vermont Avenue NW., Washington, D.C. 20420, 202-389-3042.

SUPPLEMENTARY INFORMATION: Section 503 of the Veterans' Disability Compensation, Housing, and Memorial Benefits Amendments of 1981 (Pub. L. 97-66, 95 Stat. 1026) increases the maximum allowable loan terms for various VA guaranteed mobile home loans. The maximum loan term for the purchase of a single-wide mobile home or a single-wide mobile home and a lot is increased from 15 years and 32 days to 20 years and 32 days. The loan term for the purchase of a double-wide mobile home is increased from 20 years and 32 days to 23 years and 32 days. Finally, the maximum loan term for the purchase of a double-wide mobile home and a lot is increased from 20 years and 32 days to 25 years and 32 days. No change is made in the maximum loan term of 15 years and 32 days for the purchase of a lot on which to place a veteran's previously acquired mobile home.

These statutory changes should assist veterans wishing to purchase a mobile home or a mobile home and a lot by lengthening maximum loan terms which thereby will lower the veteran's monthly payments. They should also assist in the "pooling" of VA mobile home loans in the secondary market since VA maximum loan terms for the acquisition of a mobile home or a mobile home and a lot are now identical with loans of the same type insured by the Department of Housing and Urban Development.

This amendment is within the exceptions to the general Veterans Administration policy of prior publication of proposed rules, as contained in 38 CFR 1.12. The changes are those required by statute, Pub. L. 97-66. Therefore, the VA finds that publication for advance notice and comment is unnecessary, would serve little purpose, and would not be in the public interest. Since a proposed notice will not be published, the amendment is not subject to the requirements of the Regulatory Flexibility Act, 5 U.S.C. 601-612.

This regulation has been reviewed under Executive Order 12291, entitled Federal Regulation. This regulation is not considered major as defined in that Executive Order. It is designed to assure that the Veterans Administration field offices comply with the new statutory provisions for the allowable maximum terms for guaranteed mobile home loans.

It will not impact on the public or private sectors as a major rule. It will not have an annual effect on the economy of 100 million or more dollars, cause a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or have significant adverse effects on competition, employment, investment productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

The official program number and title of the VA program affected by this action as set forth in OMB Circular A-89, Catalog of Federal Domestic Assistance, is 64.119, Veterans Housing—Mobile Home Loans.

This amendment is adopted under authority granted to the Administrator by sections 210(c) and 1819 (d) and (g) of title 38, United States Code.

Approved: March 3, 1982.

Robert P. Nimmo,
Administrator.

PART 36—LOAN GUARANTY

The Veterans Administration is amending 38 CFR Part 36 as follows:

In § 36.4204, paragraph (c) is revised to read as follows:

§ 36.4204 Loan purposes, maximum loan amounts and terms.

(c) The maximum permissible loan terms shall not exceed:

(1) 20 years and 32 days in the case of a loan to purchase a single-wide mobile home or a single-wide mobile home and lot;

(2) 15 years and 32 days in the case of a loan to purchase a lot on which to place a mobile home already owned by the veteran;

(3) 23 years and 32 days in the case of a loan to purchase a double-wide mobile home, or 25 years and 32 days in the case of a loan to purchase a double-wide mobile home and lot; or

(4) In the case of a used mobile home the maximum term set forth in paragraph (c) (1) or (3) of this section or the remaining physical life expectancy of the unit as established by the Administrator, whichever is less. (38 U.S.C. 1819(a) (1) and (2), (d)(1), (e)(4)(B)).

[FR Doc. 82-7779 Filed 3-22-82; 8:45 am]

BILLING CODE 8320-01-M

**ENVIRONMENTAL PROTECTION
AGENCY****40 CFR Part 123**

[SW-6-FRL-2069-2]

**Texas; Phase II, Components A and B,
Interim Authorization of State
Hazardous Waste Management
Program****AGENCY:** Environmental Protection
Agency.**ACTION:** Approval of State program.**SUMMARY:** The purpose of this notice is to grant Phase II Interim Authorization for Components A and B to the State of Texas for its hazardous waste management program.**EFFECTIVE DATE:** March 23, 1982.**FOR FURTHER INFORMATION CONTACT:**H. J. Parr, Hazardous Materials Branch,
U.S.E.P.A., Region 6, 1201 Elm Street,
Dallas, Texas 75270, (214) 767-2645.**SUPPLEMENTARY INFORMATION:** In the May 19, 1980 Federal Register (45 FR 33063), the Environmental Protection Agency promulgated regulations, pursuant to Subtitle C of the Resource Conservation and Recovery Act of 1976 (as amended), to protect human health and the environment from the improper management of hazardous waste. Included in these regulations, which became effective 6 months from the date of promulgation, were provisions for a transitional stage in which states would be granted interim program authorization. The interim authorization program will be implemented in two phases corresponding to the two stages in which an underlying Federal program will take effect.

The State of Texas received Interim Authorization for Phase I on December 24, 1980.

In the January 26, 1981 Federal Register (46 FR 7965), the Environmental Protection Agency announced the availability of portions of the second phase of Interim Authorization. EPA's decision to make the second phase of Interim Authorization available in components was based on the desire to proceed with authorizing State programs as expeditiously as possible and because some of the subparts of the federal regulations containing standards for hazardous waste treatment, storage and disposal facilities (40 CFR Part 264) are to be promulgated at different times rather than in one single promulgation as previously anticipated.

On November 13, 1981, EPA published a notice in the Federal Register inviting the public to offer comments on the Texas Application for Interim

Authorization Phase II, Components A and B of its Hazardous Waste Management Program at a public hearing to be conducted by Region 6 on December 21, 1981. This notice also invited the public to submit written comments on the Texas application to Region 6 by the close of the public hearing.

On January 25, 1982 EPA announced in the Federal Register an extension of the public comment period of the Texas Phase II application until February 24, 1982. The 30 day extension was made because substantial revisions and an addition were made to the Texas application subsequent to the notice in the Federal Register of November 13, 1981. The revisions were made to the Memorandum of Agreement (MOA) between the State and EPA and the addition was a Memorandum of Understanding (MOU) entered into among the Texas Department of Health (TDH), the Texas Department of Water Resources (TDWR), and the Texas Railroad Commission (TRC). The revisions to the MOA made procedural changes in the Texas Phase II application. The MOU which was executed after the application was submitted, became effective on January 1, 1982, and clarifies the divisions of responsibility among TDH, TDWR, TRC with respect to oil and gas related wastes.

Discussion

Texas, long in the vanguard of states which recognized the need for hazardous waste management, was also among the first group of states authorized to operate Phase I of the RCRA program on December 24, 1980. On May 11, 1981, the State of Texas submitted to me the first draft application for Interim Authorization for Phase II, Components A and B of the RCRA program. Included with its Phase II application Texas requested authorization to operate the temporary federal permit program for new land disposal facilities promulgated on February 13, 1981 in 40 CFR Part 267. EPA policy, explained in the preamble to 40 CFR Part 267, was not in favor of authorizing State programs to operate this temporary portion of the RCRA permit program. EPA has considered the Texas request, which has been joined in by a number of other states, and has decided not to change this policy at this time, but instead will expedite the publication of final land disposal regulations which will be available for state authorization.

During our review of the Texas draft application, which included a complete submission by the two state agencies

with jurisdiction in hazardous waste management, the Texas Department of Water Resources (TDWR) and the Texas Department of Health (TDH), we realized that the nature of the problems identified in the Texas program resulted from the fact that it predated the RCRA regulatory scheme for hazardous waste management and represented a different approach to the administration of a permit program from that established by EPA in the RCRA Phase II permitting program. I wish to commend the State of Texas for the enormous effort expended in its final application which resulted in the reshaping of its program into one which meets federal statutory requirements and is substantially equivalent to the federal program.

In our comments on the Texas draft application, we identified major problem areas which had to be addressed in the State's final application for Phase II, Components A and B. These major problems involved two important parts of the Texas application: the Memorandum of Agreement (MOA) between the State and the Regional Office, and State permitting procedures. The MOA did not address procedures for program reporting, permit processing and responsibilities for permit enforcement. The state agencies' permitting procedures did not provide, in the manner required by RCRA section 7004(b)(2), for hearing notices, opportunity to request hearings, or opportunity to participate in hearings. In addition, the TDH did not provide that a draft permit and fact sheet could be available prior to the permit hearing. TDWR did not provide for response to comments of persons not parties to the permit hearings. Both TDH and TDWR had standing requirements which might operate to restrict persons, not party to a permit hearing, from participation in the hearing. In summary, the Texas permit process was a more formal adjudicatory process than that of the federal program and did not appear to meet many of the federal requirements for public participation in the permit issuance process.

Texas submitted its final application on October 26, 1981. Problems identified with the MOA were completely remedied in the MOA submitted with the State's final application. The revised MOA contained terms and conditions which defined the State and EPA's responsibilities for reporting, permit issuance and permit enforcement.

The final application submitted by Texas addressed many, but not all, of the issues concerning permitting procedures. The Program Description and Attorney General's Statement

clarified that State administrative procedures are interpreted to provide that any person who is or may be affected by a proposed permit may request a hearing. This is in agreement with EPA's interpretation of the provision in RCRA § 7004(b)(2) which establishes the circumstances under which a hearing on a proposed permit must be held. The Attorney General's statement also demonstrated that Texas rules permit any person, including those who are not parties, to comment at a hearing on a proposed permit.

While most of the notice requirements established by RCRA section 7004(b)(2) to inform the public and local and state government of proposed permits were met by TDH and TDWR in the State's final application, TDWR did not require the radio broadcasting of proposed permit notices as required by RCRA. In addition, the TDH permitting program did not provide for a document meeting the requirements of a draft permit to be available and noticed to the public. The TDWR permit procedures included a provision allowing for comment on a proposed permit but did not require any response to significant comments by persons not made parties to the hearing.

Prior to the public hearing which EPA held on the Texas Phase II application both TDWR and TDH submitted amendments to the MOA which resolved outstanding issues concerning the Texas permit procedures. TDWR submitted an amendment providing assurance that notice of proposed permits and hearings on proposed permits will be announced on local radio stations according to the mandate of RCRA section 7004(b)(2). The TDH submitted an amendment to the MOA which provided assurance that that agency would prepare, notice and provide to the public a document corresponding to a draft permit and fact sheet prior to a hearing on the proposed permit in accordance with all of the requirements of 40 CFR 124.6, 124.8 and 124.10. These amendments insured that the State permit procedures met virtually all of the federal requirements for public participation in the permit process. The only issue outstanding after these revisions to the MOA concerned the lack of response by TDWR to persons, not parties to their permit hearings, who make substantial comments. EPA regulations, at 40 CFR 124.17(a), require response to substantial comments at the time the permit decision is made. TDWR has provided assurances in a letter of clarification to EPA on January 29, 1982, that the program will respond to all substantial comments in the same manner and

under the same certification of authority in RCRA as that provided to EPA to meet the same requirement in its application for primacy in the Underground Injection Control Program. While the Texas permitting procedures are not identical to EPA's, the differences reflect state administrative and permitting processes which predate EPA's, and which are upon close scrutiny substantially equivalent to EPA requirements.

The amendments to the Texas MOA were introduced into the record at the hearing on the Texas Application on December 21, 1981. At that time EPA announced that it would extend the public comment period to allow comments on amendments and an addition to the MOA. These were: (1) Permit procedures amendments, (2) an amendment to the MOA which provided for the voluntary suspension of any portion of State authorization in the event that any portion of the federal permit program is suspended pursuant to the policy of the Administrator announced in the *Federal Register* on February 24, 1982 (47 FR 8010), and (3) a Memorandum of Understanding between TDH, TDWR and the Texas Railroad Commission, executed after the submission of the final application, which outlined each State Agency's jurisdiction over oil and gas wastes.

The extended public comment period was noticed on January 25, 1982 in the *Federal Register* (47 FR 3378) ended on February 24, 1982. After careful review of the application, the additional revisions and clarifications and all comments, written and oral, I find that the vast majority of comments support authorization of the Texas Application. There is substantial support for the procedural amendments which Texas has offered to meet federal permit procedure requirements and no significant opposition to these or other issues presented in the Texas Application.

EPA has proposed to temporarily suspend the regulations for existing storage surface impoundments and existing incinerators pending EPA review of their cost effectiveness. Pending a final decision, EPA has tentatively decided to authorize states to permit all facilities covered by components A and B. See 47 FR 8010. If EPA does suspend the regulations for these facilities, the State's ability to issue State RCRA permits for these facilities (existing storage surface impoundments and existing incinerators) will automatically be suspended.

I conclude that the Texas Application for Interim Authorization to operate the RCRA Phase II, Components A and B program meets all of the statutory and regulatory requirements and as such I approve this authorization.

Responsiveness Summary

The public hearing on the Texas application for Phase II authorization was held by Region 6 on the evening of December 21, 1981, in Austin, Texas. Seven presentations were made. In addition, Region 6 received eighteen written comments on the Texas application by the close of the public hearing. Five of the eighteen comments were submitted as supplements to comments presented at the public hearing. Region 6 received one written comment during the extended 30-day comment period which closed on February 24, 1982. All comments, if they complied with the time constraints of the *Federal Register* notices, whether presented at the hearing or in writing, were reviewed in reaching a decision on the Texas application for Phase II Interim Authorization, Components A and B.

Of the twenty-one public comments received by Region 6 (seven at the hearing and fourteen in writing) on the Texas application, fourteen comments favored granting the State Phase II authorization for Components A and B without restrictions. One commenter favored granting authorization only as it applies to new facilities (those facilities not included in the proposed suspension discussed in the October 20, 1981 *Federal Register*). One commenter favored granting the State conditional approval of Phase II, Components A and B if EPA would the require time schedules to correct any possible deficiencies. Copies of the complete Responsiveness Summary including detailed descriptions of each comment and a full discussion of each response can be obtained free of charge by contacting the person listed above.

(Solid Waste Disposal Act as amended by the Resource Conservation and Recovery Act of 1976 and the Solid Waste Disposal Act Amendments of 1980. 42 U.S.C. 6901 *et seq.*)

Dated: February 25, 1982.

Frances E. Phillips,
Acting Regional Administrator.

Certification: Texas Application for Interim Authorization, Under the Regulatory Flexibility Act

Pursuant to the provisions of 5 U.S.C. 605(b), I hereby certify that this authorization will not have a significant economic impact on a substantial number of small entities. The authorization suspends the applicability of

certain Federal regulations in favor of the State program, thereby eliminating duplicative requirements for handlers of hazardous wastes in the State. It does not impose any new burdens on small entities. This rule, therefore, does not require a regulatory flexibility analysis.

Dated: March 13, 1982.

Anne M. Gorsuch,
Administrator.

[FR Doc. 82-7673 Filed 3-22-82; 8:45 am]

BILLING CODE 6560-38-M

INTERSTATE COMMERCE COMMISSION

49 CFR Part 1065

[Ex Parte No. 55 (Sub-No. 49)]

Deletion of Gateway Elimination Rules

AGENCY: Interstate Commerce Commission.

ACTION: Removal of final rules.

SUMMARY: The Commission is removing rules adopted in 1974 which established procedures for eliminating gateways for irregular-route motor carriers of property. Since it appears that there are no authorities remaining which timely meet the filing requirements, and since later Commission policy has eliminated remaining gateway restrictions and circuitous route limitations, the rules have no further applicability.

EFFECTIVE DATE: April 22, 1982.

FOR FURTHER INFORMATION:

Mary Kelly, 202-275-7292.

SUPPLEMENTARY INFORMATION: The Commission adopted rules which established procedures for the elimination of gateways in Ex Parte No. 55 (Sub-No. 8), *Gateway Elimination*, 119 M.C.C. 530 (1974), 39 FR 7794 (1974), amended at 39 FR 17444 (1974). Qualifying for these procedures were certificates issued to carriers pursuant to an application pending before the Commission on or before November 23, 1973. It appears that there are no authorities remaining which timely meet the filing requirements of 49 CFR 1065. We note that remaining gateway restrictions and circuitous route limitations were eliminated in Ex Parte No. MC-142, *Elimination of Gateway Restrictions and Circuitous Route Limitations*, 45 FR 86741, December 31, 1980, pursuant to section 6 of the Motor Carrier Act of 1980, Pub. L. No. 96-296, and 49 CFR 1042 was amended to reflect the permissible scope of service under tacked authorities.

Removal of this Part will have no effect on gateway eliminations involved in consolidation, merger and control proceedings. We will continue to decide

gateway elimination applications which are directly related to acquisition proceedings filed under 49 U.S.C. 11343 and 11344 pursuant to our policy set forth at 39 FR 42958 (1974), as modified by case law.

Removal of this Part will have no legal effect on any person. Notice and comment, therefore, are unnecessary, and are not required under the Administrative Procedure Act. We are merely deleting a rule that has no further use or effect.

This action will have no effect on the human environment or conservation of energy resources. We are not required to make a regulatory flexibility analysis of this action since prior notice and comment are not mandated by 5 U.S.C. 553. However, this action will have no adverse effect on small entities since it merely removes a rule that has ceased to have purpose.

PART 1065—[REMOVED]

It is ordered:

Part 1065 of Title 49, Code of Federal Regulations, is removed.

(49 U.S.C. 10321, 5 U.S.C. 553)

Decided: March 16, 1982.

By the Commission, Chairman Taylor, Vice Chairman Gilliam, Commissioners Gresham, Clapp, and Sterrett.

Agatha L. Mergenovich,
Secretary.

[FR Doc. 82-7761 Filed 3-22-82; 8:45 am]

BILLING CODE 7035-01-M

49 CFR Parts 1201, 1206, and 1207

[No. 38685]

Financial Statement Classification of Deferred Income Taxes

AGENCY: Interstate Commerce Commission.

ACTION: Final rule.

SUMMARY: This rule revises the Uniform Systems of Accounts for railroads and motor carriers of passengers and property, as it relates to the financial statement classification of deferred income taxes. This rule was prompted by the issuance of Financial Accounting Standard No. 37, "Balance Sheet Classification of Deferred Income Taxes." The objective is to adopt a generally accepted accounting principle (GAAP) applicable to this regulated industry, thereby keeping our accounting systems in alignment with GAAP. Accounting Series Circular No. 183 initiated this abridged rulemaking proceeding, pursuant to 49 CFR 1200.2.

DATES: Comments are due 45 days after March 23, 1982.

Effective for reporting years beginning after December 24, 1980.

ADDRESS: Send comments, and 10 copies, to: Office of the Secretary, Interstate Commerce Commission, Washington, D.C. 20423.

FOR FURTHER INFORMATION CONTACT:

Bryan Brown, Jr., (202) 275-7448.

SUPPLEMENTARY INFORMATION: On September 12, 1980, the Commission's Bureau of Accounts issued Accounting Series Circular No. 183 (ASC), "Balance Sheet Classification of Deferred Income Taxes", which stated that the provisions of Financial Accounting Standard No. 37 (FAS No. 37) of the same title would be adopted. FAS No. 37 was issued by the Financial Accounting Standards Board in July 1980, and set forth new criteria for classifying deferred income taxes in a balance sheet. The objective of this rule is to adopt these provisions, thereby maintaining our accounting systems and reports in accordance with generally accepted accounting principles (GAAP).

FAS No. 37 provides that a deferred charge or credit that is related to an asset or liability shall be classified as current or noncurrent based on the classification of the related asset or liability. A deferred charge or credit that is not related to an asset or liability because (a) there is no associated asset or liability or (b) reduction of an associated asset or liability will not cause the timing difference to reverse shall be classified based on the expected reversal date of the specific timing difference.

The Uniform Systems of Accounts (USOAs) and carrier annual reports already provide for a classification of deferred income taxes on a current and noncurrent basis. However, the texts of the deferred income tax accounts in the USOAs are hereby revised to include the classification criteria specified in FAS No. 37 (See Appendices A, B, and C). Certain editorial revisions will also be made to carrier annual reports.

Under the abridged rulemaking procedures set forth in 49 CFR 1200.2, carriers were allowed 45 days to comment on the provisions contained in the ASC. No responses were received during this period, which implies general acceptance.

This rule shall be effective for reporting years beginning after December 24, 1980.

We therefore adopt the amendments set forth in the appendices to this notice.

This action does not appear to affect significantly the quality of the human environment or the conservation of energy resources.

Regulatory Flexibility Act

Pursuant to 5 U.S.C. 605(b), the Chairman of the Commission has certified that the requirements of the Regulatory Flexibility Act do not apply because this Final Rule, if promulgated, will not have a significant economic impact upon a substantial number of small entities. This rule requires only an accounting classification change of information already captured. It will also enable carriers to use the generally accepted accounting principle required for other businesses around the country. The cost and time related to this accounting change are very minimal.

(49 U.S.C. 10321 and 11145 and 5 U.S.C. 553)

Decided: March 16, 1982.

By the Commission, Chairman Taylor, Vice Chairman Gilliam, Commissioners Gresham, Clapp, and Sterrett.
Agatha L. Mergenovich,
Secretary.

Appendix A

PART 1201—RAILROAD COMPANIES

Subpart A—Uniform System of Accounts

1. Revise 49 CFR Part 1201 Instruction 1-10, "Accounting for income taxes", paragraph (b), to read as follows:

1-10 Accounting for income taxes.

(b) Under the interperiod tax allocation method of accounting the tax effect of timing differences (see definition 20) originating in the current accounting period are allocated to income tax expense of future periods when the timing differences reverse. Similar timing differences originating and reversing in the current accounting period should be combined into groups and the current tax rates applied to determine the tax effect of each group. A carrier shall not apply other than current tax rates in determining the tax effect of reversing differences except upon approval of the Commission. When determining the amount of deferred taxes, rather than computing state and other taxes individually by jurisdiction, the Federal income tax rate may be increased by a percent equivalent to the effect of taxes imposed by the jurisdictions. In classifying a deferred charge or credit as current or noncurrent a carrier shall follow the classification criteria used for the related asset or liability which caused the timing difference. A deferred charge or credit that is not related to an asset or liability because (a) there is no associated asset or liability or (b) reduction of an associated asset or liability will not cause the timing difference to reverse shall be classified based on the

expected reversal date of the specific timing difference. Such classification disregards any additional timing differences that may arise and is based on the criteria used for classifying other assets and liabilities.

2. Revise the text of account 714, "Deferred income tax debits," as follows:

714 Deferred income tax debits.

This account shall include the current portion of deferred income tax debits and credits determined in accordance with Instruction 1-10, when the balance is a net debit. A net credit balance shall be included in account 762, "Deferred income tax credits".

3. Revise the text of account 744, "Accumulated deferred income tax debits", as follows:

744 Accumulated deferred income tax debits.

This account shall include the amount of deferred noncurrent income tax debits and credits determined in accordance with Instruction 1-10 when the balance is a net debit. A net credit balance shall be included in account 786, "Accumulated deferred income tax credits".

4. Revise the text of account 762, "Deferred income tax credits," as follows:

762 Deferred income tax credits.

This account shall include the current portion of deferred income tax charges and credits determined in accordance with Instruction 1-10 when the balance is a net credit. A net debit balance shall be included in account 714, "Deferred income tax debits".

5. Revise the text of account 786, "Accumulated deferred income tax credits," as follows:

786 Accumulated deferred income tax credits.

(a) This account shall be credited with the noncurrent portions of deferred income tax debits and credits when the balance is a net credit, as determined by Instruction 1-10. A net debit balance shall be included in account 744, "Accumulated deferred income tax debits".

(b) This account shall be credited with the amount of investment tax credits utilized in the current year for income tax purposes but deferred for accounting purposes (see Instruction 1-10).

(c) This account shall be concurrently debited with amounts credited to account 557, "Provision for deferred taxes," representing amortization of amounts for investment tax credits deferred in prior accounting periods.

(d) This account shall be maintained in such a manner as to show separately:

(1) the unamortized balance of deferred income taxes and deferred investment tax credit separately as of the beginning and as of the end of each year (2) the entries that affected the account balance, and (3) the current year's net credits or charges applicable to timing differences and deferred investment tax credits.

Note A.—For definitions of income tax terminology see Definition 20. Account 557, "Provision for deferred taxes", and account 591, "Provision for deferred taxes—Extraordinary item," shall concurrently be charged (credited) with the net effect of material timing effects. Other related deferred income tax balance sheet accounts are:

Account 714, "Deferred income tax debit."

Account 744, "Accumulated deferred income tax debits."

Account 762, "Deferred income tax credits."

Appendix B

PART 1206—COMMON AND CONTRACT MOTOR CARRIERS OF PASSENGERS

1. Revise 49 CFR Part 1206 Instruction 2-32, "Accounting for income taxes," paragraph (b), to read as follows:

2-32 Accounting for income taxes.

(b) Under the interperiod tax allocation method of accounting the tax effect of timing differences (see definition 1-41) originating in the current accounting period are allocated to income tax expense of future periods when the timing differences reverse. Similar timing differences originating and reversing in the current accounting period should be combined into groups and the current tax rates applied to determine the tax effect of each group. A carrier shall not apply other than current tax rates in determining the tax effect of reversing differences except upon approval of the Commission. When determining the amount of deferred taxes, rather than computing state and other taxes individually by jurisdiction, the Federal income tax rate may be increased by a percent equivalent to the effect of taxes imposed by the jurisdictions. In classifying a deferred charge or credit as current or noncurrent a carrier shall follow the classification criteria used for the related asset or liability which caused the timing difference. A deferred charge or credit that is not related to an asset or liability because (a) there is no associated asset or liability or (b) reduction of an associated asset or liability will not cause the timing difference to reverse shall be classified based on the expected reversal date of the specific

timing difference. Such classification disregards any additional timing differences that may arise and is based on the criteria used for classifying other assets and liabilities.

2. Revise the heading and text of account 1195, "Deferred income tax charges", as follows:

1195 Deferred income tax debits.

This account shall include the current portion of deferred income tax debits and credits determined in accordance with Instruction 2-32, when the balance is a net debit. A net credit balance shall be included in account 2185, "Deferred income tax credits".

3. Revise the heading and text of account 1895, "Accumulated deferred income tax charges", as follows:

1895 Accumulated deferred income tax debits.

This account shall include the noncurrent amount of deferred income tax debits and credits determined in accordance with Instruction 2-32, when the balance is a net debit. A net credit balance shall be included in account 2460, "Accumulated deferred income tax credits".

4. Revise the text of account 2185, "Deferred income tax credits", as follows:

2185 Deferred income tax credits.

This account shall include the current portion of deferred income tax charges and credits determined in accordance with Instruction 2-32 when the balance is a net credit. A net debit balance shall be included in account 1195, "Deferred income tax debits".

5. Revise the text of account 2460, "Accumulated deferred income tax credits", as follows:

2460 Accumulated deferred income tax credits.

(a) This account shall be credited with the noncurrent portions of deferred income tax debits and credits when the balance is a net credit, as determined by Instruction 2-32. A net debit balance shall be included in account 1895, "Accumulated deferred income tax debits".

(b) This account shall be credited with the amount of investment tax credits utilized in the current year for income tax purposes but deferred for accounting purposes (see Instruction 2-32).

(c) This account shall be concurrently debited with amounts credited to account 3040, "Provision for deferred taxes," representing amortization of amounts for investment tax credits deferred in prior accounting periods.

(d) This account shall be maintained in such a manner as to show separately:

(1) the unamortized balance of deferred income taxes and deferred

investment tax credits separately as of the beginning and as of the end of each year, (2) entries which affected the account balance, and (3) the current year's net credits or charges applicable to timing differences and deferred investment tax credits.

Note A.—For definitions of income tax terminology see Definition 1-41. Account 8040, "Provision for deferred taxes", and account 9060, "Provision for deferred taxes—extraordinary items" shall concurrently be charged (credited) with the net effect of material timing effects. Other related deferred income tax balance sheet accounts are:

Account 1195, "Deferred income tax debits."

Account 1895, "Accumulated deferred income tax debits."

Account 2185, "Deferred income tax credits."

Appendix C

PART 1207—CLASS I AND CLASS II COMMON AND CONTRACT MOTOR CARRIERS OF PROPERTY

1. Revise 49 CFR Part 1207 Instruction 31, "Accounting for income taxes", paragraph (b), to read as follows:

31 Accounting for income taxes.

(b) Under the interperiod tax allocation method of accounting the tax effect of timing differences (see definition 39) originating in the current accounting period are allocated to income tax expense of future periods when the timing differences reverse. Similar timing differences originating and reversing in the current accounting period should be combined into groups and the current tax rates applied to determine the tax effect of each group. A carrier shall not apply other than current tax rates in determining the tax effect of reversing differences except upon approval of the Commission. When determining the amount of deferred taxes, rather than computing state and other taxes individually by jurisdiction, the Federal income tax rate may be increased by a percent equivalent to the effect of taxes imposed by the jurisdiction. In classifying a deferred charge or credit as current or noncurrent a carrier shall follow the classification criteria used for the related asset or liability which caused the timing difference. A deferred charge or credit that is not related to an asset or liability because (a) there is no associated asset or liability or (b) reduction of an associated asset or liability will not cause the timing difference to reverse shall be classified based on the expected reversal date of the specific timing difference. Such classification disregards any additional timing differences that may arise and is based

on the criteria used for classifying other assets and liabilities.

2. Revise the heading and text of account 1170, "Deferred income tax charges," as follows:

1170 Deferred income tax debits (Classes I and II).

This account shall include the current portion of deferred income tax debits and credits determined in accordance with Instruction 31 when the balance is a net debit. A net credit balance shall be included in account 2190, "Deferred income tax credits".

3. Revise the heading and text of account 1520, "Accumulated deferred income tax charges," as follows:

1520 Accumulated deferred income tax debits (Classes I and II).

This account shall include the noncurrent amount of income tax debits and credits determined in accordance with Instruction 31 when the balance is a net debit. A net credit balance shall be included in account 2420, "Accumulated deferred income tax credits".

4. Revise the text of account 2190, "Deferred income tax credits", as follows:

2190 Deferred income tax credits (Classes I and II).

This account shall include the current portion of deferred income tax charges and credits determined in accordance with Instruction 31 when the balance is a net credit. A net debit balance shall be included in account 1170, "Deferred income tax debits".

5. Revise the text of account 2420, "Accumulated deferred income tax credits", as follows:

2420 Accumulated deferred income tax credits (Classes I and II).

(a) This account shall be credited with the noncurrent portions of deferred income tax debits and credits when the balance is a net credit, as determined by Instruction 31. A net debit balance shall be included in account 1520, "Accumulated deferred income tax debits".

(b) This account shall be credited with the amount of investment tax credits utilized in the current year for income tax purposes but deferred for accounting purposes (see Instruction 31).

(c) This account shall be concurrently debited with amounts credited to account "provision for deferred taxes," representing amortization of amounts for investment tax credits deferred in prior accounting periods.

(d) This account shall be maintained in such a manner as to show separately:

(1) The unamortized balance of deferred income taxes and deferred investment tax credit separately as of

the beginning and as of the end of each year, (2) the entries which affected the account balance, and (3) the current year's net credits or charges applicable to timing differences and deferred investment tax credits.

Note A.— For definitions of income tax terminology see Definition 39. Account 8740/9740, "Provision for deferred taxes", and account 8851/9851, "Provision for deferred taxes—extraordinary items" shall concurrently be charged (credited) with the net effect of material timing effects. Other related deferred income tax balance sheet accounts are:

Account 1170, "Deferred income tax debits."

Account 1520, "Accumulated deferred income tax debits."

Account 2190, "Deferred income tax credits."

[FR Doc. 82-7776 Filed 3-22-82; 8:45 am]

BILLING CODE 7035-01-M

Proposed Rules

Federal Register

Vol. 47, No. 56

Tuesday, March 23, 1982

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1306

Ban of Urea-Formaldehyde Foam Insulation; Extension of Time

AGENCY: Consumer Product Safety Commission.

ACTION: Extension of time to promulgate or withdraw proposed ban.

SUMMARY: The Commission extends the time for promulgating a final ban of urea-formaldehyde (U.F.) foam insulation, or for withdrawing its proposed ban, to April 20, 1982.¹ The Commission voted on February 22, 1982, to issue the ban, to address the risks of illness which could be caused by formaldehyde gas emitted from the U. F. foam insulation. This extension is to allow time for the Commission to include in the Federal Register notice issuing the ban its responses to late comments filed by interested members of the public and to provide for a promulgation date that is ten days after the ban is published.

DATES: The time during which the Commission must either issue a final ban of U. F. foam insulation or withdraw the proposed ban is extended for good cause to April 20, 1982.

FOR FURTHER INFORMATION CONTACT: Harleigh Ewell, Attorney, Office of the General Counsel, Consumer Product Safety Commission, Washington, D.C. 20207, telephone (301) 492-6980.

SUPPLEMENTARY INFORMATION: On February 5, 1981, the Commission proposed a ban of urea-formaldehyde (U.F.) foam insulation (46 FR 11188). The ban was proposed on the basis of the Commission's preliminary finding that the product posed an unreasonable risk of injury from irritation and cancer

because of the release of formaldehyde gas from the product after it is installed. A detailed discussion of the Commission's reasons for proposing the ban was contained in the proposal notice.

On November 18, 1981, the Commission published a request for public comment on additional data that it had received concerning these proposals (46 FR 56762). Comments on these additional data were received until December 21, 1981.

On January 29, 1982, the Commission staff transmitted to the Commission a voluminous briefing package discussing the issue associated with the proposed ban. A number of parties submitted comments on the Commission staff's briefing package, and some of these parties asked that an additional comment period be established for the purpose of allowing comment on the staff's analysis of the issues and comments.

The Commission decided not to establish an additional comment period for the submission of additional comments on the proposed ban. However, as has been its practice in the past, the Commission considered late-filed comments to the extent practicable. Some of the late comments that were received were lengthy and addressed a number of issues.

The Commission held a public meeting on February 22, 1982, at which it voted to ban U. F. foam insulation. However, it was necessary subsequently to revise the draft notice that would issue the ban to formally address the additional comments that has been received.

Also, in the proposed ban, the Commission stated that the actual date of promulgation of any such ban would be ten days after the ban was published in the Federal Register.

For these reasons, which the Commission determines to be good cause, the Commission extends the date established under 15 U.S.C. 2058(a)(1), by which it must either issue a final ban of U. F. foam insulation or withdraw the proposed ban, until April 20, 1982. For good cause, this date may be further extended.

Dated: March 18, 1982.

Sadye E. Dunn,
Secretary, Consumer Product Safety Commission.

[FR Doc. 82-7699 Filed 3-18-82; 11:42 am]

BILLING CODE 6355-01-M

COMMODITY FUTURES TRADING COMMISSION

17 CFR Part 1

Minimum Financial and Related Reporting Requirements for Futures Commission Merchants

AGENCY: Commodity Futures Trading Commission.

ACTION: Proposed rules.

SUMMARY: The Commodity Futures Trading Commission ("Commission") is proposing to amend certain of its minimum financial and related reporting requirements for futures commission merchants ("FCMs"). The proposed amendments would allow those FCMs which are also registered as brokers or dealers with the Securities and Exchange Commission ("SEC") to comply with the Commission's minimum adjusted net capital requirement by complying with the SEC's minimum net capital requirement, so long as such FCMs maintain a level of adjusted net capital which exceeds the amount required to be maintained by FCMs which are not also registered as brokers or dealers. This action is a continuation of previous cooperative efforts between the Commission and the SEC which are intended to eliminate, to the extent practicable, duplicative or undue regulatory burdens on FCM/broker-dealers.

DATE: Comments must be submitted on or before April 22, 1982.

ADDRESS: Comments should be sent to: Commodity Futures Trading Commission, 2033 K Street, NW., Washington, D.C. 20581. Attention: Secretariat.

FOR FURTHER INFORMATION CONTACT: Gary C. Miller, Assistant Chief Accountant, Division of Trading and Markets, Commodity Futures Trading Commission, 2033 K Street, NW., Washington, D.C. 20581. Telephone: (202) 254-8955.

¹ Commissioners R. David Pittle, Edith Barksdale Sloan, and Samuel Zagoria voted for the extension. Commissioner Stuart M. Statler, who voted not to issue the ban, abstained, and Chairman Nancy Harvey Steorts voted not to extend.

SUPPLEMENTARY INFORMATION:

I. Proposed Amendment to Minimum Adjusted Net Capital Requirement

Since December 31, 1980, all FCMs have been required to maintain a minimum level of adjusted net capital computed according to what had previously been referred to as the "alternative" computation, which is the greatest of: (1) \$50,000 (\$100,000 for each FCM which is not a member of a contract market), or (2) four percent of the funds required to be segregated by the FCM pursuant to the Commodity Exchange Act, as amended ("Act"), and the regulations promulgated thereunder, or (3) for those FCMs which are also registered as brokers or dealers, four percent of aggregate debit items computed in accordance with the SEC formula for determination of reserve requirements (Exhibit A to SEC Rule 15c3-3, 17 CFR 240.15c3-3).¹ Prior to December 31, 1980, the "basic" adjusted net capital computation used to determine the required minimum level of adjusted net capital was the greater of: (1) \$50,000 (\$100,000 for non-member FCMs), or (2) six and two-thirds percent of the FCM's aggregate indebtedness. After December 31, 1980, all references to aggregate indebtedness were eliminated from the Commission's minimum financial and related reporting requirements.

Although the Commission has eliminated all references to aggregate indebtedness in its minimum financial and related reporting requirements for FCMs, the SEC has maintained six and two-thirds percent of aggregate indebtedness as the basic net capital requirement for brokers and dealers. Further, the SEC recently adopted an amendment to its alternative net capital computation, effective May 1, 1982, which reduces the amount of net capital required for a broker or dealer electing to operate under the SEC's alternative net capital computation from four percent of aggregate debit items to two percent.²

¹45 FR 79416 (December 1, 1980). At the same time that the Commission adopted those changes to its minimum financial and related reporting requirements, the Commission proposed to increase the minimum dollar amounts of adjusted net capital required to be maintained by FCMs to \$100,000 for firms which are members of at least one contract market and \$150,000 for non-members. 45 FR 79498 (December 1, 1980). The Commission still has that proposal under consideration.

²47 FR 3512 (January 25, 1982). The SEC also amended its net capital definition with respect to two items unique to the securities business: (1) Receivables arising out of "free shipments" of mutual fund shares (see 47 FR 3512, at 3517, 3518) and (2) "short securities differences" (see 47 FR 3512, at 3515-16, 3518). No changes are needed in the Commission's regulations as a result of those two amendments because all deductions which a broker or dealer must make from its net worth in

Because of the current difference between the Commission's rules and the SEC's rules regarding aggregate indebtedness, and because of the difference in the Commission's rules and the SEC's rules, as effective May 1, 1982, regarding aggregate debit items, there are FCM/broker-dealers with adjusted net capital which meets the minimum net capital requirement of the SEC but does not meet the Commission's requirement as it now stands, even though the firm's adjusted net capital is in excess of the Commission's principal requirement, which is four percent of the funds required to be segregated under the Act and the Commission's regulations (come May 1, 1982, more FCM/broker-dealers would be in that situation). This circumstance could arise if, for example, and FCM/broker-dealer was carrying \$50,000,000 in customer funds, had aggregate indebtedness of \$45,000,000 and aggregate debit items amounted to \$200,000,000. For such a hypothetical firm, four percent of the funds required to be segregated would amount to \$2,000,000, six and two-thirds percent of aggregate indebtedness would amount to \$3,000,000, and four percent of aggregate debit items would amount to \$8,000,000 (two percent of aggregate debit items would be half as much, or \$4,000,000). As long as such a hypothetical firm maintained net capital of \$3,000,000 (if it was using the SEC's basic computation) or \$4,000,000 (if it elected to operate under the SEC's amended alternative computation), it would be in compliance with the SEC's regulations (those amounts would exceed the minimum amount required of an FCM which was not also a broker or dealer and was carrying the same amount of customer funds by \$1,000,000 and \$2,000,000, respectively). Such a firm, however, would need \$8,000,000 to be in compliance with the Commission's regulations (based on four percent of aggregate debit items), which is \$6,000,000 more than an FCM which is not also a broker or dealer would need if it was carrying the same amount of customer funds. Even if the Commission simply amended its regulations so that an amount of adjusted net capital equal to two percent of aggregate debit items were satisfactory, this would still require the hypothetical firm to maintain

computing net capital under SEC regulations are incorporated by reference in the Commission's financial rules (in the Commission's terminology, such items constitute required adjustments to net capital). Likewise, further rule changes proposed by the SEC (see 47 FR 3521, 47 FR 3531 and 47 FR 3534, all published on January 25, 1982) would also be incorporated by reference in the Commission's financial rules. See 17 CFR 1.17(c)(5)(v) and (xiv) (1981).

\$4,000,000 of adjusted net capital, which would be \$1,000,000 more than the amount required by the SEC's basic computation method, and \$2,000,000 more than would be required of an FCM which is not also a broker or dealer and which carries the same amount of customer funds.

In the Commission's view, a firm such as the hypothetical firm discussed in the preceding paragraph would face an undue burden both with respect to the amount of adjusted net capital which it would be required to maintain and with respect to duplicative computational and recordkeeping requirements if such a firm were required to maintain adjusted net capital equal to four percent of aggregate debit items, or even two percent of aggregate debit items. In the example given, this would require an FCM/broker-dealer to maintain either four times or twice the amount, respectively, of adjusted net capital as would be required of such a firm if it were not registered as a broker or dealer, and also would require maintenance of \$5,000,000 and \$1,000,000, respectively, of adjusted net capital beyond the amount of net capital required under the SEC's basic computation. The Commission believes that such a result is not needed to achieve the essential purpose of the minimum financial requirement for FCMs, which is to require FCMs to maintain at all times adjusted net capital equal to the greater of the required minimum dollar amount, or four percent of the funds required to be segregated. The Commission also believes that such a result would be contrary to one of the Commission's stated goals, which is to prevent the imposition of excessive financial requirements on FCM/broker-dealers so as to put such firms at a competitive disadvantage to other FCMs.³ Further, if the Commission did not amend its regulations, FCM/broker-dealers could be required to maintain adjusted net capital according to two different methods, necessitating duplicative computational and recordkeeping requirements. This would not be consistent with previous cooperative efforts between the Commission and the SEC directed towards the elimination of duplicative regulatory burdens.

The Commission has determined, therefore, to propose amendments to the minimum financial and related reporting requirements for FCMs to allow those FCMs which are also registered as brokers or dealers to comply with the Commission's minimum adjusted net

³See 43 FR 39956, at 39962 (September 8, 1978).

capital requirement by maintaining the amount of net capital required by the regulations of the SEC, so long as the amount of net capital maintained exceeds the amount required to be maintained by FCMs which are not registered as brokers or dealers. FCM/broker-dealers would have to maintain an amount of adjusted net capital at least equal to the minimum dollar amount or four percent of the funds required to be segregated, and thus FCM/broker-dealers would not have an advantage over other FCMs. On the other hand, if an FCM/broker-dealer maintains the amount of net capital which the SEC deems necessary and such an amount exceeds what would be required by the Commission for such a firm if it were only an FCM, the Commission's regulations should not place such a firm at a competitive disadvantage to other FCMs by requiring an even higher amount of net capital to be maintained.

The Commission is proposing to amend § 1.17(a)(1) of its regulations by eliminating the words "4 percent of aggregate debit items computed in accordance with the formula for determination of reserve requirements (Exhibit A to Rule 15c3-3, 17 CFR 240.15c3-3)" and substituting in their place "the amount of net capital required by Rule 15c3-1(a) of the regulations of the Securities and Exchange Commission (17 CFR 240.15c3-1(a))" as the last clause of § 1.17(a)(1). Confirming changes to other provisions of § 1.17 and to a provision of the early warning system (17 CFR 1.12 (1981)) which refer to the required minimum amount of adjusted net capital would also be made,⁴ as well as appropriate changes to Commission Form 1-FR, the basic financial reporting form for FCMs.⁵

⁴ Paragraph (e) of § 1.17, referring to withdrawal of equity capital, and paragraphs (b)(2)(vi)(C), (b)(2)(vii), (b)(2)(viii), (b)(3)(ii) and (b)(3)(v) of § 1.17, referring to subordination agreements, would be amended, as well as § 1.12(b) of the early warning system, with appropriate references to the corresponding SEC rules.

⁵ Amendments would be made in what are currently Items 24C and 27 of the Statement of the Computation of the Minimum Capital Requirements (as a result of previous amendments to Form 1-FR made in connection with the Commission's adoption of regulations to govern a pilot program of trading commodity options on domestic exchange, those items have been renumbered as 22C and 25, respectively. 46 FR 54500, 54536 (November 3, 1981). A change would also be required in Item 4 of the Statement of the Computation of the Minimum Capital Requirements due to a proposed change in treatment of certain current tax liabilities discussed *infra*. Of course, FCM/broker-dealers retain the option of filing a copy of Part II of their FOCUS Report in lieu of Form 1-FR. 17 CFR 1.10(h)(1981). The changes to the Form 1-FR which would be necessitated by the proposed amendments to the regulations discussed herein are not being published in this release since those changes are of a minor,

The Commission is proposing to amend its minimum financial and related reporting requirements by means of general phrasing which incorporates by reference the appropriate SEC rules, rather than by amending the Commission's rules to conform to specific requirements currently set forth in the SEC's rules, so that any future change in the SEC's net capital requirement would be incorporated by reference into the Commission's rules, and would not require a further rulemaking proceeding by the Commission. The general phrasing which the Commission is now proposing would also eliminate any problem caused by the fact that the SEC still allows the aggregate indebtedness method of net capital computation.

II. Other Amendments

The recent SEC amendments to its net capital requirements for brokers and dealers made two substantive changes to those requirements in addition to lowering the percentage of aggregate debit items used in the SEC's alternative net capital computation. After its own consideration of the issues involved, and in view of the Commission's continuing commitment to cooperative efforts with the SEC concerning financial regulations, the Commission has determined to propose similar amendments.

The first proposal concerns the treatment of certain current tax liabilities.⁶ The Commission's regulations do not allow an FCM to exclude current tax liabilities (in contrast to the treatment allowed for deferred tax liabilities) from the firm's liabilities for purposes of computing net capital, even if the current tax liability is based on income related to an asset which must be deducted from current assets for purposes of computing net capital.⁷ Although this may appear to constitute a "double deduction," the Commission previously has not allowed an offset for current tax liabilities because a current tax liability must be paid by the FCM regardless of whether the asset generating the income upon which the tax liability is based has been converted into cash, and the Commission believes that such

technical nature and because Form 1-FR does not appear in the Code of Federal Regulations. Anyone interested in further information regarding the changes to Form 1-FR may contact Mr. Miller at the address or telephone number listed in this release. Form 1-FR is available upon request from the Commission.

⁶ The SEC's discussion of this issue can be found in 47 FR 3512, at 3516-17.

⁷ 17 CFR 1.17(c)(2)(ii) (1981), as amended, 46 FR 54500, 54517 (November 3, 1981).

treatment could continue to be justified under a strict liquidity test. The Commission further believes, however, that such treatment appears to be unnecessary to protect a firm's solvency. Accordingly, the Commission is proposing an amendment to its financial rules which would permit an FCM to exclude from liabilities for purposes of computing net capital any current tax liability based upon accrued income which is directly related to an asset required to be deducted pursuant to § 1.17. The Commission intends, however, to interpret this provision narrowly if it is adopted.

The second proposal concerns subordinated debt.⁸ The Commission's subordination agreement rules are deemed "satisfactory subordination agreements" and the subordinated debts which are governed by those agreements can be excluded from liabilities for purposes of computing net capital. Section 1.17(h)(2)(vii) prohibits any prepayment of subordinated debt for one year following the date upon which the governing subordination agreement became effective, a provision which is designed to insure the adequacy and permanence of subordinated debt, and to prevent circumvention of the general requirement of a one year minimum term (see § 1.17(h)(2)(i)(A)). The SEC has now determined to permit the use of what it refers to as "Revolving Subordinated Loan Agreements," which would have no restriction as to when prepayment of subordinated debt could be made, provided certain other conditions are met. The Commission believes that subordination agreements could be approved without restriction as to when prepayment could be made, so long as such prepayments (deemed "special prepayments") are subject to the following conditions, and subject to approval by the designated self-regulatory organization(s) involved and the Commission:

1. Any proposed special prepayment, together with contemplated prepayments and scheduled repayments of capital during the succeeding six months, would not result in a firm's adjusted net capital being less than the greatest of (1) twice the minimum dollar amount (\$100,000 for members, \$200,000 for non-members), or (2) ten percent of the funds required to be segregated under the Act and the regulations promulgated thereunder, or (3) for securities brokers or dealers, the amount of net capital required by the regulations of the Securities and Exchange Commission before such a special prepayment would be permitted; and

⁸ The SEC's discussion of this issue can be found in 47 FR 3512, at 3516.

2. Pre-tax losses during the latest three-month period were less than fifteen percent of current excess adjusted net capital.

The conditions which would apply to a special prepayment involve higher levels of adjusted net capital than those applicable to the present prepayment provision. The Commission believes such higher levels are appropriate to the situation and they are generally in line with the SEC's provision in this area.

A satisfactory subordination agreement, therefore, would, if the amendment were adopted, be permitted to contain either the current prepayment provision, the new special prepayment provision, both such prepayment provisions, or neither provision. A subordination agreement containing the special prepayment provision described in this release would, of course, be subject to all other provisions of the Commission's regulations regarding subordination agreements.

III. Other Matters

A. Contract Market Rules

The Commission wishes to reiterate that central to the operation of the financial surveillance system for FCMs are the requirements in § 1.52(a) of the regulations (17 CFR 1.52(a)(1981)) that each contract market have in effect, and be responsible for enforcing, financial and reporting rules for their member FCMs which are at least as stringent as those contained in §§ 1.10 and 1.17 of the Commission's regulations, and that each contract market's definition of adjusted net capital be the same as that provided in § 1.17(c). Most of the contract markets' rules in this regard incorporate, by reference, the requirements of §§ 1.10 and 1.17 and, hence, any amendments to § 1.17 would be incorporated automatically into the rules of those contract markets upon the effective date of such amendments. Two contract markets do not follow this approach, however, and instead have detailed financial and reporting rules. If the proposed change in the treatment of certain current tax liabilities is adopted by the Commission, the definition of adjusted net capital would be affected, and the rules of those two contract markets would have to be amended so that their definition of adjusted net capital would remain the same as the Commission's definition. Those two contract markets should begin the preparations necessary to effectuate an appropriate change in their rules in the event such a change is adopted.

B. Certification Under the Regulatory Flexibility Act

The Commission does not believe that the proposed rule amendments would have significant economic impact on small entities. As discussed above, the only regulated entities which would be affected by the proposed rule amendments would be FCMs, principally FCM/broker-dealers.⁹ The proposed rule amendments are of a liberalizing nature and they would relieve burdens and restrictions heretofore imposed on FCMs. Accordingly, pursuant to Section 3(a) of the Regulatory Flexibility Act, 94 Stat. 1168 (5 U.S.C. 605(b)), the Chairman, on behalf of the Commission, certifies that the rule amendments proposed herein, if promulgated, will not have a significant economic impact on a substantial number of small entities. However, the Commission particularly invites comments from any firms or other persons which believe that promulgation of these rule amendments might have a significant economic impact upon their activities.

In consideration of the foregoing, the Commission, pursuant to the authority contained in Sections 4d, 4f and 8a of the Act, 7 U.S.C. 6d, 6f and 12a (1976 & Supp. III 1979), hereby proposes to amend 17 CFR Chapter I in the manner set forth below.

PART 1—GENERAL REGULATIONS UNDER THE COMMODITY EXCHANGE ACT

1. 17 CFR Part 1 is proposed to be amended by revising paragraph (b) of § 1.12 to read as follows:

§ 1.12 Maintenance of minimum financial requirements by futures commission merchants.

(b) Each person registered as a futures commission merchant, or who files an application for registration as a futures commission merchant, who knows or should have known that its adjusted net capital at any time is less than the greatest of 150 percent of the appropriate minimum dollar amount required by § 1.17, or 6 percent of the funds required to be segregated pursuant to Section 4d(2) of the Act and these regulations, or, for securities brokers or dealers, the amount of net capital specified in Rule 17a-11(b) of the Securities and Exchange Commission (17 CFR 240.17a-11(b)), must file written

⁹ The Commission has recently published its proposed determination that a registered FCM not be considered a "small entity" within the meaning of the Regulatory Flexibility Act, Pub. L. 96-354, 94 Stat. 1165, 1166, (5 U.S.C. 601(3) and (6)). 46 FR 23940, 23941 (April 29, 1981).

notice to that effect as set forth in paragraph (g) of this section within five (5) business days of such event. Such applicant or registrant must also file a Form 1-FR (or, if such applicant or registrant is registered with the Securities and Exchange Commission as a securities broker or dealer, it may file (in accordance with § 1.10(h)) a copy of its Financial and Operational Combined Uniform Single Report under the Securities Exchange Act of 1934, Part II, in lieu of Form 1-FR) or such other financial statement designated by the Commission and/or the designated self-regulatory organization, if any, as of the close of business for the month during which such event takes place and as of the close of business for each month thereafter until three (3) successive months have elapsed during which the applicant's or registrant's adjusted net capital is at all times equal to or in excess of the minimums set forth in this paragraph (b) which are applicable to such applicant or registrant. Each financial statement required by this paragraph (b) must be filed within 30 calendar days after the end of the month for which such report is being made.

2. 17 CFR Part 1 is proposed to be amended further by revising paragraphs (a)(1), (c)(2)(v), (c)(4)(iv)(A) and (c)(4)(iv)(C), by redesignating paragraph (c)(4)(v) as paragraph (c)(4)(vi), by adding a new paragraph (c)(4)(v), by revising paragraphs (e) and (h)(2)(vi)(C), by revising paragraph (h)(2)(vii) and redesignating paragraph (h)(2)(vii) as paragraph (h)(2)(viii)(A), by adding a new paragraph (h)(2)(vii)(B), and by revising paragraphs (h)(2)(viii), (h)(3)(ii) and (h)(3)(v) of § 1.17 to read as follows:

§ 1.17 Minimum financial requirements—futures commission merchants.

(a)(1) Except as provided in paragraph (a)(2) of this section, each person registered as a futures commission merchant must maintain adjusted net capital equal to or in excess of the greatest of \$50,000 (\$100,000 for each person registered as a futures commission merchant who is not a member of a designated self-regulatory organization), or 4 percent of the funds required to be segregated pursuant to the Act and these regulations, or, for securities brokers and dealers, the amount of net capital required by Rule 15c3-1(a) of the regulations of the Securities and Exchange Commission (17 CFR 240.15c3-1(a)).

(c) * * *

(2) * * *

(v) Include fixed assets and assets which otherwise would be considered noncurrent to the extent of any long-term debt adequately collateralized by assets acquired for use in the ordinary course of the trade or business of an applicant or registrant and any other long-term debt adequately collateralized by assets of the applicant or registrant if the sole recourse of the creditor for nonpayment of such liability is to such asset: *Provided*, Such liabilities are not excluded from liabilities in the computation of net capital under paragraph (c)(4)(vi) of this section;

(4) ***

(iv) ***

(A) The aggregate amount resulting from applying to the amount of the deductions computed in accordance with paragraph (c)(5) of this section the appropriate Federal and State tax rate(s) applicable to any unrealized gain on the asset on which the deduction was computed;

(C) Any deferred tax liability related to unrealized appreciation in value of any asset(s) which has been otherwise excluded from current assets in accordance with the provisions of this section;

(v) Excludes any current tax liability related to income accrued which is directly related to an asset otherwise deducted pursuant to this section; and

(vi) Excludes liabilities which would be classified as long term in accordance with generally accepted accounting principles to the extent of the net book value of plant, property and equipment which is used in the ordinary course of any trade or business of the applicant or registrant which is a reportable segment of the applicant's or registrant's overall business activities, as defined in generally accepted accounting principles, other than in the commodity futures, commodity option, security and security option segments of the applicant's or registrant's business activities: *Provided*, That such plant, property and equipment is not included in current assets pursuant to paragraph (c)(2)(v) of this section.

(e) No equity capital of the applicant or registrant or a subsidiary's or affiliate's equity capital consolidated pursuant to paragraph (f) of this section, whether in the form of capital contributions by partners (including amounts in the commodities, options and securities trading accounts of partners which are treated as equity capital but excluding amounts in such trading accounts which are not equity

capital and excluding balances in limited partners' capital accounts in excess of their stated capital contributions), par or stated value of capital stock, paid-in capital in excess of par or stated value, retained earnings or other capital accounts, may be withdrawn by action of a stockholder or partner or by redemption or repurchase of shares of stock by any of the consolidated entities or through the payment of dividends or any similar distribution, nor may any unsecured advance or loan be made to a stockholder, partner, sole proprietor, or employee if, after giving effect thereto and to any other such withdrawals, advances or loans and any payments of payment obligations (as defined in paragraph (h) of this section) under satisfactory subordination agreements and any payments of liabilities excluded pursuant to paragraph (c)(4)(vi) of this section which are scheduled to occur within six months following such withdrawal, advance or loan, either adjusted net capital of any of the consolidated entities would be less than the greatest of 120 percent of the appropriate minimum dollar amount required by § 1.17 or 7 percent of the amount required to be segregated pursuant to the Act and these regulations or, for securities brokers or dealers, the amount of net capital specified in Rule 15c3-1(e), of the Securities and Exchange Commission (17 CFR 240.15c3-1(e)), or in the case of any applicant or registrant included within such consolidation, if equity capital of the applicant or registrant (inclusive of satisfactory subordination agreements which qualify as equity under paragraph (d) of this section) would be less than 30 percent of the required debt-equity total as defined in paragraph (d) of this section: *Provided*, That this provision shall not preclude an applicant or registrant from making required tax payments or preclude the payment to partners of reasonable compensation. The Commission may, upon application of the applicant or registrant, grant relief from this paragraph (e) if the Commission deems it to be in the public interest or for the protection of nonproprietary accounts.

(h) ***

(2) ***

(vi) ***

(C) The secured demand note agreement may also provide that, in lieu of the procedures specified in the provisions required by paragraph (h)(2)(vi)(B) of this section, the lender, with the prior written consent of the applicant or registrant and the

designated self-regulatory organization, or, if the applicant or registrant is not a member of a designated self-regulatory organization, then the Commission, may reduce the unpaid principal amount of the secured demand note: *Provided*, That after giving effect to such reduction the adjusted net capital of the applicant or registrant would not be less than the greater of 7 percent of the funds required to be segregated pursuant to the Act and these regulations, or, for securities brokers or dealers, the amount of net capital specified in Rule 15c3-1d(b)(6)(iii) of the regulations of the Securities and Exchange Commission (17 CFR 240.15c3-1d(b)(6)(iii)): *Provided*, further, That no single secured demand note shall be permitted to be reduced by more than 15 percent of its original principal amount and after such reduction no excess collateral may be withdrawn. No designated self-regulatory organization shall consent to a reduction of the principal amount of a secured demand note if, after giving effect to such reduction, adjusted net capital would be less than 120 percent of the appropriate minimum dollar amount required by this section.

(vii) *Permissive prepayments and special prepayments.* (A) An applicant or registrant at its option, but not at the option of the lender, may, if the subordination agreement so provides, make a payment of all or any portion of the payment obligation thereunder prior to the scheduled maturity date of such payment obligation (hereinafter referred to as a "prepayment"), but in no event may any prepayment be made before the expiration of one year from the date such subordination agreement became effective: *Provided, however*, That the foregoing restriction shall not apply to temporary subordination agreements which comply with the provisions of paragraph (h)(3)(v) of this section nor shall it apply to "special prepayments" made in accordance with the provisions of paragraph (h)(2)(vi)(B) of this section. No prepayment shall be made if, after giving effect thereto (and to all payments of payment obligations under any other subordinated agreements then outstanding, the maturity or accelerated maturities of which are scheduled to fall due within six months after the date such prepayment is to occur pursuant to this provision, or on or prior to the date on which the payment obligation in respect to such prepayment is scheduled to mature disregarding this provision, whichever date is earlier) without reference to any projected profit or loss of the applicant or registrant, the adjusted net capital of the applicant or registrant is less than the greater of 7

percent of the funds required to be segregated pursuant to the Act and these regulations or, for securities brokers or dealers, the amount of net capital specified in Rule 15c3-1d(b)(7) of the regulations of the Securities and Exchange Commission (17 CFR 240.15c3-1d(b)(7)), or its adjusted net capital is less than 120 percent of the appropriate minimum dollar amount required by this section. Notwithstanding the above, no prepayment shall occur without the prior written approval of the designated self-regulatory organization and the Commission.

(B) An applicant or registrant at its option, but not at the option of the lender, may, if the subordination agreement so provides, make a payment at any time of all or any portion of the payment obligation thereunder prior to the scheduled maturity date of such payment obligation (hereinafter referred to as a "special prepayment"). No special prepayment shall be made if, after giving effect thereto (and to all payments of payment obligations under any other subordinated agreements then outstanding, the maturity or accelerated maturities of which are scheduled to fall due within six months after the date such special prepayment is to occur pursuant to this provision, or on or prior to the date on which the payment obligation in respect to such special prepayment is scheduled to mature disregarding this provision, whichever date is earlier) without reference to any projected profit or loss of the applicant or registrant, the adjusted net capital of the applicant or registrant is less than the greater of 10 percent of the funds required to be segregated pursuant to the Act and these regulations or, for securities brokers or dealers, the amount of net capital specified in Rule 15c3-1d(c)(5)(ii) of the regulations of the Securities and Exchange Commission (17 CFR 240.15c3-1d(c)(5)(ii)), or its adjusted net capital is less than 200 percent of the appropriate minimum dollar amount required by this section, nor shall any special prepayment be made if pre-tax losses during the latest three-month period were greater than 15 percent of current excess adjusted net capital. Notwithstanding the above, no prepayment shall occur without the prior written approval of the designated self-regulatory organization and the Commission.

(viii) *Suspended repayment.* (A) The payment obligation of the applicant or registrant in respect of any subordination agreement shall be suspended and shall not mature if, after

giving effect to payment of such payment obligation (and to all payments of payment obligations of the applicant or registrant under any other subordination agreement(s) then outstanding which are scheduled to mature on or before such payment obligation), the adjusted net capital of the applicant or registrant would be less than the greater of 6 percent of the funds required to be segregated pursuant to the Act and these regulations or, for securities brokers or dealers, the amount of net capital specified in Rule 15c3-1d(b)(8)(i) of the regulations of the Securities and Exchange Commission (17 CFR 240.15c3-1d(b)(8)(i)), or its adjusted net capital would be less than 120 percent of the minimum dollar amount required by this section: *Provided*, That the subordination agreement may provide that if the payment obligation of the applicant or registrant thereunder does not mature and is suspended as a result of the requirement of this paragraph (h)(2)(viii) of this section for a period of not less than six months, the applicant or registrant shall then commence the rapid and orderly liquidation of its business, but the right of the lender to receive payment, together with accrued interest or compensation, shall remain subordinate as required by the provisions of this section.

(3) * * *

(ii) *Notice of maturity or accelerated maturity.* Every applicant or registrant shall immediately notify the designated self-regulatory organization and the Commission if, after giving effect to all payments of payment obligations under subordination agreements then outstanding which are then due or mature within the following six months without reference to any projected profit or loss of the applicant or registrant, its adjusted net capital would be less than 120 percent of the minimum dollar amount required by this section, or its adjusted net capital would be less than the greater of 6 percent of the funds required to be segregated pursuant to the Act and these regulations or, for securities brokers or dealers, the amount of net capital specified in Rule 15c3-1d(c)(2) of the regulations of the Securities and Exchange Commission (17 CFR 240.15c3-1d(c)(2)).

(v) *Temporary Subordinations.* To enable an applicant or registrant to participate as an underwriter of securities or undertake other extraordinary activities and remain in compliance with the adjusted net capital

requirements of this section, an applicant or registrant shall be permitted, on no more than three occasions in any 12-month period, to enter into a subordination agreement on a temporary basis which has a stated term of no more than 45 days from the date the subordination agreement became effective: *Provided*, That this temporary relief shall not apply to any applicant or registrant if the adjusted net capital of the applicant or registrant is less than the greater of 7 percent of the funds required to be segregated pursuant to the Act and these regulations or, for securities brokers or dealers, the amount of net capital specified in Rule 15c3-1d(c)(5)(i) of the Securities and Exchange Commission (17 CFR 240.15c3-1d(c)(5)(i)), or its adjusted net capital is less than 120 percent of the appropriate minimum dollar amount required by this section, or the amount of equity capital as defined in paragraph (d) of this section is less than the limits specified in paragraph (d) of this section. Such temporary subordination agreement shall be subject to all the other provisions of this section.

Issued in Washington, D.C., on March 17, 1982, by the Commission.

Jane K. Stuckey,
Secretary of the Commission.

[FR Doc. 82-7782 Filed 3-22-82; 8:46 a.m.]

BILLING CODE 6351-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Subchapter F

Review of Blood Regulations; Public Meetings

AGENCY: Food and Drug Administration.

ACTION: Notice of meetings on regulations.

SUMMARY: The Food and Drug Administration (FDA) announces that two public meetings will be held for review of current blood regulations. The first meeting will be held to discuss the blood derivative and source plasma regulations, and the second meeting will be held to discuss the whole blood regulations.

DATES:

April 12-13, 1982, from 8:30 a.m. to 5 p.m., regarding blood derivative and source plasma regulations.

April 20-21, 1982, from 8:30 a.m. to 5 p.m., regarding whole blood regulations.

ADDRESSES: The April 12-13, 1982 meeting will be held in Rm. 121, Bldg. 29, National Institutes of Health, 8800 Rockville Pike, Bethesda, MD 20205. The April 20-21, 1982 meeting will be held at the Lister Hill Auditorium, National Library of Medicine, Bldg. 38A, 8600 Rockville Pike, Bethesda, MD 20205.

FOR FURTHER INFORMATION CONTACT: Mary Ann Tourault, Bureau of Biologics (HFB-200), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, 301-496-5241.

SUPPLEMENTARY INFORMATION: The purpose of these meetings is to review current blood and blood product requirements listed in Subchapter F of Title 21 of the Code of Federal Regulations with regard to their scientific validity and economic impact on industry and the public. This action is intended to highlight regulations which are unnecessarily costly, burdensome, inefficient, or otherwise unsuitable from a regulatory standpoint and in need of revision. The Executive Order 12291 and the Paperwork Reduction Act of 1980 require the review of certain existing regulations imposing economic burdens. In addition, the Regulatory Flexibility Act requires a periodic review of regulations that impose significant economic impact upon a substantial number of small businesses, small organizations, or small governmental organizations. All of these reviews are conducted to determine whether existing rules should be continued without change, amended, or rescinded.

Individuals or organizations intending to present changes in the blood and blood product regulations are requested to submit a written summary of comments before the meetings. The summary of comments should identify sections of the Code of Federal Regulations to be changed, the reasons for the change economic data supporting the change, and the suggested proposed revision.

Persons planning to attend are requested to contact Mary Ann Tourault (address above) for additional information.

Dated: March 17, 1982.

William F. Randolph,
Acting Associate Commissioner for
Regulatory Affairs.

[FR Doc. 82-7667 Filed 3-18-82; 1:46 pm]

BILLING CODE 4160-01-M

DEPARTMENT OF STATE

22 CFR Part 41

[Docket No. SD-175]

Bureau of Consular Affairs; Nonimmigrant Classification of Students

AGENCY: Department of State.

ACTION: Proposed rule.

SUMMARY: The Department proposes to amend § 41.45 to implement the provisions of section 2(a) of the Immigration and Nationality Act Amendments of 1981, Pub. L. 97-116, which are to become effective on June 1, 1982. The proposals would limit the F-1 nonimmigrant visa classification to aliens destined to full courses of study at academic institutions designated in the law or in language training programs. The Department also proposes to create a new § 41.68 relating to the new M-1 classification for aliens coming to the United States for full courses of study at an established vocational or other recognized nonacademic institution (other than a language training program) and M-2 classification for the alien spouse or minor children accompanying or following to join an alien classified M-1. In addition, to implement changes made by Pub. L. 97-116, the Department proposes to add a new classification symbol in § 41.12; amend the table of contents to add the new § 41.68 and amend the subject title of § 41.45.

DATES: Written comments are invited from interested persons and must be received on or before April 23, 1982.

ADDRESS: Send comment to Cornelius D. Scully, III, Director, Office of Legislation, Regulations and Advisory Assistance, Visa Services, Bureau of Consular Affairs, Department of State, Washington, D.C. 20520.

FOR FURTHER INFORMATION CONTACT: Gerald M. Brown, Legislation and Regulations Division, Visa Services. (202) 632-1900.

SUPPLEMENTARY INFORMATION: The Immigration and Nationality Act Amendments of 1981 approved on December 29, 1981 included in section 2(a) an amendment of section 101(a)(15)(F)(i) of the Act to limit the classification of nonimmigrants thereunder to otherwise qualifying aliens seeking to enter the United States temporarily and solely to pursue a full course of study at an established college, university, seminary, conservatory, academic high school, elementary high school, or other academic institution or in a language

training program. The same section added a new subparagraph (M) to section 101(a)(15) of the Act to establish a new nonimmigrant classification for certain aliens seeking to enter the United States temporarily and solely to pursue a full course of study at an established vocational or other recognized nonacademic institution (other than a language training program) and the spouse or minor children accompanying or following to join any such alien. These regulations are proposed for administering the amendments to section 101(a)(15) of the Act and include the conditions which otherwise qualified aliens will be required to meet to obtain a nonimmigrant visas solely for the purpose of study in the United States. The Form I-20M-N (Certificate of Eligibility) referred to in the proposed new § 41.46 is the document which the Immigration and Naturalization Service is proposing in its regulations for use by an authorized official of an established vocational or other recognized nonacademic institutions approved by the Service for attendance by foreign students, in certifying the alien's eligibility and acceptance for admission. Other technical changes are made to sections in Part 41 affected by Pub. L. 97-116.

PART 41—VISAS: DOCUMENTATION OF NONIMMIGRANTS UNDER THE IMMIGRATION AND NATIONALITY ACT, AS AMENDED

In light of these proposals, Part 41 is proposed to be amended as follows:

§ 41.12 [Amended]

1. In the list of classification of symbols in § 41.12, amend line 17 (Student) to read "Student—Academic or language training program".

2. In the list of classification of symbols in § 41.12, after line 40 (Spouse or minor child * * * L-2), insert the following

Class	Citation	Symbol to be inserted in visa
Vocational or other recognized nonacademic student.	101(A)(15)(M); 95 Stat. 1611.	M-1
Spouse or minor child of alien classified M-1.	95 Stat. 1611	M-2

3. Revise § 41.45 and the undesignated center heading preceding it to read as follows:

Students—Academic, Language Training Programs

§ 41.45 Students in colleges, universities, seminaries, conservatories, academic high schools, elementary schools, other academic institutions, and in language training programs.

(a) An alien shall be classifiable as a nonimmigrant student under section 101(a)(15)(F)(i) of the Act upon establishing to the satisfaction of the consular officer that the provisions of that section have been met and that the alien:

(1) Will attend, and has been accepted for attendance by, a college, university, seminary, conservatory, academic high school, elementary school, or other academic institution or in a language training program in the United States which has been approved by the Attorney General for the purposes of section 101(a)(15)(F)(i) of the Act, as evidenced by the presentation of Form I-20A-B (Certificate of Eligibility) properly and completely filled out and signed by the alien and by an official of the accepting school (the Form I-20A, when properly executed and presented by an alien in support of an application for a student visa under this section, shall be accepted by the consular officer as prima facie evidence that the designated college, university, seminary, conservatory, academic high school, elementary school, or other academic institution or institution providing language training has been approved by the Attorney General for the attendance of nonimmigrant students, and that the visa applicant has been accepted for attendance at such institution);

(2) Is in possession of sufficient funds to cover expenses while in the United States or other arrangements have been made to provide those expenses;

(3) Has sufficient scholastic preparation and knowledge of the English language (unless the alien is going to an institution exclusively to participate in an English language training program) to enable the undertaking of a full course of study given in the English language which the accepting institution is equipped to offer, or has (i) accepted the alien expressly for a full course of study in a language with which the alien is sufficiently familiar, or (ii) has made special arrangements for tutoring the alien in the English language and the consular officer is satisfied that the applicant will be able, with such tutoring, to undertake a full course of study in the accepting institution; and

(4) Intends in good faith and will be able to depart from the United States upon the termination of the student

status (consular officers are authorized in borderline cases to require the posting of a bond with the Attorney General in a sufficient sum to insure that upon the alien's conclusion of studies, or upon the alien's failure to maintain student status, or any status subsequently acquired under section 248 of the Act, the alien will depart from the United States). If the alien is otherwise qualified for classification as a nonimmigrant student under this section, but intends to study the English language exclusively while in the United States, such alien may be classified as a nonimmigrant student under the provisions of section 101(a)(15)(F)(i) of the Act even though no credits are given by the institution for such study. The approved school must be equipped to offer a full course of study in the English language and must have accepted the applicant expressly for that course.

(b) An alien shall also be classifiable as a nonimmigrant under section 101(a)(15)(F)(ii) of the Act if it is established to the satisfaction of the consular officer that such alien qualifies under the provisions of that section and that the alien: (1) Is in possession of sufficient funds to cover expenses while in the United States, or that other arrangements have been made to provide for such expenses; and (2) intends in good faith and will be able to depart from the United States upon the termination of the status of the principal alien

4. Immediately before § 41.66 add a new undesignated center heading to read "Fiancee or Fiance".

5. Immediately before § 41.67 add a new undesignated center heading to read "Executives, Managers, and Specialists".

6. Immediately after § 41.67 add the following new undesignated center heading and section to read as follows:

Students—Vocational

§ 41.68 Students in established vocational or other recognized nonacademic institutions, other than in language training programs.

(a) An alien shall be classifiable as a nonimmigrant student under section 101(a)(15)(M)(i) of the Act upon establishing to the satisfaction of the consular officer that the provisions of that section have been met and that the alien:

(1) Will attend and has been accepted for attendance solely for the purpose of pursuing a full course of study (other than a language training program) by an established vocational or other recognized nonacademic institution in the United States which has been approved by the Attorney General for

the purposes of section 101(a)(15)(M)(i) of the Act, as evidenced by the presentation of Form I-20M-N (Certificate of Eligibility) properly and completely filled out and signed by the alien and by an official of the accepting institution (the Form I-20M, when properly executed and presented by an alien in support of an application for a student visa under this section, shall be accepted by the consular officer as prima facie evidence that the designated vocational or other recognized nonacademic institution which has issued the document has been approved by the Attorney General for the attendance of nonimmigrant students pursuant to section 101(a)(15)(M)(i) of the Act and that the visa applicant has been accepted for attendance at such institution);

(2) Is in possession of sufficient funds to cover expenses while in the United States or other arrangements have been made to provide for those expenses;

(3) Has sufficient knowledge of the English language to enable such an alien to undertake a full course of study in the accepting institution, or, of knowledge of the English language is inadequate to enable such alien to pursue a full course of study given in the English language, the accepting institution is equipped to offer and has accepted the alien expressly for a full course of study in a language with which the alien is sufficiently familiar; and (4) intends in good faith and will be able to depart from the United States upon the termination of student status.

(b) An alien shall also be classifiable as a nonimmigrant under section 101(a)(15)(M)(ii) of the Act if it is established to the satisfaction of the consular officer that such alien qualifies under the provisions of that section and that the alien: (1) Is in possession of sufficient funds to cover expenses while in the United States, or that other arrangements have been made to provide for such expenses; and (2) intends in good faith and will be able to depart from the United States upon the termination of the status of the principal alien.

(Sec. 104, 66 Stat. 174 (8 U.S.C. 1104); sec. 109(b)(1), 91 Stat. 847)

Dated: March 4, 1982.
Diego C. Asencio,
Assistant Secretary for Consular Affairs.

[FR Doc. 82-7662 Filed 3-22-82; 8:45 am]

BILLING CODE 4710-06-M

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[LR-4-82]

Travel Expenses of Members of Congress; Public Hearing on Proposed Regulations

AGENCY: Internal Revenue Service, Treasury.

ACTION: Notice of public hearing on proposed regulations.

SUMMARY: This document provides notice of a public hearing on proposed regulations relating to travel expenses of members of Congress.

DATES: The public hearing will be held on May 11, 1982, beginning at 10:00 a.m. Outlines of oral comments must be delivered or mailed by April 27, 1982.

ADDRESS: The public hearing will be held in the I.R.S. Auditorium, Seventh Floor, 7400 Corridor, Internal Revenue Building, 1111 Constitution Avenue, N.W., Washington, D.C. The outlines should be submitted to the Commissioner of Internal Revenue, Attn: CC:LR:T (LR-4-82), Washington, D.C. 20224.

FOR FURTHER INFORMATION CONTACT: Charles Hayden of the Legislation and Regulation Division, Office of Chief Counsel, Internal Revenue Service, 1111 Constitution Avenue, N.W., Washington, D.C. 20224, 202-566-4691, not a toll-free call.

SUPPLEMENTARY INFORMATION: The subject of the public hearing is proposed regulations under section 274 of the Internal Revenue Code of 1954. The proposed regulations appeared in the *Federal Register* for Thursday, January 21, 1982 (47 FR 3006).

The rules of § 601.601(a)(3) of the "Statement of Procedural Rules" (26 CFR Part 601) shall apply with respect to the public hearing. Persons who have submitted written comments within the time prescribed in the notice of proposed rulemaking and also desire to present oral comments at the hearing on the proposed regulations should submit an outline of the comments to be presented at the hearing and the time they wish to devote to each subject by April 27, 1982. Each speaker will be limited to 10 minutes for an oral presentation exclusive of time consumed by questions from the panel for the government and answers to those questions.

Because of controlled access restrictions, attendees cannot be admitted beyond the lobby of the Internal Revenue Building until 9:45 a.m.

An agenda showing the scheduling of the speakers will be made after outlines are received from the speakers. Copies of the agenda will be available free of charge at the hearing.

This document does not meet the criteria for significant regulations set forth in paragraph 8 of the Treasury Directive for improving government regulations appearing in the *Federal Register* for Wednesday, November 8, 1978.

By direction of the Commissioner of Internal Revenue:

David E. Dickinson,

Director, Legislation and Regulations Division.

[FR Doc. 82-7774 Filed 3-22-82; 8:45 am]

BILLING CODE 4830-01-M

DEPARTMENT OF THE INTERIOR

Office of Surface Mining Reclamation and Enforcement

30 CFR Part 931

Public Comment and Opportunity for Public Hearing on a Modified Portion of the New Mexico Permanent Regulatory Program

AGENCY: Office of Surface Mining Reclamation and Enforcement (OSM), Interior.

ACTION: Notice of receipt of permanent program modification; public comment period and opportunity for public hearing.

SUMMARY: OSM is announcing procedures for the public comment period and for a public hearing on the substantive adequacy of a program amendment submitted to satisfy a condition imposed by the Secretary of the Interior on the approval of the New Mexico Permanent Regulatory Program (hereinafter referred to as the New Mexico program) under the Surface Mining Control and Reclamation Act of 1977 (SMCRA).

DATES: Written comments must be received on or before 4:00 p.m. on April 22, 1982 to be considered in the Secretary's decision on whether the proposed amendment satisfies the condition.

A public hearing on the proposed modification has been scheduled for 1:00-4:00 p.m., April 16, 1982, at the address listed below under "ADDRESSES." Any person interested in making an oral or written presentation at the hearing should contact Mr. Robert Hagen at the address below by April 7, 1982. If no person has contacted Mr. Hagen by this date to

express an interest to participate in this hearing, the hearing will be cancelled. A notice announcing any cancellation will be published in the *Federal Register*.

ADDRESSES: The public hearing will be held at the State of New Mexico, Energy and Minerals Dept., Mining and Minerals Division, Map Room, 525 Camino De Los Marquez, Santa Fe, NM 87501. Written comments should be mailed or hand-delivered to Robert Hagen, State Office Director, Office of Surface Mining Reclamation and Enforcement, 219 Central N.W., Albuquerque, New Mexico 87102, Telephone (505) 766-1486.

Copies of the New Mexico proposed modification to the program, a listing of any scheduled public meetings and all written comments received in response to this notice will be available for review at the OSM Headquarters Office, the OSM State Office and the Office of the State Regulatory Authority listed below, Monday through Friday, 8:00 a.m. to 4:00 p.m., excluding holidays.

Office of Surface Mining Reclamation and Enforcement, Administrative Record Room, 1100 "L" Street, N.W., Washington, D.C.

Office of Surface Mining Reclamation and Enforcement, State Office, 219 Central, N.W., Albuquerque, New Mexico 87102

Energy and Minerals Department, Division of Mining and Minerals Department, First Northern Plaza, East, Room 200, Santa Fe, New Mexico 87501, Telephone: (505) 827-5451

FOR FURTHER INFORMATION CONTACT: Robert Hagen, State Office Director, Office of Surface Mining, 219 Central, N.W., Albuquerque, New Mexico 87102 (505) 766-1484; FTS 474-1486.

SUPPLEMENTARY INFORMATION: On February 28, 1980, OSM received a proposed regulatory program from the State of New Mexico. On December 31, 1980, following a review of the proposed program as outlined in 30 CFR 732, the Secretary approved the proposed program conditioned on the correction of 12 minor deficiencies (45 FR 86459-86490).

In accepting the Secretary's conditional approval, New Mexico agreed to submit provisions to satisfy conditions "a"- "d" and "f"- "i" by July 1, 1981, and a provision to meet condition "e" by February 28, 1982. Subsequently, New Mexico requested that the deadline for the State to meet conditions "a"- "d" and "f"- "i" be extended until February 28, 1982. On October 30, 1981 (46 FR 54070), OSM announced its decision to grant New Mexico's request. The State

recently asked for a second extension that would establish a new deadline for the State to meet conditions "a"- "c" and "e"- "1". Accordingly, on February 23, 1982, OSM issued a proposed rule to extend the deadline for the State to meet those 11 conditions until March 15, 1983.

On February 28, 1982, New Mexico submitted to OSM a policy statement to satisfy condition "d". That condition specifies that the approval found in § 931.10 will terminate on February 28, 1982, unless New Mexico submits to the Secretary by that date copies of fully implemented regulations which include the requirements for posting and publishing notices of show cause orders that may be issued in accordance with 30 CFR 843.13(c)(1)-(3) and (d), or otherwise amends its program to accomplish the same result.

To satisfy this condition, the State submitted a statement of its procedures for posting and publishing notices of show cause orders. The statement, signed by Mr. Emery C. Arnold, Director of the New Mexico Mining and Minerals Department, and dated February 19, 1982, is included in the New Mexico administrative record and is available for public inspection at the OSM addresses listed above under "ADDRESSES." The Secretary seeks public comment on whether the provision submitted by the State corrects the program deficiency identified in condition "d". If the material submitted by the State is approved, the condition as specified in 30 CFR 931.11(d) will be removed.

The public comment period announced today does not address the other 11 conditions on the approval of the New Mexico program. As stated above, OSM has proposed an extension until March 15, 1983, of the deadline for the State to meet those 11 conditions.

Additional Determinations

1. *Compliance with the National Environmental Policy Act.* The Secretary has determined that, pursuant to section 702(d) of SMCRA, 30 U.S.C. 1292(d), no environmental impact statement need be prepared on this rulemaking.

2. *Compliance with the Regulatory Flexibility Act.* The Secretary hereby determines that this proposed rule will not have a significant economic impact on small entities within the meaning of the Regulatory Flexibility Act, 5 U.S.C. 601 et seq.

3. *Compliance with Executive Order No. 12291.* Regulations concerning satisfaction of conditions of approval of State regulatory programs under SMCRA have been granted a categorical exemption from the requirement to

prepare a Regulatory Impact Analysis pursuant to Executive Order No. 12291, by a letter from the Office of Management and Budget dated August 28, 1981.

Dated: March 16, 1982.

J. S. Griles,

Acting Director, Office of Surface Mining.

[FR Doc. 82-7797 Filed 3-22-82; 8:45 am]

BILLING CODE 4310-05-M

VETERANS ADMINISTRATION

38 CFR Part 3

Veterans Benefits; Evidence of Marriage and Birth

AGENCY: Veterans Administration.

ACTION: Proposed regulation amendments.

SUMMARY: The Veterans Administration is proposing to amend its adjudication regulations governing evidence of marriage and birth. The proposed amendment would require that a claimant submit documentary evidence of marriage and birth without exception. The need for this change results from our obligation to preserve the integrity of Veterans Administration benefits provisions.

DATES: Comments must be received on or before April 22, 1982. It is proposed to make this change effective the date of final approval.

ADDRESSES: Interested persons are invited to submit written comments, suggestions, or objections regarding the proposal to the Administrator of Veterans Affairs (271A), Veterans Administration, 810 Vermont Avenue, NW., Washington, D.C. 20420. All written comments received will be available for public inspection at the above address only between the hours of 8 a.m. and 4:30 p.m. Monday through Friday (except holidays) until May 3, 1982. Persons visiting the Veterans Administration Central Office in Washington, D.C. for the purpose of inspecting comments will be received by the Central Office Veterans Services Unit in room 132. Visitors to a VA field station will be informed that the records are available for inspection only in Central Office and will be furnished the address and room number.

FOR FURTHER INFORMATION CONTACT: T. H. Spindle, Jr. (202-389-3005).

SUPPLEMENTARY INFORMATION: Under 38 CFR 3.205(a), the certified statement of a veteran or surviving spouse claimant may be accepted to establish the claimant's marriage without requiring

the claimant to submit corroborating evidence, such as a marriage certificate. Under 38 CFR 3.209, the certified statement of a veteran may be accepted as proof of birth of a veteran's child without requiring the veteran to submit corroborating evidence such as a birth certificate. In the case of a deceased veteran, § 3.209 permits the Veterans Administration to accept a similar statement from a child's surviving parent.

These liberal provisions for establishing marriage and birth make it quite easy for a dishonest claimant to defraud the Veterans Administration. Consequently, we are proposing to amend §§ 3.205 and 3.209 so as to require evidence, such as a marriage or birth certificate, to support a claim for benefits based on marriage or birth of a child.

The Administrator hereby certifies that these proposed rules, if promulgated, will not have a significant economic impact, on a substantial number of small entities as they are defined in the Regulatory Flexibility Act (RFA), 5 U.S.C. 601-612. The reason for this certification is that these regulations deal with the type of evidence which must be submitted by individuals applying for Veterans Administration benefits. Any impact upon small entities would be incidental and slight. Pursuant to 5 U.S.C. 605(b), these proposed rules are therefore exempt from the initial and final regulatory flexibility analyses requirements of sections 603 and 604.

In accordance with Executive Order 12291, Federal regulation, we have determined that these proposed regulation changes are nonmajor for the following reasons:

(1) They will not have an effect on the economy of \$100 million or more.

(2) They will not cause a major increase in costs or prices.

(3) They will not have significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

Catalog of Federal Domestic Assistance Program numbers are 64.104, 64.105, 64.109 and 64.110.

Approved: March 1, 1982.

By direction of the Administrator,
Charles T. Nagel,
Deputy Administrator.

PART 3—ADJUDICATION

The Veterans Administration proposes to amend 38 CFR Part 3 as follows:

1. Section 3.205 is amended as follows:

(a) By inserting the legal citation "(38 U.S.C. 210(c))" following paragraph (c).

(b) By revising the introductory portion of paragraph (a) preceding subparagraph (1) as set forth below:

§ 3.205 Marriage.

(a) *Proof of marriage.* Marriage is established by one of the following types of evidence:

2. Section 3.209 is amended as follows:

(a) By inserting the words "or she" following the word "he" in paragraph (e) and inserting the legal citation "(38 U.S.C. 310(c))" following paragraph (g).

(b) By revising the introductory portion preceding paragraph (a) as set forth below:

§ 3.209 Birth.

Age or relationship is established by one of the following types of evidence. If the evidence submitted for proof of age or relationship indicates a difference in the name of the person as shown by other records, the discrepancy is to be reconciled by an affidavit or certified statement identifying the person having the changed name as the person whose name appears in the evidence of age or relationship.

§ 3.210 [Amended]

3. Section 3.210 is amended by removing the words "his widow" and inserting the words "the veteran's surviving spouse" in paragraph (c)(1)(ii).

[FR Doc. 82-7777 Filed 3-22-82; 8:45 am]

BILLING CODE 8320-01-M

VETERANS ADMINISTRATION**DEPARTMENT OF DEFENSE****38 CFR Part 21****Veterans' Educational Assistance Program; Advance Payments**

AGENCY: Veterans Administration and Department of Defense.

ACTION: Proposed regulation.

SUMMARY: The proposed regulation, adopted jointly by the Veterans Administration and the Department of Defense, permits the advance payment of educational assistance allowance to participants in the Post-Vietnam Era Veterans' Educational Assistance Program following breaks in enrollment of more than 30 days. Currently, a break must be more than a calendar month before the Veterans Administration may make an advance payment. This has

resulted in some instances where an individual could not be paid for the interval between terms and could not receive an advance payment for the next term. This proposal eliminates this inequity.

DATES: Comments must be received on or before April 22, 1982. It is proposed to make this proposal effective the date of final approval.

ADDRESSES: Send written comments to: Administrator of Veterans Affairs (271A), Veterans Administration, 810 Vermont Avenue, N.W., Washington, D.C. 20420.

Comments will be available for inspection at the address shown above until May 3, 1982.

FOR FURTHER INFORMATION CONTACT: June C. Schaeffer (225), Assistant Director for Policy and Program Administration, Education Service, Department of Veterans Benefits, Veterans Administration, 810 Vermont Avenue, N.W., Washington, D.C. 20420 (202-389-2092).

SUPPLEMENTARY INFORMATION: Section 21.5135 is amended to permit the Veterans Administration to make an advance payment of educational assistance allowance to an individual when there are breaks in enrollment of more than 30 days. This will bring the policy for the Post-Vietnam Era Veterans' Educational Assistance Program into agreement with the policy used for paying survivors' and dependents' educational assistance, and assistance under chapter 34, title 38, United States Code.

The agencies have determined that this proposed regulation is not a major rule as that term is defined by Executive Order 12291, Federal Regulation. The annual effect on the economy will be less than \$100 million. It will not result in any major increases in costs or prices for anyone. It will have no significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

The Administrator of Veterans Affairs and the Secretary of Defense hereby certify that this proposed regulation, if promulgated, will not have a significant economic impact on a substantial number of small entities as they are defined in the Regulatory Flexibility Act (RFA), 5 U.S.C. 601-612. Pursuant to 5 U.S.C. 605(b), this proposed regulation therefore is exempt from the initial and final regulatory flexibility analyses requirements of sections 603 and 604. The reason for this certification is that the proposed

regulation will affect only individual Veterans Administration benefit recipients. It will have no significant direct impact on small entities (i.e., small businesses, small private and nonprofit organizations, and small governmental jurisdictions).

The Catalog of Federal Domestic Assistance number for the program affected by this proposed regulation is 64.120.

Additional Comment Information

Interested persons are invited to submit written comments, suggestions or objections regarding these documents to the Administrator of Veterans Affairs (271A), Veterans Administration, 810 Vermont Avenue, N.W., Washington, D.C. 20420. All written comments received will be available for public inspection at the above address only between the hours of 8 a.m. and 4:30 p.m. Monday through Friday (except holidays) until May 3, 1982. Any person visiting the Veterans Administration Central Office in Washington, D.C. for the purpose of inspecting any such comments will be received by the Central Office Veterans Services Unit in room 132. Visitors to VA field stations will be informed that the records are available for inspection only in Central Office and will be furnished the address and room number.

Approved: December 15, 1981.

Robert P. Nimmo,

Administrator of Veterans Affairs.

Approved: March 3, 1982.

R. Dean Tice,

Deputy Assistant Secretary of Defense.

PART 21—VOCATIONAL REHABILITATION AND EDUCATION

The Veterans Administration is proposing to amend 38 CFR Part 21 as follows:

In § 21.5135, paragraph (f) is revised to read as follows:

§ 21.5135 Advance payments.

(f) *Time of payment.* The Veterans Administration will authorize and advance payment only for—

(1) The beginning of an ordinary school year; or

(2) The beginning of any other enrollment period which begins after a break in enrollment of 30 days or longer, provided the individual is not eligible for payment for the break. (38 U.S.C. 1641, 1780(d))

[FR Doc. 82-7778 Filed 3-22-82; 8:45 am]

BILLING CODE 8320-01-M

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[A-5-FRL-2071-2]

Approval and Promulgation of Implementation Plans; Minnesota

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of proposed rulemaking.

SUMMARY: This notice proposes to approve amended and new rules adopted by the State of Minnesota (State) as revisions to the Minnesota State Implementation Plan (SIP). These rules were submitted by the Minnesota Pollution Control Agency (MPCA) on January 23, 1981, and regulate emissions from many source categories within the State. The purpose of this notice is to discuss EPA's evaluation of the rules and to solicit public comments on the rules and EPA's proposed action to approve the rules.

DATE: Comments on the rules and EPA's proposed action must be received by April 22, 1982.

ADDRESSES: Copies of the rules are available at the following addresses. Environmental Protection Agency, Region V, Air Programs Branch, 230 South Dearborn Street, Chicago, Illinois 60604.

Minnesota Pollution Control Agency, 1935 West County Road B-2, Roseville, Minnesota 55113.

Comments should be sent to: Gary Gulezian, Chief, Regulatory Analysis Section, Air Programs Branch, EPA, Region V, 230 South Dearborn Street, Chicago, Illinois 60604.

FOR FURTHER INFORMATION CONTACT: Delores Sieja, Regulatory Analysis Section, Air Programs Branch, EPA, Region V, 230 South Dearborn Street, Chicago, Illinois 60604, (312) 886-6038.

SUPPLEMENTARY INFORMATION: On January 28, 1972, the State of Minnesota submitted its SIP to the EPA for approval pursuant to section 110 of the Clean Air Act. This submittal included, among other things, State rules APC-1 through APC-16. EPA approved these rules as part of the Federally approved Minnesota SIP on May 13, 1972 (37 FR 10874).

On January 23, 1981, the Minnesota Pollution Control Agency (MPCA) submitted new rules and amendments to some of its previously approved rules. In a November 20, 1981 notice (46 FR 57061), EPA proposed to approve some of the rules as part of Minnesota's strategy to control particulates in the primary and secondary nonattainment

areas within the Twin Cities Seven County Metropolitan Area and the City of Duluth. Among the rules reviewed in this notice were APC-4, APC-24, APC-32 and APC-33. Rules APC-4, APC-24, and APC-32 were reviewed only as they relate to particulate control. Rule APC-33 was reviewed in its entirety but on November 17, 1981, the MPCA submitted amendments to APC-33. Therefore, today, EPA is proposing to approve (1) the remainder of rules APC-4, APC-24, and APC-32, which control emissions other than particulate; (2) the amendments to APC-33; and (3) rules APC-8, and APC-12, APC-13, APC-15, APC-16, APC-19 and APC-39 as revisions to the Minnesota SIP.

Following is a review of the rules.

1. *Rules APC-4, APC-13, APC-15, APC-16 and APC-24.* These rules contain standards for existing and new sources. EPA will not take action on the limits as they apply to new sources that fall under the requirements of the Standards of Performance for New Stationary Sources (NSPS) because the State has been granted delegation to enforce the NSPS requirements as of September 20, 1977.

a. *APC-4 Standards of Performance for Fossil Fuel Burning Indirect Heating Equipment.* This rule was amended by a restructuring into the following categories: (1) definitions, (2) determination of applicable standards of performance, (3) particulate, sulfur dioxide and nitrogen dioxide standards for indirect heating equipment which commences construction or modification before and after August 17, 1971, (4) stack height provisions, and (5) performance test methods and procedures.

Particulate. In a November 20, 1981 Federal Register (46 FR 57061) EPA proposed to approve the particulate standards for indirect heating equipment.

Sulfur dioxide (SO₂). The SO₂ standards for indirect heating equipment which commences construction or modification before August 17, 1971 vary depending on equipment size and the particular geographic location of the source. Sources in attainment areas have been operating in compliance with the standards in this rule since June 4, 1976, and no violation of the SO₂ National Ambient Air Quality Standards (NAAQS) have been recorded. Therefore, EPA believes these standards will ensure continued attainment and maintenance of the SO₂ NAAQS. For nonattainment areas, the applicable limits were part of the control strategy adopted to demonstrate attainment of the SO₂ NAAQS by December 31, 1982 (46 FR 20996).

Nitrogen dioxide (NO₂). This rule does not contain any NO₂ standards for indirect heating equipment installed before August 17, 1971. This is acceptable to EPA since there are no NO₂ nonattainment areas within the State and the NO₂ NAAQS has been attained and maintained with the current SIP requirements.

b. *APC-13 Standards of Performance for Storage Vessels for Petroleum Liquids.* This rule was amended by a restructuring into the following categories: (1) Definitions, (2) standards of performance for storage vessels for petroleum refineries which commence construction or modification before and after June 11, 1973, (3) monitoring requirements, and (4) exception provisions.

The standards of performance for storage vessels for petroleum refineries vary depending on the capacity of the vessel and whether construction or modification was commenced before or after June 11, 1973. Storage vessels with a storage capacity greater than 40,000 gallons which commence construction or modification after June 11, 1973 fall under the State's NSPS delegation and EPA takes no action on this portion of the rule. All other storage vessels covered by the rule have been operating in compliance with the standards in this rule since March 12, 1976 and no violation of the ozone NAAQS have been recorded. Therefore, EPA believes these standards will ensure continued attainment and maintenance of the ozone NAAQS.

c. *APC-15 Standards of Performance for Sulfuric Acid Plants.* This rule was amended by a restructuring into the following categories: (1) definitions, (2) standards of performance for sulfuric acid production units which commence construction or modification before and after August 17, 1971, (3) continuous emission monitoring requirements, (4) performance test methods and procedures, and (5) exception provisions. This rule provides standards of performance for sulfur dioxide and acid mist.

Sulfur dioxide. The only sulfuric acid plant in the State of Minnesota has been operating in compliance with the SO₂ limits in this rule since December 18, 1975. This SO₂ limit was part of the control strategy adopted to demonstrate attainment of the SO₂ NAAQS by December 31, 1982 (46 FR 20996).

Acid mist. The acid mist limit for sulfuric acid production units which commence construction or modification before August 17, 1971, was approved on May 31, 1972 (37 FR 10874).

d. *APC-16 Standards of Performance for Nitric Acid Plants.* This rule was amended by restructuring it into the following categories: (1) Definitions, (2) standards of performance for nitric acid production units which commence construction or modification before and after August 17, 1971, (3) emission monitoring requirements, and (4) performance test methods and procedures.

The standards of performance for nitric acid plants are based on mass and opacity limits. The only nitric acid plant in the State of Minnesota has been operating in compliance with the standards in this rule since December 18, 1975 and no violations of the NO_x NAAQS have been recorded. Therefore, EPA believes that these standards will ensure continued attainment and maintenance of the NO_x NAAQS.

e. *APC-24 Standards of Performance for Petroleum Refineries.* This rule contains (1) particulate, sulfur dioxide and carbon monoxide standards of performance for affected facilities at petroleum refineries which commence construction or modification before and after June 11, 1973, (2) definitions, (3) exemptions, and (4) performance test methods and procedures.

Particulate. In a November 20, 1981 Federal Register (46 FR 57601) EPA proposed to approve the particulate standards for affected facilities at petroleum refineries.

Sulfur Dioxide. Affected facilities at petroleum refineries which commence construction or modification before June 11, 1973. The SO₂ standards for fuel gas combustion devices and indirect heating equipment were utilized in the control strategy which demonstrated attainment of the SO₂ NAAQS by December 31, 1982 (46 FR 20996).

Affected facilities at petroleum refineries which commence construction or modification after June 11, 1973. The SO₂ standard for indirect heating equipment of less than 250 million BTU per hour were utilized in the control strategy adopted to demonstrate attainment of the SO₂ NAAQS by December 31, 1982 (46 FR 20996).

The SO₂ standards for indirect heating equipment of more than 250 million BTU per hour fall under the State's NSPS delegation and EPA takes no action on this portion of the rule.

Carbon monoxide (CO). This rule contains a CO standard for only fluid catalytic cracking unit catalyst regenerators which commence construction or modification after June 11, 1973. This falls under the State's NSPS delegation and EPA takes no action on this portion of the rule.

2. *Rules APC-8, APC-12, APC-19, APC-32, and APC-39.* a. *APC-8 Open Burning.* This rule was amended by a restructuring into the following categories: (1) Definitions, (2) open burning restrictions and exemptions, (3) open burning by permit requirements, (4) liability, conflicting laws and diseased shade tree open burning site provisions.

This rule describes activities for which an open burning permit is required and sources that are exempt from permitting. Sources that are exempt from this rule are minor and are expected to have an insignificant impact on air quality. For activities that require a permit, the permit will be issued only if certain conditions are implemented to reduce emissions into the atmosphere.

This rule has been in effect at the State since March 12, 1976, and the specified provisions have helped to contribute to the maintenance of the TSP, SO₂, and CO NAAQS.

b. *APC-12 Standards of Performance for Motor Vehicles and Stationary Internal Combustion Engines.* This rule was amended by a restructuring into the following categories: (1) Definitions, (2) standards of performance for motor vehicles, trains, boats, construction equipment and stationary internal combustion engines, (3) exemptions, and (4) requirements for air pollution control systems.

The standards of performance limit the amount of visible air contaminants and SO₂ emissions that may be discharged by motor vehicles, trains, boats, construction equipment and stationary internal combustion engines. Air pollution control system requirements include keeping these systems intact and in working condition when operating motor vehicles.

This rule has been in effect in the State since June 4, 1976, and the specified standards and requirements have helped to contribute to the maintenance of the TSP, SO₂, and CO NAAQS.

c. *APC-19 Permits for Indirect Sources.* This rule contains (1) definitions, (2) description of sources required to obtain a permit, (3) assessment and permit procedures, and (4) standards for issuance and permit conditions.

The provisions of this rule apply to indirect sources in the metropolitan areas of Duluth, Moorhead, St. Cloud, Rochester and Twin Cities.

As defined in this rule, an indirect source is a facility, building structure, or installation which attracts or may attract mobile source activity that results in emissions of a pollutant for which there is a State standard. All indirect sources, regardless of whether

or not a permit is required for their operation, must not allow violations of any ambient air quality standard.

This rule has been in effect in the State since February 18, 1975, and the specified provisions have contributed to maintenance of the NAAQS.

d. *APC-32 Standards of Performance for Fossil Fuel Burning Direct Heating Equipment.* This rule contains (1) definitions, (2) determination of applicable standards of performance, (3) particulate and sulfur dioxide standards for fossil fuel-burning direct heating equipment, and (4) performance test methods.

Particulate. In a November 20, 1981, Federal Register (46 FR 57601) EPA proposed to approve the particulate standards for direct heating equipment.

Sulfur dioxide. The sulfur dioxide limits vary depending on equipment size and on the particular geographic location of the source. Sources in attainment areas have been operating in compliance with the standards in this rule since January 24, 1977, and no violation of the SO₂ NAAQS have been recorded. Therefore, EPA believes that these standards will ensure continued attainment and maintenance of the SO₂ NAAQS. For nonattainment areas the applicable limit was part of the control strategy adopted to demonstrate attainment of the SO₂ NAAQS by December 31, 1982 (46 FR 20996).

e. *APC-39 Emergency Episodes.* This rule contains (1) applicability requirements, (2) definitions, (3) episode levels and declaration provisions, (4) control directives, and (5) the MPCA's emergency powers to protect the public health.

The rule requires a facility with 250 or more tons of emissions per year, located within or having air pollutant emissions affecting any area within the State of Minnesota, to take specific action during cases of air pollution episodes. The type of action varies depending on the (1) pollutant, (2) type of emission facility and (3) stage of the air pollution episode (alert, warning, or emergency).

This rule meets the requirements as described in 40 CFR 51.18 and contains control actions which will prevent ambient pollution concentrations from reaching levels which could cause significant harm to human health.

3. *APC-33 Standards of Performance for Coal Handling Facilities Within Designated Areas.* In the November 20, 1981 notice (46 FR 57661), EPA proposed to approve this rule. EPA had determined that the standards of performance for coal handling facilities and pneumatic coal-cleaning equipment and thermal dryers at any coal handling

facility represent Reasonable Available Control Technology (RACT).

On November 17, 1981, the MPCA submitted amendments to APC-33. EPA is proposing to approve these amendments as a revision to the Minnesota SIP because they still represent RACT and add clarity to the standards for certain coal handling facilities. Specifically, if fugitive emissions from these facilities exceed 20 percent opacity, the operation must control those emissions by either installing control equipment or using dust suppression methods.

Pursuant to the provisions of 5 U.S.C. 605(b), the Administrator certified on January 27, 1981 (46 FR 8709) that approvals of SIPs under sections 110 and 172 of the Act will not, if promulgated, have a significant economic impact on a substantial number of small entities. Today's action proposes to approve a State action under sections 110 and 172 of the Act. It imposes no new requirements beyond those which the State has already imposed.

The Office of Management and Budget has exempted this rule from the requirements of section 3 of Executive Order 12291.

Dated: February 12, 1982.

Valdas V. Adamkus,
Regional Administrator.

[FR Doc. 82-7682 Filed 3-22-82; 8:45 am]

BILLING CODE 6560-38-M

40 CFR Part 86

[AMS-FRL-2079-2]

Control of Air Pollution From New Motor Vehicles and New Motor Vehicle Engines; Revised Gaseous Emission Regulations for 1984 and Later Model Year Light-Duty Trucks and Heavy-Duty Engines

AGENCY: Environmental Protection Agency.

ACTION: Extension of Comment Period and Request for Comments.

SUMMARY: On January 13, 1982 EPA published a Notice of Proposed Rulemaking (NPRM) entitled Revised Gaseous Emission Regulations for 1984 and Later Model Year Light-Duty Trucks and Heavy-Duty Engines (47 FR 1642). A public hearing concerning this NPRM was held on February 18, 1982.

At the public hearing, EPA raised several questions concerning the key issues of the NPRM. The testifiers were unable to respond completely to some questions at that time, and committed to including full answers in their final written submissions. Subsequently, the

Engine Manufacturers Association (EMA) has requested that the comment period for this action be extended three weeks. EMA has asked for this extension specifically to prepare comments on the issues and questions raised by EPA at the public hearing.

In addition, during the course of the hearing, two important issues arose related to the emission standards and emission test procedures for both heavy-duty gasoline-fueled engines (HDGEs) and heavy-duty diesel engines (HDDEs). The Engine Manufacturers Association and the Motor Vehicle Manufacturers Association each submitted modified engine test cycles which they recommend be adopted in place of EPA's current 1984 cycles. Also, the question of separate standards for HDGEs and HDDEs was raised. These areas were discussed with several of the public hearing participants, but were not specifically addressed by all participants or the public at large.

In recognition of the importance of complete and well-prepared comments, and to allow additional specific comments on the issues mentioned above, EPA has decided to extend the comment period for three weeks.

DATES: Comments on the subject NPRM plus additional comments requested below should be submitted on or before April 12, 1982.

ADDRESSES: Written comments should be submitted (preferably 4 copies) to: Central Docket Section (A-130), Environmental Protection Agency, Attn: Docket No. A-81-11, 401 M Street, SW., Washington, D.C. 20460.

Docket No. A-81-11 is located in the U.S. EPA, Central Docket Section, West Tower Lobby, Gallery 1, 401 M Street, SW., Washington, D.C. The docket may be inspected between 8 a.m. and 4 p.m. on weekdays. As provided in 40 CFR, Part 2, a reasonable fee may be charged for photocopying.

FOR FURTHER INFORMATION CONTACT: Mr. Glenn W. Passavant, Emission Control Technology Division, U.S. Environmental Protection Agency, 2565 Plymouth Road, Ann Arbor, MI 48105, Telephone: (313) 668-4408.

SUPPLEMENTARY INFORMATION: EPA is seeking additional comment on two issues related specifically to the heavy-duty engine emission control program and arising from comments on the proposed rule.

Optional Engine Test cycles

In the NPRM, EPA requested specific comments and amendments to the EPA transient test procedures for HDGEs and HDDEs which are currently scheduled to take effect in the 1984 model year (47 FR

1643). In response to this request, and as a direct result of ongoing test procedure evaluation efforts by the heavy-duty engine manufacturers, two alternative heavy-duty engine test cycles (one each for HDGEs and HDDEs) have been suggested. The suggested emission test cycle for HDGEs is available at section IV-D-2 of Public Docket A-81-11. The suggested emission test cycle for HDDEs is available at section II-D-35 of Public Docket A-81-20.

EPA requests additional comments on the appropriateness of adopting the suggested cycles as replacements or options to the current 1984 cycles. Based on data submitted to date, EPA believes that the suggested cycles may serve as acceptable replacements or options to the current 1984 test cycles for HDGEs and HDDEs. In addition, EPA has performed preliminary statistical analyses of the suggested alternative cycles which indicate that these cycles are statistically very similar to the current 1984 cycles. Therefore, if they are adopted as replacement or optional test cycles, the applicable emission standards for each engine type (HDGE and HDDE) are expected to be the same for either test cycle. Specific comment is also requested on how these potential test procedure changes might affect the comparability of emission results from the cycles. If the comments and EPA's ongoing analysis indicate the need for adjustment factors with the optional test cycles, then those factors could be included in the final rule.

Separate Standards for HDGEs and HDDEs

In the NPRM, EPA proposed revised 1984 heavy-duty engine emission standards of 1.3 g/BHP-hr for hydrocarbons (HC) and 35 g/BHP-hr for carbon monoxide (CO). The statutory standards currently promulgated for 1984 are 1.3 g/BHP-hr HC and 15.5 g/BHP-hr for CO. Testimony at the public hearing indicated that HDDEs could meet the statutory standards while HDGEs will have trouble meeting the proposed revised standards (especially HC). Consequently, EPA is considering establishing separate emission standards for gasoline-fueled and diesel heavy-duty engines. EPA's authority to promulgate emission standards at different levels for HDGEs and HDDEs is found in section 202(a)(3) of the Clean Air Act as amended in 1977. EPA requests public comment on the appropriateness, impact, and acceptability of establishing different levels of emission standards for gasoline-fueled and diesel heavy-duty engines.

Date: March 12, 1982.

Kathleen M. Bennett,
Assistant Administrator for Air, Noise and
Radiation.

[FR Doc. 82-7700 Filed 3-22-82; 8:45 am]

BILLING CODE 6560-26-M

FEDERAL MARITIME COMMISSION

46 CFR Part 549

[General Order 29; Docket No. 82-16]

Removal of Regulations Governing Level of Military Rates

AGENCY: Federal Maritime Commission.

ACTION: Proposed rule.

SUMMARY: This rule proposes to make permanent the suspension of regulations governing rates quoted for the transportation of U.S. Defense Department cargoes pursuant to Military Sealift Command requests for proposals. This action is taken in light of the determination that military rates are no longer so low as to be detrimental to the commerce of the United States, and with a view towards lessening the regulatory burden on U.S. flag operators.

DATE: Comments due on or before April 22, 1982.

ADDRESSES: Comments (original and 15 copies) to: Francis C. Hurney, Secretary, Federal Maritime Commission, 1100 L Street, N.W., Washington, D.C. 20573.

FOR FURTHER INFORMATION CONTACT:

Francis C. Hurney, Secretary, Federal Maritime Commission, 1100 L Street, N.W., Washington, D.C. 20573, (202) 523-5725.

SUPPLEMENTARY INFORMATION: Notice is hereby given that the Federal Maritime Commission proposes to make permanent the suspension of its regulations governing the level of military rates by removing Part 549 of Title 46 of the Code of Federal Regulations, Federal Maritime Commission General Order 29.

The Commission's General Order 29 (46 CFR Part 549) governing the level of military rates was published in the *Federal Register* on December 2, 1972 (37 FR 25720). The Commission's proposal to temporarily suspend General Order 29, and the reasons therefor, were published in the *Federal Register* on February 4, 1981 (46 FR 10767). The final rule suspending General Order 29 during the period October 1, 1981 through September 30, 1982 was published in the *Federal Register* on April 3, 1981, (46 FR 20199).

The Commission has continued to monitor the level of military rates. Nothing has occurred which would

suggest lifting the suspension. On the contrary, the Commission has concluded that the appropriate course is to propose making the suspension permanent through the removal of 46 CFR Part 549, General Order 29. This proposed action is not to be construed as an indication that the Commission is no longer concerned with the level of military rates. The Commission still considers charging non-compensatory rates for the carriage of military cargoes to be detrimental to the commerce of the United States, and will continue to monitor these rates for potential violations of the Shipping Act, 1916.

Pursuant to the Regulatory Flexibility Act (5 U.S.C. 601 *et seq.*), the Commission certifies that the proposed rule will not, if adopted, have a significant economic impact on a substantial number of small entities. The primary impact of this proposed rule will be on carriers publishing military cargo rates and the Military Sealift Command, none of which are generally considered to be small entities within the meaning of the Act.

PART 549—REGULATIONS GOVERNING LEVEL ON MILITARY RATES [REMOVED]

Therefore, pursuant to sections 18(b)(5) and 43 of the Shipping Act, 1916 (46 U.S.C. 817 and 841(a)), it is proposed that Title 46 CFR be amended to remove Part 549.

By the Commission.

Francis C. Hurney,
Secretary.

[FR Doc. 82-7796 Filed 3-22-82; 8:45 am]

BILLING CODE 6730-01-M

DEPARTMENT OF COMMERCE

National Oceanic and Atmospheric Administration

50 CFR Part 285

Atlantic Tuna Fisheries

AGENCY: National Oceanic and Atmospheric Administration (NOAA), Commerce.

ACTION: Notice of intent to prepare an Environmental Impact Statement.

SUMMARY: NOAA intends to prepare an Environmental Impact Statement (EIS) on proposed revisions to the regulations implementing the Atlantic Tunas Conservation Act. The proposed revisions are broad enough that NOAA has decided to prepare a new EIS rather than a supplement to the current EIS.

DATE: Comments may be submitted anytime and will be considered to the extent practicable.

ADDRESS: Comments should be directed to Mr. Allen E. Peterson, Director, Northeast Region, National Marine Fisheries Service, 14 Elm Street, Federal Building, Gloucester, MA 01930.

FOR FURTHER INFORMATION CONTACT:

Mr. Allen E. Peterson, Jr., Director, Northeast Region, National Marine Fisheries Service, 14 Elm Street, Federal Building, Gloucester, MA 01930; telephone 617/291-3600.

SUPPLEMENTARY INFORMATION: The National Marine Fisheries Service (NMFS) in NOAA intends to prepare a draft environmental impact statement (DEIS) on proposed revisions to the regulations governing the U.S. bluefin tuna fishery. These regulations are being developed under the provisions of the Atlantic Tunas Conservation Act (16 U.S.C. 971-971h) to implement recommendations made by the International Commission for the Conservation of Atlantic Tunas (ICCAT) in November 1981. NOAA previously prepared a DEIS (March 1980), Final Environmental Impact Statement (FEIS) (June 1980), and Environmental Assessment (December 1980) on regulations governing this fishery. The proposed revisions are sufficiently broad to warrant preparation of a regular DEIS rather than a supplemental document.

The primary objective of this revision is to implement the ICCAT recommendation requiring a 2-year moratorium on bluefin tuna fishing in the western Atlantic Ocean during the 1982 and 1983 seasons except as necessary to enable scientific monitoring of the stock. Negotiations with Japan and Canada, the other two Nations currently fishing the stock, established an annual total harvest of 1,160 mt in the western Atlantic, of which 605 mt or 51.2 percent was allocated to the United States. The DEIS will analyze various management measures to determine the most appropriate means of distributing the 605 mt among user groups and fulfilling our international treaty obligations. Among the issues and alternatives to be addressed are: Four different quotas for each user group (rod and reel, other handgear, purse seine in the directed fishery, and purse seine and swordfish longline in the incidental fishery) within the confines of the 605 mt allocation; several commencement dates for the hand-gear fishery in the Gulf of Mexico that will protect the spawning stock from fishing pressure and postpone harvest until later in the season when flesh quality improves; several alternatives regarding quotas for

harpoon and charter boats; a proposal to end the current arrangement of separate northern and southern management areas; an alternative to discontinue the operation of buy boats; several alternatives on the catch rate of giant tunas in the hand-gear fishery; and several different levels of incidental catch by purse-seine vessels. For each of these issues, the status quo also will be analyzed.

Implementation of the proposed revisions should improve the current state of the bluefin stock by decreasing fishing mortality and maintaining a scientific monitoring program. It has been estimated that stock size could decrease by up to 40 percent if the ICCAT recommendations are not implemented in 1982.

The schedule for preparing both the DEIS and FEIS will be compressed to enable implementation of the regulations by June 10, 1982, the anticipated date of fishing under the current regulations. We estimate that the DEIS will be available to the public in April, 1982. The normal 45-day DEIS review period may be reduced to 33 days so the DEIS and regulation preparation schedules can proceed in

unison. A series of public hearings will be held on the Atlantic and Gulf coasts during this review period. Scoping meetings have already been held in Toms River, NJ, and on Long Island, NY. The FEIS cooling-off period will probably run for about 5 days prior to June 10 and then continue for the remaining 20 days while comments also are being accepted on the interim final regulations.

To ensure that all of the relevant issues are identified, NMFS will request your comments on the proposed allocation of 605 mt and the various management measures to be considered. Because of the compressed DEIS schedule, comments received in response to this notice will be considered in conjunction with comments received on the DEIS. Comments should be directed to Mr. Allen E. Peterson at the address provided above.

(16 U.S.C. 971-971h)

Dated: March 18, 1982.

Robert K. Crowell,

Deputy Executive Director, National Marine Fisheries Service.

[FR Doc. 82-7802 Filed 3-22-82; 8:45 am]

BILLING CODE 3510-22-M

Notices

Federal Register

Vol. 47, No. 56

Tuesday, March 23, 1982

This section of the FEDERAL REGISTER contains documents other than rules or proposed rules that are applicable to the public. Notices of hearings and investigations, committee meetings, agency decisions and rulings, delegations of authority, filing of petitions and applications and agency statements of organization and functions are examples of documents appearing in this section.

DEPARTMENT OF AGRICULTURE

Federal Grain Inspection Service

Federal Grain Inspection Service Advisory Committee; Meeting

Pursuant to the provisions of section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92-463), notice is hereby given of the following committee meeting:

Name: Federal Grain Inspection Service Advisory Committee.

Date: April 14, 1982.

Place: U.S. Department of Agriculture, 1400 Independence Avenue, SW., Room 2096 South Building, Washington, D.C. 20250. Time: 8:30 a.m.

Purpose: To enable the members to discuss and provide advice to the Administrator of the Federal Grain Inspection Service with respect to the efficient and economical implementation of the U.S. Grain Standards Act of 1976, in order to assure the normal movement of grain in an orderly and timely manner.

The agenda will include reports by the Subcommittees established January 27: (1) Conflicts of interest involving boards of trade and chambers of commerce operating as official agencies, (2) whether the term "surveillance" better describes what is now referred to as "supervision" by the Federal Grain Inspection Service of official agency activities, and (3) whether dead insects and hidden infestations should be considered in determining insect infestation. Other agenda items will include user fees for administrative and supervisory costs, research activities, and a discussion of sorghum and sunflower standards.

The meeting will be open to the public, but space and facilities are limited. Public participation will be limited to written statements submitted before or at the meeting unless their participation is otherwise requested by the Committee Chairman. Persons, other than members, who wish to address the

Committee at the meeting, should contact Dr. Kenneth A. Gilles, Administrator, FGIS, U.S. Department of Agriculture, Washington, D.C. 20250, telephone (202) 382-0219.

Dated: March 17, 1982.

D. R. Galliat,

Acting Administrator.

[FR Doc. 82-7671 Filed 3-22-82; 8:45 am]

BILLING CODE 3410-EN-M

CIVIL AERONAUTICS BOARD

[Docket No. 40545]

Airport Slot Allocations; Request for Comments on CAB Recommendation to FAA

Dated: March 19, 1982.

AGENCY: Civil Aeronautics Board.

ACTION: Request for public comments.

SUMMARY: The CAB invites comments on a recommendation that it is considering making to the Federal Aviation Administration. The FAA administers the allocation of operating rights, or "slots," at the nation's airports that has been made necessary by the shortage of air traffic controllers. The CAB's recommendation will address concerns that the method currently being used by the FAA unnecessarily frustrates the procompetitive policies of the Airline Deregulation Act.

DATES: Comments by: April 5, 1982.

Reply comments by: April 12, 1982.

Comments and other relevant information received after these dates will be considered by the Board only to the extent practicable.

ADDRESSES: Twenty copies of comments should be sent to Docket 40545, Civil Aeronautics Board, 1825 Connecticut Avenue, NW., Washington, D.C. 20428. Individuals may submit their views as consumers without filing multiple copies. Comments may be examined in Room 711, Civil Aeronautics Board, 1825 Connecticut Avenue, NW., Washington, D.C. as soon as they are received.

FOR FURTHER INFORMATION CONTACT:

Susan B. Jollie, Associate General Counsel, Antitrust Division, Civil Aeronautics Board, 1825 Connecticut Avenue, NW., Washington, D.C. 20428; (202) 673-6011.

SUPPLEMENTARY INFORMATION: At the request of the Federal Aviation Administration (FAA), the Board

recently has been examining the procedures that the FAA has been using over the past several months to restrict access into and out of the nation's 22 busiest airports under its Interim Operations Plan. The current version of the plan is set out in Special Federal Aviation Regulation No. 44-3, 47 FR 7816, February 18, 1982 (hereafter "SFAR 44-3"). To aid it in its review, the Board has decided to request comments from the airline industry, communities, air transport users, and other interested persons who might assist the Board in making informed recommendations to the FAA on possible changes to the Interim Operations Plan. The Board is concerned with the economic effects that the FAA's restrictions have had—on individual air carriers and communities, and on competition in the airline industry in general. We have already recommended to FAA that it broaden the definition of "new entrant." By this notice we are requesting specific comments on whether to recommend further assistance for new entrants and on whether special consideration should be given to carriers and communities that demonstrate unusual hardships. Commenters are also welcome to address any related areas of concern.

Background

As is well known, the restrictions imposed by the Interim Operations Plan were mandated by last year's walkout by air traffic controllers. That action substantially curtailed the ability of the National Air Traffic Control (ATC) System to handle normal traffic levels in a safe and efficient manner, and the FAA consequently determined that it was necessary to restrict aircraft operations. The FAA thus implemented the Interim Operations Plan in order to allocate operating rights to the various users of the national airspace (commercial air carriers, air taxis, general aviation, and the military) until such time as the capacity of the ATC System could be restored to a level where demand could be accommodated.

The new feature of SFAR 44-3 is the distribution of slots that are newly available, whether as a result of expanded capacity or, on occasion, the return of existing slots. It is generally not contemplated that any slots will be taken away from current users. In distributing new slots, some priority is given new entrants. SFAR 44-3 defines a

new entrant as a carrier that had an application for operating authority on file with the Board prior to August 3, 1981, and who was not operating on February 17, 1982. Other new entrants are treated like incumbents. As a group, new entrants are eligible to receive up to 40 percent of the new capacity at each airport, subject to a proviso that no single new entrant will be allocated more than 20 percent. The order for the allocation of the incremental slots to the new entrants is determined by a random draw (lottery). The remaining slots are then allocated to incumbent carriers, also by lottery, subject to a restriction that no carrier may receive more than 2 to 4 slots per turn depending upon the total number of slots available at the airport. In addition, those new entrants that do not receive any slots in the first allocation are permitted to participate in the lottery for the remaining slots along with the incumbent carriers.

SFAR 44-3 also provides for the allocation of new capacity at the various Air Route Traffic Control Centers. These cover various regions throughout the country. Flights are limited not only to the capacity of the origin and destination airports, but also to the capacity of each region through which they pass. Allocations of regional capacity are first made for flights to and from the 22 restricted airports. Remaining capacity is then allocated to carriers who have requested slots within each regional control center area, to the extent their requests can be accommodated. If there is more demand for a particular flight segment than the system can be handled, allocations are made by random draw.

Under SFAR 44-3 the incremental operating rights, to the extent they are available, are granted for the following scheduling periods: April 25 through May 31, 1982 (already allocated), June 1 through July 31, 1982, and August 1 through October 30, 1982.

In SFAR 44-3, the FAA also announced that it was withdrawing its opposition to an agreement that various carriers had filed with the Board for approval under section 412 of the Federal Aviation Act and antitrust immunity under section 414. The agreement would enable them to trade slots at each of the 22 restricted airports. By Order 82-3-43, the Board indicated that it would approve an agreement that would permit the voluntary exchange of slots both within and between the 22 restricted airports. The Board also stated that it might permit the carriers to engage in two-for-one or multiple exchanges. The slot exchange agreement should help those carriers that now hold

slots to mitigate the various operational and marketing difficulties they have experienced.

The Board's Concerns

The Board does not question the FAA's determination that there has been a need to restrict access under its Interim Operations Plan. However, we are concerned that the FAA's method of allocation among users may, over time, erode the important progress that has been made toward achieving the goals set forth in the Airline Deregulation Act. For the past several years, the Board has sought to promote competition in the airline industry by either eliminating or substantially loosening the significant regulatory barriers to entry that were once pervasive. We have taken these steps because, if the airline industry is to be truly competitive—that is, if deregulation is to be successful—it is imperative that actual and potential competitors be able to respond both rapidly and meaningfully to new competitive opportunities. Ease of entry is one of the hallmarks of deregulation, and the air carriers that have been formed or have begun jet service since passage of the Deregulation Act in 1978 have played a key role in spurring competition. Yet, the limits to access under the Interim Operations Plan have resulted in significant new regulatory barriers to entry. As a consequence, to the extent possible, we want to ensure that the anticompetitive effects of these restrictions are minimized. Otherwise, we are concerned that much of our recent effort to deregulate the airline industry might be undone.

The Board has already recommended to the FAA that it amend SFAR 44-3 to broaden the definition of "new entrant." The new definition would encompass all air carriers that have begun or will begin service with large aircraft since October 24, 1978. A carrier would remain in that class until it had provided services for 36 months, after which it would be treated as an incumbent. All carriers meeting this definition would be placed in the SFAR 44-3 new entrant priority pool for the slot lotteries. For each lottery period, a new entrant could not request slots at more than three airports that it was not already serving. While carriers operating only aircraft of 60 seats or less are excluded from the definition of "new entrant," they might qualify for special consideration under any of the three categories detailed below. However, the Board expects the FAA's new tower-to-tower program to provide the most relief for these carriers.

Because of the small number of new air carrier slots expected to be available under SFAR 44-3 in the next few

allocation periods, the Board requests comments on whether the procompetitive goals of the Airline Deregulation Act are best served by awarding air carriers additional slots in certain limited cases. The particular cases in which the Board seeks comments on shifting slots are: (1) New entrants with only a few large aircraft, (2) hardship air carriers, and (3) hardship communities. These cases are discussed below. It appears that only a limited number of additional slots, perhaps as few as 150 nationwide, might accommodate these goals. A single carrier might need as few as 10 or 15. Some slots could be taken out of the general aviation pool and given to commercial air carriers. It has been suggested that the FAA does not have the legal authority to make such awards. The Board believes that the FAA does have this authority, as discussed in the attached General Counsel's memorandum (Appendix A). The current FAA policy is to make general aviation and commercial aviation absorb slot restraints in a roughly similar manner. We invite comments on the legal necessity and desirability of such a policy, and on whether allocations from the general aviation pool should be made for the purposes discussed here.

New Entrants With Not More Than Eight Large Aircraft

The Interim Operations Plan has had an especially severe effect on new entrants. The inability of these carriers to obtain enough slots has hampered their efforts to become competitively viable. Moreover, it has probably been a factor in the investment community's reluctance to support other prospective airlines.

Some people argue that there is a critical number of aircraft that a new carrier needs in order to begin profitable operations. We seek comment on an allocation scheme that would accommodate a new entrant's aircraft acquisitions until it had a given number of large aircraft. At this point the Board sees eight as about the right number, but is open to suggestion and argument on the figure. These carriers would ordinarily participate in each SFAR 44-3 slot lottery along with the rest of the new entrants and all other carriers. They would then be entitled to as many additional slots from the general aviation pool as they needed to make reasonable use of large aircraft acquired since the previous lottery. "Reasonable use" and the total number of new slots thus needed by a carrier would be determined on the basis of the nature and scope of the carrier's operations.

This determination could be a two-step process. First, aircraft utilization could be measured in block hours. A qualifying carrier would be entitled to operate its new equipment at 85 percent, or some other predetermined fraction, of the average utilization rate of its existing fleet. (The rate for a carrier that previously had no large aircraft would have to be based on some other factor, such as the average for all other new entrants with small fleets.) The second step would be to determine the number of slots needed to achieve this target utilization rate. Other factors being equal, a long-haul carrier does not need as many slots as a short-haul carrier, so the correlation between block hours and needed slots is not direct. An adjustment for the average stage length in the carrier's existing system could be made at this point. The Board is inclined to leave some room for administrative flexibility to consider a carrier's particular needs, however, rather than prescribing a mathematically precise computation of slot entitlements.

New entrants qualifying under such a program should be able to estimate delivery dates for their new aircraft, or acquisition dates for aircraft that they plan to lease, well before each slot lottery. It appears, therefore, that the award of additional slots from the general aviation pool could be made only once for each lottery period. If that were not the case, however, there could be a special procedure for awarding necessary slots at other times. Such a scheme would not be unfair to the other carriers participating in the lotteries, because it would not affect the number of slots available to them.

The Board also invites comments on whether the definition of "new entrant" should be expanded, for this program, to include commuter air carriers beginning service after October 24, 1978, with the reference to "large aircraft" correspondingly removed.

Once acquired by a carrier under this program, slots would have no special status. Thus, they would not affect the carrier's eligibility to participate in the next lottery, or the 20/40 percent new entrant preference already accorded in SFAR 44-3. Similarly, carriers could trade these slots to other carriers just like any other slots.

Hardship Carriers

In addition to assistance from new entrants, the Board seeks comments on whether there is a need to introduce some flexibility in slot allocations to accommodate some unique circumstances encountered by incumbent carriers. While most incumbents should be aided

substantially by the slot exchange program, some carriers that were undergoing a major route restructuring at the time of the controllers' walkout may have lost an extremely high percentage of their slots and thus fallen well below their normal base. The Board therefore seeks comments on a procedure under which the Board would identify incumbent carriers who should receive special treatment. For this procedure, a new entrant would be considered an incumbent if, at the time of the controller walkout, it already had eight large aircraft (or whatever number is selected as the limit for the aircraft-utilization entitlements proposal discussed above).

This "hardship carrier" proposal raises issues of Broad procedures, criteria for identifying qualifying carriers and awarding them slots, and the source of the slots. The procedure could involve a carrier's applying to the Board for additional slots, with copies of the application served on all carriers serving the affected airports. There would be 5 days for those carriers and other interested persons to file comments or objections. The Board might hold an oral argument on a highly expedited schedule, and would issue a brief decision.

The key eligibility criterion for this hardship relief could be that the carrier had not merely experienced unusual difficulties directly related to the controllers' walkout, but that the effect of the walkout on that carrier's operations was significantly worse than on other carriers. The effect of the walkout could be measured by the percentage reduction, between months that are 1 year apart, in the carrier's domestic system departures, available seats, or available seat-miles at the affected airports. (The change in departures from December 1980 to December 1981, for example, is shown in Appendix B.) Hardship status could be accorded to all carriers that experienced a reduction of more than some specified level, such as 15 percent. Alternatively, it could be accorded to the five or 10 or some other number of carriers that experienced the most severe percentage reductions, regardless of what those percentages were. Under either approach, such rules as the following should be considered: (1) Hardship awards of slots would be made only once to any qualifying carrier. (2) The number of slots given to one carrier would be limited to 25, with at most 10 at any given airport and at most three at any hour at any given airport. (The Board invites comments on what other figures might be substituted.) (3) Relief under the hardship program would be

limited to the extent necessary to bring qualifying carriers up to the level of the carrier that came closest without qualifying for relief.

As for the source of slots to implement this "hardship carrier" proposal, there are two main alternatives. Under the first, the Board would be given control of up to 25 percent (or some other portion) of the incremental slots for each allocation period, which would then be held out of the lottery and awarded by the Board as needed to qualifying carriers. (This pool could also be used for new entrants if no slots were available from general aviation for the new entrant program discussed above.) Any unused slots would be returned by the Board to the lottery. Under the second alternative, the Board would identify qualifying carriers and the FAA would award them slots out of the general aviation pool. These two approaches could be combined, resulting in a scheme analogous to the special treatment for new entrants proposed above, whereby carriers would first participate in the lottery and then have their further needs accommodated by the general aviation pool.

Hardship Communities

It is possible for a community to lose service as a result of slot limitations even though access to its own airport is not restricted. This could happen when a carrier providing service from that community to a slot-restricted hub decided to drop that service in order to use its slots at the hub to fly between the hub and another city instead. There could be another carrier that was willing to provide replacement service to the original community, but was unable to do so because it had no slots at the hub. If the original community were covered by the essential air service (EAS) guarantees of the Federal Aviation Act's section 419 small communities program, service levels could generally be maintained either by the Board's requiring the exiting carrier to continue service or the FAA's providing necessary slots as it had done in a number of recent cases. Communities that are not covered by the EAS program and those with levels of air service that exceed the levels defined in our essential air service program, however, receive no comparable protection under the current scheme. The Board has already received requests from two such communities—Evansville, Indiana, and Burlington, Vermont—for slot allocations to be given to a particular carrier to provide service to a major community of interest.

In light of these circumstances, the Board requests comments on a plan to provide slot relief for communities that are currently unprotected by the EAS guarantees and have undergone severe hardships. The eligibility determination could be based on whether the community has lost, within a 30-day period, either one-third of its airline capacity to all hubs, or one-half its capacity in any major market. A "major market" could be defined as any one that accounted for more than one-fifth of all the community's local and connecting traffic. (Most communities have only one or two such markets.) The Board could also find eligible any community demonstrating that its percentage loss of capacity since the controllers' walkout had been twice, or some other predetermined multiple of, the national average.

A community that qualified for hardship relief under this proposal would be entitled to have the Board allocate slots to carriers that were willing to serve it. If more than one carrier were willing to provide replacement service, there would also be a need to select a carrier or carriers. This might be done by an abbreviated hearing procedure at the Board. The carrier threatening to depart, however, would not be able to get any slots under this procedure. Otherwise, it would have an incentive to threaten to leave a market merely to increase its total number of slots.

There are three possible sources for the slots needed to implement this "hardship community" proposal. The first would be to take them from the pool allocated to the Board as discussed above for hardship carriers. The second would be to have a separate, similar pool for communities. Finally, the slots could be taken from the general aviation pool. Moreover, a Board pool and the general aviation pool could be combined sequentially, as also discussed above.

The Board has not reached any conclusion, and invites comment, on its authority to classify communities in ways other than those required for the essential air service program in section 419 of the Federal Aviation Act. If the Board adopted such a program, it would make recommendations to the FAA similar to those it has made concerning EAS allocations.

Requests for Comments

Accordingly, the Civil Aeronautics Board, to enable it to make an informed recommendation to the FAA, requests public comments on the proposals described above for awarding additional airport slots to (1) new entrants with not more than eight large aircraft, (2)

hardship carriers, and (3) hardship communities. For each of these three proposals, the Board especially invites comments in the following areas:

A. The general merits of the proposal;

B. The details of the proposal, including the various numerical thresholds and alternative approaches described in the proposal;

C. Any important details that may have been omitted from the proposal, with special attention to any problems of timing or logistics; and

D. Any changes needed in the FAA's Air Route Traffic Control Center (ARTCC) capacity allocation procedures that would be made necessary as a result of implementing the Board's proposal on the allocation of individual airport slots.

By the Civil Aeronautics Board:

Phyllis T. Kaylor,
Secretary.

Appendix A—Memorandum

To: The Board

From: General Counsel.

Question presented: Does the FAA have the authority to revise the allocation of airport slots to provide additional slots for air carriers?

Answer: Yes.

Discussion:

The FAA has ample authority to revise the present allocation of air navigation rights between commercial air carriers and general aviation. Section 307(a) of the Federal Aviation Act (49 U.S.C. 1348(a)) authorizes the Secretary of Transportation "to develop plans for and formulate policy with respect to the use of the navigable airspace; and assign by rule, regulation, or order the use of the navigable airspace under such terms, conditions, and limitations as he may deem necessary in order to insure the safety of aircraft and the efficient utilization of such airspace." [Emphasis added].

The Department of Transportation (DOT), through the Federal Aviation Administration (FAA), has used this authority to apportion flights between scheduled air carriers, scheduled air taxis, and other users (including general aviation) at four crowded airports under the High Density Rule (14 CFR 93.121 *et seq.*). Recently, the Eighth Circuit has affirmed the FAA's authority to allocate "slots" at Washington National Airport based upon its responsibility for "the efficient utilization of airspace." *Northwest Airlines v. Goldschmidt*, 645 F.2d 1309 (8th Cir. 1981). The Court there agreed with the Secretary of Transportation's arguments that he "has responsibility and authority not only for aviation safety but also for airspace management." *Id.* at 1316.

When the High Density Rule was proposed, some commenters had objected that it discriminated against certain classes of users and that it terminated a long established policy of "first come-first served." In adopting the Rule, the FAA noted:

This rule grants a greater priority to certificated air carriers, who provide common

carrier service in accordance with the policy of recognizing a national interest in maintaining a public mass air transportation system, offering service on equal terms to all who would travel. For the traveler today, there is frequently no feasible alternative mode of travel. The concept of "first come-first served" remains as the fundamental policy governing the use of air space so long as capacity is adequate to meet the demands of all users without unreasonable delay or inconvenience. When capacity limitations compel a choice, however, the public service offered by the common carrier must be preferred.

33 FR 17897, December 13, 1968.

If DOT may give preference to common carrier service when limiting and allocating operating rights at heavily used airports, it may surely do so elsewhere to deal with chronic congestion from air traffic control capacity limitations.

Courts have recognized the validity of DOT/FAA giving a preference to common carriers over private users where total operations press the limits of capacity. When FAA first adopted the High Density Rule, the Aircraft Owners and Pilots Association (AOPA) sought a preliminary injunction against the Rule alleging an unlawful restriction of their right to fly. The injunction was denied and summary judgment entered for the Government by the U.S. District Court for the District of Columbia, and that decision was affirmed on appeal to the D.C. Circuit of Appeals. *AOPA v. Volpe*, No. 927-69 (D.D.C., May 14, 1969), *aff'd* No. 23146 (D.C. Cir. November 19, 1969). In another case, the Port Authority of New York, with the tacit acquiescence of the FAA, imposed a \$25 take-off-and-landing fee on general aviation aircraft using the major New York airports during peak traffic hours. AOPA challenged the fee as unlawful discriminatory, but the Court held that "no genuine basis appears for denying the FAA and airport owners the power to differentiate among kinds of flights." *AOPA v. Port Authority of N.Y.*, 305 F. Supp. 93, 106 (E.D.N.Y. 1969). Since the common carriers serve the interests of more people in access to navigable airspace, the Court found that "[t]he efficient utilization of air space in the interest of the greatest number of users of the air space plainly justifies the * * * distinction between large and small aircraft * * *." *Id.* at 107.

The recent decision of the Ninth Circuit Court of Appeals in *Santa Monica Airport Association v. City of Santa Monica*, 481 F. Supp. 927 (C.D. Cal. 1979), *aff'd* 659 F.2d 100 (9th Cir. 1981), does not detract from the FAA's authority to allocate flights between common carriers and general aviation. The *Santa Monica* decision applies only to the powers of the city as airport proprietor; it does not restrict the powers of the FAA or DOT. If anything, it implicitly reaffirms those powers. *Santa Monica* held that the city, as proprietor of the local airport, could not categorically forbid all jet operations without regard to whether they met the objective noise level standard in effect for propeller aircraft. Such a ban, the Court held, would impermissibly burden interstate commerce and violate Equal Protection. Thus, the city's

powers were very limited precisely because airspace management is an area preempted by federal control, except for the local proprietor's authority to control noise, ground congestion, and other strictly proprietary matters. See *City of Burbank v. Lockheed Air Terminal, Inc.*, 411 U.S. 624 (1973). The fact that Santa Monica could not show a preference to certain types of operations does not mean that DOT would be similarly restricted, provided the restriction was reasonably related to "efficient utilization of the airspace" or other responsibilities under the Federal Aviation Act. Thus, the authority of DOT/FAA to differentiate between general aviation and common carriers, and give preference to the latter, in the interest of efficient airspace management, has been consistently recognized by the agency itself and the courts.

David M. Kirstein.

Appendix B

TOTAL DEPARTURES AT 22 AFFECTED AIRPORTS—DECEMBER 1981 COMPARED WITH DECEMBER 1980

Carrier	December 1981	December 1980	December 1981 as a percent of December 1980
Pan American	7,336	9,221	79.6
Trans World	21,924	26,448	82.9
Eastern	44,192	52,404	84.3
Northwest	13,113	15,332	85.5
Texas Int'l	6,604	7,418	89.0
United	38,364	42,714	89.8
Delta	44,909	49,124	91.4
Brant	15,515	16,669	93.1
American	30,594	32,676	93.6
US Air	21,550	22,835	94.4
Republic	23,948	25,037	94.9
Western	9,708	10,212	95.1
Ozark	8,626	8,865	97.3
Continental	11,355	7,185	158.0
	^a 11,459	^a 10,740	^a 106.7
Piedmont	7,504	6,746	111.2
Southwest	410	484	84.7
Air California	2,156	2,220	97.1
Air Florida	3,502	3,188	109.8
Pacific			
Southwest	6,106	4,880	125.1
New York Air	4,073	432	942.8
Midway	1,695		
People Express	2,743		

¹ Republic and Hughes AirWest were combined.
^a Continental flight attendants were on strike from December 5th to the 16th, November figures are shown.

[FR Doc. 82-7793 Filed 3-19-82; 10:46 am]

BILLING CODE 6320-01-M

DEPARTMENT OF COMMERCE

International Trade Administration

University of Minnesota; Decision on Application for Duty-Free Entry of Scientific Article

The following is a decision on an application for duty-free entry of a scientific article pursuant to section 6(c) of the Educational, Scientific, and Cultural Materials Importation Act of 1966 (Pub. L. 89-651, 80 Stat. 897) and the regulations issued thereunder as amended (15 CFR 301).

A copy of the record pertaining to this decision is available for public review between 8:30 a.m. and 5:00 p.m. in Room 2097 of the Department of Commerce Building, 14th and Constitution Avenue NW., Washington, D.C. 20230.

Docket No.: 81-00388. Applicant: University of Minnesota, 103 Shepherd Laboratories, 100 Union Street SE., Minneapolis, MN 55455. Article: JEM-100CX-SCH Specimen Cooling Holder; and JEM-100CX-SCSH Common Specimen Holder. Manufacturer: JEOL Ltd., Japan. Intended use of article: See Notice on page 56631 in the Federal Register of November 18, 1981.

Comments: No comments have been received with respect to this application. Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, is being manufactured in the United States. Reasons: The application relates to an accessory for an instrument that had been previously imported for the use of the applicant institution. The article is being furnished by the manufacturer which produced the instrument with which the article is intended to be used and is pertinent to the applicant's purposes.

The Department of Commerce knows of no similar accessory being manufactured in the United States, which is interchangeable with or can be readily adapted to the instrument with which the foreign article is intended to be used.

(Catalog of Federal Domestic Assistance Program No. 11.105, Importation of Duty-Free Educational and Scientific Materials.)

Frank W. Creel,

Acting Director, Statutory Import Programs Staff.

[FR Doc. 82-7765 Filed 3-22-82; 8:45 am]

BILLING CODE 3510-25-M

Pennsylvania State University; Decision on Application for Duty-Free Entry of Scientific Article

The following is a decision on an application for duty-free entry of a scientific article pursuant to section 6(c) of the Educational, Scientific, and Cultural Materials Importation Act of 1966 (Pub. L. 89-651, 80 Stat. 897) and the regulations issued thereunder as amended (15 CFR 301).

A copy of the record pertaining to this decision is available for public review between 8:30 A.M. and 5:00 P.M. in Room 2097 of the Department of Commerce Building, 14th and Constitution Avenue NW., Washington, D.C. 20230.

Docket No.: 81-0039. Applicant: The Pennsylvania State University, The Milton S. Hershey Medical Center, 500 University Drive, Hershey, PA 17033. Article: TMR 32/200 Spectrometer with Accessories. Manufacturer: Oxford Research Systems, United Kingdom. Intended use of article: See Notice on page 56632 in the Federal Register of November 18, 1981. Advice submitted by: Department of Health and Human Services: January 18, 1982.

Comments: No comments have been received with respect to this application. Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, is being manufactured in the United States. Reasons: The foreign article has a large-bore magnet (20 cm.) able to receive human limbs and intact small animals for *in vivo* metabolism studies. The Department of Health and Human Services advises in its memorandum dated January 18, 1982 that (1) the capability of the foreign article described above is pertinent to the applicant's intended purpose and (2) it knows of no domestic instrument or apparatus of equivalent scientific value to the foreign article for the applicant's intended use.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, which is being manufactured in the United States.

(Catalog of Federal Domestic Assistance Program No. 11.105, Importation of Duty-Free Educational and Scientific Materials.)

Frank W. Creel,

Acting Director, Statutory Import Programs Staff.

[FR Doc. 82-7764 Filed 3-22-82; 8:45 am]

BILLING CODE 3510-25-M

State University of New York; et al.; Consolidated Decision on Applications for Duty-Free Entry of Scientific Articles

The following is a consolidated decision on applications for duty-free entry of scientific articles pursuant to section 6(c) of the Educational, Scientific, and Cultural Materials Importation Act of 1966 (Pub. L. 89-651, 80 Stat. 897) and the regulations issued thereunder as amended (15 CFR 301).

A copy of the record pertaining to each of the applications in this consolidated decision is available for public review between 8:30 A.M. and 5:00 P.M. in Room 2097 of the Department of Commerce Building, 14th

and Constitution Avenue, N.W., Washington, D.C. 20230.

Decision: Applications denied. Applicants have failed to establish that instruments or apparatus of equivalent scientific value to the foreign articles for such purposes as the foreign articles are intended to be used are not being manufactured in the United States.

Reasons: Section 301.8 of the regulations provides in pertinent part:

The applicant shall on or before the 20th day following the date of such notice, inform the Deputy Assistant Secretary whether it intends to resubmit another application for the same article for the same intended purposes to which the denied application relates. The applicant shall then resubmit the new application on or before the 90th day following the date of the notice of denial without prejudice to resubmission, unless an extension of time is granted by the Deputy Assistant Secretary in writing prior to the expiration of the 90-day period.

* * * if the applicant fails, within the applicable time periods specified above, to either (a) inform the Deputy Assistant Secretary whether it intends to resubmit another application for the same article to which the denial without prejudice to resubmission relates, or (b) resubmit the new application, the prior denial without prejudice to resubmission has the effect of a final decision by the Deputy Assistant Secretary on the application within the context of Subsection 301.11 (Emphasis added).

The meaning of the subsection is that should an applicant either fail to notify the Deputy Assistant Secretary of its intent to resubmit another application for the same article to which the denial without prejudice relates within the 20-day period, or fails to resubmit a new application within the 90-day period, the prior denial without prejudice to resubmission will have the effect of a final denial of the application.

None of the applicants to which this consolidated decision relates has satisfied the requirements set forth above; therefore, the prior denials without prejudice have the effect of a final decision denying their respective applications.

Subsection 301.8 further provides:

* * * the Deputy Assistant Secretary shall transmit a summary of the prior denial without prejudice to resubmission, to the Federal Register for publication, to the Commissioner of Customs, and to the applicant."

Docket Number: 80-00262. Applicant: State University of New York Upstate Medical Center, 750 East Adams Street, Syracuse, NY 13210. Article: Radiation Therapy Simulator, Therasim 750. Date of Denial Without Prejudice to Resubmission: August 6, 1981.

Docket Number: 80-00453. Applicant: Iowa State University, Ames, IA 50011.

Article: NMR Spectrometer, Model WM-300 and Accessories. Date of Denial Without Prejudice to Resubmission: September 15, 1981.

Docket Number: 80-00462. Applicant: Medical University of South Carolina, 171 Ashley Avenue, Charleston, SC 29403. Article: TP-11 Radiotherapy Planning System. Date of Denial Without Prejudice to Resubmission: August 5, 1981.

Docket Number: 81-00041. Applicant: Medical College of Georgia, 1120 15th Street, Augusta, GA 30912. Article: TP-11 Radiation Therapy Planning System. Date of Denial Without Prejudice to Resubmission: August 4, 1981.

Docket Number: 81-00045. Applicant: Southern California Permanente Medical Group, 1510 North Edgemont Avenue, Los Angeles, CA 90027. Article: TP-11 Computer & Treatment Planning System. Date of Denial Without Prejudice to Resubmission: August 6, 1981.

Docket Number: 81-00046. Applicant: Baptist Medical Center, 800 Prudential Drive, Jacksonville, FL 32207. Article: Radiation Treatment Planning System, TP-11. Date of Denial Without Prejudice to Resubmission: August 4, 1981.

Docket Number: 81-00058. Applicant: Arizona State University, Department of Chemistry, Tempe, AZ 85281. Article: Mass Spectrometer, MAT 312. Date of Denial Without Prejudice to Resubmission: August 19, 1981.

Docket Number: 81-00059. Applicant: University of Colorado, Health Sciences Center, 4200 East Ninth Avenue, Denver, CO 80262. Article: MM165F Mass Spectrometer with DS 2050 Data System. Date of Denial Without Prejudice to Resubmission: August 12, 1981.

Docket Number: 81-00103. Applicant: U.S. Department of Justice, Immigration & Naturalization Service, 425 I Street, N.W., Room 6225, Washington, D.C. 20536. Article: Comparison Projector and Accessories. Date of Denial Without Prejudice to Resubmission: August 6, 1981.

Docket Number: 81-00146. Applicant: Sandia National Laboratories, Albuquerque, NM 87185. Article: Xenon Chloride Laser. Date of Denial Without Prejudice to Resubmission: August 24, 1981.

Docket Number: 81-00150. Applicant: San Diego State University, Department of Civil Engineering, San Diego, CA 92182. Article: Geonor Consolidometer. Date of Denial Without Prejudice to Resubmission: August 26, 1981.

Docket Number: 81-00167. Applicant: NASA/Goddard Space Flight Center, Greenbelt Road, Greenbelt, MD 20771. Article: Micro-Measurement Instrument, Model 75-1002, 112/1037M with

Accessories. Date of Denial Without Prejudice to Resubmission: September 21, 1981.

Docket Number: 81-00189. Applicant: Wesley Medical School, 550 North Hillside, Wichita, KS 67214. Article: Teletherapy Treatment Planning Simulator, Therasim 750. Date of Denial Without Prejudice to Resubmission: September 15, 1981.

(Catalog of Federal Domestic Assistance Program No. 11.105, Importation of Duty-Free Educational and Scientific Materials.)

Frank W. Creel,
Acting Director, Statutory Import Programs Staff.

[FR Doc. 82-7766 Filed 3-22-82; 8:45 am]
BILLING CODE 3510-25-M

Yale University; Decision on Application for Duty-Free Entry of Scientific Article

The following is a decision on an application for duty-free entry of a scientific article pursuant to section 6(c) of the Educational, Scientific, and Cultural Materials Importation Act of 1966 (Pub. L. 89-651, 80 Stat. 897) and the regulations issued thereunder as amended (15 CFR 301).

A copy of the record pertaining to this decision is available for public review between 8:30 a.m. and 5:00 p.m. in Room 2097 of the Department of Commerce Building, 14th and Constitution Avenue, N.W., Washington, D.C. 20230.

Docket Number: 82-00010. Applicant: Yale University, Molecular Biophysics & Biochemistry, P.O. Box 6666, 260 Whitney Avenue, New Haven, CT 06511. Article: Rotating Anode X-ray Generator, GX 21, Type RA-6 and Accessories. Manufacturer: Elliott Brothers London Ltd., United Kingdom. Intended Use of Article: See Notice on page 57718 in the Federal Register of November 25, 1981. Advice Submitted by: Department of Health and Human Services: January 27, 1982.

Comments: No comments have been received with respect to this application. Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, is being manufactured in the United States. Reasons: The foreign article provides a small focused spot and a rotating target for maximum x-ray beam intensity (15 kilowatts at a 0.5 x 10 mm focus). The Department of Health and Human Services advises in its memorandum dated January 27, 1982 that (1) the capability of the foreign article described above is pertinent to the applicant's intended purpose and (2)

it knows of no domestic instrument or apparatus of equivalent scientific value to the foreign article for the applicant's intended use.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, which is being manufactured in the United States.

(Catalog of Federal Domestic Assistance Program No. 11.105, Importation of Duty-Free Educational and Scientific Materials.)

Frank W. Creel,

Acting Director, Statutory Import Programs Staff.

[FR Doc. 82-7767 Filed 3-22-82; 8:45 am]

BILLING CODE 3510-25-M

Commercial News USA Magazine; Publication Fee for Participating Firms

Commercial News USA is an export magazine of the Department of Commerce, used to promote the overseas sale of U.S.-manufactured products. Descriptions published in Commercial News USA are received through, and meet the requirements of, two Commerce programs, the New Product Information Service and the International Market Search. The magazine is distributed to U.S. Embassies and Consulates abroad to be used as a source document for the Posts' commercial newsletters, which in turn distribute the information to key individuals in government and business. Interested parties in foreign countries are urged to contact the U.S. manufacturers directly for further information on listed products.

Before January 1, 1982, products were published in Commercial News USA for participating firms free of charge. At the beginning of this calendar year, Commerce began charging firms \$25 (minimum) in order to recover some of the publication costs for the magazine.

Imposition of this fee was announced in advance through Commerce District offices throughout the United States and in other publications of the Department. This notice is being published in the Federal Register to further announce the imposition of this fee to the general public.

For further information contact Ann H. Watts, (202) 377-5131.

Donald V. Earnshaw,

Deputy Assistant Secretary for Export Development.

[FR Doc. 82-7691 Filed 3-22-82; 8:45 am]

BILLING CODE 3510-25-M

National Bureau of Standards

Data Encryption Standard—FIPS PUB 46; Request for Comments

Under the provisions of Pub. L. 89-306 (79 Stat. 1127; 40 U.S.C. 759(f)) and Executive Order 11717 (38 FR 12315, dated May 11, 1973), the Secretary of Commerce is authorized to establish uniform automatic data processing standards. Within this authorization, the Data Encryption Standard was issued as Federal Information Processing Standard 46 on January 15, 1977.

This standard requires review by NSB five years after its effective date, taking into account technological trends and other factors, to determine whether the standard should be affirmed, revised, or withdrawn. This review process is now underway. In order to ensure that all parties have an opportunity to present their views, NBS is soliciting comments on the standard. Comments on the standard will be carefully considered when reviewing the adequacy, implementation and use of the standard. Specific recommendations for improving the standard will be considered.

Interested parties may submit their written comments to: Director, Institute for Computer Sciences and Technology, National Bureau of Standards, Washington, D.C. 20234, Attention: FIPS 46 Review. Comments to be considered must be received on or before June 21, 1982.

Dated: March 17, 1982.

Ernest Ambler,
Director.

[FR Doc. 82-7686 Filed 3-22-82; 8:45 am]

BILLING CODE 3510-CN-M

Federal Information Processing Standards 60-1, 61, 62, 63; Technical Verification Guidance

This notice provides technical verification guidance for Federal Information Processing Standards 60-1, 62, and 63 which were issued by the Secretary of Commerce under the provisions of Pub. L. 89-306 (79 Stat. 1127; 40 U.S.C. 759(f)) and Executive Order 11717 (38 FR 12315, dated May 11, 1973). This is the sixth such technical verification notice providing specific guidance concerning technical interface implementation approaches. The first such notice was published in the Federal Register on August 13, 1980 (45 FR 53856-53857) and set out the paragraph numbering system that would be followed in listing and responding to questions in that first notice and subsequent notices. The second notice was published in the Federal Register on

October 17, 1980 (45 FR 68989-68990). The third notice was published in the Federal Register on December 16, 1980 (45 FR 82687-82689). The fourth notice was published in the Federal Register on March 6, 1981 (46 FR 15526-15528) and was the subject of two correction notices, both on March 15, 1981 (46 FR 18575). The fifth notice was published in the Federal Register on June 30, 1981 (46 FR 33576).

FIPS 60-1, 61, 62, and 63 are intended to achieve full plug-to-plug interchangeability of peripheral components. This general intent is the basis for this guidance.

6.1 With regard to the identifying information provided on the Verification List, must the description for an adapter to connect a FIPS-conforming subsystem to a computer system include more information than the model or series of computer to which the adapter connects?

No. There are many ways of connecting and interfacing adapters to computer systems. These ways may be dependent on the computer vendor's hardware and software, which may change from time to time. The verification list is not designed to track such changes. Current information concerning the interaction and requirements of computer vendor hardware and software with adapter vendor hardware and software should be obtained from the appropriate vendor.

6.2 Do FIPS 60-1 and 63 apply to electronic "solid-state" subsystems which do not employ moving magnetic media?

No. The FIPS recognize that there are many types of peripheral equipment which may connect to a computer system through a conforming channel. FIPS 60-1 and 63 refer synonymously to disks and rotating mass storage equipment. Subsystems which do not employ moving magnetic media are clearly not covered by FIPS 60-1 and 63, nor are there operational specifications standards for such subsystems. Thus, it is clear that no requirement for conformance with I/O channel interface standards exists for such subsystems.

6.3 Does the presence or absence of "cache" memory either in a control unit or on the channel side of the interface (for example, in an adapter) affect the requirement for conformance with FIPS-60-1, 61, 62 and 63?

No. A cache memory is added in order to reduce the delay time between a request for information transfer over the channel and the actual initiation of that transfer. The presence of cache does not affect the channel interface and may be

regarded as being an internal design detail. The presence or absence of cache is irrelevant to the determination of whether the channel or the control unit conforms to FIPS 60-1, 61, 62, and 63.

6.4 How does the Verification List apply to computer systems which can employ channel interfaces which are verified with respect to FIPS 60-1, 61, and 63, as appropriate, but which require a non-conforming interface to access a relatively small amount of disk storage to perform, for example, as storage for page swapping or for system resident software?

As stated in the Explanation paragraph of FIPS 60-1: "The Government's intent in employing this I/O Channel Interface standard is to reduce the cost of satisfying the Government's data processing requirements through increasing its available alternative sources of supply for computer system components at the time of initial system acquisition, as well as in system replacement and augmentation and in system component replacement." (Underlining added for emphasis)

For those systems where the central processor architecture encompasses a limited amount of disk storage connected via a non-conforming interface, this central processor disk storage may be determined by NBS not to be a system component. If so, the Verification List tabulation of conforming channel interfaces will include a footnote identifying the model number of the central processing unit and the related non-conforming portion of the system configuration which includes the maximum number of disk subsystems and disk spindles that may be connected by means of a non-conforming interface to function as an integral part of the central processor architecture. In order to be so listed, such system configurations must rely operationally on the I/O Channel Interface of FIPS 60-1, 61, and 63 for interoperation with all disks whose function is not an integral part of the central processor architecture, e.g., for application program files, general data storage, and input/output functions. Configurations which exceed these constraints may be employed only if a specific waiver is granted in accordance with the provisions set forth in FIPS 60-1.

Because it is possible to respond fully to the foregoing questions in such a brief fashion, NBS has decided not to avail itself of the opportunity to summarize the guidance provided for in the interim revision of FIPS PUBS 60-1 through 63. The guidance provided in response to questions 6.1 through 6.4 is, therefore,

considered complete. Requests for additional FIPS 60-1 through 63 verification guidance should be addressed to the Director, Institute for Computer Sciences and Technology, National Bureau of Standards, Washington, D.C. 20234, Attention: FIPS 60-1 through 63 Verification Guidance.

Dated: March 17, 1982.

Ernest Ambler,
Director.

[FR Doc. 82-7687 Filed 3-22-82; 8:45 am]

BILLING CODE 3510-CN-M

Office of the Secretary

Advisory Panels for the Mid-Atlantic, New England and Western Pacific Fishery Management Councils; Re-establishment

In accordance with the provisions of the Federal Advisory Committee Act, 5 U.S.C. App. (1976) and Office of Management and Budget Circular A-63 of March 1974 (as revised), and after consultation with GSA, the Department has determined that the re-establishment of the charters for the Advisory Panels (APs) for the Mid-Atlantic, New England and Western Pacific Fishery Management Councils (FMCs) are in the public interest in connection with the performance of duties imposed on the Department by law.

The President signed the Magnuson Fishery Conservation and Management Act, as amended, into law on April 13, 1976. The Act mandated the establishment of eight Regional Fishery Management Councils to serve as the instruments of Federal-State-private interaction in the conduct of fishery management in the U.S. Fishery Conservation Zone (FCZ). The Act also authorized the establishment of such APs as are deemed by the Councils to be necessary or appropriate to assist them in carrying out their functions under the Act.

The APs for both the Mid-Atlantic and New England Fishery Management Councils were established by charters dated December 20, 1977, and the AP for the Western Pacific Fishery Management Council was established by a charter dated October 26, 1977. These panels are expected to continue with a balanced representation of members, who are appointed by the parent Councils. The purpose of each Panel is to advise the respective Council on the assessments and specifications contained in the fishery management plans (FMPs) for fisheries within the Councils' geographic area of concern, with particular regard to (1) the extent

to which the fishing vessels of the U.S. will harvest resources considered in the FMPs; (2) the effect of such FMPs on local economies and social structures; (3) potential conflicts between user groups of a given fishery resource; and (4) enforcement problems peculiar to each fishery with emphasis on the expected need for enforcement resources. Research indicates that the functions of these Panels cannot be accomplished by any other organization element or other committee of the Department.

These Panels have produced several oral and written reports on the topics listed above. The APs for both the Mid-Atlantic and New England FMCs are currently addressing five fishery management units each; and the Western Pacific FMC is currently addressing three fishery management units, all selected by the Councils for management plan development. The management plans for each Panel are in the developmental state.

These APs will continue to operate in compliance with the provisions of the Federal Advisory Committee Act (FACA). Copies of each AP charter will be filed with the appropriate committees of the Congress and with the Library of Congress. Inquiries regarding this notice may be addressed to the Committee Liaison Officer, National Oceanic and Atmospheric Administration, U.S. Department of Commerce, Rockville, Maryland 20852, or Mrs. Yvonne Barnes, Committee Management Analyst, U.S. Department of Commerce, Washington, D.C. 20230.

Dated: March 16, 1982.

Dennis C. Boyd,

Executive Director, Information Resources Management.

[FR Doc. 82-7690 Filed 3-22-82; 8:45 am]

BILLING CODE 3510-CW-M

National Oceanic and Atmospheric Administration

Mid-Atlantic Fishery Management Council; Public Meeting

AGENCY: National Marine Fisheries Service, NOAA.

SUMMARY: The Mid-Atlantic Fishery Management Council, established by section 302 of the Magnuson Fishery Conservation and Management Act (Pub. L. 94-265), will meet to discuss the Bluefish and Fluke Fishery Management Plans (FMPs); status of other FMPs; foreign fishing applications as well as other fishery management and administrative matters.

DATES: The public meetings will convene on Wednesday, April 21, 1982, at approximately noon and will adjourn on Thursday, April 22, 1982, at approximately 5 p.m. The meetings may be lengthened or shortened depending upon progress on the agenda.

ADDRESS: The meetings will take place at the Sheraton-Fountainebleau Inn and Spa, 10100 Ocean Highway, Ocean City, Maryland.

FOR FURTHER INFORMATION:

Mid-Atlantic Fishery Management Council, Room 2115—Federal Building, 300 South New Street, Dover, Delaware 19901, Telephone: (302-674-2331).

Dated: March 18, 1982.

Jack L. Falls,

Chief, Administrative Support Staff, National Marine Fisheries Service.

[FR Doc. 82-7763 Filed 3-22-82; 8:45 am]

BILLING CODE 3510-22-M

COMMITTEE FOR THE IMPLEMENTATION OF TEXTILE AGREEMENTS

Adjusting the Import Restraint Level for Certain Cotton Apparel Products from India

March 18, 1982.

AGENCY: Committee for the Implementation of Textile Agreements.

ACTION: Increasing the consultation level for cotton skirts in Category 342, produced or manufactured in India and exported during the agreement year which began on January 1, 1982, from 39,326 dozen to 84,270 dozen.

(A detailed description of the textile categories in terms of T.S.U.S.A. numbers was published in the *Federal Register* on February 28, 1980 (45 FR 13172), as amended on April 23, 1980 (45 FR 27463), August 12, 1980 (45 FR 53506), December 24, 1980 (45 FR 85142), May 5, 1981 (46 FR 25121), October 5, 1981 (46 FR 48963), October 27, 1981 (46 FR 52409), and February 9, 1982 (47 FR 5926)).

SUMMARY: Pursuant to the terms of the Bilateral Cotton, Wool and Man-Made Fiber Textile Agreement of December 30, 1977, as amended, between the Governments of the United States and India, the consultation level established for cotton apparel products in Category 342 is being increased to 84,270 dozen for the agreement year which began on January 1, 1982 and extends through December 31, 1982, at the request of the Government of India.

EFFECTIVE DATE: March 18, 1982.

FOR FURTHER INFORMATION CONTACT:

Ross Arnold, International Trade Specialist, Office of Textiles and Apparel, U.S. Department of Commerce, Washington, D.C. 20230 (202/377-4212).

SUPPLEMENTARY INFORMATION: On December 18, 1981, there was published in the *Federal Register* (46 FR 61685) a letter dated December 15, 1981 from the Chairman of the Committee for the Implementation of Textile Agreements to the Commissioner of Customs, which established levels of restraint for certain specified categories of cotton, wool and man-made fiber textile products, including Category 342, produced or manufactured in India, which may be entered into the United States for consumption, or withdrawn from warehouse for consumption, during the twelve-month period which began on January 1, 1982 and extends through December 31, 1982. In the letter published below, in accordance with the terms of the bilateral agreement, the Chairman of the Committee for the Implementation of Textile Agreements directs the Commissioner of Customs to increase the twelve-month level previously established for Category 342 to 84,270 dozen.

Arthur Garel,

Acting Chairman, Committee for the Implementation of Textile Agreements.

UNITED STATES DEPARTMENT OF COMMERCE

March 18, 1982.

Commissioner of Customs,
Department of the Treasury,
Washington, D.C. 20229.

Dear Mr. Commissioner: This directive amends, but does not cancel, the directive issued to you on December 15, 1981 by the Chairman of the Committee for the Implementation of Textile Agreements concerning imports into the United States of certain cotton, wool and man-made fiber textile products, produced or manufactured in India.

Effective on March 18, 1982, paragraph 1 of the directive of December 15, 1981 is amended to increase the level of restraint for cotton textile products in Category 342 to 84,270 dozen.¹

The action taken with respect to the Government of India and with respect to imports of cotton textile products from India has been determined by the Committee for the Implementation of Textile Agreements to involve foreign affairs functions of the United States. Therefore, these directions to the Commissioner of Customs, which are necessary for the implementation of such actions, fall within the foreign affairs exception to the rule-making provisions of 5

¹ The level of restraint has not been adjusted to reflect any imports after December 31, 1981.

U.S.C. 553. This letter will be published in the *Federal Register*.

Sincerely,

Arthur Garel,

Acting Chairman, Committee for the Implementation of Textile Agreements.

[FR Doc. 82-7766 Filed 3-22-82; 8:45 am]

BILLING CODE 3510-25-M

DEPARTMENT OF DEFENSE

Department of the Air Force

USAF Scientific Advisory Board; Meeting

March 12, 1982.

The dates for the meeting of the USAF Scientific Advisory Board Arnold Engineering Development Center Advisory Group as published in the *Federal Register*, Volume 47, No. 37, Page 8039, Wednesday, February 24, 1982 have been changed. The new meeting dates are May 13-14, 1982. All other information remains the same.

For further information contact the SAB Secretariat at (202) 697-8845.

Winnibel F. Holmes,

Air Force Federal Register Liaison Officer.

[FR Doc. 82-7697 Filed 3-22-82; 8:45 am]

BILLING CODE 3910-01-M

DEPARTMENT OF EDUCATION

National Board of the Fund for the Improvement of Postsecondary Education; Closed Meeting

AGENCY: National Board of the Fund for the Improvement of Postsecondary Education.

ACTION: Notice of closed meeting.

SUMMARY: This notice sets forth the proposed agenda of a forthcoming meeting of the National Board of the Fund for the Improvement of Postsecondary Education. This notice also describes the functions of the Board. Notice of this meeting is required under the Federal Advisory Committee Act (Pub. L. 92-463, section 10(a)(2)).

DATES: May 6, 1982 at 5:00 p.m. through May 8, 1982 at 2:00 p.m.

ADDRESS: Belmont Conference Center, 6555 Belmont Woods, Elkridge, Maryland.

FOR FURTHER INFORMATION CONTACT: Sven Groennings, Director, Fund for the Improvement of Postsecondary Education, 7th & D Streets, SW., Washington, D.C. 20202 (202-245-8091).

SUPPLEMENTARY INFORMATION: The National Board of the Fund for the

Improvement of Postsecondary Education is established under section 1003 of the Higher Education Amendments of 1980, Title X (20 U.S.C. 1135-1). The National Board of the Fund is established to "advise the Secretary and the Director of the Fund for the Improvement of Postsecondary Education * * * on the selection of projects under consideration for support by the Fund in its competitions."

The meeting of the National Board is closed to the public. The proposed agenda includes: Reviewing and evaluating grant applications submitted to the Fund under the Comprehensive Program.

The meeting of the National Board of the Fund will be closed to the public from 5:00 p.m., May 6 until the conclusion of the agenda, approximately 2:00 p.m., May 8, for review, discussion or consideration of proposals submitted to the Fund for the awards of grants or contracts. The meeting will be closed under the authority of section 10(d) of the Federal Advisory Committee Act (Pub. L. 92-463; 5 U.S.C. Appendix I) and under exemptions (4) and (6) of section 552(b) of the Government in the Sunshine Act (Pub. L. 94-409; 5 U.S.C. 552b(c) (4) and (6)). Discussions of the applications and the qualifications of proposed staff will disclose commercial or financial information obtained from applicants which is confidential or disclose information of a personal nature where disclosure of such matters to the public would constitute a clearly unwarranted invasion of personal privacy if conducted in open session.

A summary of the activities at the closed session and related matters which are informative to the public consistent with the policy of Title 5 U.S.C. 552b(c) will be available to the public within fourteen days of the meeting.

Records are kept of all Board proceedings, and are available for public inspection at the Fund for the Improvement of Postsecondary Education, Room 3100, Regional Office Building, 7th and D Streets, SW., Washington, D.C. 20202 from the hours of 8:00 a.m. to 4:30 p.m.

Dated: March 12, 1982.

Thomas P. Melady,
Assistant Secretary for Postsecondary Education.

[FR Doc. 82-7695 Filed 3-22-82; 8:45 am]

BILLING CODE 4000-01-M

DEPARTMENT OF ENERGY

Economic Regulatory Administration

[ERA Docket No. 82-CERT-004]

Jones & Laughlin Steel Corp., Division of Jones & Laughlin Steel Inc.; Certification of Eligible Use of Natural Gas To Displace Fuel Oil

On February 11, 1982, Hones & Laughlin Steel Corporation, Division of Jones & Laughlin Steel Incorporated (J&L), 3 Gateway Center, 9N, Pittsburgh, Pennsylvania 15263, filed with the Administrator of the Economic Regulatory Administration (ERA) pursuant to 10 CFR Part 595 an application for certification of an eligible use of approximately 185,000 Mcf of natural gas per month to displace the use of approximately 1,289,450 gallons (30,701 barrels) of No. 6 fuel oil (1.2-1.9 percent sulfur) per month at its Aliquippa Works located in Aliquippa, Pennsylvania. The eligible seller of the natural gas is American Energy Services, Inc., and the natural gas will be transported by Columbia Gas Transmission Corporation and distributed by Columbia Gas of Pennsylvania, Inc. Notice of that application was published in the *Federal Register* (47 FR 9047, March 3, 1982) and an opportunity for public comment was provided for a period of ten (10) calendar days from the date of publication. No comments were received.

The ERA has carefully reviewed J&L's application in accordance with 10 CFR Part 595 and the policy considerations expressed in the Final Rulemaking Regarding Procedures for Certification of the Use of Natural Gas to Displace Fuel Oil (44 FR 47920, August 16, 1979). The ERA has determined that J&L's application satisfies the criteria enumerated in 10 CFR Part 595 and, therefore, has granted the certification and transmitted that certification to the Federal Energy Regulatory Commission. More detailed information, including a copy of the application, transmittal letter, and the actual certification is available for public inspection at the ERA, Natural Gas Branch Docket Room, Room 6013, RG-631, 2000 M Street, NW, Washington, D.C. 20461, from 8:00 a.m. to 4:30 p.m., Monday through Friday, except Federal holidays.

Issued in Washington, D.C., March 16, 1982.

James W. Workman,
Director, Office of Fuels Programs, Economic Regulatory Administration.

[FR Doc. 82-7701 Filed 3-22-82; 8:45 am]

BILLING CODE 6450-01-M

[ERA Docket No. 82-CERT-005]

Long Island Lighting Co.; Certification of Eligible Use of Natural Gas To Displace Fuel Oil

On February 12, 1982, Long Island Lighting Company (LILCO), 250 Old Country Road, Mineola, New York 11501, filed with the Administrator of the Economic Regulatory Administration (ERA) pursuant to 10 CFR Part 595 an application for certification of an eligible use of approximately 50,000 dekatherms (approximately 50,000 Mcf) of natural gas per day. This gas is estimated to displace the use of approximately 540,000 barrels of residual fuel oil (1.5 percent sulfur) and 40,000 barrels of No. 2 fuel oil (0.3 percent sulfur) at the E. F. Barrett Electric Plant in Island Park, New York, and 155,000 barrels of residual fuel oil (1.0 percent sulfur) at the Glenwood Plant in Glenwood Landing, New York. The eligible seller of the natural gas is Equitable Gas Company and the natural gas will be transported by Texas Eastern Transmission Corporation. Notice of that application was published in the *Federal Register* (47 FR 9048, March 3, 1982), and an opportunity for public comment was provided for a period of ten (10) calendar days from the date of publication. No comments were received.

The ERA has carefully reviewed LILCO's application in accordance with 10 CFR Part 595 and the policy considerations expressed in the Final Rulemaking Regarding Procedures for Certification of the Use of Natural Gas to Displace Fuel Oil (44 FR 47920, August 16, 1979). The ERA has determined that LILCO's application satisfies the criteria enumerated in 10 CFR Part 595 and, therefore, has granted the certification and transmitted that certification to the Federal Energy Regulatory Commission. More detailed information, including a copy of the application, transmittal letter, and the actual certification is available for public inspection at the ERA, Natural Gas Branch Docket Room, Room 6013, RG-631, 2000 M Street, NW., Washington, D.C. 20461, from 8:00 a.m. to 4:30 p.m., Monday through Friday, except Federal holidays.

Issued in Washington, D.C., March 16, 1982.

James W. Workman,
Director, Office of Fuels Programs, Economic Regulatory Administration.

[FR Doc. 82-7702 Filed 3-22-82; 8:45 am]

BILLING CODE 6450-01-M

Office of Energy Research**Energy Research Advisory Board; Meeting**

Pursuant to the provisions of the Federal Advisory Committee Act (Pub. L. 92-463, 86 Stat. 770), notice is hereby given of the following meeting:

Name: Energy Research Advisory Board.
Date and Time: Thursday, April 8, 1982—9:00 am to 5:00 pm. Friday, April 9, 1982—9:00 am to 5:00 pm.

Place: U.S. Department of Energy, Forrestal Building, Room 6E-069, 1000 Independence Avenue, SW, Washington, DC 20585.

Contact: Gloria Decker, Information Management Systems Branch, U.S. Department of Energy, Forrestal Building, Room 4D-024, 1000 Independence Avenue, SW, Washington, DC 20585, Telephone: 202-252-8990.

Tentative Agenda for Portion of Meeting Which Will Be Open to the Public:

- Status Reports from Conservation and Solar Panels
- Discussion of Preliminary Report on Multiprogram Laboratories
- Briefing on FY 83 budget
- Public Comment (10 minute rule)

In addition to the above, the Board plans to discuss the advanced isotope separation program. This portion of the meeting, tentatively scheduled for April 8, 1982 from 3:00 to 5:00 p.m., will be closed. A determination to close this portion of the meeting was made in the interest of national security, pursuant to the provisions of section 624 of the Department of Energy Organization Act, Pub. L. 95-91. Since aspects of the discussion of advanced isotope separations processes are classified information.

Public Participation: With the exception stated above, the meeting is open to the public. Written statements may be filed with the Board either before or after the meeting. Members of the public who wish to make oral statements pertaining to agenda items listed in the open portion of the meeting should contact Gloria Decker at the address or telephone number listed above. Requests must be received at least 5 days prior to the meeting and reasonable provisions will be made to include the presentation on the agenda. The Chairperson of the Board is empowered to conduct the meeting in fashion that will facilitate the orderly conduct of business. **Transcripts:** For the open portion of the meeting, transcripts will be available for public review and copying at the Public Reading Room, Room 1E-190, Forrestal Building, 1000 Independence Avenue, SW., Washington, DC, between 8:00 am and 4:00 pm, Monday through Friday, except Federal holidays.

Issued at Washington, DC on March 18, 1982.

Howard H. Raiken,
Deputy Advisory Committee Management Officer.

[FR Doc. 82-7706 Filed 3-22-82; 8:45 am]

BILLING CODE 6450-01-M

Federal Energy Regulatory Commission

[Docket No. ER82-229-000]

Alabama Power Co.; Order Accepting for Filing and Suspending Revised Rates, Granting Interventions, and Establishing Price Squeeze and Hearing Procedures

Issued: March 18, 1982.

On January 18, 1982, Alabama Power Company (APC) tendered for filing increased rates for service to its 16 cooperative and 9 municipal wholesale customers.¹ APC states that the proposed rates would result in an increase in revenues of approximately \$9,431,000 (9.11%) for the twelve month period ending December 31, 1982. APC requests that these rates have an effective date of March 19, 1982, and be suspended until May 1, 1982.²

Notice of APC's filing was issued on January 21, 1982, with responses due by February 12, 1982. On February 12, 1982, the Alabama Electric Cooperative, Inc. (AEC) and 11 Alabama distribution cooperatives (collectively, the Cooperatives)³ filed a petition to intervene, protest, motion for a five-month suspension of an hearing on the proposed rate increase. The Cooperative's request for a maximum suspension is based on allegations of excessive Period II cost of service expenses including an excessive rate of return on equity. More specifically, the Cooperatives allege (1) excessive operation and maintenance (O&M)

¹ See Attachment A for customers and rate schedule designations.

² In Docket No. ER81-95-000, APC's last rate filing, the Commission approved a settlement agreement which provided that if APC filed a change of rates prior to May 1, 1982, it would be permitted to request the first possible effective date, so long as it also requested suspension of such rates until at least May 1, 1982. *Alabama Power Company*, 16 FERC ¶61,023, ¶63,018.

³ AEC is a non-profit electric cooperative. Nine of the Cooperatives are members of AEC. They are Baldwin County Electric Membership Corporation, Central Alabama Electric Cooperative, Clarke-Washington Electric Membership Corporation, Coosa Valley Electric Cooperative, Inc., Dixie Electric Cooperative, Inc., Pea River Electric Cooperative, Inc., Pioneer Electric Cooperative, Inc., Tallapoosa River Electric Cooperative, Inc., and Wiregrass Electric Cooperative, Inc. The other two cooperatives are Black Warrior Electric Membership Corporation and Tombigbee Electric Cooperative, Inc.

expenses, (2) excessive coal inventories, (3) a possibly defective cash working capital study, (4) arbitrary functionalization and allocation of general plant, (5) an unsubstantiated increase in nuclear fuel disposal costs, (6) improper inclusion of certain bond issues in the capital structure, and (7) an unsupported allowance in the requested return on equity for underwriting costs and market pressure. The Cooperatives also allege price squeeze.

A timely petition to intervene, protest and request for fuel clause investigation was also filed by the Alabama Municipal Electric Authority (AMEA) and thirteen Alabama municipalities (collectively, the Municipalities).⁴ The Municipalities also seek maximum suspension of the proposed rates. In support thereof they allege (1) APC's estimate of an approximate \$9.4 million revenue increase is substantially understated, due to its failure to account for fuel clause billing increases since its last rate filing, (2) APC seeks to have its wholesale customers subsidize its retail customers, (3) APC may be seeking double recovery of certain costs, and (4) price squeeze.

The Municipalities also state that APC's filing contains undocumented, excessive, or unsupportable cost of service items, including (1) rate of return on equity, (2) debt and equity issuances improperly included in capital structure, (3) failure to credit wholesale customers with the benefits of investment tax credit amortization, (4) line loss factor, (5) materials and supplies, (6) nuclear plant amortization costs, (7) fossil fuel inventories, (8) O&M expenses, and (9) improper allocation of costs between retail and wholesale customers. The Municipalities also aver that APC's proposed rate design improperly reduces the voltage discount to customers who, in reliance on APC's previous rate design, have invested in facilities enabling them to take power from APC at higher voltages.

Lastly, the Municipalities request an investigation of APC's fuel adjustment clause. In that connection, it is stated that APC's fuel clause provides for recovery of the entire energy cost (as distinguished from the fuel component of that cost) of energy dispatched to APC from the Southern Company system power pool on an "economic

⁴ The thirteen Municipalities, all members of AMEA, are the City of Alexander City, City of Dothan, City of Fairhope, The Utilities Board of the City of Foley, City of Lafayette, City of Lanett, Electric Board of the City of Luverne, City of Opelika, City of Piedmont, the Utilities Board of the City of Sylacauga, City of Troy, and the Utilities Board of the City of Tuskegee.

dispatch" basis. The Municipalities question whether APC's purchases from its affiliates via Southern Company's power pool are "economic dispatch" purchases. It is also alleged that APC's methodology for determining charges and credits to wholesale customers under the fuel adjustment clause is improper.

A timely protest and petition for leave to intervene was also filed by the Secretary of the Army on behalf of the Department of Defense (DOD). DOD makes no specific allegations, but notes that, as a customer of APC, its interests will be affected by the outcome of this proceeding.

An untimely petition to intervene, protest, motion for five month suspension and hearing was filed by the Attorney General of Alabama on behalf of the State of Alabama, its agencies and citizens (Alabama). Alabama states that it has not had time to fully review APC's filing, but notes several cost of service matters in addition to those addressed by the Cooperatives and the Municipalities, which Alabama believes require an evidentiary hearing. These matters include (1) inclusion of unappropriated, undistributed subsidiary earnings in the common equity component of capital structure, (2) treatment of certain leases as long-term debt, (3) inclusion of non-investor-supplied funds in rate base, (4) the amount of accumulated deferred federal income taxes, and (5) increases in numerous administrative and general expenses.

On February 17, 1982, an untimely letter requesting intervenor status was filed by Mr. R. S. Crowder, a private citizen from Birmingham, Alabama. In support of his request, Mr. Crowder states that he is a retail customer of APC's and that he is concerned that APC's charges be properly allocated between its wholesale and retail customers.

On March 1, 1982, APC filed responses to the petitions to intervene, opposing the late intervention of Mr. Crowder and the purported⁵ late intervention of DOD, opposing the requests for a five month suspension, and arguing that any relief granted as a result of an investigation of its fuel clause should have prospective effect only.

Discussion

The Commission finds that good cause exists to accept the late filed interventions of Alabama and Mr. Crowder. The Commission further finds

that participation in this proceeding by each of the petitioners is in the public interest. Accordingly, their petitions to intervene will be granted.

With respect to APC's fuel adjustment clause, the Commission notes that the same issues raised by the Municipalities were raised in the previous APC rate filing in Docket No. ER81-95-000 and in Docket Nos. ER78-77 and EL78-27. Because the proceedings in those dockets were eventually settled without deciding the fuel adjustment clause issues, the Commission finds it appropriate to consider these matters, including any limitations on available relief, along with the other matters raised by the petitioners, during the evidentiary proceeding ordered below.

Having considered the matters addressed by the intervenors, our analysis indicates that APC's proposed rates have not been shown to be just and reasonable and may be unjust, unreasonable, unduly discriminatory or preferential, or otherwise unlawful. However, we find on the basis of preliminary review that the proposed rates may not result in substantially excessive revenues, as defined in *West Texas Utilities Company*, Docket No. ER82-223-000 (February 26, 1982). Thus, for the reasons stated in *West Texas*, and consistent with the settlement agreement approved in Docket No. ER81-95-000, we shall suspend the rates to become effective, subject to refund, on May 1, 1982.

In light of the intervenors' price squeeze allegations, we shall institute price squeeze procedures and phase those procedures in accordance with the Commission's policy established in *Arkansas Power and Light Company*, Docket No. ER79-339 (August 6, 1979). As we have noted in prior orders, this procedure will allow a decision first to be reached on the cost of service, capitalization, and rate of return issues. If, in the view of the intervenors or staff, a price squeeze persists, a second phase of the proceeding may follow.

The Commission orders:

(A) APC's revised rates are hereby accepted for filing and are suspended to become effective, subject to refund, on May 1, 1982.

(B) Pursuant to the authority contained in and subject to jurisdiction conferred upon the Federal Energy Regulatory Commission by section 402(a) of the Department of Energy Organization Act and by the Federal Power Act, particularly section 205 and 206 thereof, and pursuant to the Commission's Rules of Practice and Procedure and the regulations under the Federal Power Act (18 CFR, Chapter I), a

public hearing shall be held concerning the justness and reasonableness of APC's rates.

(C) The petitions to intervene in this proceeding are hereby granted subject to the Commission's Rules of Practice and Procedure and the regulations under the Federal Power Act; *Provided, however*, that participation by such intervenors shall be limited to the matters set forth in their petitions to intervene; and *provided, further*, that the admission of such intervenors shall not be construed as recognition that they might be aggrieved by any order of the Commission in this proceeding.

(D) We hereby order initiation of price squeeze procedures and further order that the proceeding be phased so that the price squeeze procedures begin after issuance of a Commission opinion establishing the rate which, but for a consideration of price squeeze, would be just and reasonable. The presiding judge may order a change in this schedule for good cause. The price squeeze portion of this case shall be governed by the procedures set forth in § 2.17 of the Commission's regulations as they may be modified prior to the initiation of the price squeeze phase of this proceeding.

(E) The Commission staff shall serve top sheets in this proceeding on or before March 30, 1982.

(F) A presiding administrative law judge, to be designated by the Chief Administrative Law Judge, shall convene a conference in this proceeding to be held within approximately fifteen (15) days after service of top sheets, in a hearing room of the Federal Energy Regulatory Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426. The presiding judge is authorized to establish procedural dates and to rule on all motions (except motions to consolidate or sever and motions to dismiss) as provided for in the Commission's Rules of Practice and Procedure.

(G) The Secretary shall promptly publish this order in the *Federal Register*.

By the Commission.
Kenneth F. Plumb,
Secretary.

Alabama Power Company, Docket No. ER82-229-000, Rate Schedule Designations

Filed: January 18, 1982.

Designations and Descriptions

FPC Electric Tariff Original Volume No. 1

(1) Fifth Revised Sheet No. 2 (Supersedes Fourth Revised Sheet No. 2)—Table of Contents.

⁵ Contrary to APC's assertion, DOD's petition was timely filed on February 12, 1982.

- (2) Eighth Revised Sheet No. 5 (Supersedes Seventh Revised Sheet No. 5 and Sixth Revised Sheet No. 5-A)—Revision No. 5 Rate Schedule REA-1.
- (3) Eighth Revised Sheet No. 7 (Supersedes Seventh Revised Sheet No. 7)—Fuel Cost Adjustment.
- (4) Fifth Revised Sheet No. 7-A (Supersedes Fourth Revised Sheet No. 7-A)—Fuel Cost Adjustment.
- (5) First Revised Sheet No. 7-B (Supersedes Original Sheet No. 7-B)—Fuel Cost Adjustment.
- (6) Eighth Revised Sheet No. 8 (Supersedes Seventh Revised Sheet No. 8 and Sixth Revised Sheet No. 8-A)—Revision No. 5, Rate Schedule MUN-1.
- (7) Eighth Revised Sheet No. 10 (Supersedes Seventh Revised Sheet No. 10)—Fuel Cost Adjustment.
- (8) Fifth Revised Sheet No. 10-A (Supersedes Fourth Revised Sheet No. 10-A)—Fuel Cost Adjustment.
- (9) First Revised Sheet No. 10-B (Supersedes Original Sheet No. 10-B)—Fuel Cost Adjustment.
- (10) Fifth Revised Sheet No. 32 (Supersedes Fourth Revised Sheet No. 32)—Index of Purchasers, Revision No. 5, Rate Schedules, REA-1 and MUN-1.
- (11) Fifteenth Revised Sheet No. 34 (Supersedes Fourteenth Revised Sheet No. 34)—Index of Purchasers, Rate Schedule, REA-1 and MUN-1.
- (12) Seventeenth Revised Sheet No. 35 (Supersedes Sixteenth Revised Sheet No. 35)—Index of Purchasers, Rate Schedule, REA-1 and MUN-1.
- (13) Ninth Revised Sheet No. 36 (Supersedes Eighth Revised Sheet No. 36)—Index of Purchasers, Rate Schedule, REA-1 and MUN-1.
- (14) Seventeenth Revised Sheet No. 37 (Supersedes Sixteenth Revised Sheet No. 37)—Index of Purchasers, Rate Schedule, REA-1 and MUN-1.
- (15) Fifteenth Revised Sheet No. 38 (Supersedes Fourteenth Revised Sheet No. 38)—Index of Purchasers, Rate Schedule, REA-1 and MUN-1.
- (16) Eleventh Revised Sheet No. 39 (Supersedes Tenth Revised Sheet No. 39)—Index of Purchasers, Rate Schedule, REA-1 and MUN-1.
- (17) Second Revised Sheet No. 40 (Supersedes First Revised Sheet No. 40 and Supplement No. 1)—Index of Purchasers, Rate Schedule, REA-1 and MUN-1.
- (18) Supplement No. 13 to Rate Schedule FPC No. 120 (Supersedes Supplement Nos. 10 and 11)—Revision No. 5, Rate Schedule MUN-1 (City of Foley).
- (19) Supplement No. 14 to Rate Schedule FPC No. 120 (Supersedes Supplement No. 12)—Fuel Cost Adjustment (City of Foley).

[FR Doc. 82-7749 Filed 3-22-82; 8:45 am]

BILLING CODE 6717-01-M

[Docket No. GP80-6-000]**Arkansas-Louisiana Gas Co., a Division of Arkla, Inc.; Two-Party Protest**

Issued: March 19, 1982.

On March 9, 1982, Arkansas-Louisiana Gas Co. (ARKLA), a division of Arkla,

Inc., filed with the Federal Energy Regulatory Commission (Commission), pursuant to §§ 154.94(j)(3) and 157.40(1)(c)(v)(B) of the Commission's regulations, a supplement to its October 12, 1979 evidentiary submission and a protest to Rimrock Gas Company's (Rimrock) claimed contractual authority to charge and collect the maximum lawful price under section 108 of the Natural Gas Policy Act of 1978 (NGPA), 15 U.S.C. 3301-3432 (Supp. III 1979), for stripper well natural gas sold to ARKLA under a 1960 contract, as amended.

ARKLA contends that there is no area rate clause, other indefinite price escalator clause or other pricing provision in the contract which would allow Rimrock to charge and ARKLA to pay maximum lawful prices under the NGPA and particularly maximum lawful prices under NGPA section 108.

Any person desiring to participate who is not already a party or participant in this proceeding shall file a petition to intervene, in accordance with § 1.8 of the Commission's Rules of Practice and Procedure, on or before April 7, 1982.

Kenneth F. Plumb,
Secretary.

[FR Doc. 82-7750 Filed 3-22-82; 8:45 am]

BILLING CODE 6717-01-M

[Docket No. ER82-160-001]**Central Telephone & Utilities Corp., Western Power Division; Compliance Filing**

March 18, 1982.

Take notice that on March 10, 1982, Central Telephone & Utilities Corporation, Western Power Division filed revised cost of service statements and rates (St.'s AV, BG, BJ, BK, BL) pursuant to the Commission's order issued February 16, 1982.

Any person desiring to be heard or to protest this filing should file comments with the Federal Energy Regulatory Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426, on or before April 2, 1982. Comments will be considered by the Commission in determining the appropriate action to be taken. Copies of this filing are on file with the Commission and are available for public inspection.

Kenneth F. Plumb,
Secretary.

[FR Doc. 82-7752 Filed 3-22-82; 8:45 am]

BILLING CODE 6717-01-M

[Docket No. ER82-380-000]**Duke Power Co.; Filing**

March 18, 1982

Take notice that Duke Power Company (Duke Power) tendered for filing on March 15, 1982, a supplement to Duke's Interconnection Agreement with Yadkin, Inc. Duke states that this agreement is on file with the Commission and has been designated Duke Rate Schedule FERC No. 11.

Duke indicates that this amendment also supersedes Service Schedule F to the prior contract dated June 14, 1961, as amended, and restates the rate form of Service Schedule F to be the same as that of Duke's Rate Schedule No. 10, Resale Service, Municipalities and Public Utility Companies, both of which are currently being collected subject to refund in Docket No. ER81-550-000 pending a Settlement Agreement by the parties. Duke represents that Service Schedule F and Rate Schedule No. 10 are the same rate in different form and that no change in revenue is produced by the restatement. Duke proposes an effective date of December 1, 1981.

According to Duke copies of this filing were mailed to the customer and the North Carolina Utilities Commission.

Any person desiring to be heard or to protest said filing should file a petition to intervene or protest with the Federal Energy Regulatory Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426, in accordance with §§ 1.8 and 1.10 of the Commission's Rules of Practice and Procedure (18 CFR 1.8, 1.10). All such petitions or protests should be filed on or before April 6, 1982. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a petition to intervene. Copies of this filing are on file with the Commission and are available for public inspection.

Kenneth F. Plumb,
Secretary.

[FR Doc. 82-7753 Filed 3-22-82; 8:45 am]

Billing Code 6717-01-M

[Docket No. RP82-51-000]**Mid Louisiana Gas Co.; Proposed Change in Rates**

March 17, 1982.

Take notice that Mid Louisiana Gas Company (Mid Louisiana) on March 9, 1982, tendered for filing as a part of First Revised Volume No. 1 of its FERC Gas Tariff, Fourth Revised Sheet No. 26a and

Sixth Revised Sheet No. 26b to become effective March 2, 1982.

Mid Louisiana states that the purpose of the filing is to permit Mid Louisiana to charge prospectively the appropriate ceiling prices for its pipeline owned production under the Natural Gas Policy Act of 1978 (NGPA). Mid Louisiana states that it currently is pricing its own production in accordance with Commission Order Nos. 58 and 98, which were vacated on March 2, 1982 by the U.S. Court of Appeals for the Fifth Circuit in *Mid Louisiana Gas Company, et al. v. FERC*, Nos. 80-3804 & 4010. Mid Louisiana further states that, in making the instant filing, it does not waive any rights it may have to make a filing to charge and collect NGPA prices for company owned production retroactively to December 1, 1978, the effective date of Title II of the NGPA.

Copies of the filing were served upon the company's jurisdictional customers and interested state commissions.

Any person desiring to be heard or to protest said filing should file a petition to intervene or protest with the Federal Energy Regulatory Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426, in accordance with §§ 1.8 and 1.10 of the Commission's Rules of Practice and Procedure (18 CFR 1.8, 1.10). All such petitions or protests should be filed on or before March 24, 1982. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a petition to intervene. Copies of this filing are on file with the Commission and are available for public inspection.

Kenneth F. Plumb,
Secretary.

[FR Doc. 82-7751 Filed 3-22-82; 8:45 am]

BILLING CODE 6717-01-M

[Docket No. ER82-379-000]

Ohio Power Co.; Filing

March 18, 1982

Take notice that American Electric Power Service Corporation (AEP) on March 12, 1982, tendered for filing on behalf of its affiliate Ohio Power Company (OPCO) Modification No. 4 dated January 1, 1982 to the Operating Agreement dated December 1, 1965 between The Toledo Edison Company and OPCO, OPCO's Rate Schedule FERC No. 35.

Sections 1 and 2 of Modification No. 4 provides for an increase in the demand charge for Short Term and Limited Term Power to \$1.25 per kilowatt per week

and \$6.50 per kilowatt per month respectively, when OPCO is the supplying party. Both schedules proposed to become effective January 1, 1982. These demand rates are substantially the same as the recently filed Short Term and Limited Term demand charges between Ohio Power Company and Cleveland Electric Illuminating Company (Docket ER82-197-000) which has been accepted by the Commission and made effective January 1, 1982 by letter Order dated February 23, 1982.

AEP requests an effective date of January 1, 1982, and therefore requests waiver of the Commission's notice requirements.

Copies of the filing were served upon the Toledo Edison Company and the Public Utilities Commission of Ohio.

Any person desiring to be heard or to protest said filing should file a petition to intervene or protest with the Federal Energy Regulatory Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426, in accordance with §§ 1.8 and 1.10 of the Commission's Rules of Practice and Procedure (18 CFR 1.8, 1.10). All such petitions or protests should be filed on or before April 6, 1982. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a petition to intervene. Copies of this filing are on file with the Commission and are available for public inspection.

Kenneth F. Plumb,
Secretary.

[FR Doc. 82-7754 Filed 3-22-82; 8:45 am]

BILLING CODE 6717-01-M

[Docket Nos. ER81-450-000, et al.]

Union Electric Co.; Order Denying Petition for Reconsideration of Summary Disposition

Issued: March 18, 1982.

On January 25, 1982, Union Electric Company (Union) filed a petition for reconsideration of the Commission's order of July 2, 1981, in Docket No. ER81-450-000. The July 2, 1981 order provided that the rate increase proposed by Union in this docket be accepted for filing and suspended for one day. The order also granted certain summary dispositions, including the deduction from rate base of accumulated deferred income taxes (ADIT) associated with normalization of AFUDC and capitalized taxes and pensions. Union seeks reconsideration of this one summary disposition item, stating that

either the Commission erred in its summary disposition of this issue or the Commission has since established a new policy inconsistent with the summary disposition.

Union relies on *Northern States Power Company*, Docket No. ER79-616, Opinion No. 34 (December 3, 1981) to support its position. According to Union, the Commission in Opinion No. 134 established its clear intent to require such rate base deductions only if the tax benefits were related to an actual rate base item. Union contends that since CWIP is not yet an actual rate base item, the deduction of the related deferred taxes should not be required. Union requests that the Commission either (1) reverse the ruling in the July 2, 1981 order in this case with regard to deferred taxes and allow Union immediately to file new tariff sheets reflecting this decision,¹ or (2) acknowledge that Union may litigate the issue in this proceeding.

After careful review of Union's arguments, we conclude that the facts in this case are not directly analogous to those underlying *Northern States Power Company*, Opinion No. 134, *supra*, and that Union has misconstrued the implications of that opinion. In *Northern States*, we determined that deduction from rate base of ADIT related to a cancelled nuclear plant was improper because the plant was never placed in service and its cost would never be included in rate base. We further noted that since the company would not earn a return on the plant investment, it would have no corresponding tax obligation nor would it receive associated tax compensation from its ratepayers.

In this case, however, Union seeks to include in rate base ADIT balances associated with construction work in progress which, according to the company's own design, ultimately will be included in rate base, thus generating a return to Union and creating an associated tax liability. Thus, the distinction between the rate (and tax) consequences applicable to abandoned plant and plant under construction is significant; it renders the approach followed in Opinion No. 134 inapposite in this proceeding.² Furthermore, no questions of fact or law remain to be

¹ Union notes that revenues collected under the revised tariff sheets would remain subject to refund pending the outcome of proceedings in Docket Nos. ER81-450-000, et al.

² For a discussion of the distinctions between Opinion No. 134, and this situation, including the limitations of and rationale underlying Opinion No. 134, see Order No. 144, Final Rule, Docket Nos. RM80-42, et al., pp. 114-115, 15 FERC ¶ 10,000 (1981) and Order No. 144-A, "Order Denying Rehearing, Lifting Stay, And Clarifying Order," Docket Nos. RM80-42, et al., 18 FERC ¶ 61,163 (February 22, 1982).

pursued at hearing and we emphasize that the intent of summary disposition, in addition to expediting clearly appropriate refunds, is to preclude unnecessary litigation of settled matters. Thus, we shall deny Union's petition for reconsideration.

The Commission orders:

(A) Union's petition for reconsideration of summary disposition is hereby denied in its entirety.

(B) The Secretary shall promptly publish this order in the Federal Register.

By the Commission.
Kenneth F. Plumb,
Secretary.

[FR Doc. 82-7755 Filed 3-22-82; 8:45 am]
BILLING CODE 6717-01-M

[Docket No. GP82-15-000, et al.]

State of Kentucky et al.; Petitions for Withdrawal of Notices of Increased Production and Seasonally Affected Filings

March 17, 1982.

In the matter of the State of Kentucky, section 108 NGPA notice of increased production and seasonally affected filings, Ashland Exploration, Inc., D.C. Polley No. 1 Well FERC No. 80-02663, Docket No. GP82-15-000; State of West Virginia, section 108 NGPA notice of increased production and seasonally affected filings, Ashland Exploration, Inc., Eastern Gas & Fuel No. 48 Well FERC No. 81-45358, Docket No. GP82-16-000; and State of West Virginia, section 108 NGPA notice of increased production and seasonally affected filings, Ashland Exploration, Inc., Eastern Gas & Fuel No. 36 Well FERC No. 81-47136, Docket No. GP82-17-000.

Take notice that on December 21, 1981, Ashland Exploration, Inc. (Ashland), P.O. Box 391, Ashland, Kentucky 41101, filed with the Federal Energy Regulatory Commission (Commission) petitions for withdrawal of section 108 Notices of Increased Production and section 108 Seasonally Affected Filings under the Natural Gas Policy Act of 1978 (NGPA) for the three wells referenced above.

Ashland states that the Commission, in an Order issued October 30, 1981, in Docket No. GP81-29, stated that a staff audit "found the individual well records reflected readings, from royalty meters located at each well, which have been proportionately adjusted so that the total volume * * * for all the wells in the gathering system equals the volume of gas recorded on the common sales meter." Ashland further states that it

has reviewed production records and has determined that certain of its filings previously made have been based on proportionately adjusted readings as opposed to actual well readings.

As a result of this review, Ashland states it discovered that the D.C. Polley No. 1 well, the Eastern Gas & Fuel No. 48 well, and the Eastern Gas & Fuel No. 36 well did, in fact, exceed the 60 Mcf per day stripper well production limit in the ninety-day periods set forth in the previous respective section 108 Notices of Increased Production and Seasonally Affected Filings for the referenced wells. In light of this fact, Ashland requests that it be allowed to withdraw these filings.

With respect to the question of refunds arising out of Ashland's request for withdrawal of the subject filings, notice is hereby given that the question of whether refunds, plus interest computed under 18 CFR 154.102(d), will be required is a matter subject to the review and final decision of the Commission.

Any person desiring to be heard or to protest this proceeding should file, within 30 days after publication of this notice in the Federal Register, with the Federal Energy Regulatory Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426, a petition to intervene or a protest in accordance with § 1.8 or § 1.10 of the Commission's Rules of Practice and Procedure (18 CFR 1.8 or 1.10). All protests filed with the Commission will be considered but will not make the protestants parties to the proceeding. Any person wishing to become a party to a proceeding or to participate as a party in any hearing must file a petition to intervene in accordance with the Commission's Rules.

Kenneth F. Plumb,
Secretary.

[FR Doc. 82-7756 Filed 3-22-82; 8:45 am]
BILLING CODE 6717-01-M

[Docket Nos. RP80-101-006, et al.]

Texas Gas Transmission Corp., et al.; Filing of Pipeline Refund Reports and Refund Plans

March 17, 1982.

Take notice that the pipelines listed in the Appendix hereto have submitted to the Commission for filing proposed refund reports or refund plans. The date of filing, docket number, and type of filing are also shown on the Appendix.

Any person wishing to do so may submit comments in writing concerning the subject refund reports and plans. All such comments should be filed with or

mailed to the Federal Energy Regulatory Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426, on or before April 1, 1982. Copies of the respective filings are on file with the Commission and available for public inspection.

Kenneth F. Plumb,
Secretary.

APPENDIX

Filing date and company	Docket No.	Type filing
Jan. 12, 1982: Texas Gas Transmission Corp.	RP80-101-006	Report.
Mar. 1, 1982: Granite State Gas Transmission, Inc.	RP82-18-001	LFUT Report.
Mar. 4, 1982: East Tennessee Natural Gas Co.	RP71-15-012	Report.
Mar. 5, 1982: Algonquin Gas Transmission Co.	CP77-337-012	Report.
Mar. 5, 1982: Columbia Gulf Transmission Co.	RP80-145-006	Report.
Mar. 8, 1982: Southern Natural Gas Co.	RP72-91-004	Report.
Mar. 10, 1982: Algonquin Gas Transmission Co.	RP82-19-001	LFUT Report.

[FR Doc. 82-7757 Filed 3-22-82; 8:45 am]
BILLING CODE 6717-01-M

[Docket No. CP81-322-001]

Texas Gas Transmission Corp.; Petition To Amend

March 17, 1982.

Take notice that on March 8, 1982, Texas Gas Transmission Corporation (Petitioner), P.O. Box 1160, Owensboro, Kentucky 42302, filed in Docket No. CP81-322-001 a petition to amend the order issued August 12, 1981, in said docket pursuant to section 7(c) of the Natural Gas Act so as to remove the maximum daily volume limitation and instead to authorize only that Petitioner would transport on an interruptible basis a daily volume of gas not to exceed a total of 15,000,000 Mcf during the primary term of the transportation agreement, all as more fully set forth in the petition to amend which is on file with the Commission and open to public inspection.

Petitioner states that by order issued August 12, 1981, it was authorized to construct and operate certain interconnecting facilities and to transport on an interruptible basis up to 50,000 Mcf of natural gas per day for Natural Gas Pipeline Company of America (Natural) from a point of receipt in Vermilion Parish, Louisiana, to a point of delivery at the interconnection of the systems of Petitioner and Dow Intrastate Gas

Company (Dow Intrastate) in Lafayette Parish, Louisiana. Petitioner explains that Dow Chemical Company (Dow), the ultimate recipient of the gas, failed to take the 50,000 Mcf per day maximum daily volume anticipated by Petitioner and Natural, the seller of the gas, during the first few months that the transportation arrangement took place, therefore, Natural has requested that Petitioner transport volumes above the 50,000 Mcf per day limitation for the remainder of the term of the transportation agreement in order that the full 15,000,000 Mcf purchased from Natural by Dow may be transported and delivered by the expiration of the sales and transportation certificates, July 31, 1982.

Petitioner requests herein amendment of the subject order to omit any reference to maximum daily volumes and to provide instead only that Petitioner would transport on an interruptible basis a daily volume of gas not to exceed a total of 15,000,000 Mcf during the 363 day term of the transportation arrangement.

Any person desiring to be heard or to make any protest with reference to said petition to amend should on or before April 1, 1982, file with the Federal Energy Regulatory Commission, Washington, D.C. 20426, a petition to intervene or a protest in accordance with the requirements of the Commission's Rules of Practice and Procedure (18 CFR 1.8 or 1.10) and the Regulations under the Natural Gas Act (18 CFR 157.10). All protests filed with the Commission will be considered by it in determining the appropriate action to be taken but will not serve to make the protestants parties to the proceeding. Any person wishing to become a party to a proceeding or to participate as a party in any hearing therein must file a petition to intervene in accordance with the Commission's Rules.

Kenneth F. Plumb,
Secretary.

[FR Doc. 82-7756 Filed 3-22-82; 8:45 am]
BILLING CODE 6717-01-M

Office of Hearings and Appeals

Issuance of Proposed Decisions and Orders; Period of February 15 Through February 26, 1982

During the period of February 15 through February 26, 1982, the proposed decisions and orders summarized below were issued by the Office of Hearings and Appeals of the Department of Energy with regard to applications for exception.

Under the procedural regulations that apply to exception proceedings (10 CFR

Part 205, Subpart D), any person who will be aggrieved by the issuance of a proposed decision and order in final form may file a written notice of objection within ten days of service. For purposes of the procedural regulations, the date of service of notice is deemed to be the date of publication of this Notice or the date an aggrieved person receives actual notice, whichever occurs first.

The procedural regulations provide that an aggrieved party who fails to file a Notice of Objection within the time period specified in the regulations will be deemed to consent to the issuance of the proposed decision and order in final form. An aggrieved party who wishes to contest a determination made in a proposed decision and order must also file a detailed statement of objections within 30 days of the date of service of the proposed decision and order. In that statement of objections, the aggrieved party must specify each issue of fact or law that it intends to contest in any further proceeding involving the exception matter.

Copies of the full text of these proposed decisions and orders are available in the public docket room of the Office of Hearings and Appeals, Room 1111, New Post Office Building, 12th & Pennsylvania Avenue, NW., Washington, D.C. 20461, Monday through Friday, between the hours of 1:00 p.m. and 5:00 p.m., except federal holidays.

George B. Breznay,
Director, Office of Hearings and Appeals.
March 17, 1982.

Champlin Petroleum Co., Washington, D.C.,
BEE-1677, crude oil.

Champlin Petroleum Company filed an Application for Exception from the provisions of 10 CFR 211.69. The exception request, if granted, would permit the firm to recover entitlements overpayments resulting from the submission of erroneous entitlements reports to the DOE during the period February 1976 through September 1980. On February 26, 1982, the Department of Energy issued a Proposed Decision and Order which determined that the exception request be denied.

Johnson Oil Co., Salt Lake City, Utah, DEE-3708, crude oil.

Johnson Oil Company filed an Application for Exception from the provisions of 10 CFR 211.67. The exception request, if granted, would relieve the firm of any entitlements purchase obligations pertaining to its crude oil receipts and runs to stills during the period December 1978 through June 1980. On February 23, 1982, the Department of Energy issued a Proposed Decision and Order which

determined that the exception request be denied.

[FR Doc. 82-7703 Filed 3-22-82; 8:45 am]
BILLING CODE 8450-01-M

Issuance of Proposed Decision and Order, Week of March 1 through March 5, 1982

During the week of March 1 through March 5, 1982, the proposed decision and order summarized below was issued by the Office of Hearings and Appeals of the Department of Energy with regard to an application for exception.

Under the procedural regulations that apply to exception proceedings (10 CFR Part 205, Subpart D), any person who will be aggrieved by the issuance of a proposed decision and order in final form may file a written notice of objection within ten days of service. For purposes of the procedural regulations, the date of service of notice is deemed to be the date of publication of this Notice or the date an aggrieved person receives actual notice, whichever occurs first.

The procedural regulations provide that an aggrieved party who fails to file a Notice of Objection within the time period specified in the regulations will be deemed to consent to the issuance of the proposed decision and order in final form. An aggrieved party who wishes to contest a determination made in a proposed decision and order must also file a detailed statement of objections within 30 days of the date of service of the proposed decision and order. In the statement of objections, the aggrieved party must specify each issue of fact or law that it intends to contest in any further proceeding involving the exception matter.

Copies of the full text of this proposed decision and order are available in the Public Docket Room of the Office of Hearings and Appeals, Room 1111, New Post Office Building, 12th and Pennsylvania Avenue, NW., Washington, D.C. 20461, Monday through Friday, between the hours of 1:00 p.m. and 5:00 p.m., except federal holidays.

George B. Breznay,
Director, Office of Hearings and Appeals.
March 17, 1982.

Silver Eagle Refining Co., Labarge, Wyo.,
BEE-1694, crude oil.

Silver Eagle Refining Company filed an Application for Exception from the provisions of 10 CFR 211.67. The exception request, if granted, would result in the issuance of additional entitlements to Silver Eagle equal in value to entitlements that the firm was unable to sell for the month of January 1980.

On March 4, 1982, the Department of Energy issued a Proposed Decision and Order which determined that the exception request be denied.

[FR Doc. 82-7704 Filed 3-22-82; 8:45 am]

BILLING CODE 6450-01-M

FEDERAL MARITIME COMMISSION

Agreements Filed

The Federal Maritime Commission hereby gives notice that the following agreements have been filed with the Commission for approval pursuant to section 15 of the Shipping Act, 1916, as amended (39 Stat. 733, 75 Stat. 763, 46 U.S.C. 814).

Interested parties may inspect and obtain a copy of each of the agreements and the justifications offered therefor at the Washington Office of the Federal Maritime Commission, 1100 L Street, N.W., Room 10327; or may inspect the agreements at the Field Offices located at New York, N.Y.; New Orleans, Louisiana; San Francisco, California; Chicago, Illinois; and San Juan, Puerto Rico. Interested parties may submit comments on each agreement, including requests for hearing, to the Secretary, Federal Maritime Commission, Washington, D.C. 20573, within 20 days after the date of the Federal Register in which this notice appears. Comments should include facts and arguments concerning the approval, modification, or disapproval of the proposed agreement. Comments shall discuss with particularity allegations that the agreement is unjustly discriminatory or unfair as between carriers, shippers, exporters, importers, or ports, or between exporters, from the United States and their foreign competitors, or operates to the detriment of the commerce of the United States, or is contrary to the public interest, or is in violation of the Act.

A copy of any comments should also be forwarded to the party filing the agreements and the statement should indicate that this has been done.

Agreement No.: T-4027-1.

Filing party: Mr. Randall V. Adams, Accounting/Traffic, Port of Palm Beach, P.O. Box 9935, Riviera Beach, Florida 33404.

Summary: Agreement No. T-4027-1 amends the basic Agreement No. T-4027 between the Port of Long Beach (Port) and Lund and Pullara, Inc. (L&P), providing for the lease by the Port to L&P of office space in the Port's Maritime Office Building. The modification provides for the inclusion of a "Utility Cost" in the original lease. The cost shall be assessed to L&P

pursuant to Tenant's percentage share as defined in section 9.02 of the lease.

Agreement No.: T-4032.

Filing party: Mr. Randall V. Adams, Accounting/Traffic, Port of Palm Beach, P.O. Box 9935, Riviera Beach, Florida 33404.

Summary: Agreement No. T-4032, between the Port of Palm Beach (Port) and Palm Beach Shipping Agency, Inc. (PBSAI), provides for the lease by the Port to PBSAI of office space in the Port's soon to be completed Maritime Office Building. The premises will be used in connection with PBSAI's steamship agency business. The term of the lease shall be for three years with an option to renew for two consecutive terms of two years each. As rental for the premises PBSAI will pay an annual amount of \$7,105 to the Port.

Agreement Nos.: 8760-12 and 9247-9.

Filing party: Henri P. Blok, Secretary, Pacific-India/Pakistan/Ceylon/Burma Agreements, 417 Montgomery Street, San Francisco, California 94104.

Summary: Agreements Nos. 8760-12 and 9247-9 modify, respectively, the basic agreements of the West Coast United States and Canada/India, Pakistan, Bangladesh, Sri Lanka and Burma Rate Agreement and the India Pakistan, Bangladesh, Sri Lanka and Burma/West Coast United States and Canada Rate Agreement to conform to the requirements of 46 CFR 528 (General Order 7, Revised).

Agreement No.: 10440.

Filing party: R. J. Finnan, Chief Tariff Publishing Officer, Lykes Bros. Steamship Co., Inc., 300 Poydras Street, New Orleans, Louisiana 70130.

Summary: Agreement No. 10440 is a proposal between Lykes Bros. Steamship Co., Inc. (Lykes) and Lineas Navieras Bolivianas, (Linabol) applicable to cargo transported "in the foreign commerce of the United States and the Republic of Bolivia, via ports on the West Coast of South America, to and from U.S. ports on the Gulf of Mexico." The agreement permits Linabol to charter space on Lykes' vessels, enables the parties to rationalize sailings and capacity, and provides each party with associate line status so they may operate under equal conditions in the trade. No joint solicitation or booking is permitted, although the parties may individually contract to use the same U.S. agent, upon obtaining each other's approval. The parties will submit semiannual operating reports to the Commission summarizing carryings under the agreement, and the agreement will remain in effect for a period of 36 months from the date of approval.

By the Federal Maritime Commission.

Dated: March 18, 1982.

Francis C. Hurney,

Secretary.

[FR Doc. 82-7748 Filed 3-22-82; 8:45 am]

BILLING CODE 6730-01-M

Inactive Tariffs; Cancellation

By Notice published in the Federal Register on September 3, 1981, the Commission notified the carriers named therein of its intent to cancel their domestic offshore tariffs 30 days thereafter, in the absence of a showing of good cause why such tariffs should not be cancelled. Seven carriers replied to this Notice requesting that their tariffs not be cancelled. Accordingly, the tariffs of the following carriers will be retained in the Commission's files as active:

Alexander & Associates, 112 Erie Avenue, Seattle, Washington 98122
Cargomatic Express, Inc., 8440 S.W. 107 Avenue, 104, Miami, Florida 33173
Container Marine Transport, Inc., 90 West Street, New York, New York 10006

Mercantile Freight Service, Inc., 2280 Alahao Place, Honolulu, Hawaii 96819
Sause Bros. Ocean Towing Co., Inc., Suite 1480 Lloyd Building, 700 N.E. Multnomah Street, Portland, Oregon 97232

Thru Island Express, Inc., 63-69 Hook Road, Bayonne, New Jersey 07002
West India Line, Post Office Box 10355, 153 East Port Road, West Palm Beach, Florida 33404

Gulf Caribbean Marine Lines, Inc., Post Office Box 3110, Jacksonville, Florida 32203 has voluntarily cancelled its effective tariff. The remaining carriers failed to respond to this Notice.

Accordingly, by authority delegated by § 9.04 of Commission Order No. 1 (Revised) dated November 12, 1981, the tariffs of the carriers listed in Appendix I are hereby cancelled.

Daniel J. Connors,

Director, Bureau of Tariffs.

Appendix I

Ace Shipping Co. Inc., Suite 203, 1200 Biscayne Boulevard, Miami, Florida 33132—FMC-F No. 1
Alltrans Alaska Freight, Inc., 650 South Othello Street, Seattle, Washington 98108—FMC-F No. 1
American International Shipping Co., Suite 914, 677 Ala Moana Boulevard, Honolulu, Hawaii 96813—FMC-F No. 7
Australia-Far East Shipping, Inc., 2302 East Del Amo Boulevard, Compton, California 90220—FMC-F No. 1
Barton Export Boxing Corp., Maracibo Street, Building 19 C-D, Port Newark, New Jersey 07114—FMC-F No. 1
Caribbean Steamship Corp., San Miguel Building—Suite 312, Kennedy Avenue—

KM. 2.5 P.O. Box 4423, San Juan Industrial Development, San Juan, Puerto Rico 00905—FMC-F No. 1

Caribe Cargo Services, Inc., 6331 N.W. 74th Avenue, Miami, Florida 33166—FMC-F No. 1

CMC Ocean Freight Express, Post Office Box 4035, Carolina, Puerto Rico 00630—FMC-F No. 2

Consolidated Freight Forwarders, Inc., 2792 N.W. 24th Street, Miami, Florida 33142—FMC-F No. 1

Dillingham Pacific Lines, Inc., Post Office Box 3288, Pier 24, Honolulu, Hawaii 96801—FMC-F No. 1

Drake Motor Lines, Inc., 20 Olney Avenue, Cherry Hill, New Jersey 08002—FMC-F No. 4

Gaynar Shipping Corporation, One World Trade Center, New York, New York 10048—FMC-F No. 1

The Great Norwegian Trading Company, 3579 East 11th Avenue, Hialeah, Florida 33013—FMC-F No. 1

Guam Fast Freight, 744 Naakea Place, Honolulu, Hawaii 96825—FMC-F No. 1

Guam Marianas Freight, 300 Market Street, Oakland, California 94607—FMC-F No. 1

Husky Barge Lines, 3115 Mt. View Drive, Anchorage, Alaska 99503—FMC-F No. 3

International Marine Transport Services, Inc., Post Office Box 7667, St. Thomas, Virgin Islands 00801—FMC-F No. 2

International Marine Transport Services, Inc., Post Office Box 3272, Old San Juan Puerto Rico 00904—FMC-F No. 3

Inter-Ports Service, Inc., Post Office Box 475, St. Just, Puerto Rico 00750—FMC-F No. 4

Inter-Ports Service, Inc., Post Office Box 475, St. Just, Puerto Rico—FMC-F No. 5

Island Transport Services, Inc., Post Office Box 970, Christiansted, St. Croix, Virgin Islands 00820—FMC-F No. 1

La Grande Shipping Co., Inc., 520 Paterson Plank Road, Jersey City, New Jersey 07307—FMC-F No. 1

Loux & Sons Drayage, 200 3rd Street, Oakland, California 94607—FMC-F No. 3

Malabe Shipping Co., Inc., 45 Bergen Street, Brooklyn, New York 11201—FMC-F No. 4

Pacific Hauling Service, Inc., 3579 East Cliff Drive, Salt Lake City, Utah 84117—FMC-F No. 2

Pan-American Express Co., Inc., 508 West 126th Street, New York, New York 10027—FMC-F No. 2

P.R.V.I. Consolidators Corp., 515 Gardner Avenue, Brooklyn, New York 11222—FMC-F No. 1

Rodriguez Trucking, Inc., 515 Marcy Avenue, Brooklyn, New York 11206—FMC-F No. 2

Seaway Distribution Corporation, Post Office Box 30505, Honolulu, Hawaii 96819—FMC-F No. 2

Transcaribbean Consolidated Freight Co., 264 40th Street, Brooklyn, New York 11220—FMC-F No. 1

Trans-Freight, Inc., Post Office Box 522458, Miami, Florida 33152—FMC-F No. 1

Unifreight Corporation, G.P.O. Box 6001, San Juan, Puerto Rico 00936—FMC-F No. 2

Vanleigh Transport Corp., Post Office Box 3680, Carolina, Puerto Rico 00630—FMC-F No. 1

[FR Doc. 82-7747 Filed 3-22-82; 8:45 am]

BILLING CODE 6730-01-M

[Docket No. 82-15]

Kerr Steamship Company, Inc. v. the Board of Commissioners of the Port of New Orleans and Ryan-Walsh Stevedoring Co., Inc.; Filing of Complaint and Assignment

Notice is given that a complaint filed by Kerr Steamship Company, Inc. against The Board of Commissioners of the Port of New Orleans and Ryan-Walsh Stevedoring Co., Inc. was served March 11, 1982. Complainant alleges that respondents have violated sections 16 and 17 of the Shipping Act, 1916 by seeking to enforce assessment of demurrage charges against complainant for which complainant alleges it has no obligation to pay.

This proceeding has been assigned to Administrative Law Judge Charles E. Morgan. Hearing in this matter, if any is held, shall commence within the time limitations prescribed in 46 CFR 502.61. The hearing shall include oral testimony and cross-examination in the discretion of the presiding officer only upon proper showing that there are genuine issues of material fact that cannot be resolved on the basis of sworn statements, affidavits, depositions, or other documents or that the nature of the matter in issue is such that an oral hearing and cross-examination are necessary for the development of an adequate record.

Francis C. Hurney,
Secretary.

[FR Doc. 82-7746 Filed 3-22-82; 8:45 am]

BILLING CODE 6730-01-M

FEDERAL RESERVE SYSTEM

Alden Bancshares, Inc.; Formation of Bank Holding Company

Alden Bancshares, Inc., Alden, Kansas, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 80 percent or more of the voting shares of Alden State Bank, Alden, Kansas. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Kansas City. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 13, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing,

identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7713 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

American Bancshares of Arkansas; Formation of Bank Holding Company

American Bancshares of Arkansas, Charleston, Arkansas, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 80 per cent or more of the voting shares of American State Bank, Charleston, Arkansas. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of St. Louis. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 15, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7714 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

The Bancshares, Inc.; Formation of Bank Holding Company

The Bancshares, Inc., Scottsburg, Indiana, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 100 per cent of the voting shares, less directors' qualifying shares, of The Scott County State Bank, Scottsburg, Indiana, the successor by merger with the Scottsburg Bank, Scottsburg, Indiana. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or

at the Federal Reserve Bank of St. Louis. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 15, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7723 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Caneyville Bancshares, Inc.; Formation of Bank Holding Company

Caneyville Bancshares, Inc., Caneyville, Kentucky, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 80 percent or more of the voting shares of Bank of Caneyville, Caneyville, Kentucky ("Bank"). The factors that are considered in acting on the application are set forth in Section 3(c) of the Act (12 U.S.C. 1842(c)).

Caneyville Bancshares, Inc., Caneyville, Kentucky, has also applied, pursuant to section 4(c)(8) of the Bank Holding Company Act (12 U.S.C. 1843(c)(8)) and § 225.4(b)(2) of the Board's Regulation Y (12 CFR 225.4(b)(2)), for permission to acquire voting shares of Caneyville Insurance Agency, Inc., Caneyville, Kentucky.

Applicant states that the proposed subsidiary would operate solely as an insurance sales agency, selling credit life and health insurance to persons involved in, and only upon transactions related to, extensions of credit by Bank. These activities would be performed from offices of Applicant's subsidiary in Caneyville, Kentucky, and the geographic areas to be served are all areas from which Bank derives its customers. Such activities have been specified by the Board in § 225.4(a) of Regulation Y as permissible for bank holding companies, subject to Board approval of individual proposals in accordance with the procedures of § 225.4(b).

Interested persons may express their views on the question whether consummation of the proposal can "reasonably be expected to produce benefits to the public, such as greater convenience, increased competition, or

gains in efficiency, that outweigh possible adverse effects, such as undue concentration of resources, decreased or unfair competition, conflicts of interests, or unsound banking practices." Any request for a hearing on this question must be accompanied by a statement of the reasons a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute, summarizing the evidence that would be presented at a hearing, and indicating how the party commenting would be aggrieved by approval of the proposal.

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of St. Louis.

Any views or requests for hearing should be submitted in writing and received by the Reserve Bank not later than April 14, 1982.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7724 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Carbondale Bancshares, Inc.; Formation of Bank Holding Company

Carbondale Bancshares, Inc., Carbondale, Kansas, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 80 percent or more of the voting shares of State Bank of Carbondale, Carbondale, Kansas. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Kansas City. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 13, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve Systems, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7725 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

CITBA Financial Corp.; Formation of Bank Holding Company

Citba Financial Corporation, Mooresville, Indiana, has applied for the board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 100 percent of the voting shares of Citizens Bank, Mooresville, Indiana. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The Application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Chicago. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 14, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7715 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Citicorp; Acquisition of Bank

Citicorp, New York City, New York, has applied for the Board's approval under section 3(a)(3) of the Bank Holding Company Act (12 U.S.C. 1842(a)(3)) to acquire 100 per cent of the voting shares of Citibank (Delaware), Wilmington, Delaware. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of New York. Any person wishing to comment on the application should submit views in writing to the Reserve Bank to be received not later than April 15, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7726 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Consolidated Holding Co.; Formation of Bank Holding Company

Consolidated Holding Company, Oldham, South Dakota, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 94 per cent or more of the voting shares of American State Bank, Oldham, South Dakota. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Minneapolis. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 15, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7716 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

De Kalb County Bancshares, Inc.; Formation of Bank Holding Company

De Kalb County Bancshares, Inc., Clarksdale, Missouri, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 91.63 percent or more of the voting shares of Clarksdale Bank, Clarksdale, Missouri. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Kansas City. Any person wishing to comment on the application should submit views in writing to the Secretary, Board of Governors of the Federal Reserve System, Washington, D.C. 20551 to be received not later than April 15, 1982.

Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7727 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Delhi Bancshares, Inc.; Formation of Bank Holding Company

Delhi Bancshares, Inc., Delhi, Louisiana, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 100 per cent of the voting shares of Guaranty Bank & Trust Company, of Delhi, Delhi, Louisiana. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Dallas. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 13, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7717 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Financial Services of Lowry, Inc.; Formation of Bank Holding Company

Financial Services of Lowry, Inc., Lowry, Minnesota, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 82 per cent or more of the voting shares of Lowry State Bank, Lowry, Minnesota. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Minnesota. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 13, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7718 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

First National Bancorp; Acquisition of Bank

First National Bancorp, Gainesville, Georgia, has applied for the Board's approval under section 3(a)(3) of the Bank Holding Company Act (12 U.S.C. 1842(a)(3)) to acquire 100 percent of the voting shares of the successor by merger to First Bank of Habersham, Cornelia, Georgia. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Atlanta. Any person wishing to comment on the application should submit views in writing to the Reserve Bank to be received not later than April 15, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,

Assistant Secretary of the Board.

[FR Doc. 82-7728 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

First Selmer Bancshares, Inc.; Formation of Bank Holding Company

First Selmer Bancshares, Inc., Selmer, Tennessee, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding

company by acquiring 100 percent of the voting shares of the successor by merger to First National Bank of Selmer, Selmer, Tennessee. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of St. Louis. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 15, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,
Assistant Secretary of the Board.

[FR Doc. 82-7729 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

MPS Bancorp, Inc., Acquisition of Bank

MPS Bancorp, Inc., Mount Prospect, Illinois, has applied for the Board's approval under section 3(a)(3) of the Bank Holding Company Act (12 U.S.C. 1842(a)(3)) to acquire 100 percent of the voting shares less directors' qualifying shares, of Tollway-Arlington National Bank of Arlington Heights, Arlington Heights, Illinois. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Chicago. Any person wishing to comment on the application should submit views in writing to the Secretary, Board of Governors of the Federal Reserve System, Washington, D.C. 20551, to be received not later than April 15, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,
Assistant Secretary of the Board.

[FR Doc. 82-7730 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Mercantile Texas Corp., Acquisition of Bank Holding Company

Mercantile Texas Corporation, Dallas, Texas, has applied for the Board's approval under section 3(a)(5) of the Bank Holding Company Act (12 U.S.C. 1842(a)(5)) to merge with State National Financial Corporation, Corsicana, Texas, which owns The State National Bank of Corsicana, Corsicana, Texas. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

Mercantile Texas Corporation, Dallas, Texas, is also engaged in the following nonbank activities: Data processing; investment advisor; credit related insurance, financial services; small business investment company. In addition to the factors considered under section 3 of the Act (banking factors), the Board will consider the proposal in the light of the company's nonbanking activities and the provisions and prohibitions in section 4 of the Act (12 U.S.C. 1843).

The application may be inspected at the offices of the Board of Governors or the Federal Reserve Bank of Dallas. Any person wishing to comment on the application should submit views in writing to the Secretary, Board of Governors of the Federal Reserve System, Washington, D.C. 20551, to be received not later than April 15, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,
Assistant Secretary of the Board.

[FR Doc. 82-7731 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Mid-Nebraska Bancshares, Inc.; Proposed Acquisition of Ord Insurance, Inc.

Mid-Nebraska Bancshares, Inc., Ord, Nebraska, has applied, pursuant to section 4(c)(8) of the Bank Holding Company Act (12 U.S.C. 1843(c)(8)) and § 225.4(b)(2) of the Board's Regulation Y (12 CFR 225.4(b)(2)), for permission to acquire all of the assets of Ord Insurance, Inc., Ord, Nebraska.

Applicant states that the proposed subsidiary would engage in the sale of general insurance in a community with a population of 5,000 or less. These

activities would be performed from offices of Applicant's subsidiary in Ord, Nebraska, and the geographic area to be served is Valley County, Nebraska. Such activities have been specified by the Board in § 225.4(a) of Regulation Y as permissible for bank holding companies, subject to Board approval of individual proposals in accordance with the procedures of § 225.4(b).

Interested persons may express their views on the question whether consummation of the proposal can "reasonably be expected to produce benefits to the public, such as greater convenience, increased competition, or gains in efficiency, that outweigh possible adverse effects, such as undue concentration of resources, decreased or unfair competition, conflicts of interests, or unsound banking practices." Any request for a hearing on this question must be accompanied by a statement of the reasons a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute, summarizing the evidence that would be presented at a hearing, and indicating how the party commenting would be aggrieved by approval of the proposal.

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Kansas City.

Any person wishing to comment on the application should submit views in writing to the Reserve Bank to be received no later than April 15, 1982.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,
Assistant Secretary of the Board.

[FR Doc. 82-7732 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Mt. Vernon Bancorp, Inc.; Formation of Bank Holding Company

Mt. Vernon Bancorp, Inc., Mt. Vernon, Illinois, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring at least 80 percent of the voting shares of First Bank and Trust Co., Mt. Vernon, Illinois. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of St. Louis. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be

received not later than April 15, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,
Assistant Secretary of the Board.

[FR Doc. 82-7733 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

NBE Bancshares, Inc.; Formation of Bank Holding Company

NBE Bancshares, Inc., Earlville, Illinois, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 100 percent of the voting shares of the successor by merger to National Bank of Earlville, Earlville, Illinois. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Chicago. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 13, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,
Assistant Secretary of the Board.

[FR Doc. 82-7734 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Rocky Financial Corp.; Formation of Bank Holding Company

Rocky Financial Corporation, Rocky, Oklahoma, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 100 percent of the voting shares of The State Bank of Rocky, Rocky, Oklahoma. The factors that are considered in acting on the application are set forth in section 3(c)

of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Kansas City. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 15, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,
Assistant Secretary of the Board.

[FR Doc. 82-7719 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Salem Financial Corp.; Formation of Bank Holding Company

Salem Financial Corporation, Goshen, Indiana, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 100 percent of the voting shares of Salem Bank and Trust Company, Goshen, Indiana. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Chicago. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 15, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,
Assistant Secretary of the Board.

[FR Doc. 82-7720 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Security National Corp.; Formation of Bank Holding Company

Security National Corporation, Washington, D.C., has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12

U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 100 percent of the voting shares of Security Bank, N.A., Washington, D.C. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Richmond. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 13, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,
Assistant Secretary of the Board.

[FR Doc. 82-7721 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

Southern Bancorporation, Inc.; Proposed Acquisition of Family Budget Finance of Tifton, Inc.

Southern Bancorporation, Inc., Greenville, South Carolina, has applied, pursuant to section 4(c)(8) of the Bank Holding Company Act (12 U.S.C. 1843(c)(8)) and 225.4(b)(2) of the Board's Regulation Y (12 CFR 225.4(b)(2)), for permission to indirectly acquire substantially all of the assets of Family Budget Finance of Tifton, Inc., Tifton, Georgia.

Applicant states that the business proposed to be acquired engages in the activities of making or acquiring for its own account, or for the account of others, loans and other extensions of credit such as would be made by a consumer finance company acting as agent for the sale of credit life, credit accident and health insurance and property and casualty insurance in connection with extensions of credit made by the company. These activities would be performed from offices of Applicant's subsidiary in Tifton, Georgia, and the geographic areas to be served are Tifton, Georgia and surrounding area. Such activities have been specified by the Board in § 225.4(a) of Regulation Y as permissible for bank holding companies, subject to Board approval of individual proposals in accordance with the procedures of § 225.4(b).

Interested persons may express their views on the question whether consummation of the proposal can "reasonably be expected to produce benefits to the public, such as greater convenience, increased competition, or gains in efficiency, that outweigh possible adverse effects, such as undue concentration of resources, decreased or unfair competition, conflicts of interests, or unsound banking practices." Any request for a hearing on this question must be accompanied by a statement of the reasons a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute, summarizing the evidence that would be presented at a hearing, and indicating how the party commenting would be aggrieved by approval of the proposal.

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Atlanta.

Any person wishing to comment on the application should submit views in writing to the Reserve Bank to be received no later than April 13, 1982.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,
Assistant Secretary of the Board.

[FR Doc. 82-7735 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

State Bancshares, Inc., Formation of Bank Holding Company

State Bancshares, Inc., Benkelman, Nebraska, has applied for the Board's approval under section 3(a)(1) of the Bank Holding Company Act (12 U.S.C. 1842(a)(1)) to become a bank holding company by acquiring 90 percent of the voting shares of the State Bank, Benkelman, Nebraska. The factors that are considered in acting on the application are set forth in section 3(c) of the Act (12 U.S.C. 1842(c)).

The application may be inspected at the offices of the Board of Governors or at the Federal Reserve Bank of Kansas City. Any person wishing to comment on the application should submit views in writing to the Reserve Bank, to be received not later than April 8, 1982. Any comment on an application that requests a hearing must include a statement of why a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute and summarizing the evidence that would be presented at a hearing.

Board of Governors of the Federal Reserve System, March 16, 1982.

Theodore E. Downing, Jr.,
Assistant Secretary of the Board.

[FR Doc. 82-7722 Filed 3-22-82; 8:45 am]

BILLING CODE 6210-01-M

GENERAL SERVICES ADMINISTRATION

Transportation and Public Utilities Service

[E-82-10]

Delegation of Authority to the Secretary of Energy

1. *Purpose.* This delegation authorizes the Secretary of Energy to represent the consumer interests of the executive agencies of the Federal Government in proceedings before the Illinois Commerce Commission involving electric rates, Case No. 82-0026.

2. *Effective date.* This delegation is effective immediately.

3. Delegation.

a. Pursuant to the authority vested in the Administrator of General Services by the Federal Property and Administrative Services Act of 1949, 63 Stat. 377, as amended, particularly sections 201(a)(4) and 205(d) (40 U.S.C. 481(a)(4) and 486(d)), authority is delegated to the Secretary of Energy to represent the consumer interests of the executive agencies of the Federal Government in proceedings before the Illinois Commerce Commission involving the application of the Commonwealth Edison Company for an increase in its electric rates in Case No. 82-0026.

b. The Secretary of Energy may redelegate this authority to any officer, official, or employee of the Department of Energy.

c. This authority shall be exercised in accordance with the policies, procedures, and controls prescribed by the General Services Administration (GSA), and shall be exercised in cooperation with the responsible officers, officials, and employees thereof.

d. The Department of Energy shall add to its service list in this case so that GSA will receive copies of testimony, briefs, and other Department of Energy filings.

Dated: March 12, 1982.

Allan W. Beres,
Commissioner, Transportation and Public Utilities Service.

[FR Doc. 82-7666 Filed 3-22-82; 8:45 am]

BILLING CODE 6820-AM-M

[E-82-11]

Delegation of Authority to the Secretary of Energy

1. *Purpose.* This delegation authorizes the Secretary of Energy to represent the consumer interests of the executive agencies of the Federal Government in proceedings before the Idaho Public Utilities Commission involving electric rates, Docket Nos. U-1006-185 and U-1006-185A.

2. *Effective date.* This delegation is effective immediately.

3. Delegation.

a. Pursuant to the authority vested in the Administrator of General Services by the Federal Property and Administrative Services Act of 1949, 63 Stat. 377, as amended, particularly sections 201(a)(4) and 205(d) (40 U.S.C. 481(a)(4) and 486(d)), authority is delegated to the Secretary of Energy to represent the consumer interests of the executive agencies of the Federal Government in proceedings before the Idaho Public Utilities Commission involving the application of the Idaho Power Company for an increase in its electric rates in Docket Nos. U-1006-185 and U-1006-185A.

b. The Secretary of Energy may redelegate this authority to any officer, official, or employee of the Department of Energy.

c. This authority shall be exercised in accordance with the policies, procedures, and controls prescribed by the General Services Administration (GSA), and shall be exercised in cooperation with the responsible officers, officials, and employees thereof.

d. The Department of Energy shall add GSA to its service list in this case so that GSA will receive copies of testimony, briefs, and other Department of Energy filings.

Dated: March 12, 1982.

Allan W. Beres,
Commissioner, Transportation and Public Utilities Service.

[FR Doc. 82-7665 Filed 3-22-82; 8:45 am]

BILLING CODE 6820-AM-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Consumer Participation; Open Meetings

AGENCY: Food and Drug Administration

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the following consumer exchange meetings:

Buffalo District Office, Chaired by Lois M. Meyer, Consumer Affairs Officer

Date: Tuesday, March 30, 1982, 1:30 p.m.
Address: First Floor Conference Rm., Clinton County Government Center, 137 Margaret St., Plattsburgh, NY 12901.

For further information contact: Lois M. Meyer, Consumer Affairs Officer, Food and Drug Administration, 599 Delaware Ave., Buffalo, NY 14202, 716-846-4483.

Buffalo District Office, Chaired by Robert L. Hart, Supervisory Consumer Safety Officer, Albany Resident Post, and Lois M. Meyer, Consumer Affairs Officer

Date: Thursday, April 1, 1982, 10 a.m.
Address: Downstairs Conference Rm., Colonie Public Library, 629 Albany Shaker Rd., Loudonville, NY 12211.

For further information contact: Lois M. Meyer, Consumer Affairs Officer, Food and Drug Administration, 599 Delaware Ave., Buffalo, NY 14202, 716-846-4483.

Houston Station, Chaired by Anthony J. Whitehead, Station Director

Date: Monday, April 5, 1982, 10:30 a.m. to 12 m.
Address: Library, Westend Park Senior Citizens Center, 1226 NW. 18th St., San Antonio, TX 78207.

For further information contact: Juan A. Tijerina, Consumer Affairs Officer, Food and Drug Administration, 419 S. Main, Rm. 301, San Antonio, TX 78204, 512-229-6737.

Houston Station, Chaired by Anthony J. Whitehead, Station Director

Date: Monday, April 5, 1982, 2:30 p.m. to 4 p.m.
Address: V.F.W. Hall, Old Elementary School Bldg., 211 W. College, Devine, TX 78016.
For further information contact: Juan A. Tijerina, Consumer Affairs Officer, Food and Drug Administration, 419 S. Main, Rm. 301, San Antonio, TX 78204, 512-229-6737.

SUPPLEMENTARY INFORMATION: The purpose of these meetings is to encourage dialogue between consumers and FDA officials, to identify and set priorities for current and future health concerns, to enhance understanding and exchange information between local consumers and FDA's District Offices, and to contribute to the agency's policymaking decisions on vital issues.

Dated: March 17, 1982.

William F. Randolph,
Acting Associate Commissioner for
Regulatory Affairs.

[FR Doc. 82-7672 Filed 3-18-82; 4:54 pm]

BILLING CODE 4160-01-M

National Institutes of Health

Board of Scientific Counselors, Division of Cancer Biology and Diagnosis; Meeting

Pursuant to Pub. L. 92-463, notice is hereby given of the meeting of the Board of Scientific Counselors, DCBD, National Cancer Institute, May 20, 1982. This meeting will be open to the public in Building 31, Conference Room 7, National Institutes of Health, Bethesda, Maryland 20205, from 9:00 a.m. to adjournment for concept review of proposed DCBD research projects.

Mrs. Winifred Lumsden, Committee Management Officer, National Cancer Institute, Building 31, Room 10A06, National Institutes of Health, Bethesda, Maryland 20205 (301/496-5708) will provide summaries of the meeting and rosters of committee members, upon request.

Dr. Alan S. Rabson, Director, Division of Cancer Biology and Diagnosis, National Cancer Institute, Building 31, Room 3A-03, National Institutes of Health, Bethesda, Maryland 20205 (301/496-4345) will furnish substantive program information.

Dated: March 10, 1982.

Betty J. Beveridge,
Committee Management Officer, NIH.

[FR Doc. 82-7689 Filed 3-22-82; 8:45 am]

BILLING CODE 4140-01-M

Board of Scientific Counselors, Division of Resources, Centers, and Community Activities; Meeting

Pursuant to Pub. L. 92-463, notice is hereby given of the meeting of the Board of Scientific Counselors, Division of Resources, Centers, and Community Activities, National Cancer Institute, National Institutes of Health, May 6-7, 1982, Building 1, Wilson Hall, Bethesda, Maryland 20205. The entire meeting will be open to the public from 8:30 a.m. to adjournment on May 6 and from 8:30 a.m. to adjournment on May 7, to discuss the current and future programs of the Division of Resources, Centers, and Community Activities, as well as to review the program concepts of that Division. Attendance by the public will be limited to space available.

Mrs. Winifred Lumsden, Committee Management Officer, National Cancer Institute, Building 31, Room 10A06, National Institutes of Health, Bethesda, Maryland 20205 (301/496-5708) will provide summaries of the meeting and rosters of committee members, upon request.

Dr. Robert G. Burnight, Executive Secretary, Board of Scientific Counselors, DRCCA, National Cancer

Institute, Blair Building, Room 614C, National Institutes of Health, Bethesda, Maryland 20205 (301/427-8630) will furnish substantive program information.

Dated: March 10, 1982.

Betty J. Beveridge,
Committee Management Officer, NIH.

[FR Doc. 82-7688 Filed 3-22-82; 8:45 am]

BILLING CODE 4140-01-M

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[CA 12252]

California; Order Providing for Opening of Lands

March 12, 1982.

By virtue of the authority contained in Section 24 of the Act of June 10, 1920, 41 Stat. 1075, as amended, 16 U.S.C. 818 (1970), and in accordance with the authority delegated to me by the State Director, California State Office, Bureau of Land Management, dated January 13, 1977 (42 FR 3901), as amended, and pursuant to the determination of the Federal Energy Regulatory Commission it is ordered as follows:

1. By order dated February 17, 1982, the Federal Energy Regulatory Commission vacated the land withdrawal in part for Power Project No. 564 as to the following described lands:

Mount Diablo Meridian

T. 26 S., R. 33 E.,

Sec. 18, Lots 5, 6, 7, 8, 9, 10, 11 (Formerly described as a portion of the W 1/2 W 1/2 W 1/2 NW 1/4 NE 1/4);

The area aggregates approximately 0.48 acres in Kern County, California.

These lands remain segregated from the operation of the Public Land Laws and the Mining Laws by virtue of PLO 548 which withdrew the land for Flood Control Purposes for use by the Corps of Engineers; these lands are further segregated from the Public Land Laws by Reservoir Site Reserve 17 and Powersite Classification 267. Simultaneously with, and at such time as PLO 548, Reservoir Reserve 17 and Powersite Classification 267 are restored to the operation of the Public Land Laws these lands withdrawn as a part of Power Project No. 564 shall be restored to the operation of the Public Land Laws.

Inquiries concerning the land should be addressed to the Bureau of Land Management, Federal Office Building,

Room E-2841, 2800 Cottage Way,
Sacramento, California 95825.

Joan B. Russell,

Chief, Lands Section, Branch of Lands and
Minerals Operations.

[FR Doc. 82-7696 Filed 3-22-82; 8:45 am]

BILLING CODE 4310-84-M

[CA 9649]

California; Order Providing for Opening of Lands

March 12, 1982.

By virtue of the authority contained in Section 24 of the Act of June 10, 1920, 41 Stat. 1075, as amended, 16 U.S.C. 818 (1970), and in accordance with the authority delegated to me by the State Director, California State Office, Bureau of Land Management, dated January 13, 1977 (42 FR 3901), as amended, and pursuant to the determination of the Federal Energy Regulatory Commission it is ordered as follows:

1. By order dated March 2, 1982, the Federal Energy Regulatory Commission vacated the land withdrawal in part for Power Project No. 2279 as to the following described land:

Mount Diablo Meridian

T. 26 N., R. 12 E.,

Sec. 31, S $\frac{1}{2}$ S $\frac{1}{2}$ SE $\frac{1}{4}$ NE $\frac{1}{4}$.

The area aggregates 10 acres within the Plumas National Forest, Plumas County, California.

This land shall immediately, upon publication in the *Federal Register*, become available for consummation of a pending Forest Service Exchange Application CA 9649.

Inquiries concerning the land should be addressed to the Bureau of Land Management, Federal Office Building, Room E-2841, 2800 Cottage Way, Sacramento, California 95825.

Joan B. Russell,

Chief, Lands Section, Branch of Lands and
Minerals Operations.

[FR Doc. 82-7695 Filed 3-22-82; 8:45 am]

BILLING CODE 4310-84-M

Office of Surface Mining Reclamation and Enforcement

State of Montana Reclamation Plan; Abandoned Mine Lands Reclamation Program

AGENCY: Office of Surface Mining
Reclamation and Enforcement (OSM),
Interior.

ACTION: Notice of availability of findings
of no significant impact (FONSI)
addressing environmental assessments
(EAs) for development of two (2)

abandoned mine land projects under the
State of Montana Reclamation Plan.

SUMMARY: OSM has prepared EAs on
projects submitted in the Federal Grant
Application submitted by the State of
Montana to the Office of Surface
Mining.

A FONSI has been made on the two
(2) reclamation projects indicated below
and included in the grant application
developed under Title IV of the Surface
Mining Control and Reclamation Act of
1977 (SMCRA), 30 U.S.C. 1231-1234.

ADDRESS: Copies of the EAs and FONSI
are available for inspection or may be
obtained at the following location
between the hours of 8:00 a.m. and 4:00
p.m.: Office of Surface Mining, Wyoming
State Office, Freden Building, 935
Pendell Blvd., Mills, Wyoming 82644.

FOR FURTHER INFORMATION CONTACT:
William Thomas, Wyoming State Office
Director, Office of Surface Mining, U.S.
Department of the Interior, P.O. Box
1420, Mills, Wyoming 82644; Telephone
(301) 261-5550.

Reclamation projects included in the
FONSI and this location are:
Heal Property, Centerville, Montana.
Klein Mine, Roundup, Montana.

Dated: March 18, 1982.

J. Steven Griles,

Acting Director, Office of Surface Mining.

[FR Doc. 82-7745 Filed 3-22-82; 8:45 am]

BILLING CODE 4310-05-M

Office of the Secretary

Alaska Land Use Council; Notice of Call for Work Program Items, FY 82-83

As required by the operating
procedures of the Alaska Land Use
Council, which was established under
the Alaska National Interest Lands
Conservation Act, Pub. L. 96-487, the
Council shall issue a call for
recommended items to be included in
the work program for the coming year.
Each item submitted for the work
program must include a brief description
of the work to be accomplished, the
completion date, the anticipated
product, the estimated cost, and nature
of the Council's involvement. The
Cochairmen, after consultation with the
Council's Staff Committee, will prepare
a recommended work program
considering the requirements of
ANILCA, projected Council resources,
special requests, and recommendations
from the public and Council members.
The proposed work program will be
submitted in May to the Council for
adoption. Any interested party having a
proposed work program item should
submit the information to the

Cochairmen prior to April 15, 1982.

Submittals should be sent to: The
Cochairmen, Alaska Land Use Council,
P.O. Box 120, Anchorage, AK 99510.
Anyone having questions regarding the
Council's work program may call the
Council office at (907) 272-3422 or FTS
271-5485.

William P. Horn,

Deputy Under Secretary.

March 17, 1982.

[FR Doc. 82-7698 Filed 3-22-82; 8:45 am]

BILLING CODE 4310-10-M

INTERNATIONAL COMMUNICATION AGENCY

Culturally Significant Objects Imported for Exhibition; Determination

Notice is hereby given of the following
determination: Pursuant to the authority
vested in me by the act of October 19,
1965 (79 Stat. 985, 22 U.S.C. 2459) and
Executive Order 12047 of March 27, 1978
(43 FR 13359, March 29, 1978), I hereby
determine that the objects in the exhibit,
"Mauritshuis: Dutch Painting of the
Golden Age From the Royal Picture
Gallery, The Hague" (included in the
list¹ filed as a part of this
determination) imported from abroad for
the temporary exhibition without profit
within the United States are of cultural
significance. These objects are imported
pursuant to an agreement between the
foreign lender and the participating
museums in the United States. I also
determine that the temporary exhibition
or display of the listed exhibit objects at
the National Gallery of Art, Washington,
D.C., beginning on or about April 20,
1982, to on or about October 31, 1982;
the Kimbell Art Museum, Forth Worth,
Texas, beginning on or about November
20, 1982, to on or about January 30, 1983;
The Art Institute of Chicago, Chicago,
Illinois, beginning on or about February
26, 1983, to on or about May 29, 1983;
and the Los Angeles County Museum of
Art, Los Angeles, California, beginning
on or about June 30, 1983, to on or about
September 11, 1983, is in the national
interest.

Public notice of this determination is
ordered to be published in the *Federal
Register*.

Dated: March 19, 1982.

Charles Z. Wick,

Director.

[FR Doc. 82-7869 Filed 3-22-82; 8:45 am]

BILLING CODE 8230-01-M

¹ An itemized list of objects included in the
exhibit is filed as part of the original document.

INTERSTATE COMMERCE COMMISSION

[Ex Parte No. 387 (Sub-No. 101)]

Boston and Maine Corporation, Exemption for Contract Tariff ICC-BM- C-0013

AGENCY: Interstate Commerce Commission.

ACTION: Notice of provisional exemption.

SUMMARY: Petitioners are granted a provisional exemption under 49 U.S.C. 10505 from the notice requirements of 49 U.S.C. 10713(e). The contract tariff to be filed may become effective on one day's notice. This exemption may be revoked if protests are filed within 15 days of publication in the Federal Register.

FOR FURTHER INFORMATION CONTACT: Donald J. Shaw, Jr. or Jane F. Mackall (202) 275-7656.

SUPPLEMENTARY INFORMATION: The Boston and Maine Corporation, Robert W. Meserve and Benjamin H. Lacy, Trustees, (BM) filed a petition on March 9, 1982 seeking an exemption under 49 U.S.C. 10505 from the statutory notice provisions of 49 U.S.C. 10713(e). Petitioners request that we permit contract tariff ICC-BM-C-0013 to become effective on one day's notice. The tariff was filed to become effective on April 9, 1982. The tariff provides for the track storage of pulp, paper and paper products in equipment carrying BM markings.

Under 49 U.S.C. 10713(e), contracts must be filed on not less than 30 days' notice. There is no provision for waiving this requirement. Cf. former section 10762(d)(1). However, the Commission has granted relief under our section 10505 exemption authority in exceptional situations.

The petition shall be granted. Due to the economic downturn, the BM has excess equipment, and the paper industry has excess production. The contract allows the shippers to store their shipments in boxcars until needed at destination. This eliminates the need for making a shipment to a storage warehouse and reshipping when the product is needed. It also permits utilization of idle boxcars. One shipper has developed a production problem and requires immediate storage. Advancement of the effective date would permit immediate use of the boxcars. We find this to be the type of exception circumstances which warrants a provisional exemption.

Petitioner's contract tariff ICC-BM-C-0013 may become effective on one day's notice. We will apply the following

conditions which have been imposed in similar exemption proceedings:

If the Commission permits the contract to become effective on one day's notice, this fact neither shall be construed to mean that this is a Commission approved contract for purposes of 49 U.S.C. 10713(g) nor shall it serve to deprive the Commission of jurisdiction to institute a proceeding on its own initiative or on complaint, to review this contract and to disapprove it.

Subject to compliance with these conditions, under 49 U.S.C. 10505(a) we find that the 30 day notice requirement in these instances is not necessary to carry out the transportation policy of 49 U.S.C. 10101a and is not needed to protect shippers from abuse of market power. Further, we will consider revoking this exemption under 49 U.S.C. 10505(c) if protests are filed within 15 days of publication in the Federal Register.

This action will not significantly affect the quality of the human environment or conservation of energy resources.

(49 U.S.C. 10505)

Dated: March 16, 1982.

By the Commission, Division 1, Commissioners Clapp, Taylor, and Sterrett. Commissioner Taylor is assigned to this Division for the purpose of resolving the votes. Since there was no tie in this matter, Commissioner Taylor did not participate.

Agatha L. Mergenovich,
Secretary.

[FR Doc. 82-7680 Filed 3-22-82; 8:45 am]

BILLING CODE 7035-01-M

[Docket No. AB-43 (Sub-No. 82)A]

Illinois Central Gulf Railroad Co.— Abandonment—Between Milepost 256.88 in Madison County and Milepost 257.52 at Alton, Ill.; Findings

Notice is hereby given pursuant to 49 U.S.C. 10903 that the Commission, Review Board Number 3, has issued a certificate authorizing the Illinois Central Gulf Railroad Company to abandon a 0.64 mile line of railroad extending from railroad milepost 256.88 in Madison County, IL to milepost 257.52 at Alton, IL, subject to certain conditions. Since no investigation was instituted, the requirement of § 1121.38(b) of the Regulations that publication of notice of abandonment decisions in the Federal Register be made only after such a decision becomes administratively final was waived.

Upon receipt by the carrier of an actual offer of financial assistance, the carrier shall make available to the offeror the records, accounts, appraisals, working papers, and other documents used in preparing Exhibit I (§ 1121.45 of

the Regulations). Such documents shall be made available during regular business hours at a time and place mutually agreeable to the parties.

The offer must be filed with the Commission and served concurrently on the applicant, with copies to the Section of Finance, Interstate Commerce Commission, Washington, D.C. 20423, no later than 10 days from publication of this Notice. The offer, as filed, shall contain information required pursuant to § 1121.38(b) (2) and (3) of the Regulations. If no such offer is received, the certificate of public convenience and necessity authorizing abandonment shall become effective 30 days from the service date of the certificate.

Agatha L. Mergenovich,
Secretary.

[FR Doc. 82-7681 Filed 3-22-82; 8:45 am]

BILLING CODE 7035-01-M

Motor Carriers; Finance Applications; Decision-Notice

As indicated by the findings below, the Commission has approved the following applications filed under 49 U.S.C. 10924, 10926, 10931 and 10932.

We find:

Each transaction is exempt from section 11343 (formerly section 5) of the Interstate Commerce Act, and complies with the appropriate transfer rules.

This decision is neither a major Federal action significantly affecting the quality of the human environment nor a major regulatory action under the Energy Policy and Conservation Act of 1975.

Petitions seeking reconsideration must be filed within 20 days from the date of this publication. Replies must be filed within 20 days after the final date for filing petitions for reconsiderations; any interested person may file and serve a reply upon the parties to the proceeding. Petitions which do not comply with the relevant transfer rules at 49 CFR 1132.4 may be rejected.

If petitions for reconsideration are not timely filed, and applicants satisfy the conditions, if any, which have been imposed, the application is granted and they will receive an effective notice. The notice will indicate that consummation of the transfer will be presumed to occur on the 20th day following service of the notice, unless either applicant has advised the Commission that the transfer will not be consummated or that an extension of time for consummation is needed. The notice will also recite the compliance requirements which must be met before the transferee may commence operations.

Applicants must comply with any conditions set forth in the following decision-notices within 30 days after publication, or within any approved extension period. Otherwise, the decision-notice shall have no further effect.

It is Ordered:

The following applications are approved, subject to the conditions stated in the publication, and further subject to the administrative requirements stated in the effective notice to be issued hereafter.

By the Commission, Review Board No. 3, Members Krock, Joyce, and Dowell.

MC-FC-78781. By decision of March 8, 1982, Review Board Number 3 modified the prior decision-notice published November 21, 1980, and authorized the additional transfer of Permits No. MC-138336 and Subs 1, 10, and 14, and Certificates No. MC-142948 Subs 8 and 10, from The Grader Line, Inc. (Nashville, TN) to Tennessee Western Corporation, d.b.a. Tennessee Western Express, (Nashville, TN). Operating rights summary: dry cleaning and laundry equipment, materials, supplies, and parts from Louisville, KY, to WA, OR, CA, NM, AZ, UT, NV, GA, FL, and TX, under contract with W. M. Cissell Manufacturing Co.; water heaters and water heater parts, from Ashland City, TN, to NV, CA, OR, WA, NM, AZ, under contract with State Industries, Inc.; rovings, glass fibre, and related commodities, from Irwindale and Huntington Beach, CA, to AR, CO, FL, IL, IN, KS, LA, MN, NY, PA, TN, TX, VA, WA, OR, MO, and OH; pens, stationery, and related commodities, from Reliance Pen & Pencil facilities at Lewisburg, TN, to Los Angeles, CA; and from Reliance facilities at Los Angeles, CA, to Lewisburg, TN, and AZ, CO, ID, MT, NM, NV, OR, TX, UT, WA, and WY. Representative: Lawrence C. Goddard, 107 Music City Circle, Suite 309, Nashville, TN 37214

MC-FC-78982. (Correction), published in the February 9, 1982, issue of the Federal Register at page 10098. Notice approving the transfer to Marathan Bus Lines, Inc. of South Amboy, NJ of Certificate No. MC-140797 (Sub-No. 3) issued June 18, 1981 to Blue & Gray Transit, Inc. of Brooklyn, NY, should not have imposed a condition against incidental charter operations.

MC-FC-79639. By decision of March 8, 1982, issued under 49 U.S.C. 10926 and the transfer rules at 49 CFR 1132, Review Board Number 3 approved the transfer to GENE COLLETT AND WILLIAM E. CRAVEN, of Atlanta, GA, of Permit No. MC-152288 Sub 1F and 2 issued to NEAL TRANSPORT, INC., of

Powder Springs, GA, authorizing the transportation of (1) *copper wire, copper rods, wire processing machinery and empty reels*, between points in the United States, under continuing contract(s) with LARCON WIRE CORPORATION and LARIBEE WIRE INSULATED PRODUCTS, both of Atlanta, GA, and (2) such commodities as are dealt in or used by producers of bakery products between points in the United States, under continuing contract(s) with COUNTRY HOME BAKERY, INC., of Atlanta, GA. Representative: Phillip L. Martin, 2220 Parklake Dr., N.E., Suite 115, Atlanta, GA 30345. TA lease is not sought. Transferee is not a carrier.

MC-FC-79654. By decision of March 10, 1982, issued under 49 U.S.C. 10926 and the transfer rules at 49 CFR 1132, Review Board Number 3 approved the transfer to CONTAINER CARRIERS, INC., of Houston, TX, of Permit No. MC-136689 and Subs 2, 3, 4, 7, 8, 11, and 12, issued to SLAUGHTER TRANSPORTATION CORPORATION, of Houston, TX, authorizing *liquid cooking oils, animal litter, deodorants, bleaching and cleaning compounds, and foodstuffs*, from Houston, TX, to points in LA, NM, OK, and from New Orleans to Houston, TX, under contract with The Clorox Co.; *plastic bottles*, from facilities of Sewald Plastics at Reserve, LA, to (1) facilities of Clorox Co., under contract with Clorox; (2) facilities of Houston Distilled Water Company at Houston, TX, under contract with Houston Distilled Water. Representative: Claude W. Ferebee, 3910 FM 1960 W., Suite 106, Houston, TX 77068. TA lease is not sought. Transferee is a carrier.

MC-FC-79657. By decision of March 8, 1982, issued under 49 U.S.C. 10926 and the transfer rules at 49 CFR 1132, Review Board Number 3 approved the transfer to SAFETY TRANSIT TOURS OF EDEN, INC., of Eden, NC, of Certificate No. MC-114057 (Sub-Nos. 1 and 3) issued February 9, 1955 and December 12, 1979, respectively to R. H. GAULDIN, d.b.a. SAFETY TRANSIT LINES, of Eden, NC, authorizing the transportation (1) under the Sub-1 certificate by regular routes, of *passengers and their baggage, and express, newspapers and mail, in the same vehicle with passengers*, generally between various points in NC and VA, and (2) under the Sub-3 certificate of *passengers and their baggage in special operations, in round-trip tours*, beginning and ending at points in Rockingham County, NC and extending to points in the United States (except AK and HI). Representative: Archie W.

Andrews, 617 F. Lynrock Terrace, Eden, NC 27288.

MC-FC-79660. By decision of March 10, 1982, issued under 49 U.S.C. 10926 and the transfer rules at 49 CFR 1132, Review Board Number 3 approved the transfer to ON TIME FREIGHT SYSTEMS INC., of Omaha, NE, of Certificate No. MC-138069 (Sub-No. 17) and a portion of Certificate No. MC-138069 (Sub-No. 11X), issued to LUCIUS, INC., of Denver, CO. The operating rights to be transferred authorize the transportation of (1) *food and related products*, between St. Louis, MO, Cincinnati, OH, and points in IL, IN, KY, LA, MI, TX, and CA, on the one hand, and, on the other, points in Pueblo County, CO; and (2) *such commodities* as are dealt in by retail chain grocery and food business houses, between Chicago, IL, and points in Brown County, WI, on the one hand, and, on the other, points in KS, MO, CO, and NE. Representative: Steven K. Kuhlmann, 717 17th Street, Suite 2600, Denver, CO 80202.

Note.—TA has not been filed. Transferee was granted authority in No. MC-FC-79312 to operate as a common carrier.

MC-FC-79664. By decision of March 8, 1982, issued under 49 U.S.C. 10926 and the transfer rules at 49 CFR 1132, Review Board Number 3 approved the transfer to GLENN PHILLIPS AND CECIL BLANTON, a partnership, d.b.a. ALASKA MOBILE HOME MOVERS, of Anchorage, AK, of Certificate No. MC-119558 (Sub-No. 6) which cancelled Subs 1 and 5 Certificates issued to RAY CUNNINGHAM, d.b.a. ALASKA MOBILE HOME MOVERS, of Anchorage, AK, authorizing the transportation of (A) *Buildings*, in sections mounted on wheeled undercarriages with hitch-ball connector, between points in AK; and (B) *Mobile homes*, between ports of entry in AK on the United States-Canada Boundary line, on the one hand, and, on the other, points in AK (except that area southeast of Yakutat Bay); the authority in (B) above is restricted to traffic originating at or destined to points in Canada. (C) *Mobile homes*, (1) between points in AK (except points in that area southeast of Yakutat Bay), on the one hand, and, on the other, points in CO, ID, IN, KS, MI, MN, MT, NE, OK, SD, WA, and WI, (2) between points in AK, and (3) between points in that part of AK west of an imaginary line constituting a southbound extension of the Alaska-Canada (Yukon) Boundary line, on the one hand, and, on the other, Haines, AK. Representative: Arthur R. Hauver, Esq., 750 West Second Ave.,

Suite 200, Anchorage, AK 99501. TA lease is sought. Transferee is not a carrier.

MC-FC-79670. By decision of March 10, 1982, issued under 49 U.S.C. 10926 and the transfer rules at 49 CFR 1132, Review Board Number 3 approved the transfer to LEWIS F. McDONALD, INC., of Certificate No. MC-61699 (Sub-No. 2) issued to LEWIS FRANK McDONALD, FARMERS AND MERCHANTS BANK, ADMINISTRATOR, authorizing the transportation of (1) *fruit containers, fruit packing supplies and box and basket materials*, from Winchester, VA, to points in WV, MD, and PA, within 150 miles of Winchester; (2) *spray materials, feed and seed*, from Baltimore, MD, to Winchester, VA; (3) *barrels* (a) from Baltimore, MD, to Winchester, Bristol and Covington, VA and (b) from Washington, DC, Hagerstown, MD and Martinsburg, WV, to Winchester, VA; (4) *fruit packing supplies*, from Biglerville, PA, to Winchester, VA; (5) *apples*, from Winchester, VA, to Washington, DC and Baltimore, MD; (6) *cooperage stock*, from Winchester, VA, to Baltimore, MD and Tablers and Romney, WV; and (7) *fruit packing supplies* (except in bulk), from the plant site of the Inland Container Corporation at or near Newark, DE, to the plant site of Fruit and Produce Packaging Company at Winchester, VA. Representative: Frank B. Hand, Jr., 523 S. Cameron St., Winchester, VA 22601.

Note.—Transferee is a non-carrier.
Agatha L. Mergenovich,
Secretary.

[FR Doc. 82-7674 Filed 3-22-82; 8:45 am]
BILLING CODE 7035-01-M

Motor Carriers; Finance Applications; Decision-Notice

The following applications, filed on or after July 3, 1980, seek approval to consolidate, purchase, merge, lease operating rights and properties, or acquire control of motor carriers pursuant to 49 U.S.C. 11343 or 11344. Also, applications directly related to these motor finance applications (such as conversions, gateway eliminations, and securities issuances) may be involved.

The applications are governed by Special Rule 240 of the Commission's Rules of Practice (49 CFR 1100.240). See Ex Parte 55 (Sub-No. 44), *Rules Governing Applications Filed By Motor Carriers Under 49 U.S.C. 11344 and 11349*, 363 I.C.C. 740 (1981). These rules provide among other things, that opposition to the granting of an application must be filed with the Commission in the form of verified

statements within 45 days after the date of notice of filing of the application is published in the *Federal Register*. Failure seasonably to oppose will be construed as a waiver of opposition and participation in the proceeding. If the protest includes a request for oral hearing, the request shall meet the requirements of Rule 242 of the special rules and shall include the certification required.

Persons wishing to oppose an application must follow the rules under 49 CFR 1100.241. A copy of any application, together with applicant's supporting evidence, can be obtained from any applicant upon request and payment to applicant of \$10.00, in accordance with 49 CFR 1100.241(d).

Amendments to the request for authority will not be accepted after the date of this publication. However, the Commission may modify the operating authority involved in the application to conform to the Commission's policy of simplifying grants of operating authority.

We find, with the exception of those applications involving impediments (e.g., jurisdictional problems, unresolved fitness questions, questions involving possible unlawful control, or improper divisions of operating rights) that each applicant has demonstrated, in accordance with the applicable provisions of 49 U.S.C. 1130, 11302, 11343, 11344, and 11349, and with the Commission's rules and regulations, that the proposed transaction should be authorized as stated below. Except where specifically noted this decision is neither a major Federal action significantly affecting the quality of the human environment nor does it appear to qualify as a major regulatory action under the Energy Policy and Conservation Act of 1975.

In the absence of legally sufficient protests as to the finance application or to any application directly related thereto filed within 45 days of publication (or, if the application later becomes unopposed), appropriate authority will be issued to each applicant (unless the application involves impediments) upon compliance with certain requirements which will be set forth in a notification of effectiveness of the decision-notice. To the extent that the authority sought below may duplicate an applicant's existing authority, the duplication shall not be construed as conferring more than a single operating right.

Applicant(s) must comply with all conditions set forth in the grant or grants of authority within the time period specified in the notice of effectiveness of this decision-notice, or

the application of a non-complying applicant shall stand denied.

Dated: March 17, 1982.

By the Commission, Review Board Number 3, Members Krock, Joyce, and Dowell.

MC-F-13679 SUDDATH VAN LINES, INC.—Purchase (Portion)—Plymouth Van Lines, Inc. (Supplemental) (Previously published in the *Federal Register* on August 24, 1978.

Note.—By decision of January 20, 1982, the Commission authorized Suddath Van Lines, Inc. to purchase certain authority of Plymouth Van Lines, Inc., conditioned on this republication. The purpose of this republication is to reflect that the Plymouth Van Lines authority which Suddath Van Lines proposes to purchase in No. MC-65748 (Sub-No. 5G) in part authorizes the transportation of household goods between points in NC, on and east of U.S. Highway 25 on the one hand, and on the other, points in CA, MN, NV and VT. The NC boundary was previously inadvertently described as U.S. Highway 21. Any interested person concerned with service to the area between U.S. Highways 21 and 25, who is not already a party to this proceeding may file a petition for leave to intervene within 30 days of this publication, setting forth its interests in and the manner in which it has been prejudiced by the grant of authority.

OP2-53A

Decided: March 12, 1982.

By the Commission, Review Board No. 1, Members Parker, Chandler, and Fortier.

MC-F-14816, filed March 2, 1982. CM INDUSTRIES, INC., (applicant) of P.O. Box 43050, St. Paul, MN 55164—continuance in control—CONTINENTAL MOTOR FREIGHT, INC. (Continental), 1219 Marquette Avenue, Minneapolis, MN 55402. Representative: Robert S. Lee, 1600 TCF Tower, Minneapolis, MN 55402, (612) 333-1341. Applicant, a non-carrier holding company and in turn, Mario J. Bonello, Frank A. Bonello, and Julius F. Bonello, the individuals in control of applicant, seek authority to continue in control of Continental Motor Freight, Inc. Upon the institution by Continental of operations in interstate or foreign commerce. Applicant presently controls Century-Mercury Motor Freight, Inc., (control approved in MC-F-13657) which holds authority in MC-108223 and subs thereto.

Note.—Continental has filed a directly related application, its initial application, docketed in MC-160803, published in the same *Federal Register* issue.

Agatha L. Mergenovich,
Secretary.

[FR Doc. 82-7676 Filed 3-22-82; 8:45 am]
BILLING CODE 7035-01-M

[Volume No. 3]

Motor Carriers; Applications, Alternate Route Deviations, and Intrastate Applications**Motor Carrier Alternate Route Deviations—Notice**

The following letter-notices to operate over deviation routes for operating convenience only have been filed with the Commission under the Deviation Rules—Motor Carrier of Passengers (49 CFR 1042.2(c)(9)).

Protests against the use of any proposed deviation route herein described may be filed with the Commission in the manner and form provided in such rules at any time, but will not operate to stay commencement of the proposed operations, unless filed within 30 days from the date of this Federal Register notice.

Each applicant states that there will be no significant effect on either the quality of the human environment or energy policy and conservation.

Motor Carriers of Passengers

MC 1515 (deviation No. 764), GREYHOUND LINES, INC., Greyhound Tower, Phoenix, AZ 85077, filed March 5, 1982. Carrier proposes to operate as a *common carrier*, by motor vehicle, of *passengers and their baggage*, and *express and newspapers* in the same vehicle with passengers, over a deviation route as follows: From Aurora, IL, over IL Hwy 31 to Geneva, IL, and return over the same route for operating convenience only. The notice indicates that the carrier is presently authorized to transport passengers and the same property over a pertinent service route as follows: From Aurora, IL, over IL Hwy 31 to junction IL Hwy 5, then over IL Hwy 5 to unnumbered hwy southeast of DeKalb, IL, then over unnumbered hwy to junction IL Hwy 38, then over IL Hwy 38 to Geneva, IL, and return over the same route.

MC 1515 (deviation No. 765), GREYHOUND LINES, INC., Greyhound Tower, Phoenix, AZ 85077, filed March 5, 1982. Carrier proposes to operate as a *common carrier*, by motor vehicle, of *passengers and their baggage*, and *express and newspapers* in the same vehicle with passengers, over a deviation route as follows: From Beaumont, TX over US Hwy 69/287 to Port Arthur, TX, and return over the same route for operating convenience only. The notice indicates that the carrier is presently authorized to transport passengers and the same property over a pertinent service route as follows: From Beaumont, TX over Interstate Hwy 10 to Orange, TX, then over TX Hwy 87 to

Port Arthur, TX, and return over the same route.

By the Commission,
Agatha L. Mergenovich,
Secretary.

[FR Doc. 82-7679 Filed 3-22-82; 8:45 am]

BILLING CODE 7035-01-M

[Vol. No. OP-2-53]

Motor Carriers Permanent Authority Decisions; Decision-Notice

The following operating rights applications, filed on or after July 3, 1980, are filed in connection with pending finance applications under 49 U.S.C. 10926, 11343 or 11344. The applications are governed by Special Rule 252 of the Commission's General Rules of Practice (49 CFR 1100.252).

Persons wishing to oppose an application must follow the rules under 49 CFR 1100.252. Persons submitting protests to applications filed in connection with pending finance applications are requested to indicate across the front page of all documents and letters submitted that the involved proceeding is directly related to a finance application and the finance docket number should be provided. A copy of any application, together with applicant's supporting evidence, can be obtained from any applicant upon request and payment to applicant of \$10.00.

Amendments to the request for authority are not allowed. However, the Commission may have modified the application to conform to the Commission's policy of simplifying grants of operating authority.

Findings: With the exceptions of those applications involving duly noted problems (e.g., unresolved common control, unresolved fitness questions, and jurisdictional problems) we find, preliminarily, that each applicant has demonstrated that its proposed service warrants a grant of the application under the governing section of the Interstate Commerce Act. Each applicant is fit, willing, and able properly to perform the service proposed and to conform to the requirements of Title 49, Subtitle IV, United States Code, and the Commission's regulations. Except where specifically noted, this decision is neither a major Federal action significantly affecting the quality of the human environment nor a major regulatory action under the Energy Policy and Conservation Act of 1975.

In the absence of legally sufficient protests in the form of verified statements as to the finance application or to the following operating rights

applications directly related thereto filed within 45 days of publication of this decision-notice (or, if the application later becomes unopposed), appropriate authority will be issued to each applicant (except where the application involves duly noted problems) upon compliance with certain requirements which will be set forth in a notification of effectiveness of this decision-notice. Within 60 days after publication an applicant may file a verified statement in rebuttal to any statement in opposition.

Applicant(s) must comply with all conditions set forth in the grant or grants of authority within the time period specified in the notice by effectiveness of this decision-notice, or the application of a non-complying applicant shall stand denied.

To the extent that any of the authority granted may duplicate an applicant's other authority, the duplication shall be construed as conferring only a single operating right.

Decided: March 12, 1982.

By the Commission, Review Board Number 1, Members Parker, Chandler, and Fortier.

Agatha L. Mergenovich,
Secretary.

MC 160803, filed March 2, 1982. Applicant: CONTINENTAL MOTOR FREIGHT, INC., 1219 Marquette Avenue, Minneapolis, MN 55402. Representative: Robert S. Lee, 1600 TCF Tower, Minneapolis, MN 55402, (612) 333-1341. Transporting *machinery*, between Minneapolis, MN, and points in Ashland County, OH, on the one hand, and, on the other, points in the U.S. (except AK and HI).

Note.—This application is directly related to MC-F-14816, published in the same Federal Register issue.

[FR Doc. 82-7675 Filed 3-22-82; 8:45 am]

BILLING CODE 7035-01-M

[Volume No. OP1-44]

Motor Carriers; Permanent Authority Decision; Decision-Notice

Decided: March 11, 1982.

The following operating rights applications, filed on or after July 3, 1980, are filed in connection with pending finance applications under 49 U.S.C. 10926, 11343 or 11344. The applications are governed by Special Rule 252 of the Commission's General Rules of Practice (49 CFR 1100.252).

Persons wishing to oppose an application must follow the rules under 49 CFR 1100.252. Persons submitting protests to applications filed in connection with pending finance

applications are requested to indicate across the front page of all documents and letters submitted that the involved proceeding is directly related to a finance application and the finance docket number should be provided. A copy of any application, together with applicant's supporting evidence, can be obtained from any applicant upon request and payment to applicant of \$10.00.

Amendments to the request for authority are not allowed. However, the Commission may have modified the application to conform to the Commission's policy of simplifying grants of operating authority.

Findings: With the exceptions of those applications involving duly noted problems (e.g., unresolved common control, unresolved fitness questions, and jurisdictional problems) we find, preliminarily, that each applicant has demonstrated that its proposed service warrants a grant of the application under the governing section of the Interstate Commerce Act. Each applicant is fit, willing, and able properly to perform the service proposed and to conform to the requirements of Title 49, Subtitle IV, United States Code, and the Commission's regulations. Except where specifically noted, this decision is neither a major Federal action significantly affecting the quality of the human environment nor a major regulatory action under the Energy Policy and Conservation Act of 1975.

In the absence of legally sufficient protests in the form of verified statements as to the finance application or to the following operating rights applications directly related thereto filed within 45 days of publication of this decision-notice (or, if the application later becomes unopposed), appropriate authority will be issued to each applicant (except where the application involves duly noted problems) upon compliance with certain requirements which will be set forth in a notification of effectiveness of this decision-notice. Within 60 days after publication an applicant may file a verified statement in rebuttal to any statement in opposition.

Applicant(s) must comply with all conditions set forth in the grant or grants of authority within the time period specified in the notice of effectiveness of this decision-notice, or the application of a non-complying applicant shall stand denied.

To the extent that any of the authority granted may duplicate an applicant's other authority, the duplication shall be construed as conferring only a single operating right.

By the Commission, Review Board Number 1, Members Parker, Chandler, and Fortier.

Agatha L. Mergenovich,
Secretary.

MC 160581 (Sub-2), filed February 16, 1982. Applicant: PILGRIM TRANSPORT, INC., 610 West 138th St., Riverdale, IL 60627. Representative: Carl L. Steiner, 29 South LaSalle St., Chicago, IL 60603, (312) 236-9375. Transporting *metal products*, between Chicago, IL, and points in Medina County, OH, Marion County, IN, and Macomb County, MI, on the one hand, and on the other, points in the U.S. (except AK and HI).

Note.—This application is directly related to MC-F-14807, published in the Federal Register issue of March 17, 1982.

[FR Doc. 82-7677 Filed 3-22-82; 8:45 am]

BILLING CODE 7035-01-M

Motor Carriers; Permanent Authority Decisions; Decision-Notice

The following applications, filed on or after February 9, 1981, are governed by Special Rules of the Commission's Rule of Practice, see 49 CFR 1100.251. Special Rule 251 was published in the Federal Register of December 31, 1980, at 45 FR 86771. For compliance procedures, refer to the Federal Register issue of December 3, 1980, at 45 FR 80109.

Persons wishing to oppose an application must follow the rules under 49 CFR 1100.252. A copy of any application, including all supporting evidence, can be obtained from applicant's representative upon request and payment to applicant's representative of \$10.00.

Amendments to the request for authority are not allowed. Some of the applications may have modified prior to publication to conform to the Commission's policy of simplifying grants of operating authority.

Findings

With the exception of those applications involving duly noted problems (e.g., unresolved common control, fitness, water carrier dual operations, or jurisdictional questions) we find, preliminarily, that each applicant has demonstrated a public need for the proposed operations and that it is fit, willing, and able to perform the service proposed, and to conform to the requirements of Title 49, Subtitle IV, United States Code, and the Commission's regulations. This presumption shall not be deemed to exist where the application is opposed. Except where noted, this decision is neither a major Federal action significantly affecting the quality of the human environment nor a major

regulatory action under the Energy Policy and Conservation Act of 1975.

In the absence of legally sufficient opposition in the form of verified statements filed on or before 45 days from date of publication, (or, if the application later becomes unopposed) appropriate authorizing documents will be issued to applicants with regulated operations (except those with duly noted problems) and will remain in full effect only as long as the applicant maintains appropriate compliance. The unopposed applications involving new entrants will be subject to the issuance of an effective notice setting forth the compliance requirements which must be satisfied before the authority will be issued. Once this compliance is met, the authority will be issued.

Within 60 days after the publication an applicant may file a verified statement in rebuttal to any statement in opposition.

To the extent that any of the authority granted may duplicate an applicant's other authority, the duplication shall be construed as conferring only a single operating right.

Note.—All applications are for authority to operate as a motor common carrier in interstate or foreign commerce over irregular routes, unless noted otherwise. Applications for motor contract carrier authority are those where service is for a named shipper "under contract".

Please direct status inquiries to the Ombudsman's Office, (202) 275-7326.

Volume No. OP1-47

Decided: March 12, 1982.

By the Commission, Review Board No. 1, Members Parker, Chandler, and Fortier.

MC 117511 (Sub-2), filed March 3, 1982. Applicant: COX OIL & TRANSPORT COMPANY, INC., P.O. Box 167, Carmi, IL 62821. Representative: Douglas G. Brown, 913 South Sixth St., Springfield, IL 62703, (217) 753-3925. Transporting *petroleum products*, between points in Gibson and Pike Counties, IN, on the one hand, and, on the other, points in Wayne, Wabash, Edwards, White, Hamilton and Jefferson Counties, IL.

MC 124170 (Sub-198), filed March 5, 1982. Applicant: FROSTWAYS, INC., 3000 Chrysler Service Drive, Detroit, MI 48207. Representative: William J. Boyd, 2021 Midwest Road, Suite 205, Oak Brook, IL 60521, (312) 629-2900. Transporting *general commodities* (except classes A and B explosives, household goods, and commodities in bulk), between points in the U.S. (except AK and HI), under continuing contract(s) with Universal Foods Corporation, of Milwaukee, WI.

MC 129951 (Sub-12), filed March 8, 1982. Applicant: HARLEY I. KEETER, JR., 6379 Valmont Drive, Boulder, CO 80301. Representative: Harley I. Keeter, Jr. (same address as applicant), (303) 442-2131. Transporting *coke, coal products, building materials, forest products, and beel pulp products*, between points in AZ, CA, CO, ID, KS, MT, NE, ND, SD, NM, NV, OK, OR, TX, UT, WA, and WY.

MC 135530 (Sub-8), filed March 3, 1982. Applicant: LAKE CENTER INDUSTRIES TRANSPORTATION, INC., 5676 Industrial Park Road, Winona, MN 55987. Representative: John G. Grote (same address as applicant), (507) 457-3750. Transporting *nitro carbo nitrate*, between points in the U.S. (except AK and HI), under continuing contract(s) with Explo-Midwest, Inc., of Plainview, MN.

MC 143480 (Sub-3), filed March 3, 1982. Applicant: R. BROWN & SONS, INC., 11 Canyon Estates Drive, Colchester, VT 05446. Representative: Robert E. Brown, 31 Porters Point Road, Colchester, VT 05446, (802) 864-0288. Transporting *wood products*, between points in the U.S. (except AK and HI), under continuing contract(s) with Spartan Industries, Inc., of Fairfax, VT.

MC 143870 (Sub-1), filed February 24, 1982. Applicant: BRANTLEY BROTHERS MOVING & STORAGE CO., INC., 17 Frelinghuysen Ave., Newark, NJ 07114. Representative: Malachia Brantley (same address as applicant), (201) 243-1500. Transporting *household goods, electronics, and computers*, between points in NJ, AL, AZ, AR, CA, FL, GA, KY, LA, MI, MS, MO, NC, NM, SC, TN, and TX.

MC 144061 (Sub-26), filed March 8, 1982. Applicant: SICOMAC CARRIERS, INC., 1109 Goffle Rd., Hawthorne, NJ 07506. Representative: Jack L. Schiller, 123-60 83rd Ave., Kew Gardens, NY 11415, (212) 263-2078. Transporting *general commodities* (except classes A and B explosives and household goods), between points in the U.S. (except AK and HI), under continuing contract(s) with (1) Borden, Inc., of Columbus, OH, (2) ICI Americas, Inc., of Wilmington, DE, and (3) Lonza, Inc., of Fairlawn, NJ.

MC 146980 (Sub-2), filed March 5, 1982. Applicant: HOOSIER EXPRESS, INC., P.O. Box 705, Westville, IN 46391. Representative: Donald W. Smith, P.O. Box 40248, Indianapolis, IN 46240, (317) 846-6655. Transporting *metal products*, between points in the U.S. (except AK and HI), under continuing contract(s) with Liberty Steel Service, Inc., of South Bend, IN.

MC 148620 (Sub-15), filed March 8, 1982. Applicant: K.G.L. CONTRACTING SERVICES, INC., P.O. Box 8202, Pembroke Pines, FL 33024. Representative: Robert W. Gerson, 1400 Chandler Bldg., 127 Peachtree Street, N.E., Atlanta, GA 30303, (404) 658-8045. Transporting *general commodities* (except classes A and B explosives and household goods as defined by the Commission), between points in the U.S. (except AK and HI), under continuing contract(s) with Scott Paper Company, of Philadelphia, PA.

MC 148671 (Sub-1), filed March 8, 1982. Applicant: HARLAND QUACKENBUSH, d.b.a. H & D TRUCKING, 500 Dew Drop Cove, Casselberry, FL 32707. Representative: Elbert Brown, Jr., P.O. Box 1378, Altamonte Springs, FL 32701-1378, (305) 869-5936. Transporting *paper and related products*, between points in the U.S. (except AK and HI), under continuing contract(s) with Rexford Paper Company, Division of Inland Container Corporation, of Indianapolis, IN.

MC 151890 (Sub-2), filed March 5, 1982. Applicant: D & T EXPRESS, INC., 4230 Elvis Presley Blvd., Suite 400B, Memphis, TN 38116. Representative: Henry E. Seaton, 1024 Pennsylvania Bldg., 425 13th St., N.W., Washington, DC 20004, (202) 347-8862. Transporting *general commodities* (except classes A and B explosives, household goods, and commodities in bulk), between Lexington, Luray, Beech Bluff, Ralston, Terrell, Malesus, Medon, Toone, Conger, Bolivar, Middleburg, Hickory Valley, and Grand Junction, TN, Michigan City, Lamar, Hudsonville, Holly Springs, Waterford, Spraggins, Abbeville, McClary, College Hill, Oxford, Taylor, and Water Valley, MS, Deaneffield, Whitesville, Philpot, Oak Ridge, Masonville, Thompsonville, and Edgote, KY, Kenwood, Hickory Point, Doddsville, Fox Bluff, Chapmansboro, Parkburg, Deanburg, Silerton, Hornsby, Serles, and Lacy, TN, on the one hand, and, on the other, points in the U.S. (except AK and HI).

MC 153601 (Sub-8), filed March 3, 1982. Applicant: I.N.F. LTD, 80 East Little Canada Road, St. Paul, MN 55117. Representative: Melvin M. Freese, P.O. Box 43355, St. Paul, MN 55164, (612) 633-2661. Transporting *food and related products*, between points in AR, CO, IL, IN, IA, KS, KY, MI, MN, MO, MT, NE, NY, ND, OH, OK, PA, SD, TN, TX, WV, WI, and WY.

MC 154861 (Sub-7), filed March 3, 1982. Applicant: CAROLINA MOTOR EXPRESS, INC., P.O. Box 550, Forest City, NC 28043. Representative: Eric

Meierhoefer, Suite 1000, 1029 Vermont Ave., N.W., Washington, DC 20005, (202) 347-9332. Transporting *lumber and wood products*, between points in Flathead County, MT, on the one hand, and, on the other, points in VA, TN, GA, and SC.

MC 155261 (Sub-1), filed March 8, 1982. Applicant: ROBERT PARRY, 620 Powell Ave., Clarks-Summit, PA 18411. Representative: Joseph A. Keating, Jr., 121 South Main St., Taylor, PA 18517, (717) 562-1202. Transporting *salt and salt products*, between points in the U.S. (except AK and HI), under continuing contract(s) with International Salt Company, of Clarks-Summit, PA.

MC 156000, filed March 3, 1982. Applicant: FLOR-DRI SUPPLY COMPANY, INC., 4629 West Fort St., Detroit, MI 48209. Representative: William R. Ralls, 118 West Ottawa, Suite B, Lansing, MI 48933, (517) 372-6622. Transporting *beer*, (a) between Detroit, MI, on the one hand, and, on the other, points in TN, FL, KY, and Hamilton County, OH, and (b) between points in Hamilton County, OH, on the one hand, and, on the other, points in KY and TN.

MC 156510, filed March 8, 1982. Applicant: J LINE, INC., Gibson Hill Road, P.O. Box 21, Greene, RI 02827. Representative: Charles E. Werchadlo (same address as applicant), (401) 397-5037. Transporting *copper wire*, between points in the U.S. (except AK and HI), under continuing contract(s) with Collyer Insulated Wire Co., of Lincoln, RI.

MC 157410 (Sub-1), filed March 2, 1982. Applicant: LEALICE DEHONEY, d.b.a. HERITAGE TOURS, 1204 S. Third, Suite A, Louisville, KY 40203. Representative: William W. Dehoney (same address as applicant), (502) 636-9211. As a *broker*, at Louisville, KY, in arranging for the transportation of *passengers and their baggage*, in the same vehicle with passengers, in special and charter operations, between points in the U.S. (except AK and HI).

MC 158441 (Sub-1), filed February 17, 1982. Applicant: BOBBY FRYAR TRUCKING, 418 S. Seminole Drive, Chattanooga, TN 37411. Representative: Bobby Fryar (same address as applicant), (615) 867-9160. Transporting *lime stone rock*, between points in the U.S. (except AK and HI), under continuing contract(s) with Tac Industries, Inc., of Dalton, GA.

MC 160061, filed March 8, 1982. Applicant: GEAUGA TRANSFER SERVICE, INC., P.O. Box 125, Middlefield, OH 44062. Representative: Lewis S. Witherspoon, 2455 North Star

Road, Columbus, OH 43221, 1-(614) 486-0448. Transporting *commodities in bulk*, between points in the U.S. (except AK and HI), under continuing contract(s) with By-Products Management of Ohio, Inc., of Cleveland, OH.

MC 160840, filed March 4, 1982. Applicant: EDDY'S TRAVEL & CHARTER SERVICE, INC., 2428 Auburn Blvd., Sacramento, CA 95821. Representative: James H. Gulseth, 100 Bush St., 21st Floor, San Francisco, CA 94104, (415) 986-5778. As a *broker* at Sacramento, CA, in arranging for the transportation of *passengers and their baggage*, in the same vehicle with passengers, in special and charter operations, beginning and ending at points in CA and extending to points in the U.S. (including AK and HI).

MC 160851, filed March 5, 1982. Applicant: CONSTRUCTION TRANSPORT, INC., d.b.a. CTI, 1217 West Park Drive, P.O. Box 428, Huntington, IN 46750. Representative: Richard A. Huser, 1301 Merchants Plaza, Indianapolis, IN 46204-3491. Transporting *cement*, between points in Allen, Whitley, Huntington, Wabash, Wells, Miami, Howard and Madison Counties, IN, Paulding, Greene, and Lucas Counties, OH, and Monroe County, MI.

MC 160861, filed March 5, 1982. Applicant: MARVIN WARD TRUCKING, 2607 Shenandoah, Tyler, TX 75701. Representative: William Sheridan, P.O. Drawer 5049, Irving, TX 75062, (214) 255-6279. Transporting *food and other edible products and byproducts intended for human consumption* (except alcoholic beverages and drugs), *agricultural limestone and fertilizers*, and *other soil conditioners* by the owner of the motor vehicle in such vehicle, between points in the U.S. (except AK and HI).

MC 160870, filed March 5, 1982. Applicant: O/P TRANSPORTATION LTD., INC., 12290 S W Main, Tigard, OR 97223. Representative: Oliver L. Patterson (same address as applicant) (503) 684-1470. Transporting *general commodities* (except classes A and B explosives, household goods, and commodities in bulk), between points in the U.S. (including AK but excluding HI), under continuing contract(s) with East-West Consolidators, Inc., of Tualatin, OR, Marine Intermodal Cooperative Association, of Portland, OR, and Cascade West Materials, Inc., of Lake Oswego, OR.

MC 160871, filed March 5, 1982. Applicant: SWARTHOUT & FERRIS BUS SERVICE, INC., 115 Graham Road, Ithaca, NY 14850. Representative: Lawrence E. Lindeman, 4660 Kenmore

Ave., Suite 1203, Alexandria, VA 22304 (703) 751-2441. Transporting *passengers and their baggage*, in the same vehicle with passengers, in charter operations, between points in the U.S. (except AK and HI), under continuing contract(s) with Swarthout & Ferris Bus Service, of Ithaca, NY.

MC 160881, filed March 8, 1982. Applicant: LEO A. HOLT, 7311 Atlantic Avenue, Ventnor, NJ 08406. Representative: Leo A. Holt (same address as applicant) (609) 823-7849. Transporting *passengers and their baggage*, in the same vehicle with passengers, in special and charter operations, limited to the transportation of not more than 24 passengers in any one vehicle, not including the driver, in non-scheduled door-to-door service, between Atlantic City, NJ, on the one hand, and, on the other, points in CT, DE, MD, NJ, NY, PA, VA, and DC.

Volume No. OP2-52

Decided: March 11, 1982.

By the Commission, Review Board No. 1. Members Parker, Chandler, and Fortier.

MC 143023 (Sub-7), filed March 3, 1982. Applicant: CHI-WAUKEE TRUCK LINES, INC., 1501 West Pershing Rd., Chicago, IL 60609. Representative: Donald E. Weishaar, Suite 4-2777 Finley Rd., Downers Grove, IL 60515, 312-620-8664. Transporting *beverages*, between points in the U.S. (except AK and HI), under continuing contract(s) with Elmwood Distributors, Inc., and C & S Distributors, Inc., both of Chicago, IL.

MC 156133, filed February 26, 1982. Applicant: TRI STATE TIRE & RUBBER, INC., d.b.a. TANDEM TRANSPORT, 322 U.S. Highway West 20, Michigan City, IN 46360. Representative: James M. Hodge, 3730 Ingersoll Ave., Des Moines, IA 50312, 515-247-4985. Transporting *lumber, wood products, and building materials*, between the facilities of Champion International Corporation and Weyerhaeuser Company, at points in the U.S. (except AK and HI), on the one hand, and, on the other, those points in the U.S., in and east of MN, IA, MO, AR, and LA.

MC 156133 (Sub-1), filed March 3, 1982. Applicant: TRI STATE TIRE & RUBBER, INC., d.b.a. TANDEM TRANSPORT, 322 U.S. Highway West 20, Michigan City, IN 46360. Representative: James M. Hodge, 3730 Ingersoll Ave., Des Moines, IA 50312, 515-247-4985. Transporting (1) *plastic pipe, and building and insulating materials*, between the facilities of Manville Sales Corporation, at those points in the U.S., in and east of MN, IA, MO, AR, and LA, on the one hand, and, on the other, those points in the U.S., in

and east of MN, IA, MO, AR, and LA, and (2) *building materials, and refractory products*, between the facilities of General Refractories Company, at points in IL, IN, IA, KY, KS, MD, MI, MN, MO, NE, NJ, NY, OH, PA, TN, WI, and WV, on the one hand, and, on the other, points in IL, IN, IA, KY, KS, MD, MI, MN, MO, NE, NJ, NY, OH, PA, TN, WI, and WV.

MC 160472, filed March 2, 1982. Applicant: TROJAN CORPORATION, Rte. No. 3, Wolf Lake, IL 62988. Representative: Jack L. Schiller, 123-60 83rd Ave., Kew Gardens, NY 11415, 212-263-2078. Transporting *general commodities* (except household goods), between points in the U.S. (except AK and HI), under continuing contract(s) with (a) C-I-L Chemicals, Inc., of Plattsburgh, NY, (b) Cisco Corporation, of Nashville, IL, (c) Familian Sierra Craft, Inc., of Caldwell, ID, (d) International Minerals & Chem., of Des Plaines, IL, (e) Mid West Carbide Corporation, of Keokuk, IA, and (f) Nitro-chem Energy Corp., of Rolling Meadows, IL. Condition: to the extent any permit issued in this proceeding authorizes the transportation of classes A and B explosives, it shall be limited in point of time to a period expiring 5 years from its date of issuance.

Volume No. OP3-44

Decided: March 15, 1982.

By the Commission, Review Board No. 2. Members Carleton, Fisher and Williams.

MC 36485 (Sub-1), filed March 4, 1982. Applicant: P. E. BURKE MOVING & STORAGE CORP., 113 Crescent Street, Waltham, MA 02154. Representative: Gerald A. Burke (same address as applicant) (617) 894-1900. Transporting *household goods*, between points in ME, NH, VT, MA, CT, RI, NY, NJ, PA, MD, DE, VA, WV, OH, NC and DC.

MC 113624 (Sub-89), filed March 2, 1982. Applicant: WARD TRANSPORT, INC., P.O. Box 735, Pueblo, CO 81002. Representative: Leslie R. Kehl, 1660 Lincoln St., Suite 1600, Denver, CO 80264 (303) 861-4028. Transporting *general commodities* (except classes A and B explosives, and household goods), between points in the U.S. (except AK and HI), under continuing contract(s) with Wycon Chemical Company, of Houston, TX.

MC 120464 (Sub-3), filed March 4, 1982. Applicant: SYSTEM TRANSPORT, 1710 E. 29th St., Long Beach, CA 90806. Representative: Donald R. Hedrick, P.O. Box 4334, Santa Ana, CA 92702, (714) 667-8107. Transporting (1) *petroleum and related products* and (2) *chemicals and related products*, (a) between points

in CA, OR, WA, and TX, (b) between points in CA, OR, WA, and TX, on the one hand, and, on the other, points in AZ, NV, UT, and NM and (c) between points in CA, on the one hand and, on the other, points in OH, NJ, NY, and WV.

MC 123285 (Sub-15), filed March 5, 1982. Applicant: CLETEX TRUCKING, INC., P.O. Box 812, Cleburne, TX 76031. Representative: Clayte Binion, 623 S. Henderson, 2nd Fl., Fort Worth, TX 76104, (817) 332-4415. Transporting *dry commodities, in bulk*, between points in AL, AZ, AR, CA, CO, GA, IL, IA, KS, KY, LA, MN, MS, MO, MT, NE, NM, ND, OK, SD, TN, TX, UT, WI, and WY.

MC 140645 (Sub-22), filed March 8, 1982. Applicant: UNITED TRUCKING, INC., P.O. Box 398, Tallapoosa, GA 30716. Representative: Clyde W. Carver, P.O. Box 720434, Atlanta, GA 30328, (404) 256-4320. Transporting *such merchandise as is dealt in by retail paint stores*, between Charlotte, NC, Chicago, IL, Indianapolis, IN and Memphis, TN, on the one hand, and, on the other, those points in the U.S. in and east of MN, IA, MO, AR, and LA.

MC 141205 (Sub-53), filed March 9, 1982. Applicant: HUSKY OIL TRANSPORTATION COMPANY, 600 S. Cherry St., Denver, CO 80222. Representative: F. Robert Reeder, Box 11898, Salt Lake City, UT 84147, (801) 532-1234. Transporting *petroleum and petroleum products*, between points in MT, WY, UT, AZ, NM, ND, SD, OK, NE, KS, CO, CA, ID, and NV.

MC 142005 (Sub-3), filed March 8, 1982. Applicant: CHARLES D. ZEISLOFT, 403 E. Elm St., Wenonah, NJ 08090. Representative: Alan Kahn, 1430 Land Title Bldg., Philadelphia, PA 19110, (215) 561-1030. Transporting (1) *ores and minerals*, and (2) *clay, concrete, glass or stone products*, between points in NJ, on the one hand, and, on the other, points in DE, MD, NY, PA, and VA.

MC 144345 (Sub-25), filed March 8, 1982. Applicant: DON'S FROZEN EXPRESS, INC., 3820 Airport Ave., Caldwell, ID 83605. Representative: David E. Wishney, P.O. Box 837, Boise, ID 83701, (208) 336-5955. Transporting *such commodities as are dealt in or used by restaurants*, between points in Los Angeles County, CA, on the one hand, and, on the other, points in Cache County, UT, ID, NV, OR, and WA.

MC 148045 (Sub-6), filed March 8, 1982. Applicant: QUAD CITY SPOTTING SERVICE, INC., 1607 W. River Drive, P.O. Box 4168, Davenport,

IA 52808. Representative: Joseph Winter, 29 S. LaSalle St., Chicago, IL 60603, (312) 263-2306. Transporting *general commodities* (except classes A and B explosives, household goods, and commodities in bulk), between the facilities of Ralston Purina Company, at points in the U.S. (except AK and HI), on the one hand, and, on the other, points in the U.S. (except AK and HI).

MC 155004 (Sub-6), filed March 5, 1982. Applicant: JOSEPH LAND AND CO., INC., West Central Ave., P.O. Drawer 3310, Lake Wales, FL 33853. Representative: J.G. Dail, Jr., P.O. Box LL, McLean, VA 22101, (703) 893-3050. Transporting *food and related products, textile mill products, furniture and fixtures, pulp, paper and related products, chemicals, and related products* (except commodities in bulk), *rubber and plastic products, metal products, machinery, and instruments and photographic goods*, between points in AL, AZ, AR, CA, CO, CT, DE, FL, GA, IL, KS, KY, LA, MD, MI, MS, MO, NV, NJ, NM, NY, NC, OK, OR, PA, SC, TN, TX, UT, VA, WV, WI, and WY, on the one hand, and, on the other, points in AL, AZ, AR, CA, CO, CT, FL, GA, IA, IL, KS, KY, LA, MD, MA, MI, NM, MO, NV, NJ, NM, NY, OH, OK, OR, PA, SC, TN, TX, UT, VA, WA, WV, WI, and WY.

MC 157265, filed March 1, 1982. Applicant: D & B TRUCKING, INC., 1021 N. DuPage Avenue, Lombard, IL 60148. Representative: Philip A. Lee, 120 W. Madison St., Chicago, IL 60602, (312) 236-8225. Transporting *lamps, lighting fixtures and lamp shades, resistors, bearings, vinyl floor tile, molding and adhesives, curtain poles and rod-fixtures, shades and venetian blinds and kindred parts thereto, metal, metal alloys and copper sheets, fire hydrants and protective valves, plastic articles, hooks, nail and adhesives, roof-curbs, diffusers, junction boxes, steel cabinets, electrical transmission cable components and accessories, computer media and consumer products, office furniture, pneumatic tires, tubes, batteries and belting, lawn mowers, snow blowers, heaters and parts, parts for heaters, turf equipment, sprinkler systems and accessories, electrical material, and rubber articles*, between points in IL, IN, IA, KY, MI, MN, MO, OH, ND, SD, and WI.

MC 157624 (Sub-1), filed March 5, 1982. Applicant: PITTSBURGH-JOHNSTOWN-ALTOONA EXPRESS, INC., 821 Northridge Dr., Pittsburgh, PA 15216. Representative: DONALD J.

BALSLEY, Jr., 2310 Grant Bldg., Pittsburgh, PA 15219, (412) 471-1800. Transporting *general commodities* (except classes A and B explosives, household goods and commodities in bulk), between points in Allegheny, Bedford, Blair, Cambria, Fayette, Somerset, and Westmoreland Counties, PA, on the one hand, and, on the other, points in AL, AR, FL, GA, IL, IN, KY, LA, MD, MI, MS, MO, NJ, NY, NC, OH, PA, SC, TN, TX, VA, WV, WI and DC.

MC 160404, filed March 8, 1982. Applicant: ERIC MOTOR LINES, INC., P.O. Box 297, Newhall, CA 91322. Representative: Milton W. Flack, 8383 Wilshire Blvd., #900, Beverly Hills, CA 90211, (213) 655-3573. Transporting *general commodities* (except classes A and B explosives, household goods, and commodities in bulk), between points in the U.S. (except AK and HI), under continuing contract(s) with Manufacturers Coordination, Inc., of Hialeah, FL.

MC 160845, filed March 3, 1982. Applicant: ROY N. CARLSON, INC., P.O. Box 725, Stanwood, WA 98292. Representative: Michael D. Duppenhaler, 211 S. Washington St., Seattle, WA 98104, (206) 622-3220. Transporting *commodities in bulk*, between points in CA, ID, MT, OR, UT, and WA.

MC 160854, filed March 5, 1982. Applicant: JENKINS EQUIPMENT COMPANY, INC., d.b.a. JECO TRANSPORT, INC., 6020 N.E. Columbia Blvd., Portland, OR 97218. Representative: John A. Anderson, The 1515 Bldg., Suite 801, Portland, OR 97201, (503) 227-4586. Transporting *building materials, metal products, and machinery*, between points in OR, WA, ID, and CA.

MC 160855, filed March 5, 1982. Applicant: O & W TRANSPORT, INC., 1706 Elm Street, Granger, IA 50109. Representative: Ronald R. Adams, 600 Hubbell Building, Des Moines, IA 50309, (515) 244-2329. Transporting *meat and meat products*, between points in the U.S. (except AK and HI), under a continuing contract(s) with John Morrell & Co., of Chicago, IL.

MC 160864, filed March 5, 1982. Applicant: H.W.G. TRANSPORT, INC., Hwy 6 West, Iowa City, IA 52240. Representative: Norman A. Cooper, 145 W. Wisconsin Ave., Neenah, WI 54956, (414) 722-2848. Transporting *such commodities as are dealt in or used by*

grocery business houses, between points in IA, on the one hand, and, on the other, points in the U.S. (except AK and HI).

MC 160874, filed March 8, 1982.
Applicant: B & L ENTERPRISES, 81 Park Lane Drive, Kalispell, MT 59901.
Representative: Clark O. Herron (same address as applicant), (406) 752-0216.
Transporting (1) *lumber and wood products*, (2) *ores and minerals*, (3) *machinery*, and (4) *food and related products*, between points in MT, AZ, CO, ID, OR, UT, WA, and WY.

MC 160924, filed March 8, 1982.
Applicant: COMPLETE TRAILER MOVERS, INC., 405 E. Baseline Rd., Mesa, AZ 85204. Representative: Bill Swafford (same address as applicant), (602) 892-0576. Transporting *modular and mobile office buildings*, between points in AZ, NV, UT, and NM.

Agatha L. Mergenovich,
Secretary.

[FR Doc. 82-7678 Filed 3-22-82; 8:45am]

BILLING CODE 7035-01-M

DEPARTMENT OF LABOR

Employment and Training Administration

Investigations Regarding Certifications of Eligibility To Apply for Worker Adjustment Assistance

Petitions have been filed with the Secretary of Labor under section 221(a) of the Trade Act of 1974 ("the Act") and are identified in the Appendix to this notice. Upon receipt of these petitions, the Director of the Office of Trade Adjustment Assistance Employment and Training Administration, has instituted investigations pursuant to section 221(a) of the Act.

The purpose of each of the investigations is to determine whether the workers are eligible to apply for adjustment assistance under Title II, Chapter 2, of the Act. The investigations will further relate, as appropriate, to the determination of the date on which total or partial separations began or

threatened to begin and the subdivision of the firm involved.

The petitioners or any other persons showing a substantial interest in the subject matter of the investigations may request a public hearing, provided such request is filed in writing with the Director, Office of Trade Adjustment Assistance, at the address shown below, not later than April 2, 1982.

Interested persons are invited to submit written comments regarding the subject matter of the investigations to the Director, Office of Trade Adjustment Assistance, at the address shown below, not later than April 2, 1982.

The petitions filed in this case are available for inspection at the Office of the Director, Office of Trade Adjustment Assistance, Employment and Training Administration, U.S. Department of Labor, 601 D Street, NW., Washington, D.C. 20213.

Signed at Washington, D.C. this 15th day of March 1982.

Marvin M. Fooks,
Director, Office of Trade Adjustment Assistance.

APPENDIX

Petitioner: Union/workers or former workers of—	Location	Date received	Date of petition	Petition No.	Articles produced
Carnivale Bag Co. (workers).....	Brooklyn, New York.....	3/3/82	2/22/82	TA-W-13,343.....	Handbags, ladies'.
Checker Motors Corp. (AIW).....	Kalamazoo, MI.....	3/10/82	3/2/82	TA-W-13,344.....	Taxicabs also parts—auto, assemble.
Damsel Manufacturing Co., Inc. (ILGWU).....	Avenel, N.J.	2/23/82	2/19/82	TA-W-13,345.....	Apparel, children's cutting & distributing.
Haarmann Steel Corp. (company).....	Chicopee, Mass.	2/26/82	2/16/82	TA-W-13,346.....	Steel—structural, fabricated iron—misc.
Kimberly Clark Corp., Schweitzer Co-Lee Mills (UPIU).....	Lee, Mass.	2/26/82	2/4/82	TA-W-13,347.....	Paper—capicator, kraft.
Milwaukee Springs Co. (company).....	Milwaukee, Wis.	3/9/82	3/5/82	TA-W-13,348.....	Cable—automotive, control assemblies.
North Berwick Mills, Div. of Malden Mills (ILGWU).....	No. Berwick, Maine.....	2/23/82	2/19/82	TA-W-13,349.....	Fabrics—pile.
Puna Sugar Company, Ltd (ILWU).....	Keeau, Hawaii.....	3/10/82	3/3/82	TA-W-13,350.....	Sugar cane—grow sugar—raw & molasses.
Marvel Undergarment Co., Inc. (ILGWU).....	Brooklyn N.Y.	3/9/82	3/4/82	TA-W-13,351.....	Blouses—ladies'.
Rob-Anne Sportswear (ILGWU).....	Chester, Pa.	3/4/82	2/26/82	TA-W-13,352.....	Sportswear, blouses—ladies'.

[FR Doc. 82-7708 Filed 3-22-82; 8:45 am]

BILLING CODE 4510-30-M

Mine Safety and Health Administration

[Docket No. M-82-13-C]

Alabama By-Products Corp.; Petition for Modification of Application of Mandatory Safety Standard

Alabama By-Products Corporation, P.O. Box 10246, Birmingham, Alabama 35202 has filed a petition to modify the application of 30 CFR 49.6(a)(2) (mine rescue teams; equipment and maintenance requirements) to the following mines:

a. Chetopa Mine (I.D. No. 01-00323) and the Maxine Mine (I.D. No. 01-00322), both located in Jefferson County, Alabama, and

b. Mary Lee No. 1 Mine (I.D. No. 01-00515), Gorgas No. 7 Mine (I.D. No. 01-00340), Mary Lee No. 2 Mine (I.D. No. 01-00821), and Segco No. 1 Mine (I.D. No. 01-00347), all located in Walker County, Alabama.

The petition is filed under section 101(c) of the Federal Mine Safety and Health Act of 1977.

A summary of the petitioner's statements follows:

1. The petition concerns the requirement that each mine rescue station be equipped with a portable supply of liquid air, liquid oxygen, pressurized oxygen, oxygen generating or carbon dioxide absorbant chemicals, as applicable to the supplied breathing apparatus and sufficient to sustain each team for six hours while using the breathing apparatus during rescue operations.

2. All of the above listed mining operations are within two hours ground travel time of each other and are also

within two hours ground travel time of the mine rescue station and the oxygen supplier.

3. Petitioner uses liquid oxygen breathing apparatus. There is currently no feasible means by which liquid oxygen can be stored for any reasonable length of time.

4. At two of petitioner's mining operations, one of which is within five minutes ground travel time and the other within twenty minutes ground travel time of the mine rescue station, liquid oxygen is used in burning and welding operations in the surface shops. Therefore, two immediate sources of liquid oxygen are provided which can be backed up by unlimited availability from the oxygen supplier who is well within the two hour ground travel time.

5. The regulations require that mine rescue teams be stationed within two hours ground travel time of any mine they serve. In petitioner's situation not only are the mine rescue teams and rescue station within two hours time, but the source of liquid oxygen is also. In every instance, an adequate supply of liquid oxygen could be on site before the time of arrival of the mine rescue team. Petitioner therefore proposes that in lieu of storing liquid oxygen at the mine rescue station, a modification be granted with the understanding that liquid oxygen will be available to all operations within two hours ground travel time—the same response time afforded to mine rescue teams.

6. Petitioner states that the proposed alternative and conditions outlined above will provide the same degree of safety for the miners affected as that afforded by the standard.

Request for Comments

Persons interested in this petition may furnish written comments. These comments must be filed with the Office of Standards, Regulations and Variances, Mine Safety and Health Administration, Room 627, 4015 Wilson Boulevard, Arlington, Virginia 22203. All comments must be postmarked or received in that office on or before April 22, 1982. Copies of the petition are available for inspection at that address.

Dated: March 15, 1982.

Patricia W. Silvey,
Acting Director, Office of Standards,
Regulations and Variances.

[FR Doc. 82-7709 Filed 3-22-82; 8:45 am]

BILLING CODE 4510-43-M

[Docket No. M-81-265-C]

Coal Valley Mining Co.; Petition for Modification of Application of Mandatory Safety Standard

Coal Valley Mining Co., Drawer 420, Cedar Bluff, Virginia 24609 has filed a petition to modify the application of 30 CFR 75.1710 (cabs and canopies) to its No. 3A Mine located in Pike County, Kentucky. The petition is filed under section 101(c) of the Federal Mine Safety and Health Act of 1977.

A summary of the petitioner's statements follows:

1. The petition concerns the requirement that cabs or canopies be installed on the mine's electric face equipment.
2. The coal seam ranges from 38 to 50 inches in height with ascending and descending grades creating dips in the coal bed.
3. Installation of cabs or canopies would result in a diminution of safety for the miners affected because the canopies, in this mining height, could strike and dislodge roof support. In addition, the canopies cause a cramped operating compartment and reduce visibility, exposing miners to potential hazards.
4. For these reasons, petitioner requests a modification of the standard.

Request for Comments

Persons interested in this petition may furnish written comments. These comments must be filed with the Office of Standards, Regulations and Variances, Mine Safety and Health Administration, Room 627, 4015 Wilson Boulevard, Arlington, Virginia 22203. All comments must be postmarked or received in that office on or before April 22, 1982. Copies of the petition are available for inspection at that address.

Dated: March 15, 1982.

Patricia W. Silvey,
Acting Director, Office of Standards,
Regulations and Variances.

[FR Doc. 82-7711 Filed 3-22-82; 8:45 am]

BILLING CODE 4510-43-M

[Docket No. M-82-20]

Consolidation Coal Co.; Petition for Modification of Application of Mandatory Safety Standard

Consolidation Coal Company, Consol Plaza, Pittsburgh, Pennsylvania 15241 has filed a petition to modify the application of 30 CFR 77.901 (protection of low and medium-voltage three-phase circuits) to its Georgetown Preparation Plant (I.D. No. 33-00958) located in Harrison County, Ohio. The petition is

filed under Section 101(c) of the Federal Mine Safety and Health Act of 1977.

A summary of the petitioner's statements follows:

1. Petitioner requests a modification of the standard as it applies to space heaters.
2. Space heaters are only used during cold weather in order to prevent various areas from freezing. When the plant is operating, the space heaters are removed to a storage area.
3. Installation of stationary space heaters is not feasible. They cannot be mounted on the equipment. Thus, they would have to be connected to the equipment by a steel strap that would create a stumbling or tripping hazard.
4. As an alternative to the grounding procedure specified in the standard, petitioner proposes a redundant grounding system. The ground wire in the power cable would be maintained, and a second frame ground between the frame of the equipment and the closest grounded permanent metallic structure would be added. This ground wire would be limited to a maximum length of 6 feet and would be at least a 6 AWG to insure mechanical strength and good electrical conductivity.
5. Petitioner states that this alternative would provide the same protection for the miners affected as that afforded by the standard.

Request for Comments

Persons interested in this petition may furnish written comments. These comments must be filed with the Office of Standards, Regulations and Variances, Mine Safety and Health Administration, Room 627, 4015 Wilson Boulevard, Arlington, Virginia 22203. All comments must be postmarked or received in that office on or before April 22, 1982. Copies of the petition are available for inspection at that address:

Dated: March 15, 1982.

Patricia W. Silvey,
Acting Director, Office of Standards,
Regulations and Variances.

[FR Doc. 82-7710 Filed 3-22-82; 8:45 am]

BILLING CODE 4510-43-M

NUCLEAR REGULATORY COMMISSION

Applications for Licenses To Export Nuclear Facilities or Materials

Pursuant to 10 CFR 110.70(b) "Public notice of receipt of an application", please take notice that the Nuclear Regulatory Commission has received the following applications for export licenses. A copy of each application is

on file in the Nuclear Regulatory Commission's Public Document Room located at 1717 H St., NW., Washington, D.C.

A request for a hearing or a petition for leave to intervene may be filed on or before April 22, 1982. Any request for hearing or petition for leave to intervene shall be served by the requestor or petitioner upon the applicant, the Executive Legal Director, U.S. Nuclear

Regulatory Commission, Washington, D.C. 20555, the Secretary, U.S. Nuclear Regulatory Commission and the Executive Secretary, Department of State, Washington, D.C. 20520.

In its review of application for license to export production or utilization facilities, special nuclear material or source material, noticed herein, the Commission does not evaluate the health, safety or environmental effects

in the recipient nation of the facility or material to be exported. The table below lists all new applications for the week ending March 19, 1982.

Dated this 18th day of March at Bethesda, Maryland.

For the Nuclear Regulatory Commission.

Marvin R. Peterson,

Acting Assistant Director, Export/Import and International Safeguards, Office of International Programs.

FEDERAL REGISTER (EXPORT)

Name of applicant, date of application, date received, and application number	Material type	Material in kilograms		End-use	Country of destination
		Total element	Total isotope		
Exxon Nuclear, Mar. 1, 1982, Mar. 8, 1982, XSNM01936.	3.4 pct. enriched uranium.....	70,200	2,386	Two reloads of fuel for Biblis B reactor	West Germany.
Exxon Nuclear, Mar. 10, 1982, Mar. 15, 1982, XSNM01937.	4.32 pct. enriched uranium.....	81,200	3,500	Two reloads of fuel for Kuosheng No. 1.....	Taiwan.
Exxon Nuclear, Mar. 10, 1982, Mar. 15, 1982, XSNM01938.	4.3 pct. enriched uranium.....	49,000	2,100	Two reloads of fuel for Chinshan No. 2.....	Taiwan.

[FR Doc. 82-7773 Filed 3-22-82; 8:45 am]
BILLING CODE 7590-01-M

[Docket Nos. 50-317 and 50-318]

Baltimore Gas and Electric Co.; Issuance of Amendments to Facility Operating Licenses

The Nuclear Regulatory Commission (the Commission) has issued Amendment Nos. 68 and 50 to Facility Operating License Nos. DPR-53 and DPR-69 issued to Baltimore Gas and Electric Company, which revised Technical Specifications for operation of the Calvert Cliffs Nuclear Power Plant, Unit Nos. 1 and 2 located in Calvert County, Maryland. The amendments were effective on the date of issuance.

The amendments revise the Appendix A and Appendix B Technical Specifications to reflect the recent management reorganization, incorporate shift staffing requirements, and add a monthly reporting requirement concerning pressurizer safety and relief valve failures and challenges.

The application for the amendments complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Chapter I, which are set forth in the license amendments. Prior public notice of the amendments was not required since the amendments do not involve a significant hazards consideration.

The Commission has determined that the issuance of the amendments will not result in any significant environmental

impact and that pursuant to 10 CFR 51.5(d)(4) an environmental impact statement, or negative declaration and environmental impact appraisal need not be prepared in connection with issuance of the amendments.

For further details with respect to this action, see (1) the application for amendments dated January 22, 1982, (2) Amendment Nos. 68 and 50 to License Nos. DPR-53 and DPR-69, and (3) the Commission's related Safety Evaluation. All of these items are available for public inspection at the Commission's Public Document Room, 1717 H Street, N.W., Washington, D.C. and at the Calvert County Library, Prince Frederick, Maryland. A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Licensing.

Dated: at Bethesda, Maryland, this 9th day of March, 1982.

For the Nuclear Regulatory Commission.

Robert A. Clark,

Chief, Operating Reactors Branch No. 3, Division of Licensing.

[FR Doc. 82-7769 Filed 3-22-82; 8:45 am]
BILLING CODE 7590-01-M

[Docket Nos. 50-250 and 50-251]

Florida Power and Light Co.; Issuance of Amendments to Facility Operating Licenses

The Nuclear Regulatory Commission (the Commission) has issued Amendment No. 80 to Facility Operating License No. DPR-31, and Amendment No. 74 to Facility Operating License No.

DPR-41 issued to Florida Power and Light Company (the licensee), which revised Technical Specifications for operation of Turkey Point Plant, Unit Nos. 3 and 4 (the facilities) located in Dade County, Florida. The amendments are effective as of the date of issuance.

The amendments change the Technical Specifications to specify new power distribution limits related to base load and radial burndown operation.

The application for the amendments complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Chapter I, which are set forth in the license amendments. Prior public notice of these amendments was not required since the amendments do not involve a significant hazards consideration.

The Commission has determined that the issuance of these amendments will not result in any significant environmental impact and that pursuant to 10 CFR 51.5(d)(4) an environmental impact statement or negative declaration and environmental impact appraisal need not be prepared in connection with issuance of these amendments.

For further details with respect to this action, see (1) the application for amendments dated May 14, 1981, as supplemented on November 23, 1981 and January 28, 1982, (2) Amendment Nos. 80 and 74 to License Nos. DPR-31 and DPR-41, and (3) the Commission's related Safety Evaluation. All of these items are available for public inspection

at the Commission's Public Document Room, 1717 H Street, N.W., Washington, D.C. and at the Environmental and Urban Affairs Library, Florida International University, Miami, Florida 33199. A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Licensing.

Dated at Bethesda, Maryland, this 17th day of March, 1982.

For the Nuclear Regulatory Commission.

Steven A. Varga,

Chief, Operating Reactors Branch No. 1,
Division of Licensing.

[FR Doc. 82-7770 Filed 3-22-82; 8:45 am]

BILLING CODE 7590-01-M

[NUREG-0783]

Issuance and Availability; "Suppression Pool Temperature Limits for BWR Containment"

The Nuclear Regulatory Commission (NRC) staff has prepared a report entitled, "Suppression Pool Temperature Limits for BWR Containments," (NUREG-0783). This report provides the staff's partial resolution of "Unresolved Safety Issue" A-39, "Determination of Safety Relief Valve (SRV) Pool Dynamic Loads and Temperature Limits for BWR Containment."

All BWR plants are equipped with safety/relief valves (SRV's) to protect the reactor from overpressure. Plant operational transients, such as turbine trips, actuate the SRV's causing mass and energy to be released into the suppression pool through the SRV lines. Steam is then condensed in the suppression pool in a stable condition. However, an instability of steam condensation as a result of extended steam blowdown may result causing severe vibratory loads on containment structures. Current practice to prevent this phenomenon from occurring is to restrict the allowable operating temperature envelope via the plant Technical Specifications. This restriction is referred to as the pool temperature limit.

Resolution of the concern of steam condensation instability for Mark I, II and III containments has been reached and is presented in this NUREG report. Included in the report are: (1) The acceptance criteria related to the suppression pool temperature limits; (2) the events required to analyze the suppression pool temperature responses; (3) the assumptions used for the analyses; and (4) the requirements for the suppression pool temperature

monitoring system. NUREG-0783 is not a substitute for the regulations and compliance is not a requirement.

In implementing the requirements described in NUREG-0783, the staff will assure that all licensees/applicants for Mark I plants document the information related to suppression pool temperature limits in conjunction with the requirements for the Mark I Long Term Program (defined in NUREG-0661) and all applicants with Mark II and III containments document the same information during the Final Safety Analysis Report (FSAR) review.

Copies of NUREG-0783 will be available after March 1982. Copies will be sent directly to utilities, utility industry groups and associations, and environmental public interest groups. Other copies will be available for review at the NRC Public Document Room, 1717 H Street N.W., Washington, D.C. and at the Commission's Local Public Document Rooms located in the vicinity of nuclear power plants. Addresses of these Local Public Document Rooms can be obtained from the Chief, Local Public Document Room Branch, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, telephone (301) 492-7538.

Dated at Bethesda, Maryland, this 16th day of March, 1982.

For the Nuclear Regulatory Commission.

Stephen H. Hanauer,

Director, Division of Safety Technology,
Office of Nuclear Reactor Regulation.

[FR Doc. 82-7772 Filed 3-22-82; 8:45 am]

BILLING CODE 7590-01-M

[Docket Nos. 50-282 and 50-306]

Northern States Power Co.; Issuance of Amendments to Facility Operating Licenses

The Nuclear Regulatory Commission (the Commission) has issued Amendment No. 55 to Facility Operating License No. DPR-42, and Amendment No. 49 to Facility Operating License No. DPR-60 issued to Northern States Power Company (the licensee), which revised Technical Specifications for operation of Prairie Island Nuclear Generating Plant, Unit Nos. 1 and 2 (the facilities) located in Goodhue County, Minnesota. The amendments are effective as of the date of issuance.

The amendments revised the common Technical Specifications for the Prairie Island Nuclear Generating Plant Unit Nos. 1 and 2 by permitting an increase in the allowable leakage rate for the overall airlock door tests. Technical Specification 4.4.A.5.c is affected by these amendments. The amendments

also renumbers a page contained in Amendments 53 and 47, issued on December 30, 1981.

The application for the amendments complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Chapter I, which are set forth in the license amendments. Prior public notice of these amendments was not required since the amendments do not involve a significant hazards consideration.

The Commission has determined that the issuance of these amendments will not result in any significant environmental impact and that pursuant to 10 CFR 51.5(d)(4) an environmental impact statement or negative declaration and environmental impact appraisal need not be prepared in connection with issuance of these amendments.

For further details with respect to this action, see (1) the application for amendments dated February 1, 1982, (2) Amendment Nos. 55 and 49 to License Nos. DPR-42 and DPR-60, and (3) the Commission's related Safety Evaluation. All of these items are available for public inspection at the Commission's Public Document Room, 1717 H Street, N.W., Washington, D.C. and at the Environmental Conservation Library, 300 Nicollet Mall, Minneapolis, Minnesota 55401. A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Licensing.

Dated at Bethesda, Maryland, this 5th day of March, 1982.

For the Nuclear Regulatory Commission.

Robert A. Clark,

Chief, Operating Branch No. 3, Division of
Licensing.

[FR Doc. 82-7771 Filed 3-22-82; 8:45 am]

BILLING CODE 7590-01-M

OFFICE OF PERSONNEL MANAGEMENT

Excepted Service; Positions Placed or Revoked

AGENCY: Office of Personnel
Management.

ACTION: Notice.

SUMMARY: This gives notice of positions placed or revoked under Schedules A, B, and C in the excepted service, as required by Civil Service Rule VI.

FOR FURTHER INFORMATION CONTACT:
William Bohling, 202-632-6000.

SUPPLEMENTARY INFORMATION: The Office of Personnel Management published a notice updating appointing authorities established or revoked under the Expected Service provisions of 5 CFR Part 213 on September 1, 1981 (46 FR 43912). Individual authorities established or revoked under Schedules A, B, or C between that notice and February 26, 1982 appear in a listing below. Future notices will be published on the fourth Tuesday of each month. A consolidated listing of all authorities will be published as of June 30 of each year.

Schedule A

The following exceptions are established:

In the Department of Defense, National Defense University, up to 16 positions of senior policy analyst, GS-15, at the Strategic Concepts Development Center. Initial appointments to these positions may not exceed 3 years, but may be extended thereafter for additional period(s) not to exceed 1 year each. Effective October 27, 1981.

In the U.S. Government Printing Office, Office of the Assistant Public Printer (Planning), up to three positions of Research Associate at grades GS-15 and below, involved in the study and analysis of complex problems relating to the reduction of the Government's printing costs and to provision of more efficient service to customer agencies and the public. Appointments under this authority may not exceed 1 year, but may be extended for not to exceed 1 additional year. Effective August 17, 1981.

In the Department of Housing and Urban Development, one position of Special Advisor to the Regional Administrator, GS-301-14, in San Francisco. Employment under this authority may not exceed 2 years. Effective October 5, 1981.

In the General Services Administration, up to 15 positions at grades GS-14/15, to bring into the agency current industry expertise in various program areas. Appointments under this authority may not exceed 2 years. Effective January 26, 1982.

In the Department of the Air Force, up to seven positions, GS-12-15, in Headquarters Air Force Logistics Command, DCS Logistics Operation, Wright Patterson Air Force Base, Ohio, which will provide logistic support management staff guidance to classified research and development projects. Employment under this authority is not

to exceed January 31, 1985. Effective February 3, 1982. The following exceptions are revoked:

In the Department of the Interior, positions of teachers, instructor, education aid/technician, and supervisor of classrooms, GS-3/12, at schools run by the Bureau of Indian Affairs; revoked effective October 23, 1981, because the authority has expired by its own terms.

In the Department of Commerce, Office of Minority Business Enterprise, twenty-five positions of Business Management Fellowship Program Specialists, GS-11/12; revoked effective October 16, 1981, because the authority has expired by its own terms.

In the Department of Commerce, National Technical Information Service, one position of Clerk, GS-4; revoked effective October 7, 1981, because the position is no longer needed.

In the Panama Canal Commission, all positions on vessels operated by the Commission; revoked effective November 2, 1981, because the Panama Canal Commission no longer operates any vessels.

In the U.S. Government Printing Office, one Umpire; revoked effective August 18, 1981 because the position no longer exists.

In the Department of Transportation, St. Lawrence Seaway Development Corporation, one Assistant Manager, Seaway International Bridge; revoked effective August 28, 1981, because the position no longer exists.

In the Department of Transportation, Urban Mass Transportation Administration, up to six positions in grades GS-11/15, for employment in the international seminar on "The Role of Urban Transportation in Community Development." Revoked effective August 28, 1981, because the position no longer exist.

In the Environmental Protection Agency, up to 12 positions of Sanitation Facility Trainees, WG-1 through 5, to implement the Alaska Village Demonstration Projects under the Water Quality Improvement Act of 1970; revoked effective August 12, 1981, because the positions no longer exist.

In the entire executive civil service, positions at grades GS-15 and below on the staff of the Council on Wage and Price Stability, and positions in agencies which are members of the Council, when such positions are needed to carry out the agencies' responsibilities under the anti-inflation program; revoked effective February 25, 1982, because the authority has expired by its own terms.

In the entire executive civil service, positions at grades GS-16, 17 or 18 on the staff of the Council on Wage and

Price Stability; revoked February 25, 1982, because the authority has expired by its own terms.

In the entire executive civil service, one position at grade GS-16, 17 or 18 on the staff of the Council on Wage and Price Stability; revoked effective February 25, 1982, because the position ceased to exist.

In the entire executive civil service, all positions of a project nature when filled by individuals the salaries of whom are paid out of (1) funds allocated by the President under authority of Pub. L. 87-658, the Public Works Acceleration Act of 1962, approved September 14, 1962, or (2) funds allocated by the Secretary of Commerce under authority of title X of the Public Works and Economic Development Act of 1965, as amended; revoked effective July 16, 1981, because part 1 is no longer used and part 2 has expired by its own terms.

In the Department of Treasury, Staff Assistant positions established to aid in the reorganization of Bureau of Customs under Reorganization Plan No. 1 of 1965, when filled by persons with 1 year or more of current service as a Presidential appointee in a key position in the Bureau; revoked effective June 18, 1981, because the authority is no longer needed.

In the President's Commission on World Hunger, all staff positions; revoked effective June 22, 1981, because the authority has expired by its own terms.

In the President's Commission on the Coal Industry, all staff positions; revoked effective June 25, 1981, because the authority has expired by its own terms.

In the President's Commission on the Holocaust, one GS-15 Deputy Executive Director, one GS-10 Staff Assistant, and one GS-7 Secretary; revoked effective August 14, 1981, because the authority has expired by its own terms.

In the President's Commission on the Accident at Three Mile Island, all staff positions; revoked effective June 22, 1981, because the authority has expired by its own terms.

In the National Commission on Social Security, all staff positions at GS-15 and below; revoked effective June 25, 1981, because the authority has expired by its own terms.

In the Department of Health and Human Services, St. Elizabeth's Hospital, three Medical Officers (Surgical Resident); revoked effective February 25, 1982, because the positions are no longer needed.

In the Department of Health and Human Services, St. Elizabeth's Hospital, four Medical Officers (Physical

Medicine and Rehabilitation Resident); revoked effective February 25, 1982, because the positions are no longer needed.

In the Department of Health and Human Services, St. Elizabeth's Hospital, three Medical Officers (Internal Medicine Resident); revoked effective February 25, 1982, because the positions are no longer needed.

In the Department of Health and Human Services, St. Elizabeth's Hospital, two Medical Officers (Anatomical Pathology Resident); revoked effective February 25, 1982, because the positions are no longer needed.

In the Department of Health and Human Services, St. Elizabeth's Hospital, three Medical Officers (Radiology Resident); revoked effective February 25, 1982, because the positions are no longer needed.

In the Department of Health and Human Services, St. Elizabeth's Hospital, temporary positions of graduate nurses appointed as students for the purpose of receiving 12 weeks of training equivalent to psychiatric affiliation; revoked effective February 25, 1982, because positions are no longer needed.

In the Department of Health and Human Services, St. Elizabeth's Hospital, one position of Medical Officer (Ophthalmology Resident); revoked effective February 26, 1982, because the position is no longer needed.

In the Department of Health and Human Services, St. Elizabeth's Hospital, Student Medical Interns for temporary time employment; revoked effective March 1, 1982, because the positions are no longer needed.

In the Department of Health and Human Services, Public Health Service, positions of Special escorts to accompany patients of the PHS in accordance with existing laws and regulations; revoked effective February 26, 1982, because the positions are no longer needed.

In the Department of Health and Human Services, up to 30 positions of clerical assistants employed on a part-time and intermittent basis to aid cooperating clinicians in non-Federal tuberculosis sanatoria in the keeping of records and the preparation of reports in connection with research studies into the effectiveness of antimicrobial agents in the treatment of tuberculosis; revoked effective February 26, 1982, because the positions are no longer needed.

In the Department of Health and Human Services, Public Health Service, positions in the National Institute of Mental Health involving performance of various therapeutic and service

assignments under a rehabilitation program concerned with the treatment of drug addicts, when filled by persons who have a history of drug addiction and who have been successfully treated; revoked effective February 26, 1982, because the positions are no longer needed.

In the Department of Health and Human Services, up to 20 positions of HEW Fellows in grades GS-11/15; revoked effective March 4, 1982, because the positions are no longer needed.

In the Farm Credit Administration, Federal land bank association receivers and conservators; revoked effective February 24, 1982, because the positions are no longer needed.

Schedule B

The following exception is established:

In the Department of the Air Force, up to four interdisciplinary positions for the Air Research Institute at the Air University, Maxwell Air Force Base, Alabama, for employment to complete studies proposed by candidates and acceptable to the Air Force.

Employment of any one individual is not to exceed 1 year. Such employment may be extended for not to exceed 1 additional year. Total employment of any one individual under this authority may not exceed 2 years. Effective September 16, 1981. The following exceptions are revoked:

In the Export-Import Bank of the United States, up to 24 positions of Loan Specialist, GS-7-14, when occupied by persons selected jointly by commercial banks and the agency for participation in the Eximbank-Commercial Bank Orientation Program; revoked effective February 10, 1982, because the positions are no longer needed.

In the Community Services Administration, one position of Chief, Research and Plans Division; revoked effective March 3, 1982, because the position ceased to exist.

Schedule C

The following exceptions are established:

In ACTION, one Special Assistant to the Assistant Director. Effective December 7, 1981.

In the Department of Agriculture, Office of the Secretary, one Office Assistant to the Executive Assistant to the Secretary. Effective December 3, 1981.

In the Department of Agriculture, Office of the Administrator, one Confidential Assistant to the Administrator. Effective December 10, 1981.

In the Department of the Army, Office of the Secretary, one Confidential Staff Assistant in the White House Support Group. Effective December 9, 1981.

In the Department of Commerce, Office of the Secretary, one Private Secretary to the Under Secretary for Travel and Tourism. Effective December 28, 1981.

In the Department of Commerce, Office of the Under Secretary, one Confidential Assistant to the Under Secretary for Travel and Tourism. Effective December 28, 1981.

In the Department of Commerce, Office of the Under Secretary, one Confidential Assistant to the Under Secretary. Effective December 4, 1981.

In the Department of Commerce, in the International Trade Administration, one Special Assistant to the Deputy to the Deputy Assistant Secretary for Import Administration. Effective December 9, 1981.

In the Department of Commerce, Office of Administration, one Confidential Assistant to the Assistant Secretary for Administration. Effective December 28, 1981.

In the Department of Commerce, Office of Public Affairs, one Special Assistant to the Director in the National Oceanic and Atmospheric Administration. Effective December 11, 1981.

In the Consumer Product Safety Commission, Office of the Chairman, one Special Assistant. Effective December 15, 1981.

In the Department of Defense, Office of the Secretary, one Special Assistant to the Principal Deputy Assistant Secretary of Defense (Health Affairs). Effective December 7, 1981.

In the Department of Defense, Office of the Secretary, one Special Assistant to the Director, Defense Security Assistance Agency (DSAA). Effective December 3, 1981.

In the Department of Defense, Office of the Under Secretary, one Private Secretary to the Director, Defense Test and Evaluation. Effective December 28, 1981.

In the Department of Defense, Office of the Under Secretary, one Private Secretary to the Assistant Secretary of Defense (Research and Technology). Effective December 7, 1981.

In the Department of Education, Office of Legislation and Public Affairs, one Director of Editorial Services to the Assistant Secretary. Effective December 3, 1981.

In the Department of Education, Office of Special Education, one Special Assistant to the Commissioner,

Rehabilitation Services Administration. Effective December 4, 1981.

In the Department of Education, one Special Assistant to the Assistant Secretary for Civil Rights. Effective December 9, 1981.

In the Department of Education, Office of the Under Secretary, one Secretary's Regional Representative. Effective December 29, 1981.

In the Department of Education, Office of the Under Secretary, one Executive Assistant to the Under Secretary. Effective December 18, 1981.

In the Department of Education, one Special Assistant to the Deputy Under Secretary for Intergovernmental and Interagency Affairs. Effective December 31, 1981.

In the Department of Energy, one Staff Assistant to the Special Assistant to the Secretary for Programs and Policies. Effective December 10, 1981.

In the Environmental Protection Agency, Office of the Administrator, one Intergovernmental Liaison Specialist to the Director in the Office of Intergovernmental Liaison. Effective December 29, 1981.

In the Federal Emergency Management Agency, one Deputy Director, Office of Congressional Relations. Effective December 10, 1981.

In the Federal Home Loan Bank Board, Office of Examinations and Supervision, one Secretary to the Director. Effective December 10, 1981.

In the General Services Administration, Office of Program Control, one Special Assistant to the Director. Effective December 18, 1981.

In the Department of Health and Human Services, Office of Human Development Services, one Special Assistant to the Director, Office of Program Coordination and Review. Effective December 17, 1981.

In the Department of Health and Human Services, Office of the Secretary, one Confidential Assistant to the Executive Secretary. Effective December 18, 1981.

In the Department of Health and Human Services, Office of the Secretary, one Confidential Assistant to the Executive Secretary. Effective December 18, 1981.

In the Department of Health and Human Services, Office of the Associate Administrator, one Confidential Assistant to the Associate Administrator for External Affairs, Health Care Financing Administration. Effective December 11, 1981.

In the Department of Health and Human Services, Office of the Secretary, one Confidential Assistant to the Executive Assistant to the Secretary. Effective date December 15, 1981.

In the Department of Housing and Urban Development, Office of the Regional Administrator, one Special Assistant to the Regional Administrator. Effective December 18, 1981.

In the Department of Housing and Urban Development, Office of Housing, one Executive Assistant to the Deputy Assistant Secretary for Public Housing and Indian Programs. Effective December 23, 1981.

In the Department of Housing and Urban Development, one Executive Assistant to the Regional Administrator. Effective December 23, 1981.

In the Department of Housing and Urban Development, Office of Administration, one Special Assistant to the Assistant Secretary for Administration. Effective December 28, 1981.

In the U.S. International Communication Agency, Office of Personnel Services, one Staff Assistant to the Director. Effective December 3, 1981.

In the Interstate Commerce Commission, Office of the Managing Director, one Staff Advisor (Economics) to the Managing Director. Effective December 7, 1981.

In the Department of the Interior, Office of the Secretary, one Special Assistant in the Immediate Office of the Assistant Secretary-Policy, Budget and Administration. Effective December 7, 1981.

In the Department of the Interior, Office of the Secretary, one Special Assistant to the Executive Assistant to the Secretary. Effective December 7, 1981.

In the Department of the Interior, Office of the Secretary, one Special Assistant to the Director, Office of Youth Programs. Effective December 15, 1981.

In the Department of Justice, Office of Boards and Divisions, one Special Assistant to the Assistant Attorney General for Antitrust. Effective December 3, 1981.

In the Department of Justice, Office of the U.S. Attorney, one Secretary (Stenography). Effective December 3, 1981.

In the Department of Labor, Office of the Secretary, one Special Assistant to the Assistant Secretary for Policy, Evaluation and Research. Effective December 29, 1981.

In the Department of Labor, Office of the Assistant Secretary, one Special Assistant to the Assistant Secretary for Employment and Training. Effective December 9, 1981.

In the Department of Labor, Office of the Under Secretary, one Private Secretary to the Executive Assistant to

the Under Secretary. Effective December 3, 1981.

In the Department of Labor, Office of the Assistant Secretary, one Special Assistant to the Assistant Secretary for Occupational Safety and Health. Effective December 18, 1981.

In the Department of Labor, Office of the Administrator, one Confidential Staff Assistant, Wage and Hour Division. Effective December 9, 1981.

In the Department of State, Office of the Under Secretary, one Special Assistant to the Under Secretary of State for Management. Effective December 3, 1981.

In the Department of State, Bureau of Public Affairs, one Public Information Specialist to the Assistant Secretary. Effective December 31, 1981.

In the Department of Transportation, Office of the Secretary, one Special Assistant to the Director, Office of Civil Rights. Effective December 31, 1981.

In the Department of Treasury, Office of the Secretary, one Senior Assistant to the Assistant Secretary (Enforcement and Operations). Effective December 28, 1981.

In the Department of Treasury, one Secretary to the Director, Office of Revenue Sharing. Effective December 2, 1981.

In the Department of Treasury, Office of the Commissioner, one Secretary (Stenography) to the Commissioner. Effective December 4, 1981.

In the Veterans Administration, Office of the Administrator, one Confidential Assistant to the Associate Deputy Administrator for Logistics. Effective December 29, 1981.

In ACTION, one Assistant Director, Office of Recruitment and Communications. Effective January 26, 1982.

In ACTION, one Young Volunteers Program Officer for VISTA/Service Learning Programs. Effective January 7, 1982.

In the Department of Agriculture, one Confidential Assistant to the Administrator, Food and Nutrition Service. Effective January 27, 1982.

In the Department of Agriculture, one Director, Office of the Consumer Advisor. Effective January 27, 1982.

In the Department of Agriculture, Office of Science and Education Administration, one Confidential Assistant to the Director. Effective January 7, 1982.

In the Department of Commerce, Office of Congressional Operations, one Congressional Staff Assistant to the Deputy Assistant Secretary. Effective January 27, 1982.

In the Department of Energy, Office of the Federal Energy Regulatory Commission, one Advisor to the Chairman. Effective January 27, 1982.

In the Environmental Protection Agency, Office of the Congressional Liaison, three Congressional Relations Officers. Effective January 7, 1982.

In the Environmental Protection Agency, Office of Congressional Liaison, one Congressional Relations Officer. Effective January 27, 1982.

In the Federal Trade Commission Office of the Commissioner, one Assistant to the Commissioner. Effective January 27, 1982.

In the Department of Health and Human Services, Office of Public Affairs, one Special Assistant to the Assistant Secretary for Public Affairs. Effective January 26, 1982.

In the Department of Health and Human Services, Office of Refugee Resettlement, one Special Assistant to the Director. Effective January 27, 1982.

In the Department of Health and Human Services, Office of the Under Secretary, one Confidential Secretary (Steno) to the Regional Director. Effective January 11, 1982.

In the Department of Health and Human Services, Office of Intergovernmental Affairs, one Special Assistant to the Deputy Under Secretary. Effective January 11, 1982.

In the Department of Housing and Urban Development, Office of Field Coordination, one Staff Assistant (Typing). Effective January 13, 1982.

In the Department of Housing and Urban Development, one Special Assistant to the Regional Administrator. Effective January 27, 1982.

In the Department of Housing and Urban Development, one Special Assistant to the Regional Administrator. Effective January 14, 1982.

In the Department of Housing and Urban Development, one Executive Assistant to the General Deputy Assistant Secretary for Housing. Effective January 26, 1982.

In the Department of the Interior, one Special Assistant to the Special Assistant to the Secretary (Field Coordination). Effective January 4, 1982.

In the Department of the Interior, one Special Assistant to the Assistant Secretary for Territorial and International Affairs. Effective January 27, 1982.

In the Department of Justice, Office of the U.S. Attorney, one Secretary (Steno) for the Southern District of Indiana. Effective January 12, 1982.

In the Department of Labor, Office of the Secretary, one Secretary to the Secretary of Labor. Effective January 4, 1982.

In the Department of Labor, Office of Employment and Training Administration, one Confidential Staff Assistant to the Assistant Secretary. Effective January 7, 1982.

In the Department of Labor, Office of Labor-Management Relations, one Staff Assistant to the Assistant Secretary. Effective January 5, 1982.

In the Department of Labor, Office of Public Affairs, one Private Secretary to the Assistant Secretary for Public Affairs. Effective January 25, 1982.

In the Department of Labor, Office of Employment and Training Administration, one Special Assistant to the Assistant Secretary. Effective January 25, 1982.

In the Department of State, Office of Congressional Relations, one Staff Assistant to the Assistant Secretary for Congressional Relations. Effective January 4, 1982.

In the Department of Transportation, Office of the Federal Highway Administration, one Special Assistant to the Chief Counsel. Effective January 27, 1982.

In the Department of Treasury, Office of Revenue Sharing, one Assistant to the Director. Effective January 13, 1982.

In the Department of Health and Human Services, Office of the Secretary, one Special Assistant to the Secretary (Consumer Affairs). Effective May 29, 1980.

In the Department of Health and Human Services, Office of the Assistant Secretary for Services, Office of the Assistant Secretary for Legislation, one Confidential Assistant to the Deputy Assistant Secretary. Effective March 25, 1980.

In the Department of Health and Human Services, Office of the Assistant Secretary for Legislation, one Confidential Assistant to the Deputy Assistant Secretary for Legislation. Effective April 22, 1980.

In the Department of Health and Human Services, Office of the Secretary, one Special Assistant to the Director, Office of Small and Disadvantaged Business Utilization. Effective July 24, 1980.

In the Department of Health and Human Services, Office of the Secretary, one Deputy Special Assistant for Consumer Affairs to the Special Assistant to the Secretary (Consumer Affairs). Effective July 24, 1980.

In the Department of the Interior, Office of the Secretary, one Special Assistant to the Secretary (Economic Development). Effective May 19, 1980.

In the Department of the Interior, Office of the Secretary, one Staff Assistant to the Director, U.S. Fish and

Wildlife Service. Effective December 30, 1980.

In the Department of Labor, Office of the Secretary, one Confidential Staff Assistant to the Administrator, Office of Youth Programs, Employment and Training Administration. Effective December 15, 1980.

In the Federal Emergency Management Agency, Office of the Director, one Special Assistant to the Director, Congressional Relations. Effective May 7, 1980.

In the Federal Deposit Insurance Corporation, one Congressional Liaison Officer. Effective December 12, 1980.

In the General Services Administration, Office of the Administrator, one Confidential Assistant to the Executive Assistant to the Administrator. Effective May 29, 1980.

In the Selective Service System, one Administrative Assistant to the Director. Effective August 27, 1980.

In the Federal Home Loan Bank Board, one Secretary to the Director for Minority Affairs. Effective October 1, 1980.

In the Department of Housing and Urban Development, Office of the Secretary, one Special Assistant to the Regional Administrator (Boston). Effective March 6, 1980.

In the Department of Housing and Urban Development, Office of Assistant Secretary for Community Planning and Development, one Urban Policy Specialist to the Director, Legislative and Urban Policy Staff. Effective July 18, 1980.

In the Department of Housing and Urban Development, Office of the Secretary, one Staff Assistant to the Secretary. Effective August 25, 1980.

In the Department of Housing and Urban Development, Office of the Secretary, one Staff Assistant to the Regional Administrator (New York). Effective August 7, 1980.

In the Department of Education, Office of Education for Overseas Dependents, one Private Secretary to the Administrator. Effective November 26, 1980.

In the Department of Education, Office of the Secretary, one Confidential Assistant to the Executive Assistant to the Secretary. Effective November 26, 1980.

The following exceptions are revoked:

In the Department of the Interior, Office of the Secretary, one Confidential Assistant to the Assistant Secretary, Policy, Budget and Administration; revoked effective December 30, 1980, because the position is no longer needed.

In the Department of Labor, Office of the Secretary, one Private Secretary to the Deputy Assistant Secretary for Employment and Training; revoked effective December 15, 1980, because the position no longer exists.

In the Department of Education, Office of the Commissioner for Education, one Special Assistant to the Assistant Commissioner for Policy Studies; revoked effective November 26, 1980, because the position no longer exists.

In the Department of Education, Office of the Assistant Secretary for Education, one Confidential Assistant to the Deputy Assistant Secretary for Education; revoked effective November 26, 1980, because the position no longer exists.

(5 U.S.C. 3301, 3302; EO 10577, 3 CFR 1954-1958 Comp., p. 218)

Office of Personnel Management.

Donald J. Devine,
Director.

[FR Doc. 82-7685 Filed 3-22-82; 8:45 am]

BILLING CODE 6325-01-M

SECURITIES AND EXCHANGE COMMISSION

[Release No. 12300; 812-5133]

Alex. Brown Cash Reserve Fund, Inc.; Amending a Previous Order Exempting Applicant

March 15, 1982.

Notice is hereby given that Alex. Brown Cash Reserve Fund, Inc. ("Applicant"), 11 Greenway Plaza, Suite 1919, Houston, Texas 77046, an open-end, diversified, management investment company, filed an application on February 2, 1982, requesting an order of the Commission, pursuant to Section 6(c) of the Investment Company Act of 1940 ("Act"), amending a prior order of the Commission exempting Applicant from the provisions of Section 2(a)(41) of the Act and Rules 2a-4 and 22c-1 thereunder, to the extent necessary to permit Applicant to value the assets held in its Prime Series Portfolio and its Government Series Portfolio using the amortized cost method of valuation. All interested persons are referred to the application on file with the Commission for a statement of the representations contained therein, which are summarized below.

Applicant states that it is a "money market" fund designed as an investment vehicle for institutions that wish to invest short-term cash reserves. Applicant further states that its investment objective is to seek as high a

level of current income as is consistent with preservation of capital and liquidity. The Applicant seeks to achieve its objective by investing in high quality money market instruments. The money market instruments in which the Applicant invests normally have maturities of one year or less from the date of purchase. The Applicant does not maintain a dollar weighted average maturity of its portfolio securities in excess of 120 days.

Applicant states that it invests exclusively in the following types of money market instruments: (i) Securities issued or guaranteed as to principal and interest by the United States Government or by its agencies or instrumentalities; (ii) certificates of deposit, time or savings deposits, and bankers' acceptances of domestic commercial banks and savings banks that, as of their latest published report, have total assets in excess of \$1.5 billion; (iii) certificates of deposit and time or savings deposits that are insured by the Federal Deposit Insurance Corporation or the Federal Savings and Loan Insurance Corporation; (iv) commercial paper, including variable amount master demand notes, that is rated (at the time of purchase) A-1 by Standard and Poor's Corporation or Prime-1 by Moody's Investors Service, Inc., or, if not rated, is of comparable quality to rated instruments of the foregoing quality as determined by the board of directors; and (v) repurchase agreements and reverse repurchase agreements pertaining to the above securities, subject to certain restrictions set forth in Applicant's current prospectus. On August 13, 1981 (see Investment Company Act Release No. 11907), the Commission granted an order permitting Applicant to value its portfolio securities using the amortized cost method of valuation.

The board of directors of Applicant, at a meeting held on December 1, 1981, reclassified four billion of the Applicant's shares of common stock as "Government Series". The Applicant's common stock and its existing portfolio have been designated the "Prime Series" Portfolio. The Government Series Portfolio will limit its portfolio investments to marketable securities and instruments issued or guaranteed by the United States Government or any of its agencies or instrumentalities.

As here pertinent, section 2(a)(41) of the Act defines value to mean: (1) With respect to securities for which market quotations are readily available, the market value of such securities, and (2) with respect to other securities and assets, fair value as determined in good faith by the board of directors. Rule 22c-

1 provides, in part, that no registered investment company or principal underwriter therefor issuing any redeemable security shall sell, redeem or repurchase any such security except at a price based on the current net asset value of such security which is next computed after receipt of a tender of such security for redemption or of an order to purchase or to sell such security. Rule 2a-4 adopted under the Act provides, as here relevant, that the "current net asset value" of a redeemable security issued by a registered investment company used in computing its price for the purpose of distribution and redemption shall be an amount which reflects calculations made substantially in accordance with the provisions of that rule, with estimates used where necessary or appropriate. Rule 2a-4 further provides that portfolio securities with respect to which market quotations are readily available shall be valued at current market value, and that other securities and assets shall be valued at fair value as determined in good faith by the board of directors of the registered company. The Commission has expressed the view that, among other things: (1) Rule 2a-4 requires that portfolio instruments of "money market" funds be valued with reference to market factors, and (2) it would be inconsistent, generally, with the provisions of Rule 2a-4 for a "money market" fund to value its portfolio instruments with remaining maturities in excess of sixty days on an amortized cost basis (Investment Company Act Release No. 9786, May 31, 1977).

Applicant requests an amended order of the Commission pursuant to Section 6(c) of the Act exempting it from the provisions of Section 2(a)(41) of the Act and Rules 2a-4 and 22c-1 thereunder to the extent necessary to permit the portfolio securities to be held in Applicant's Government Series Portfolio to be valued at amortized cost, whether or not market quotations are readily available.

Applicant has agreed that each of the following may be made a condition to granting of the exemptive relief requested:

1. In supervising Applicant's operations and delegating special responsibilities involving portfolio management to Applicant's investment adviser, the board of directors of Applicant undertakes—as a particular responsibility within the overall duty of care owed to its shareholders—to establish procedures reasonably designed, taking into account current market conditions and Applicant's investment objectives, to stabilize

Applicant's net asset value per share, as computed for the purpose of distribution, redemption and repurchase, at \$1.00 per share.

2. Included within the procedures to be adopted by the board of directors of the Applicant shall be the following:

(a) Review by the board of directors, as it deems appropriate and at such intervals as are reasonable in light of current market conditions, to determine the extent of deviation, if any, of the net asset value per share as determined by using available market quotations from the \$1.00 amortized cost price per share, and the maintenance of records of such review.¹

(b) In the event such deviation from the \$1.00 amortized cost price per share exceeds $\frac{1}{2}$ of 1 percent, a requirement that the board of directors will promptly consider what action, if any, should be initiated.

(c) Where the board of directors believes the extent of any deviation from the \$1.00 amortized cost price per share may result in material dilution or other unfair results to investors or existing shareholders, it shall take such action as it deems appropriate to eliminate or to reduce to the extent reasonably practicable such dilution or unfair results, which may include: redeeming shares in kind; selling portfolio instruments prior to maturity to realize capital gains or losses, or to shorten the average maturity of portfolio instruments; withholding dividends; or utilizing a net asset value per share as determined by using available market quotations.

3. Applicant will maintain a dollar-weighted average portfolio maturity appropriate to its objective of maintaining a stable net asset value per share; provided, however, that Applicant will not (a) purchase any instrument with a remaining maturity of greater than one year or (b) maintain a dollar-weighted average portfolio maturity which exceeds 120 days.²

4. Applicant will record, maintain, and preserve permanently in an easily accessible place a written copy of the

procedures (and any modifications thereto) described in paragraph 1 above, and will record, maintain and preserve for a period of not less than six years (the first two years in an easily accessible place) a written record of its board of directors' considerations and actions taken in connection with the discharge of its responsibilities, as set forth above, to be included in the minutes of the board of directors' meetings. The documents preserved pursuant to this condition shall be subject to inspection by the Commission in accordance with Section 31(b) of the Act, as if such documents were records required to be maintained pursuant to rules adopted under Section 31(a) of the Act.

5. Applicant will limit its portfolio investments, including repurchase agreements, to those United States dollar-denominated instruments which its board of directors determines present minimal credit risks, and which are of "high quality" as determined by any major rating service or, in the case of any instrument that is not rated, of comparable quality as determined by its board of directors.

6. Applicant will include in each of its quarterly reports, as an attachment to Form N-1Q, a statement as to whether any action pursuant to paragraph 2(c) above was taken during the preceding fiscal quarter and, if any such action was taken, will describe the nature and circumstances of such action.

Section 6(c) of the Act provides, in pertinent part, that the Commission, by order upon application, may conditionally or unconditionally exempt any person, security or transaction or any class or classes of persons, securities or transactions, from any provision of the Act or of any rule under the Act, if and to the extent such exemption is necessary or appropriate in the public interest and consistent with the protection of investors and the purposes fairly intended by the policy and provisions of the Act.

Notice is further given that any interested person may, not later than April 9, 1982, at 5:30 p.m., submit to the Commission in writing a request for a hearing on the application accompanied by a statement as to the nature of his/her interest, the reason for such request, and the issues, if any, of fact or law proposed to be controverted, or he/she may request that he/she be notified if the Commission shall order a hearing thereon. Any such communication should be addressed: Secretary, Securities and Exchange Commission, Washington, D.C. 20549. A copy of such request shall be served personally or by

mail upon Applicant at the address stated above. Proof of such service (by affidavit or, in the case of an attorney-at-law, by certificate) shall be filed contemporaneously with the request. As provided by Rule 0-5 of the Rules and Regulations promulgated under the Act, an order disposing of the application will be issued as of course following said date unless the Commission thereafter orders a hearing upon request or upon the Commission's own motion. Persons who request a hearing, or advice as to whether a hearing is ordered, will receive any notices and orders issued in this matter, including the date of the hearing (if ordered) and any postponements thereof.

For the Commission, by the Division of Investment Management, pursuant to delegated authority.

George A. Fitzsimmons,
Secretary.

[FR Doc. 82-7740 Filed 3-22-82; 8:45 am]

BILLING CODE 8010-01-M

[Release No. 12303; 812-5107]

American Federation of Labor and Congress of Industrial Organizations Pooled Investment Trust; Filing of an Application For an Order Exempting Applicant

March 17, 1982.

Notice is hereby given that American Federation of Labor and Congress of Industrial Organizations Pooled Investment Trust ("Trust"), 815 Sixteen Street, NW., Washington D.C. 20006, filed an application on February 5, 1982, for an order of the Commission pursuant to Section 6(c) of the Investment Company Act of 1940 ("Act") exempting the Trust from the provisions of Sections 13(a), 15(a) and (b), 17(a)(3), 22(c) and 22(e) of the Act and Rule 22c-1 thereunder. All interested persons are referred to the application on file with the Commission for a statement of the representations contained therein, which are summarized below.

The Trust states that it is a common law trust sponsored by the American Federation of Labor and Congress of Industrial Organizations ("AFL-CIO") and was created on February 1, 1982, under the laws of the District of Columbia. The Trust further states that interests in it will be represented by certificates of participation ("Certificates") all of which will be held by "labor organizations" as that term is defined in its Declaration of Trust and pension plans constituting qualified trusts ("Eligible Pension Plans") under Section 401(a) of the Internal Revenue

¹To fulfill this condition, Applicant intends to use actual quotations or estimates of market value reflecting current market conditions chosen by its board of directors in the exercise of its discretion to be appropriate indicators of value which may include, *inter alia*, (1) quotations or estimates of market value for individual portfolio instruments, or (2) values obtained from yield data relating to classes of money market instruments published by reputable sources.

²In fulfilling this condition, if the disposition of a portfolio security results in a dollar-weighted average portfolio maturity in excess of 120 days, Applicant will invest available cash in such a manner as to reduce the dollar-weighted average portfolio maturity to 120 days or less as soon as reasonably practicable.

Code of 1954 ("Code") which have beneficiaries who are represented by a labor organization. According to the application, the Trust's corpus will consist primarily of federally issued or guaranteed real estate mortgage and construction loans and certificates representing interests in one or more such loans.

The Trust states that it was created to allow new investments in an AFL-CIO sponsored non-profit investment company. According to the application, the Trust is designed to provide a relatively safe, normally diversified investment vehicle and to finance needed housing and other construction thereby creating job opportunities in the construction trades and related industries. The Trust further states that eligible labor organizations will include 101 national and international unions and 795 states and local central bodies directly affiliated with the AFL-CIO and all other unions. The Trust represents that Certificates will be sold without any sales load or commission and that the Certificates will be non-assignable and non-transferable.

The Trust states that it will be governed by a Board of Trustees ("Board") with up to seventeen members. According to the application, up to eight of the Board's trustees will be officers of the AFL-CIO or its member unions and up to eight will be management employees of one or more corporations contributing to an Eligible Pension Plan. The Trust further states that one trustee will be unaffiliated with either labor or management. According to the application, the trustees will be divided into up to three classes, two with five members and one with six. One class will stand for election each year. The Trust represents that none of the trustees will be compensated for his or her services, but that all will be entitled to reimbursement of expenses for attendance at Board meetings.

According to the application, the Trust will have no employees. The Trust states that all persons responsible for its administration and operation will be salaried employees of the AFL-CIO. The Trust represents that it will pay the AFL-CIO an annual fee equal to one-tenth of one percent of its net asset value for providing such services in quarterly installments but in no event more than the cost the AFL-CIO incurs in providing such services or a reasonable commercial fee for such services, whichever is less. The Trust states that depending upon investor interest and resulting administrative burdens, the trustees may, at a later time, consider hiring employees.

The Trust states that each Certificate will be valued at its pro rata share of the net asset value of the Trust as of the close of business at the end of each calendar quarter ("Valuation Date"). According to the application, the trustees will distribute to participating organizations the net income from the Trust's portfolio at least semiannually. The Trust further states that any order to purchase or request for redemption of Certificates made between Valuation Dates will be considered as having been made 15 days before the next ensuing Valuation Date and will be honored only as of such date.

Section 6(c) of the Act provides, in pertinent part, that the Commission, by order upon application, may conditionally or unconditionally exempt any person, security or transaction, or any class or classes of persons, securities or transactions, from any provision or provisions of the Act, if and to the extent that such exemption is necessary or appropriate in the public interest and consistent with the protection of investors and the purposes fairly intended by the policy and provisions of the Act.

The Trust requests an order pursuant to Section 6(c) of the Act exempting it, to the extent necessary to enable it to operate as herein proposed, from several specific sections of the Act. The Trust asserts that such exemptions are necessary for it to function without restructuring.

Section 13(a)(1) of the Act prohibits, in part, a change of a registered investment company's subclassification from a diversified to a non-diversified company except pursuant to a vote of a majority of its outstanding voting securities. Section 5(b) of the Act defines a diversified company to mean " * * * a management company which meets the following requirements: At least 75 per centum of the value of its total assets is represented by cash and cash items (including receivables), Government securities, securities of other investment companies, and other securities for the purposes of this calculation limited in respect of any one issuer to an amount not greater in value than five per centum of the value of the total assets of such management company and to not more than 10 per centum of the outstanding voting securities of such issuer." Section 5(b) of the Act defines a "non-diversified company" to mean any management company other than a diversified company.

The Trust proposes to invest in mortgages, which, it asserts, are available typically in large denominations and on occasion may

have a principal denomination exceeding five percent of the Trust's total assets. The Trust asserts that given the type of securities it proposes to invest in, a change from diversified to non-diversified status would not change the fundamental nature of the Trust's business. The Trust states that it is in the nature of its business to shift from diversified to non-diversified status and vice-versa. The Trust represents that its investors will be fully informed of this characteristic of its business.

Section 15(a) of the Act makes it unlawful for any person to serve or act as investment adviser of a registered investment company except pursuant to written contract that has been approved by the vote of a majority of the outstanding voting securities of such registered company, and (1) precisely describes all compensation to be paid thereunder; (2) shall continue in effect for a period more than two years from the date of its execution, only so long as such continuance is specifically approved at least annually by the board of directors or by vote of a majority of the outstanding voting securities of such company; (3) provides, in substance, that it may be terminated at any time, without the payment of any penalty, by the board of directors of such registered company or by vote of a majority of the outstanding voting securities of such company on not more than sixty days' written notice to the investment adviser; and (4) provides, in substance, for its automatic termination in the event of its assignment. Section 15(b) of the Act makes it unlawful for any principal underwriter for a registered open-end company to offer for sale, sell, or deliver after sale any security of which such company is the issuer, except pursuant to a written contract with such company, which contract (1) shall continue in effect for a period more than two years from the date of its execution, only so long as such continuance is specifically approved at least annually by the board of directors or by vote of a majority of the outstanding voting securities of such company; and (2) provides, in substance, for its automatic termination in the event of its assignment.

The Trust states that its business affairs will be conducted by employees of the AFL-CIO, which will provide such services pursuant to a written "Personal and Services Contract" at an annual fee equal to one-tenth of one percent of the Trust's net asset value in quarterly installments but in no event more than cost or a reasonable commercial fee, whichever is less. The Trust asserts that the fee arrangement, which will be fully

reviewable by its trustees, is substantially beneficial to the Trust and its certificate holders since the Trust will pay less than cost to the AFL-CIO for administrative and management services, or a reasonable commercial fee, whichever is less.

Section 17(a)(3) makes it unlawful for any affiliated person or promoter of or principal underwriter for a registered investment company or any affiliated person of such a person, promoter, or principal underwriter to borrow money from such registered company. An "affiliated person of another person" is defined in Section 2(a)(3) of the Act to include any person directly or indirectly owning, controlling, or holding with power to vote, 5 per centum or more of the outstanding voting securities of such other person.

The Trust states that it is possible that the AFL-CIO might be deemed an affiliated person or promoter or principal underwriter for the Trust and that some or all the union organizations affiliated with the AFL-CIO might be deemed affiliated persons of an affiliated person or promoter of, or principal underwriter for the Trust. In addition, the Trust states that persons holding five percent or more of the Trust's Certificates might be deemed "affiliated persons" of the Trust.

According to the application, upon receipt of a written irrevocable request for redemption, the Trust, in its discretion in exceptional circumstances involving extreme financial need of the Certificate holder and to the extent cash is available, may advance on a non-discriminatory basis to a Certificate holder up to an amount equal to approximately 80 percent of the net asset value of the Certificate holder's units as of the last Valuation Date and hold those Certificates as security for the advance. The Trust states that if a Certificate holder accepts the advance, the principal and interest on such advance shall be due and payable on the date of payment for redemption of such Certificates and that the payment for redemption shall be set-off against the amount of principal and interest due on the advance. The Trust further states that the Certificate holder shall remain obligated to the Trust for any amount of such advance remaining due after the set-off. The Trust submits that because such advances may be considered loans, an exemption from Section 17(a)(3) is necessary. The Trust submits that the terms of such advances will be reasonable and fair and, since the terms will be pre-established and will apply to all Certificate holders equally, there will

be no opportunity for overreaching on the part of any person concerned.

Section 22(c) of the Act and Rule 22c-1 thereunder provide that no registered investment company issuing a redeemable security and no principal underwriter of such company shall sell or redeem such security except at a price based on the current net asset value which is next computed after receipt of a tender of such security for redemption or of an order to purchase such security. The current net asset value of such security must be computed at least daily on each day (other than a day during which no such security was tendered for redemption and no order to purchase or sell such security was received by the investment company) in which there is a sufficient degree of trading in the investment company's portfolio securities among other things.

Section 22(e) of the Act prohibits registered investment companies from suspending the right of redemption or postponing the date of payment upon redemption of a redeemable security in accordance with its terms for more than seven days after the tender of such security for redemption.

The Trust asserts that the long-term nature of its investments will make valuation and redemption other than on a quarterly basis undesirable and unnecessary. The Trust states that the quarterly redemption date will impose no hardship on Certificate holders since they will be sizeable, well-funded unions and Eligible Pension Plans that normally can foresee their need for funds well in advance and plan around the quarterly redemption dates. The Trust further states that if a Certificate holder has extreme financial need, the Trust can, in its discretion, advance funds to the Certificate holder.

Accordingly, the Trust asserts that an order pursuant to Section 6(c) of the Act, exempting it, to the extent requested, from Sections 13(a)(1), 15(a) and (b), 17(a)(3), 22(c) and 22(e) of the Act and Rule 22c-1 thereunder, would be appropriate in the public interest and consistent with the protections of investors and the purposes fairly intended by the policy and provision of the Act.

Notice is further given that any interested person may, not later than April 12, 1982, at 5:30 p.m., submit to the Commission in writing a request for a hearing on the application accompanied by a statement as to the nature of this interest, the reason for such request, and the issues, if any, of fact or law proposed to be controverted, or he may request that he be notified if the Commission shall order a hearing

thereon. Any such communication should be addressed: Secretary, Securities and Exchange Commission, Washington, D.C. 20549. A copy of such request shall be served personally or by mail upon Applicant at the address stated above. Proof of such service (by affidavit or, in the case of an attorney-at-law, by certificate) shall be filed contemporaneously with the request. As provided by Rule 0-5 of the rules and regulations promulgated under the Act, an order disposing of the application will be issued as of course following said date unless the Commission thereafter orders a hearing upon request or upon the Commission's own motion. Persons who request a hearing, or advice as to whether a hearing is ordered, will receive any notices and orders issued in this matter, including the date of the hearing (if ordered) and any postponements thereof.

For the Commission, by the Division of Investment Management, pursuant to delegated authority.

George A. Fitzsimmons,
Secretary.

[FR Doc. 82-7741 Filed 3-22-82; 8:45 am]

BILLING CODE 8010-01-M

[Release No. 12296; 812-5086]

Cash Assets Fund; Filing of Application for an Order of the Commission Granting Exemptions

March 15, 1982.

Notice is hereby given that Cash Assets Fund ("Applicant"), 82 Devonshire Street, Boston, Massachusetts 02109, registered under the Investment Company Act of 1940 ("Act") as an open-end, diversified, management investment company, filed an application on January 18, 1982, requesting an order of the Commission pursuant to Section 6(c) of the Act, exempting Applicant from the provisions of Section 2(a)(41) of the Act and Rules 2a-4 and 22c-1 under the Act to the extent necessary to permit Applicant to value its assets pursuant to the amortized cost method of valuing portfolio securities. All interested persons are referred to the application on file with the Commission for a statement of the representations contained therein, which are summarized below.

Applicant states that it is a "money market" fund organized as a business trust under the laws of the State of Massachusetts. It is further stated that, as a so-called "series" investment company, Applicant will offer individuals, corporations, fiduciaries

and institutions a means of investing in either of two separate and distinct professionally-managed portfolios of money market instruments (referred to respectively as the "U.S. Government Portfolio" and the "Domestic Money Market Portfolio") with the objective of seeking as high a level of current income as is consistent with the preservation of capital and liquidity. Applicant further states that Fidelity Management & Research Company will serve as investment adviser to Applicant, and that Applicant's shares will be sold without a sales charge.

Applicant represents that its U.S. Government Portfolio will invest exclusively in obligations issued or guaranteed as to principal and interest by the U.S. Government, or its agencies or instrumentalities. Applicant states that its Domestic Money Market Portfolio will invest in obligations of major banks, prime commercial paper, and in U.S. Government obligations. It is also stated that Applicant may enter into repurchase agreements involving any security in which it is permitted to invest, and may purchase new issues of Government securities on a "when-issued" basis.

Applicant represents that the minimum investment in its shares is \$1,000, and that additional investments are accepted in any amount. Applicant states, in addition, that it intends to declare daily dividends of its net investment income, payable in cash at the end of each month. It is also stated that First Tennessee Bank, N.A. ("Bank") will serve as administrator for Applicant, performing services as custodian of the assets of Applicant, and as shareholders' servicing agent. Applicant states that the Bank will receive a fee at an annual rate of .25% of the average net assets of Applicant for performing these services. It is stated further that pursuant to its contract with the Bank, Applicant may purchase securities from or through the Bank, may engage in repurchase transactions with the Bank, and may place funds on deposit in accounts with the Bank subject to receipt of interest at currently available market rates. Lastly, Applicant states that investors will be able to enter into an agreement with the Bank or one of its affiliated banks pursuant to which the Bank, as agent for the investor, will automatically purchase or redeem shares of Applicant in accordance with the investor's instructions. Applicant states that the Bank may charge a fee for this service.

As here pertinent, Section 2(a)(41) of the Act defines value to mean: (1) with respect to securities for which market

quotations are readily available, the market value of such securities; and (2) with respect to other securities and assets, fair value as determined in good faith by the board of directors. Rule 22c-1 adopted under the Act provides, in part, that no registered investment company or principal underwriter therefor issuing any redeemable security shall sell, redeem, or repurchase any such security except at a price based on the current net asset value of such security which is next computed after receipt of a tender of such security for redemption or of an order to purchase or sell such security. Rule 2a-4 adopted under the Act provides, as here relevant, that the "current net asset value" of a redeemable security issued by a registered investment company used in computing its price for the purposes of distribution, repurchase and redemption shall be an amount which reflects calculations made substantially in accordance with the provisions of that rule, with estimates used where necessary or appropriate. Rule 2a-4 further states that portfolio securities with respect to which market quotations are readily available shall be valued at current market value, and that other securities and assets shall be valued at fair value as determined in good faith by the board of directors of the registered company. Prior to the filing of the application, the Commission expressed its view that, among other things: (1) Rule 2a-4 under the Act requires that portfolio instruments of "money market" funds be valued with reference to market factors, and (2) it would be inconsistent, generally, with the provisions of Rule 2a-4 for a "money market" fund to value its portfolio instruments on an amortized cost basis (Investment Company Act Release No. 9786, May 31, 1977).

Section 6(c) of the Act provides, in part, that the Commission, by order upon application, may conditionally or unconditionally exempt any person, security or transaction, or any class or classes of persons, securities or transactions, from any provision or provisions of any Act or of the rules or regulations thereunder, if and to the extent that such exemption is necessary or appropriate in the public interest and consistent with the protection of investors and the purposes fairly intended by the policy and provisions of the Act.

Applicant hereby requests an exemption from the provisions of Section 2(a)(41) of the Act and Rules 2a-4 and 22c-1 thereunder to the extent necessary to permit Applicant to value its portfolio by means of the amortized

cost method of valuation (i.e., valuing securities at cost, adjusted for amortization of premium or accretion of discount).

In support of the relief requested, Applicant states that it has been management's experience that in order to attract and retain investors in money market funds a fund must maintain a stable net asset value (preferably at \$1.00 per share) and a constant and steady flow of investment income. Applicant believes that it can provide these qualities by valuing its assets on the basis of amortized cost, and by declaring dividends on a daily basis of Applicant's net income as earned. Applicant represents that its board of trustees has determined in good faith that in light of Applicant's characteristics as described above, absent unusual or extraordinary circumstances, that the amortized cost method of valuing portfolio securities is appropriate and preferable for Applicant and reflects the fair value of such securities. It is further stated that Applicant's experience has been that, given the nature of its policies and operations, there will be a relatively negligible discrepancy between prices of its portfolio securities arrived at through market valuation methods and those computed on the basis of amortized cost.

In view of the foregoing, Applicant requests an order of the Commission exempting it from the provisions of Section 2(a)(41) of the Act and Rules 2a-4 and 22c-1 thereunder to the extent necessary to permit it to value its portfolio securities using the amortized cost method of valuation. Applicant submits that the issuance of such order, subject to the conditions enumerated below, is appropriate in the public interest and consistent with the protection of investors and the purposes fairly intended by the policy and provisions of the Act. As a prerequisite to the granting of the exemption requested herein, Applicant agrees that the following may be made conditions of the order:

1. In supervising Applicant's operations and delegating special responsibilities involving portfolio management to Applicant's investment adviser, Applicant's board of trustees undertakes—as a particular responsibility within its overall duty of care owed to Applicant's shareholders—to establish procedures reasonably designed, taking into account current market conditions and Applicant's investment objectives, to stabilize Applicant's net asset value per share, as computed for the purpose of

distribution, redemption and repurchase at \$1.00 per share.

2. Included within the procedures to be adopted by the board of trustees shall be the following:

(a) Review by the board of trustees, as it deems appropriate and at such intervals as are reasonable in light of current market conditions, to determine the extent of deviation, if any, of the net asset value per share as determined by using available market quotations from Applicant's \$1.00 amortized cost price per share, and maintenance of records of such review.¹

(b) In the event such deviation from the \$1.00 amortized cost price per share exceeds one half of 1 percent, the board of trustees will promptly consider what action, if any, should be initiated.

(c) Where the board of trustees believes the extent of any deviation from Applicant's \$1.00 amortized cost price per share may result in material dilution or other unfair results to investors or existing shareholders, it shall take such action as it deems appropriate to eliminate or to reduce to the extent reasonably practicable such dilution or unfair results, which action may include: redemption of shares in kind; the sale of portfolio securities prior to maturity to realize capital gains or losses, or to shorten Applicant's average portfolio maturity; withholding dividends; or utilizing a net asset value per share as determined by using available market quotations.

3. Applicant will maintain a dollar-weighted average portfolio maturity appropriate to its objective or maintaining a stable net asset value per share; provided, however, that Applicant will not (a) purchase any instrument with a remaining maturity at the date of acquisition of greater than one year, or (b) maintain a dollar-weighted average portfolio maturity in excess of 120 days.²

4. Applicant will record, maintain and preserve permanently in an easily accessible place a written copy of the procedures (and any modifications

thereto) described in condition 1 above, and Applicant will record, maintain and preserve for a period of not less than six years (the first two years in an easily accessible place) a written record of the board of trustees' considerations and actions taken in connection with the discharge of its responsibilities, as set forth above, to be included in the minutes of the board of trustees' meetings. The documents preserved pursuant to this condition shall be subject to inspection by the Commission in accordance with Section 31(b) of the Act as though such documents were records required to be maintained pursuant to rules adopted under Section 31(a) of the Act.

5. Applicant will limit its portfolio investments, including repurchase agreements, if any, to those U.S. dollar-denominated instruments which the board of trustees determines present minimal credit risks, and which are of high quality as determined by any major rating service, or, in the case of any instrument that is not rated, of comparable quality as determined by the board of trustees.

6. Applicant will include in each quarterly report, as an attachment to Form N-1Q, a statement as to whether any action pursuant to condition 2(c) was taken during the preceding fiscal quarter, and, if any action was taken, will describe the nature and circumstances of such action.

Notice is further given that any interested person may, not later than April 9, 1982, at 5:30 p.m. submit to the Commission in writing a request for a hearing on the application accompanied by a statement as to the nature of his/her interest, the reasons for such request, and the issues, if any, of fact or law proposed to be controverted, or he/she may request that he/she be notified if the Commission shall order a hearing thereon. Any such communication should be addressed: Secretary, Securities and Exchange Commission, Washington, D.C. 20549. A copy of such request shall be served personally or by mail upon Applicant at the address stated above. Proof of such service (by affidavit or, in the case of an attorney-at-law, by certificate) shall be filed contemporaneously with the request. As provided by Rule 0-5 of the rules and regulations promulgated under the Act, an order disposing of the application herein will be issued as of course following said date unless the Commission thereafter orders a hearing upon request or upon the Commission's own motion. Persons who request a hearing, or advice as to whether a hearing is ordered, will receive any

notices and orders issued in this matter, including the date of the hearing (if ordered) and any postponements thereof.

For the Commission, by the Division of Investment Management, pursuant to delegated authority.

George A. Fitzsimmons,
Secretary.

[FR Doc. 82-7739 Filed 3-22-82; 8:45 am]

BILLING CODE 8010-01-M

[Release No. 12297; 812-5100]

Dreyfus Institutional Money Market Fund, Inc.; Filing of Application for an Order of the Commission Granting Exemptions

March 15, 1982.

Notice is hereby given that Dreyfus Institutional Money Market Fund, Inc. (formerly, Dreyfus Money Market Instruments II, Inc.) ("Applicant"), 600 Madison Avenue, New York, New York 10022, registered under the Investment Company Act of 1940 ("Act") as an open-end, diversified, management investment company, filed an application on February 2, 1982, requesting an order of the Commission pursuant to Section 6(c) of the Act, exempting Applicant from the provisions of Section 2(a)(41) of the Act and Rules 2a-4 and 22c-1 under the Act to the extent necessary to permit Applicant to value its portfolio assets pursuant to the amortized cost method of valuing portfolio securities. All interested persons are referred to the application on file with the Commission for a statement of the representations contained therein, which are summarized below.

Applicant states that it is a "money market" fund organized under the laws of the State of Maryland, designed to provide a convenient and economical means for investing short-term funds held by banks and other institutional investors in fiduciary, advisory, agency, custodial, or other similar capacity. Applicant further states that its investment objectives is to provide the maximum level of current income consistent with the preservation of capital and the maintenance of liquidity.

Applicant states that its common stock is divided into two separate, diversified series, each having different investment policies. It is stated that Applicant's Money Market Series pursues Applicant's general investment objective by investing in short-term money market instruments consisting of securities issued or guaranteed by the U.S. Government or its agencies or

¹To fulfill this condition, Applicant will use actual quotations or estimates of market value which reflect current market conditions chosen by its board of trustees in the exercise of its discretion to be appropriate indicators of value. The quotations or estimates utilized may include, *inter alia*, (1) quotations or estimates of market value for individual portfolio instruments, or (2) values obtained from yield data relating to classes of money market instruments furnished by reputable sources.

²In fulfilling this condition, if the disposition of a portfolio instrument results in a dollar-weighted average portfolio maturity in excess of 120 days, Applicant will invest its available cash in such a manner as to reduce its dollar-weighted average portfolio maturity to 120 days or less as soon as reasonably practicable.

instrumentalities (whether or not subject to repurchase agreements), certificates of deposit and time deposits issued by domestic banks or London branches of domestic banks, bankers' acceptances, and high grade commercial paper. Applicant represents that its Government Securities Series pursues Applicant's general investment objectives by investing exclusively in securities issued or guaranteed as to principal and interest by the U.S. Government. Applicant further represents that all instruments of both of its series will have maturities not greater than one year from the date of acquisition, and that the average maturity of all of Applicant's portfolio securities will be 120 days or less. Lastly, Applicant states that all of its portfolio securities will be purchased with and payable in U.S. dollars.

As here pertinent, Section 2(a)(41) of the Act defines value to mean: (1) With respect to securities for which market quotations are readily available, the market value of such securities, and (2) with respect to other securities and assets, fair value as determined in good faith by the board of directors. Rule 22c-1 adopted under the Act provides, in part, that no registered investment company or principal underwriter thereof issuing any redeemable security shall sell, redeem, or repurchase any such security except at a price based on the current net asset value of such security which is next computed after receipt of a tender of such security for redemption or of an order of purchase or sell such security. Rule 2a-4 adopted under the Act provides, as here relevant, that the "current net asset value" of a redeemable security issued by a registered investment company used in computing its price for the purposes of distribution, repurchase and redemption shall be an amount which reflects calculations made substantially in accordance with the provisions of that rule, with estimates used where necessary or appropriate. Rule 2a-4 further states that portfolio securities with respect to which market quotations are readily available shall be valued at current market value, and that other securities and assets shall be valued at fair value as determined in good faith by the board of directors of the registered company. Prior to the filing of the application, the Commission expressed its view that, among other things: (1) Rule 2a-4 under the Act requires that portfolio instruments of "money market" funds be valued with reference to market factors, and (2) it would be inconsistent generally, with the provisions of Rule 2a-4 for a "money

market" fund to value its portfolio instruments on an amortized cost basis (Investment Company Act Release No. 9786, May 31, 1977). In view of the foregoing, Applicant requests an exemption from Section 2(a)(41) of the Act and Rules 2a-4 and 22c-1 thereunder to the extent necessary to permit Applicant to value its portfolio securities using the amortized cost method of valuation.

Section 6(c) of the Act provides, in part, that the Commission, by order upon application, may conditionally or unconditionally exempt any person, security or transaction, or any class or classes of persons, securities or transactions, from any provision or provisions of the Act or of the rules or regulations thereunder, if and to the extent that such exemption is necessary or appropriate in the public interest and consistent with the protection of investors and the purposes fairly intended by the policy and provisions of the Act.

In support of the relief requested, Applicant submits that in the experience of its investment adviser in advising other funds, it has become apparent that two qualities are helpful in order to attract investment, namely (1) stability of principal, and (2) a steady flow of investment income. It is further stated that Applicant's investors are concerned that the daily income declared by each of its series reflect income as earned and that the sales and redemption prices not fluctuate. Applicant submits that it can provide these features to investors by investing in high quality money market instruments of short duration and valuing them on the basis of the amortized cost method of valuation.

Applicant further submits that experience in the management of other funds has demonstrated that, given the nature of Applicant's policies and operations, there usually will be a negligible discrepancy between market value and the amortized cost value of such securities. Accordingly it is stated, Applicant's board of directors has determined in good faith that in light of Applicant's characteristics as described above, absent unusual or extraordinary circumstances, the amortized cost method of valuing portfolio securities is appropriate and preferable for both of Applicant's series and reflects fair value of such securities.

On the basis of the foregoing, Applicant submits that the standards for exemption expressed in Section 6(c) of the Act have been met, and that the issuance of an order subject to the conditions enumerated below, permitting Applicant to value its

portfolio securities using the amortized cost method of valuation would be appropriate in the public interest and consistent with the protection of investors and the purposes fairly intended by the policy and provisions of the Act. In addition, Applicant agrees that the following may be made conditions of the order requested:

1. In supervising Applicant's operations and delegating special responsibilities involving portfolio management to Applicant's investment adviser, Applicant's board of directors undertakes—as a particular responsibility within its overall duty of care owed to Applicant's shareholders—to establish procedures reasonably designed, taking into account current market conditions and Applicant's investment objectives, to stabilize Applicant's net asset value per share, as computed for the purpose of distribution, redemption and repurchase at \$1.00 per share.

2. Included within the procedures to be adopted by the board of directors shall be the following:

(a) Review by the board of directors, as it deems appropriate and at such intervals as are reasonable in light of current market conditions, to determine the extent of deviation, if any, of the net asset value per share as determined by using available market quotations from Applicant's \$1.00 amortized cost price per share, and maintenance of records of such review. To fulfill this condition, Applicant will use actual quotation or estimates of market value which reflect current market conditions chosen by its board of directors in the exercise of its discretion to be appropriate indicators of value. The quotations or estimates utilized may include, *inter alia*, (1) quotations or estimates of market value for individual portfolio instruments, or (2) values obtained from yield data relating to classes of money market instruments furnished by reputable sources.

(b) In the event such deviation from the \$1.00 amortized cost price per share exceeds $\frac{1}{2}$ of 1%, the board of directors will promptly consider what action, if any, should be initiated.

(c) Where the board of directors believes the extent of any deviation from Applicant's \$1.00 amortized cost price per share may result in material dilution or other unfair results to investors or existing shareholders, it shall take such action as it deems appropriate to eliminate or to reduce to the extent reasonably practicable such dilution or unfair results, which action may include: redemption of shares in kind; the sale of portfolio securities prior

to maturity to realize capital gains or losses, or to shorten Applicant's average portfolio maturity; withholding dividends; or utilizing a net asset value per share as determined by using available market quotations.

3. Applicant will maintain a dollar-weighted average portfolio maturity appropriate to its objective of maintaining a stable net asset value per share; provided, however, that Applicant will not (a) purchase any instrument with a remaining maturity at the date of acquisition of greater than one year, or (b) maintain a dollar-weighted average portfolio maturity in excess of 120 days. In fulfilling this condition, if the disposition of a portfolio instrument results in a dollar-weighted average portfolio maturity in excess of 120 days, Applicant will invest its available cash in such a manner as to reduce its dollar-weighted average portfolio maturity to 120 days or less as soon as reasonably practicable.

4. Applicant will record, maintain and preserve permanently in an easily accessible place a written copy of the procedures (and any modifications thereto) described in condition 1 above, and Applicant will record, maintain and preserve for a period of not less than six years (the first two years in an easily accessible place) a written record of the board of directors' considerations and actions taken in connection with the discharge of its responsibilities, as set forth above, to be included in the minutes of the board of directors' meetings. The documents preserved pursuant to this condition shall be subject to inspection by the Commission in accordance with Section 31(b) of the Act as though such documents were records required to be maintained pursuant to rules adopted under Section 31(a) of the Act.

5. Applicant will limit its portfolio investments, including repurchase agreements, if any, to those U.S. dollar-denominated instruments which the board of directors determines present minimal credit risks, and which are of high quality as determined by any major rating service, or, in the case of any instrument that is not rated, of comparable quality as determined by the board of directors.

6. Applicant will include in each quarterly report, as an attachment to Form N-1Q, a statement as to whether any action pursuant to condition 2(c) above was taken during the preceding fiscal quarter, and, if any action was taken, will describe the nature and circumstances of such action.

Notice is further given that any interested person may, not later than April 9, 1982, at 5:30 p.m. submit to the

Commission in writing a request for a hearing on the application accompanied by a statement as to the nature of his/her interest, the reasons for such request, and the issues, if any, of fact or law proposed to be controverted, or he/she may request that he/she be notified if the Commission shall order a hearing thereon. Any such communication should be addressed: Secretary, Securities and Exchange Commission, Washington, D.C. 20549. A copy of such request shall be served personally or by mail upon Applicant at the address stated above. Proof of such service (by affidavit or, in the case of an attorney-at-law, by certificate) shall be filed contemporaneously with the request. As provided by Rule 0-5 of the rules and regulations promulgated under the Act, an order disposing of the application herein will be issued as of course following said date unless the Commission thereafter orders a hearing upon request or upon the Commission's own motion. Persons who request a hearing, or advice as to whether a hearing is ordered, will receive any notices and orders issued in this matter, including the date of the hearing (if ordered) and any postponements thereof.

For the Commission, by the Division of Investment Management, pursuant to delegated authority.

George A. Fitzsimmons,
Secretary.

[FR Doc. 82-7738 Filed 3-22-82; 8:45 am]

BILLING CODE 8010-01-M

[Release No. 12302; 812-5087]

Gradison U.S. Government Trust; Filing of Application for an Order of the Commission Exempting Applicant From the Provisions

March 17, 1982.

Notice is hereby given that Gradison U.S. Government Trust ("Applicant"), The 580 Building, Cincinnati, Ohio 45202, registered under the Investment Company Act of 1940 ("Act") as an open-end, diversified, management investment company, filed an application on January 15, 1982, requesting an order of the Commission pursuant to Section 6(c) of the Act to exempt Applicant from the provisions of Section 2(a)(41) of the Act and Rules 2a-4 and 22c-1 thereunder, to the extent necessary to permit Applicant to value its assets using the amortized cost method of valuation. All interested persons are referred to the application on file with the Commission for a statement of the representations

contained therein, which are summarized below.

Applicant states that it is a "money market" fund organized under the laws of the State of Massachusetts as an unincorporated business trust. It is further stated that Applicant's investment objective is to seek maximum current income consistent with a high degree of safety by investing exclusively in obligations issued, guaranteed, or insured by the United States Government, its agencies, or instrumentalities, and in repurchase agreements secured by such obligations. Applicant states that Gradison & Company Incorporated will serve as Applicant's investment adviser.

Applicant represents that its board of trustees intends to establish procedures designed to stabilize, to the extent reasonably possible, the net asset value of its shares, computed for the purpose of distribution, redemption and repurchase, at \$1.00. It is further stated that experience indicates that a money market fund must be able to provide (1) stability of principal, and (2) a steady flow of predictable and competitive investment income. Applicant asserts that it can offer these features to investors by maintaining a portfolio of high quality government securities valued on the basis of the amortized cost method of valuation. Applicant states that in accordance with the amortized cost method of valuation, a portfolio security is valued at its historic cost (purchase price), and the interest to be earned on the security (plus any discount received, or minus any premium paid upon purchase) is accrued ratably over the remaining maturity of the security. It is stated that by declaring these accruals to Applicant's shareholders as a daily dividend, the value per share, will generally remain constant.

As here pertinent, Section 2(a)(41) of the Act defines value to mean: (1) With respect to securities for which market quotations are readily available, the market value of such securities, and (2) with respect to other securities and assets, fair value as determined in good faith by the board of directors. Rule 22c-1 adopted under the Act provides, in part, that no registered investment company or principal underwriter therefor issuing any redeemable security shall sell, redeem or repurchase any such security except at a price based on the current net asset value of such security which is next computed after receipt of a tender of such security for redemption or of an order to purchase or sell such security.

Rule 2a-4 adopted under the Act provides, as here relevant, that the "current net asset value" of a redeemable security issued by a registered investment company used in computing its price for the purposes of distribution, redemption and repurchase shall be an amount which reflects calculation made substantially in accordance with the provisions of that rule, with estimates used where necessary or appropriate. Rule 2a-4 further states that portfolio securities with respect to which market quotations are readily available shall be valued at current market value and other securities and assets shall be valued at fair value as determined in good faith by the board of directors of the investment company. Prior to the filing of the application, the Commission expressed its view that, among other things, (1) Rule 2a-4 under the Act requires that portfolio instruments of "money market" funds be valued with reference to market factors, and (2) it would be inconsistent generally, with the provisions of Rule 2a-4 for a "money market" fund to value its portfolio instruments on an amortized cost basis (Investment Company Act Release No. 9786, May 31, 1977). Therefore, Applicant requests that the Commission issue an order pursuant to Section 6(c) of the Act permitting it to use the amortized cost method of valuation in pricing its shares for sale, redemption and repurchase.

Section 6(c) of the Act provides, in pertinent part, that the Commission, by order upon application may conditionally or unconditionally exempt any person, security, or transaction, or any class or classes of persons, securities, or transactions, from any provision or provisions of the Act or of any rule or regulation thereunder, if and to the extent that such exemption is necessary or appropriate in the public interest and consistent with the protection of investors and the purposes fairly intended by the policy and provisions of the Act.

Applicant represents that its board of trustees has determined in good faith that, in light of Applicant's characteristics, the amortized cost method of valuation of portfolio securities is, absent unusual or extraordinary circumstances, preferable to the use of a market valuation method. Applicant states that, given the nature of its policies and operations, there should be a negligible discrepancy between prices obtained by the amortized cost method and those obtained by a market valuation method. Therefore, it is asserted, Applicant's use of the

amortized cost valuation method would not be inconsistent with the policy of the Act, as implemented by Rule 2a-4, nor would it detract from the protection of investors afforded by the Rule.

Applicant's board of trustees has determined, Applicant states, to monitor continuously values indicated by valuation methods other than the amortized cost valuation method in order to assure that the method of valuation which Applicant is utilizing approximately represents fair value in view of all pertinent factors.

1. Applicant has agreed that the following conditions may be imposed in any order of the Commission granting the exemptive relief requested:

1. In supervising Applicant's operations and delegating special responsibilities involving management of Applicant's portfolio to Applicant's investment adviser, Applicant's board of trustees undertakes—as a particular responsibility within its overall duty of care owed to Applicant's shareholders—to establish procedures reasonably designed, taking into account current market conditions and Applicant's investment objectives, to stabilize applicant's net asset value per share, as computed for the purpose of distribution, redemption and repurchase, at \$1.00 per share.

2. Included within the procedures to be adopted by the board of trustees shall be the following:

(a) Review by the board of trustees, as it deems appropriate and at such intervals as are reasonable in light of current market conditions, to determine the extent of deviation, if any, of Applicant's net asset value per share as determined by using available market quotations from the \$1.00 amortized cost price per share, and maintenance of records of such review.¹

(b) In the event such deviation from Applicant's \$1.00 amortized cost price per share exceeds $\frac{1}{2}$ of 1 percent, a requirement that the board of trustees will promptly consider what action, if any, should be initiated.

(c) Where the board of trustees believes that the extent of any deviation from Applicant's \$1.00 amortized cost price per share may result in material dilution or other unfair results to investors or existing shareholders, it

¹ To fulfill this condition, Applicant intends to use actual quotations or estimates of market value reflecting current market conditions chosen by its board of trustees in the exercise of its discretion to be appropriate indicators of value, which may include among others, (i) quotations or estimates of market value for individual portfolio instruments, or (ii) values obtained from yield data relating to classes of money market instruments published by reputable sources.

shall take such action as it deems appropriate to eliminate or to reduce to the extent reasonably practicable such dilution or unfair results, which action may include: redeeming shares in kind; selling portfolio instruments prior to maturity to realize capital gains or losses, or to shorten Applicant's average portfolio maturity; withholding dividends; or utilizing a net asset value per share as determined by using available market quotations.

3. Applicant will maintain a dollar-weighted average portfolio maturity appropriate to its objective of maintaining a stable net asset value per share; provided, however, that Applicant will not (a) purchase any instrument with a remaining maturity of greater than one year, or (b) maintain a dollar-weighted average portfolio maturity which exceeds 120 days.²

4. Applicant will record, maintain and preserve permanently in an easily accessible place a written copy of the procedures (and any modifications thereto) described in condition 1 above, and Applicant will record, maintain and preserve for a period of not less than six years (the first two years in an easily accessible place) a written record of the board of trustees' considerations and actions taken in connection with the discharge of its responsibilities, as set forth above, to be included in the minutes of the board of trustees' meetings. The documents preserved pursuant to this condition shall be subject to inspection by the Commission in accordance with Section 31(b) of the Act as though such documents were records required to be maintained pursuant to rules adopted under section 31(a) of the Act.

5. Applicant will limit its portfolio investments, including repurchase agreements, to those United States dollar-denominated instruments which the board of trustees determines present minimal credit risks, and which are of high quality as determined by any major rating service, or, in the case of any instrument that is not rated, of comparable quality as determined by Applicant's board of trustees.

6. Applicant will include in each quarterly report, as an attachment to Form N-1Q, a statement as to whether any action pursuant to condition 2(c) above was taken during the preceding fiscal quarter, and, if any action was

² In fulfilling this condition, if the disposition of a portfolio instrument results in a dollar-weighted average portfolio maturity in excess of 120 days, Applicant will invest its available cash in such a manner as to reduce the dollar-weighted average portfolio maturity to 120 days or less as soon as reasonably practicable.

taken, will describe the nature and circumstances of such action.

Notice is further given that any interested person may, not later than April 12, 1982, at 5:30 p.m., submit to the Commission in writing a request for a hearing on the application accompanied by a statement as to the nature of his/her interest, the reasons for such request, and the issues, if any, of fact or law proposed to be controverted, or he/she may request that he/she be notified if the Commission shall order a hearing thereon. Any such communication should be addressed: Secretary, Securities and Exchange Commission, Washington, D.C. 20549. A copy of such request shall be served personally or by mail upon Applicant at the address stated above. Proof of such service (by affidavit or, in the case of an attorney-at-law, by certificate) shall be filed contemporaneously with the request. As provided by Rule 0-5 of the Rules and Regulations promulgated under the Act, an order disposing of the application herein will be issued as of course following said date unless the Commission thereafter orders a hearing upon request or upon the Commission's own motion. Persons who request a hearing, or advice as to whether a hearing is ordered, will receive any notices and orders issued in this matter, including the date of the hearing (if ordered) and any postponements thereof.

For the Commission, by the Division of Investment Management, pursuant to delegated authority.

George A. Fitzsimmons,
Secretary.

[FR Doc. 7742 Filed 3-22-82; 8:45 am]

BILLING CODE 8010-01-M

SMALL BUSINESS ADMINISTRATION

Interest Rates

The interest rate on section 7(a) Small Business Administration direct business loans (as amended by Pub. L. 97-35) and the SBA share of immediate participation loans is fifteen and five-eighths (15½) percent for the fiscal quarter beginning April 1, 1982.

On a quarterly basis, the Small Business Administration also publishes an interest rate called the optional "peg" rate (13 CFR 120.3(b)(2)(iii)). This rate is a weighted average cost of money to the government for maturities similar to the average SBA loan. This rate may be used as a base rate for guaranteed fluctuating interest rate SBA loans. For the April-June quarter of 1982, this rate

will be fourteen and three-eighths (14¾) percent.

Dated: March 18, 1982.

Edwin T. Holloway,

Associate Administrator for Finance & Investment.

[FR Doc. 82-7744 Filed 3-22-82; 8:45 am]

BILLING CODE 8025-01-M

[Declaration of Disaster Loan Area #2029]

Oregon; Declaration of Disaster Loan Area

Tillamook County in the State of Oregon constitutes a disaster area as a result of damage caused by flooding which occurred on January 22, 1982. Eligible persons, firms and organizations may file applications for loans for physical damage until the close of business on May 14, 1982, and for economic injury until December 15, 1982, at the address below: Small Business Administration, Federal Building-Room 676, 1220 S.W. Third Avenue, Portland, Oregon 97204, or other locally announced locations.

Interest rates for applicants filing for assistance under this declaration are as follows:

Homeowners with credit available elsewhere—15¼%

Homeowners without credit available elsewhere—7½%

Businesses with credit available elsewhere—15¼%

Businesses without credit available elsewhere—8%

Businesses (EIDL) without credit available elsewhere—8%

Other (non-profit organizations including charitable and religious organizations)—11½%

It should be noted that assistance for agricultural enterprises is the primary responsibility of the Farmers Home Administration as specified in Pub. L. 96-302.

Information on recent statutory changes (Pub. L. 97-35, approved August 13, 1981) is available at the above-mentioned office.

(Catalog of Federal Domestic Assistance Programs Nos. 59002 and 59008)

Dated: March 15, 1982.

Robert A. Turnbull,

Acting Administrator.

[FR Doc. 82-7743 Filed 3-22-82; 8:45 am]

BILLING CODE 8025-01-M

DEPARTMENT OF THE TREASURY

Fiscal Service

[Dept. Circ. 570, 1981 Rev., Supp. No. 18]

Surety Companies Acceptable on Federal Bonds

A certificate of authority as an acceptable surety on Federal bonds is hereby issued to the following company under sections 6 to 13 of Title 6 of the United States Code. An underwriting limitation of \$504,000 has been established for the company.

Name of Company:

THE NATIONAL MUTUAL INSURANCE COMPANY

Business Address:

Insurance Square

Celina, Ohio 45822

State of Incorporation:

Ohio

Certificates of authority expire on June 30 each year, unless renewed prior to that date or sooner revoked. The certificates are subject to subsequent annual renewal so long as the companies remain qualified (31 CFR, Part 223). A list of qualified companies is published annually as of July 1 in Department Circular 570, with details as to underwriting limitations, areas in which licensed to transact surety business and other information. Federal bond-approving officers should annotate their reference copies of Treasury Circular 570, 1981 Revision, at page 33971 to reflect this addition. Copies of the circular, when issued, may be obtained from the Audit Staff, Bureau of Government Financial Operations, Department of the Treasury, Washington, D.C. 20226.

Dated: March 12, 1982.

W. E. Douglas,

Commissioner, Bureau of Government Financial Operations.

[FR Doc. 82-7692 Filed 3-22-82; 8:45 am]

BILLING CODE 4810-35-M

VETERANS ADMINISTRATION

Station Committee on Educational Allowances; Meeting

Notice is hereby given pursuant to Section V, Review Procedure and Hearing Rules, Station Committee on Educational Allowances that on April 20, 1982, at 10:00 a.m., the San Diego Regional Office Station Committee on Educational Allowances shall at Room 501, 2022 Camino Del Rio North, San Diego, California 92108 conduct a

hearing to determine whether Veterans Administration benefits to all eligible persons enrolled in Hillcrest College of Health Careers, 3300 Sixth Avenue, San Diego, California 92103 should be discontinued, as provided in 38 CFR

21.4134, because a requirement of law is not being met or a provision of the law has been violated. All interested persons shall be permitted to attend, appear before, or file statements with the committee at that time and place.

Dated: March 16, 1982.

Herbert R. Rainwater,
*Director, VA Regional Office, 2022 Camino
Del Rio North, San Diego, California 92108.*

[FR Doc. 82-7699 Filed 3-22-82; 8:45 am]

BILLING CODE 9320-01-M

Sunshine Act Meetings

Federal Register

Vol. 47, No. 56

Tuesday, March 23, 1982

This section of the FEDERAL REGISTER contains notices of meetings published under the "Government in the Sunshine Act" (Pub. L. 94-409) 5 U.S.C. 552b(e)(3).

CONTENTS

	Items
Civil Aeronautics Board.....	1
Federal Energy Regulatory Commission.....	2
Federal Mine Safety and Health Review Commission.....	3
Federal Reserve System.....	4, 5, 6
Nuclear Regulatory Commission.....	7

1

[M-345, March 18, 1982]

CIVIL AERONAUTICS BOARD.

TIME AND DATE: 3:00 p.m., March 31, 1982.

PLACE: Room 1027, 1825 Connecticut Avenue, N.W., Washington, D.C. 20428.

SUBJECT: Update of Piedmont Airlines' progress under deregulation and its plans for the future.

STATUS: Open.

PERSON TO CONTACT: Phyllis T. Kaylor, the Secretary, (202) 673-5068.

[S-422-82 Filed 3-19-82; 3:14 pm]

BILLING CODE 6320-01-M

2

FEDERAL ENERGY REGULATORY COMMISSION

TIME AND DATE: March 25, 1982, 9:00 a.m.

PLACE: 825 North Capitol Street, N.E., Washington, D.C. 20426, Room 9306.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

- (1) Docket No. CI81-14-000, Inexco Oil Company.
- (2) Docket No. RI75-112-000, Certain Pipeline and Producer Respondents.
- (3) Docket No. CP75-93-001 (Remand), Black Marlin Pipeline Company.
- (4) Docket No. IN80-1, Ship Shoal Pipeline System.

CONTACT PERSON FOR MORE INFORMATION:

Kenneth F. Plumb, Secretary, Telephone (202) 357-8400.
Kenneth F. Plumb,
Secretary.

[S-419-82 Filed 3-19-82; 9:31 am]

BILLING CODE 6717-02-M

3

FEDERAL MINE SAFETY AND HEALTH REVIEW COMMISSION

March 17, 1982.

TIME AND DATE: 10:00 a.m., Wednesday, March 24, 1982.

PLACE: Room 600, 1730 K Street, N.W., Washington, D.C.

STATUS: Open.

MATTERS TO BE CONSIDERED: The Commission will consider and act upon the following:

1. Texas Industries, Inc., Docket No. CENT 79-60-M; Petition for Discretionary Review (Issues include whether the judge erred in finding a violation of 30 CFR 56.9-5).
2. Capitol Aggregates, Inc., Docket No. CENT 79-300-M; (Issues include whether violation of 30 CFR 56.9-22 occurred due to failure to provide berms on a loading ramp).

CONTACT PERSON FOR MORE INFO:

Jean Ellen, (202) 653-5632.

[S-419-82 Filed 3-19-82; 1:58 pm]

BILLING CODE 6820-12-M

4

FEDERAL RESERVE SYSTEM Board of Governors.

TIME AND DATE: 10:00 a.m., Friday, March 26, 1982.

PLACE: 20th Street and Constitution Avenue, N.W., Washington, D.C. 20551.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

1. Personnel actions (appointments, promotions, assignments, reassignments, and salary actions) involving individual Federal Reserve System employees.
2. Any items carried forward from a previously announced meeting.

CONTACT PERSON FOR MORE INFORMATION:

Mr. Joseph R. Coyne, Assistant to the Board; (202) 452-3204.

Dated: March 18, 1982.

James McAfee,
Assistant Secretary of the Board.

[S-417-82 Filed 3-18-82; 4:15 pm]

BILLING CODE 6210-01-M

5

FEDERAL RESERVE SYSTEM Board of Governors.

TIME AND DATE: 10:00 a.m., Monday, March 29, 1982.

PLACE: 20th Street and Constitution Avenue, N.W., Washington, D.C. 20551.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

1. Proposed acquisition of computer equipment within the Federal Reserve System.
2. Personnel actions (appointments, promotions, assignments, reassignments, and salary actions) involving individual Federal Reserve System employees.
3. Any items carried forward from a previously announced meeting.

CONTACT PERSON FOR MORE INFORMATION:

Mr. Joseph R. Coyne, Assistant to the Board; (202) 452-3204.

Date: March 19, 1982.

James McAfee,
Assistant Secretary of the Board.

[S-423-82 Filed 3-19-82; 4:07 pm]

BILLING CODE 6210-01-M

6

FEDERAL RESERVE SYSTEM Board of Governors.

"FEDERAL REGISTER" CITATION OF PREVIOUS ANNOUNCEMENT: Notice forwarded to Federal Register on March 16, 1982.

PREVIOUSLY ANNOUNCED TIME AND DATE OF THE MEETING: 10:00 a.m., Wednesday, March 24, 1982.

CHANGES IN THE MEETING:

(1) One of the items announced for inclusion at this meeting was consideration of any agenda items carried forward from a previous meeting; the following such open item is added:

Proposal to adopt 1982 fee schedule for wire transfer and net settlement services. (This matter was originally announced for a meeting on Wednesday, March 17, 1982.)

(2) The following open item is deleted from the agenda:

Proposed revisions to the Federal Reserve policy on borrowing by System examiners.

CONTACT PERSON FOR MORE INFORMATION:

Mr. Joseph R. Coyne, Assistant to the Board; (202) 452-3204.

Date: March 19, 1982.

James McAfee,
Assistant Secretary of the Board.

[S-420-82 Filed 3-19-82; 2:15 pm]

BILLING CODE 6210-01-M

7

NUCLEAR REGULATORY COMMISSION

DATE: Week of March 22, 1982 (Revised) and Week of March 29, 1982.

PLACE: Commissioners' Conference Room, 1717 H Street, NW., Washington, D.C.

STATUS: Open/Closed.

MATTERS TO BE CONSIDERED:

Tuesday, March 23

1:30 p.m.: Meeting with the Advisory Panel for the Decontamination of TMI-2 (public meeting) (as announced)

3:00 p.m.: Discussion of Pending Investigation (closed meeting) (continued from 3/19)

Thursday, March 25

10:00 a.m.: Briefing on Steam Generator Problems (public meeting) (as announced)

3:00 p.m.: Affirmation/Discussion Session (public meeting). Items to be affirmed and/or discussed:

- a. Proposed Addition on 10 CFR 50.73 Establishing the Licensee Event Report (LER) System (Postponed from 3/18)
- b. Psychological Health Under the Atomic Energy Act—Draft Order
- c. Amendment to 10 CFR 35 to Require Installation of Radiation Monitors in Teletherapy Rooms and Periodic Inspection and Servicing of Teletherapy Machines

Thursday, April 1

10:00 a.m.: Discussion of Waste Confidence Proceeding (public meeting)

2:00 p.m.: Discussion of Frequency of Emergency Preparedness Exercises (public meeting)

4:00 p.m.: Affirmation/Discussion Session (public meeting). Items to be affirmed and/or discussed:

- a. 10 CFR Part 50—Proposed Rule to Clarify Applicability of License Conditions and Technical Specifications in an Emergency
- b. Final Rule—Amendment to 10 CFR 50.54(r)—Modification of Requirements for Submittal of Emergency Plans by Research and Test Reactor Licensees
- c. Advance Notice of Proposed Rulemaking on Certification of Industrial Radiographers (NDTMA Petition for Rulemaking PRM-34-2)
- d. Request for Hearing Following Denial of Renewal of Part 30 Byproducts Materials License

Friday, April 2

10:00 a.m.: Discussion of Management Organization and Internal Personnel Matters (closed meeting)

ADDITIONAL INFORMATION: By a vote of 3-0, Commissioners Gilinsky and Bradford not present, on March 18, the Commission determined pursuant to 5 U.S.C. 552b(e) and 9.107a of the Commission's Rules that Commission

business required that affirmation of Final rule on Intransit Physical Protection of Special Nuclear Material of Moderate Strategic Significance (10 CFR Part 73), held that day, and Briefing on Pending Investigation (Closed Meeting), scheduled for March 19, be held on less than one week's notice to the public.

Discussion of Waste Confidence Proceeding, scheduled for March 23, has been cancelled.

AUTOMATIC TELEPHONE ANSWERING

SERVICE FOR SCHEDULE UPDATE: (202)

634-1498. Those planning to attend a meeting should reverify the status on the day of the meeting.

CONTACT PERSON FOR MORE

INFORMATION: Walter Magee (202) 634-1410.

Dated: March 18, 1982.

Walter Magee,

Office of the Secretary.

[S-421-82 Filed 3-19-82; 2:57 pm]

BILLING CODE 7590-01-M

Estroval Tablets

Tuesday
March 23, 1982

Part II

Department of Health and Human Services

Food and Drug Administration

Topical Acne Drug Products for Over-
the-Counter Human Use; Establishment of
a Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Part 333**

[Docket No. 81N-0114]

Topical Acne Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration.
ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of a proposed rulemaking that would establish conditions under which over-the-counter (OTC) acne drug products are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by June 21, 1982 and reply comments by July 21, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on November 15, 1980 a report on OTC acne drug products from the Advisory Review Panel on OTC Antimicrobial (II) Drug Products. FDA regulations (21 CFR 330.10 (a)(6)) provide that the agency issue in the *Federal Register* a proposed order containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC acne drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions

under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgement of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the *Federal Register* a tentative final monograph for OTC acne drug products as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency's position on OTC acne drug products will be stated initially when the tentative final monograph is published in the *Federal Register* as a notice of proposed rulemaking. In that notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the *Federal Register* of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC acne drug products. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC acne drug products should be

accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC acne drug products submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after April 22, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

FDA published in the *Federal Register* of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler v. Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the *Federal Register*. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe

and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the *Federal Register* of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the *Federal Register* of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all antimicrobial active ingredients for the treatment and prevention of specific disorders such as seborrhea, dandruff, acne, athlete's foot, vaginitis, and otitis externa (swimmer's ear) was issued in the *Federal Register* of December 16, 1972 (37 FR 26842). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.'")

A subsequent request for data and information on topical antibiotic active ingredients used in OTC products for treatment and prevention of infections in minor skin wounds was published in the *Federal Register* of September 7, 1973 (38 FR 24391). The Panel's conclusions and recommendations for topical antibiotic drug products were published in the *Federal Register* of April 1, 1977 (42 FR 17642).

Products for the treatment of swimmer's ear were referred for review to the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Products. Products for the intravaginal treatment of vaginitis were referred for review to the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products. Products for the treatment of dandruff and seborrhea were referred for review to the Advisory Review Panel on OTC Miscellaneous External Drug Products.

In this document the Panel presents its conclusions and recommendations for acne drug products. The Panel's conclusions and recommendations for topical antifungal drug products are published elsewhere in this issue of the *Federal Register*.

Under § 330.10(a) (1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients contained in antimicrobial products:

Wallace Guess, Ph. D., Chairman
Frank B. Engley, Jr., Ph. D.
Paul D. Stolley, M.D., M.P.H. (resigned June 1977)
William F. Schorr, M.D. (resigned July 1977)
W. Kenneth Blaylock, M.D.
E. Dorinda Shelley, M.D.
Margaret Hitchcock, Ph. D. (resigned September 1974)
David R. Brown Sc. D. (appointed March 1975, resigned March 1976)
Eula Bingham, Ph. D. (appointed July 1976, resigned June 1977)
James E. Rasmussen, M.D. (appointed October 1976)
George B. Youngstrom, M.D. (appointed June 1977, resigned October 1979)
Anne Tucker, Ph. D. (Panel consultant from July 1978 to March 1979; appointed as a Panel member March 1979)
Zenona W. Mally, M.D. (appointed October 1979)

The Panel first convened on July 26 and 27, 1974 in an organizational meeting. Working meetings which dealt with the topic in this document were held on June 9 and 10, 1978; March 23 and 24, April 27 and 28, July 20, August 17 and 18, October 12 and 13, November 16 and 17, 1979; February 22 and 23, March 21 and 22, April 25 and 26, June 6 and 7, July 18 and 19, September 21 and 22, and November 14 and 15, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above).

The following nonvoting liaison representatives served on the Panel: Sarah Newman, nominated by an ad hoc

group of consumer organizations, served as the consumer liaison. Gavin Hildick-Smith, M.D., nominated by the Cosmetic, Toiletry and Fragrance Association, served as an industry liaison until April 1978. Michael Winrow, Ph. D., nominated by the Proprietary Association, also served as an industry liaison until April 1979, followed by Kenneth R. Johannes until January 1980, followed by C. Elizabeth McKinivan, M.D.

The following FDA employees served: Mary K. Bruch served as Executive Secretary; Michael Kennedy served as Panel Administrator in July 1974, followed by Armond M. Welch, R.Ph., until August 1978, followed by Lee Geismar, Melvin Lessing, R.Ph., M.S., served as Drug Information Analyst until October 1974, followed by Joseph Hussion, R.Ph., until July 1976, followed by Anne W. Eggers, R.Ph., M.S., until June 1978, followed by Elaine G. Euchner, R.Ph.

The following individuals were given an opportunity to appear before the Panel to express their views on acne drug products either at their own or at the Panel's request:

Eugene A. Conrad, Ph. D.
Richard Dobson, M.D.
Charles A. Evans, M.D., Ph. D.
Carol Farhi
Samuel B. Frank, M.D.
Arnold Friede
David Fulgham, M.D.
Eugene Gans, Ph. D.
George Hoffnagle, Sc. D.
Albert M. Kligman, M.D., Ph. D.
William H. Lederer, Ph. D., J.D.
James J. Leyden, M.D.
Zenona W. Mally, M.D. (before becoming a Panel member)
Philip Merker, Ph. D.
Sergio Nacht, Ph. D.
Albert Packman, D. Sc.
Peter Pochi, M.D.
Sirje M. Puhvel, Ph. D.
Alan Shalita, M.D.
Vithal Shetty, Ph. D.
John Strauss, M.D.
Harold Upjohn, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through November 15, 1980 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC acne drug products with respect to the following three categories:

Category I. Conditions under which OTC acne drug products are generally

recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC acne drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed 27 active ingredients in topically applied acne products and classified 2 ingredients in Category I, 23 ingredients in Category II, and 2 ingredients in Category III.

I. Submission of Data and Information

A. Submissions by Firms

Firms and Marketed Products

AHC Pharmacal, Miami, FL 33125.

bp Gel Medication, bp Gel Medication Strong.

Barnes-Hind Pharmaceuticals, Inc., Sunnyvale, CA 94086.

Komed Acne Lotion, Komed Mild Acne Lotion, Komex Acne Scrub.

Bowman Pharmaceuticals, Inc., Canton, OH 44702.

Bowman Drawing Paste.

Campana Corp., Batavia, IL 60510.

Cuticura Acne Cream (Cutitone).

Carter Products, Inc., Cranbury, NJ 08512.

Persol.

Chattam Drug and Chemical Co., Chattanooga, TN 37409.

Mudd.

Dermik Laboratories, Inc., Fort Washington, PA 19034.

Vlemasque.

Dome Laboratories, West Haven, CT 06516.

Acne-Dome Creme, Acne-Dome Lotion, Acne-Dome Medicated Cleanser, Vlem-Dome Wet Dressing.

Flow Pharmaceuticals, Inc., Palo Alto, CA 94303.

d-SEB.

Fox Pharmacal, Inc., North Miami, FL 33161.

Aktex.

H. B. Distributing Co., West Newton, MA 02165.

Hospital Brand Acne Cream.

Helena Rubinstein, Inc., New York, NY 10022.

Bio-Clear Medicated Cream.

Ketchum Laboratories, Inc., Amityville, NY 11701.

Propoa pH Super Cleanser.

Laboratory Robaina, Inc., Hialeah, FL 33010.

Acetolia Robaina.

Norcliff Thayer, Inc., Tuckahoe, NY 10707.

Oxy-5 Lotion, Oxy-10 Lotion.

Pennwalt Corp., Rochester, NY 14603.

Bare Face Acne Skin Medicine, Ting

Antiseptic Medicated Cream.

Poythress, William P., & Co., Inc., Richmond, VA 23261.

Bensulfoid Lotion.

Press Chemical & Pharmaceutical

Laboratories, Inc., Columbus, OH 43206.

Epsal Ointment.

Preston Pharmaceuticals, Inc., Butler, NJ 07405.

Dermakon Dandruff Shampoo, Dermakon Medicated Cream.

Purdue Frederick Co., Norwalk, CT 06856.

Betadine Skin Cleanser, Betadine Skin

Cleanser Foam.

Rorer, William H., Inc., Fort Washington, PA 19034.

Loroxide Lotion, Vanoxide Lotion.

Schattner, R., Co., Washington, DC 20016.

Chloraderm.

Smith, Kline, & French Laboratories, Philadelphia, PA 19101.

Acnomel Acne Cake, Acnomel Acne Cream.

Squibb, E. R., & Sons, Inc., New Brunswick, NJ 08903.

Epi*Clear Acne Lotion, Epi*Clear Acne

Scrub Cleanser, Epi*Clear Acne Soap,

Epi*Clear Antiseptic Lotion 5%,

Epi*Clear Antiseptic Lotion 10%,

Epi*Clear Squibb Acne Kit.

Sterling Drug, Inc., New York, NY 10016.

Campho-Phenique Liquid, pHisoAc, Stridex Medicated Pads.

Stiefel Laboratories, Inc., Oak Hill, NY 12460.

SASTid Soap, Sulfoxyl Cream Strong,

Sulfoxyl Lotion Regular, Sulfoxyl Lotion Strong.

Syntex Laboratories, Inc., Palo Alto, CA 94304.

Microsunny Acne Lotion.

Texas Pharmacal Co., San Antonio, TX 78296.

Contrablen, Liquimat, Persadox Cream,

Persadox Lotion, Sulfocin Base 4%,

Sulfocin Lotion.

Upjohn Co., Kalamazoo, MI 49001.

Plexion, Zinc Sulfide Compound Lotion, Improved.

Vick Divisions Research and Development, Division of Richardson-Merrell, Inc.,

Wilton, CT 06897.

Clearasil Regular Tinted, Clearasil Stick

Medication, Clearasil Vanishing

Formula.

Warner-Lambert Co., Morris Plains, NJ 07950.

Listerex Antibacterial Scrub Gel, Listerex

Antibacterial Scrub Lotion, Listerex

Herbal Scrub.

Westwood Pharmaceuticals, Inc., Buffalo, NY 14213.

Fostex Cake, Fostex Cream, Fostril, Pernox, Transact.

In addition, the following firms or groups provided related information:

Avon Products, Inc., Suffern, NY 10901.

Sulfur-resorcinol combinations.

Herbert Laboratories, Irvine, CA 92715.

Benzoyl peroxide 2.5 percent.

Koppers Co., Inc., Pittsburgh, PA 15219.

Resorcinol.

Miranol Chemical Co. Inc., Irvington, NJ 07111.

Miranol C2M.

Procter & Gamble Co., Cincinnati, OH 45247.

Tetracycline hydrochloride.

Proprietary Association, Washington, DC 20006.

Benzoyl peroxide safety, labeling recommendations.

Schuykill Chemical Co., Philadelphia, PA 19132.

Alcloxa, allantoin.

Sterling Drug, Inc., New York, NY 10016.

Salicylic acid.

Stiefel Laboratories, Inc., Oak Hill, NY 12460.

Antibacterial data on benzoyl peroxide-

sulfur combinations.

Vick Divisions Research and Development, Division of Richardson-Merrell, Inc.,

Wilton, CT 06897.

Benzoyl peroxide absorption, in vitro protocol for determining antibacterial activity, in vivo protocol for testing antibacterial activity, prevention of new acne lesions by topical therapeutic ingredients, resorcinol safety.

Westwood Pharmaceuticals Inc., Buffalo, NY 14213.

Laureth-4 safety, polyethylene safety.

B. Labeled Ingredients Contained in OTC Marketed Products Submitted to the Panel

The Panel has identified the following labeled ingredients in marketed products:

Alcloxa
Alcohol
Alkyl isoquinolinium bromide
Allantoin
Alpha tocopheryl acetate
Aluminum chlorhydroxide complex
Aluminum chlorhydroxy allantoinate
Aluminum hydroxide
Aluminum magnesium silicate
Aluminum oxide
Bentonite
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Benzoic acid
Benzoyl peroxide
Boric acid
Calcium phosphate
Calcium polysulfide
Calcium thiosulfate
Camphor
Carbomer 940
Carboxyvinyl polymer
Cetyl alcohol
Chlorhydroxyquinoline
Cholesterol
Citric acid
Coal tar
Colloidal alumina
Colloidal sulfur
Cosmetic colors
Dibenzothiothene
Diocetyl sodium sulfosuccinate
Edetate disodium
Epsom salts
Estrone
Glycerin
Glycerol monostearate
Glyceryl monostearate
Hexachlorophene
Hydrocarbon hydrotropes
Isopropyl
Isopropyl alcohol
Isopropyl palmitate
Magnesium sulfate
Menthol
Methylbenzethonium chloride
Methylparaben
Methyl parasept
Methyl salicylate
Micropulverized sulfur
Parachlorometaxyleneol
Phenol
Phenyl salicylate
Polyethylene
Polyethylene glycol monostearate
Polyethylene glycol 1000 monostearate
Polyoxyethylene lauryl ether

Povidone-iodine
 Precipitated sulfur
 Propylene glycol
 Propyl parasept
 Purified water
 Pyrillamine maleate
 Rescorcitol
 Resorcinol
 Resorcinol monoacetate
 Salicylic acid
 Soapless cleansers
 Sodium borate
 Sodium hydroxide
 Sodium lauryl sulfate
 Sodium phenolate
 Sodium tetraborate decahydrate
 Sodium thiosulfate
 Stearic acid
 Sulfated surfactants
 Sulfonated alkyl benzenes
 Sulfur
 Sulfur precipitated
 Tetracaine hydrochloride
 Thymol
 Water
 Wetting agents
 Zinc oxide
 Zinc stearate
 Zinc sulfide

C. Classification of Ingredients

1. *Ingredients identified by the Panel as active ingredients.* The Panel has adopted the following nomenclature for the active ingredients reviewed in this document. Other nomenclature, where needed for clarification, has been included in parentheses.

Alkyl isoquinolinium bromide
 Aluminum salts
 Alcloxa (aluminum chlorhydroxy allantoinate)
 Aluminum chlorohydrate (aluminum chlorhydroxide complex)
 Aluminum hydroxide
 Magnesium aluminum silicate (aluminum magnesium silicate)
 Benzocaine
 Benzoic acid
 Benzoyl peroxide
 Borates
 Boric acid
 Sodium borate (sodium tetraborate decahydrate)
 Calcium polysulfide
 Calcium thiosulfate
 Camphor
 Chlorhydroxyquinoline
 Chloroxylenol (parachlorometaxyleneol)
 Coal tar
 Dibenzothiophene
 Estrone
 Magnesium sulfate (Epsom salts)
 Phenolates
 Phenol
 Phenolate sodium (sodium phenolate)
 Phenyl salicylate
 Povidone-iodine
 Pyrillamine maleate
 Rescorcitol (rescorcitol)
 Resorcinol monoacetate
 Salicylic acid
 Sodium thiosulfate
 Sulfur (colloidal sulfur, micropulverized sulfur, precipitated sulfur, sulfur precipitated)

Tetracaine hydrochloride
 Thymol
 Vitamin E (alpha tocopheryl acetate)
 Zinc salts
 Zinc oxide
 Zinc stearate
 Zinc sulfide

2. *Ingredients identified by the Panel as inactive or pharmaceutically necessary ingredients.* Based on the available literature and in some cases based on concentrations reported in a submission, the Panel considers the following to be inactive ingredients when used for the treatment of acne. In general, most are used as pharmaceutical aids (solvent, vehicle, dispersant, or preservative,) or as product identification materials.

Alcohol
 Allantoin
 Aluminum oxide
 Bentonite
 Benzalkonium chloride
 Benzethonium chloride
 Calcium phosphate
 Carbomer 940
 Carboxyvinyl polymer
 Cetyl alcohol
 Cholesterol
 Citric acid
 Colloidal alumina
 Cosmetic colors
 Dioctyl sodium sulfosuccinate
 Edetate disodium
 Glycerin
 Glycerol monostearate
 Glyceryl monostearate
 Hexachlorophene
 Hydrocarbon hydrotropes
 Isopropyl alcohol (isopropyl)
 Isopropyl palmitate
 Laureth-4 (polyoxyethylene lauryl ether)
 Menthol
 Methylbenzethonium chloride
 Methylparaben (methyl parasept)
 Methyl salicylate
 Polyethylene
 Polyethylene glycol monostearate
 Polyethylene glycol 1000 monostearate
 Propylene glycol
 Propylparaben (propyl parasept)
 Purified water
 Soapless cleansers
 Sodium hydroxide
 Sodium lauryl sulfate
 Stearic acid
 Sulfated surfactants
 Sulfonated alkyl benzenes
 Water
 Wetting agents

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document includes submissions made by interested persons in response to the call-for-data notice published in the *Federal Register* of December 16, 1972 (37 FR 26842). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in

§ 330.10(a)(2), will be put on public display after April 22, 1982, in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Background

Acne affects about 80 percent of the population to some extent during adolescence (Ref. 1). Because this skin condition is common and readily recognizable by consumers, the Panel believes that safe and effective OTC acne medications should be available to the consumer.

Although much has been learned about acne in the past 30 years, much still remains unknown. Even the exact origin of the word "acne" is unknown. Some scholars believe it is a corruption of the Greek word "akne," meaning the highest point or stage (including the peak of growth in humans) (Ref. 2). Another theory is that "acne" comes from another Greek word, "aknesis," which means a rash that does not itch (Ref. 2). In fact, according to Plewig and Kligman (Ref. 3), the only undisputed fact about acne is that it does exist.

The Panel believes that the myths or misconceptions about acne need to be dispelled, including those concerning diet, sexual habits, and the belief that acne can be washed away with soap and water (Ref. 4). For years, people suffering from acne believed that eating chocolates, fatty foods, and "junk foods" either caused acne or made it worse and that abstaining from these foods would cure their acne. Unfortunately, they were often disappointed.

The role of diet is still being studied. For example, a double-blind study tested the effects of large amounts of chocolate on 65 acne patients (Ref. 5). Two kinds of candy bars that looked identical were used. One contained no chocolate; the other was an enriched chocolate bar containing 10 times the amount of chocolate as an average candy bar. The subjects ate one kind of chocolate bar daily for 4 weeks, and for the next 3 weeks they ate no candy. Then they ate the other kind of bar once daily for 4 weeks. Chocolate was found to have no effect on the clinical course of acne.

Another study was conducted with acne patients who believed that certain foods (chocolate, peanuts, milk, or cola) were causing their acne to flare (Ref. 6). These patients were fed large amounts of the suspected food for several days, but no significant change was noted in

the number or character of their acne lesions during the next several days.

According to Cunliffe and Cotterill (Ref. 2), "Iodides have also been blamed for aggravating acne but the evidence for this is rather poor * * *."

Myths about the relationship between sexual habits and the development of acne go far back in history. MacKenna cited Jonston who wrote in 1648 that acne, called "vari," infected young people who were sexually mature but who remained chaste (Ref. 7). More than a century later, according to Cunliffe and Cotterill (Ref. 2), Plenck wrote that marriage could cure acne, but Hebra disagreed. Although some sexual myths may still persist today, there is no evidence to show that they are any more than myths (Ref. 4).

* Another misconception is that acne will go away if it is ignored. Although many people no longer have significant acne by the time they are in their early twenties, a number of people still suffer from acne in their forties. The Panel believes it is particularly important that consumers realize that the treatment of acne may have to be continued for several years.

The following discussion summarizes the findings of several surveys on skin conditions.

The most recent report was published by the National Center for Health Statistics and covers the period from 1971 to 1974 (Ref. 8). The data were collected by direct physical examinations, tests, and measurements performed on samples of the population aged 1 to 74 years. Participants were chosen from the civilian noninstitutionalized population.

This report shows that significant skin disease increases rapidly with age. In children aged 1 to 5 years the rate was 142.3 per 1,000. In youths aged 12 to 17 years the rate was 362.0 per 1,000. In young adults aged 18 to 24 years the rate was 365.1 per 1,000. The rapid increase was attributed to acne vulgaris, which, as noted earlier, is common during adolescence and young adulthood. Among the individual types of skin disease that were diagnosed, acne was the most prevalent (68.1 per 1,000 population). The survey also showed that youths aged 12 to 17 years with skin problems are more likely to consult someone who is a "nonprofessional" rather than a dermatologist or other physician.

The Health Examination Survey of 1966 to 1970 (Ref. 9) presented national estimates on the prevalence of facial acne and other skin conditions among noninstitutionalized youngsters aged 12 to 17 by age, sex, geographic region, population, size of place of residence,

family income, education of parents, overall health, indication of stress, selected health habits, and physiological development. It was estimated that 28.3 per 100 youths had moderate to severe facial acne. Major findings included the following:

Facial acne (all grades combined) is about as prevalent among girls as boys in the 12-17 year age range. However, such conditions start somewhat earlier and tend to be less severe in girls than boys.

Among youths reporting they had acne, more than half (51 percent) were bothered some or a lot by the condition and (58 percent) were using some treatment for it but only 11 percent had seen a doctor about it.

White youths are slightly more likely than Negro youth to have moderate to severe facial acne but less likely to have mild conditions limited to comedones with little or no inflammatory reaction.

Facial acne is somewhat more prevalent among youths living in the South and West than those in the Northeast or Midwest. However, no consistent urban-rural differences in prevalence rates were found.

Some direct or indirect association is evident between acne prevalence in youths and the education of their parents but not their family income level. The acne prevalence rates decrease consistently with increasing education level of parents.

Facial acne is slightly more prevalent among youths whose health was rated fair-poor than among those considered in good-excellent health by either themselves or their parents.

Facial acne prevalence increases with the degree of nervousness of the youth, the association being stronger and more consistent when based on the youth's own rating of nervousness than that given by his or her parent.

The amount of food eaten particularly among boys appears to be related, directly or indirectly, to the prevalence of facial acne. Acne rates are higher among those who are said, by their parents, to eat too much than those who eat too little.

The prevalence and severity of facial acne increases with the degree of development of secondary sex characteristics among boys 12-16 years and girls 12-15 years of age.

Among girls acne tends to start after the onset of menarche for girls who reach this stage of physiological development before 13 years of age but to precede this point of development for those whose menarche onset is 14 years or later.

A report on a questionnaire survey published in 1972 stated that out of 1,023 high school students whose questionnaires were evaluated, 85.1 percent reported that they had acne (Ref. 10). Of this group, 87.7 percent had not consulted a doctor. The most frequently given reason was that the acne was not severe enough. A few students felt the treatment was too costly; the rest did not specify a reason.

About half of the students surveyed reported a seasonal change in their

acne. Among those students reporting a seasonal change, statistically significant improvement was shown during summer.

Most of the students with acne were using some kind of treatment, with girls starting treatment a little sooner than boys. However, the authors reported that only 33.4 percent of the students reported that they never missed their treatment. Statistically, the girls were significantly better than the boys in following a regular treatment schedule.

A total of 117 products was used, with 93.6 percent of the students using one or more products and only 6.4 percent using none. The products included soaps, astringents (which did not claim anti-acne properties), anti-acne preparations, complexion products, and miscellaneous products. Soaps were the most widely used (49.7 percent); anti-acne preparations were the next most widely used (28.8 percent).

People suffering from acne spend millions of dollars yearly for OTC acne preparations as well as prescription drugs (Ref. 11). "Cosmetically" accepted medications are important. In fact, dermatologists say that patient acceptance is as important as effectiveness in acne treatment. They also say that consumers want therapeutic products that work but are not too harsh or unpleasant smelling. Consumers like a product that can be easily applied, feels good, and perhaps may even have a lathering property which enhances the sense of feeling clean and leaves the skin feeling soft.

Dermatologists are often asked questions about the causes of acne, including what foods are responsible. Patients are also concerned about the possibility of scarring. They also ask what they are doing wrong, if makeup can harm the skin, and, in some cases, why they are getting acne at age 30 after having had flawless skin in adolescence. Probably the most difficult question of all to answer is: "When will the acne disappear?"

There are certain aspects of acne therapy that patients most dislike. These include the odor and the stinging and itching of acne products; the staining effect; and dryness and peeling, which to many patients means premature wrinkling. This dryness also makes it difficult to apply a water-base makeup. Patients also dislike the ashy grayness, which is produced by benzoyl peroxide products and cryotherapy and is seen mainly in black skin. Other adverse effects of acne therapy may include vaginal yeast infections as a result of taking systemic antibiotics. A less serious complaint is that having to

remember to apply or take the medication a certain number of times a day is a nuisance. Finally, patients dislike acne surgery, i.e., the comedone extraction and opening up of pustular lesions which many dermatologists routinely do at each office visit.

It has been known since the early 1970's that certain cosmetics and hair pomades can cause blackheads and whiteheads (comedogenic). It has been estimated that up to 50 percent of the popular cosmetic creams will produce comedones when tested on the inner surface of the rabbit ear once daily for 2 weeks (Ref. 3).

The term "acne cosmetica" was coined in 1972 by Kligman (Ref. 12) and refers to acneform eruptions of a low-grade, persistent nature occurring in adult women. These eruptions are caused mainly by prolonged use of cosmetics containing the offending ingredients.

The Panel agrees with the following statement by Sulzberger (Ref. 13):

"There is probably no single disease which causes more psychic trauma, more maladjustments between parents and children, more general insecurity and feelings of inferiority, and greater sums of psychic suffering than does acne vulgaris."

References

- (1) "Stubborn and Vexing, That's Acne," *FDA Consumer*, 14:14-17, 1980.
- (2) Cunliffe, W. J., and J. A. Cotterill, "The Acnes: Clinical Features, Pathogenesis and Treatment," W. B. Saunders Co. Ltd., London, pp. 2-3 and 14, 1975.
- (3) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, Berlin, pp. 1 and 227, 1975.
- (4) Fardal, R. W., "The Myths and Magic of Acne Care," *Hawaii Medical Journal*, 35:333-335, 1976.
- (5) Fulton, J. E., Jr., G. Plewig, and A. M. Kligman, "Effect of Chocolate on Acne Vulgaris," *Journal of the American Medical Association*, 210:2071-2074, 1969.
- (6) Anderson, P. C., "Foods as the Cause of Acne," *American Family Physician*, 3:102-103, 1971.
- (7) MacKenna, R. M. B., "Acne Vulgaris," *Lancet*, 1:169-176, 1957.
- (8) U.S. Department of Health, Education, and Welfare, National Center for Health Statistics, "Skin Conditions and Related Need for Medical Care Among Persons 1-74 Years," DHEW Publication No. (PHS) 79-1660, Series 11, No. 212, pp. 1-72, 1978.
- (9) U.S. Department of Health, Education, and Welfare, National Center for Health Statistics, "Skin Conditions of Youths 12-17 Years," DHEW Publication No. (HRA) 76-1639, Series 11, No. 157, 1976.
- (10) Emerson, G. W., and J. S. Strauss, "Acne and Acne Care. A Trend Survey," *Archives of Dermatology*, 105:407-411, 1972.
- (11) Shalita, A. R., "Acne Vulgaris: Not Curable but Treatable," *Modern Medicine*, 43:66-76, 1975.

(12) Kligman, A. M., and O. H. Mills, Jr., "Acne Cosmetica," *Archives of Dermatology*, 106:843-850, 1972.

(13) Sulzberger, M. B., and S. H. Zaidens, "Psychogenic Factors in Dermatologic Disorders," *Medical Clinics of North America*, 32:669-685, 1948.

B. Definitions

The Panel adopted the following definitions related to the use of acne drug products:

1. *Comedones (whiteheads and blackheads)*. Comedones are the primary lesions of acne and consist of dead cell (keratinous) debris, bacteria, sebum, and hair fragments which plug up the opening of the pilosebaceous unit. The development of the comedo is associated with an increased turnover rate of the epithelial cells lining the sebaceous follicle. The follicle becomes distended with horny material and at this early stage is known as a microcomedo, a microscopic comedo. Further distention of the sebaceous follicle results in the closed comedo.

a. *Whiteheads*. Whiteheads or closed comedones are small, whitish, firm nodules which may be difficult to see. The opening to the comedo is not visible to the naked eye. Closed comedones either rupture and become inflammatory lesions, such as papules, pustules, and nodules, or develop into open comedones. When horny material accumulates in the closed comedo, it causes the opening in the comedo to dilate, pushing horny material to the skin surface. This marks the beginning of the open comedo or blackhead.

b. *Blackheads*. Blackheads are long-lasting lesions that do not usually develop into inflammatory lesions. The tip of the blackhead appears black because of melanin, a pigment.

2. *Lesion*. In this document a lesion is considered as a characteristic area of a skin condition. Acne lesions include open and closed comedones, papules, pustules, and nodules.

3. *Nodule*. A large, red, often painful inflammatory acne lesion that contains pus and leads to scarring. Nodules are deep-seated lesions which affect the dermis. They develop from the rupture of closed comedones and are characteristic of acne conglobata. Nodules may fuse to form odd-shaped lesions. The term "cystic acne" refers to nodular inflammatory lesions and not to true cysts, which are large, round, flesh-colored, noninflammatory lesions with smooth surfaces.

4. *Papule*. A small, inflammatory lesion that appears red and raised. Papules develop from closed comedones. They may develop into pustules and nodules, or they may

resolve spontaneously after 2 to 3 weeks.

5. *Pilosebaceous unit*. Consists of a hair follicle and the associated sebaceous gland. These are connected to the surface of the skin by a duct through which the hair passes.

6. *Pustule*. A small, raised, inflammatory lesion that is filled with pus and arises from a papule. Superficial pustules resolve after a few days and rarely cause visible scarring. A deep-seated pustule takes 2 to 6 weeks to resolve, and scarring may result.

7. *Sebum*. A secretion of the sebaceous glands consisting of a mixture of fats and waxes. The severity of acne parallels the degree of sebum secretion.

C. Types of Acne

Kligman (Ref. 1) uses two major classifications of acne—true acne and drug-induced acne. The Panel has adapted these classifications to this document, citing other references when appropriate.

1. *True acne—a. Acne vulgaris*. A common skin disorder, acne vulgaris is characterized by comedones, papules, pustules, and nodules. Typically, a person with acne will have a variety of acne lesions, although in some individuals one lesion type may predominate. Acne vulgaris primarily occurs on the face, shoulders, back, and chest, but occasionally may be more widespread.

Open and closed comedones are usually the first acne lesions to occur. In the early stages, comedones are generally found on the forehead and chin. Later, papules and pustules appear on the cheeks as well. Although usually a disease of adolescence, acne does not always clear spontaneously when maturity is reached. It may persist into the third or fourth decades of the patient's life (Refs. 2 and 3). In fact, acne may even begin after the teenage years or at any age.

b. *Acne conglobata*. Acne conglobata is a severe and chronic form of acne vulgaris. The lesions tend to be particularly severe on the face, chest, and back. Lesions may also occur on the buttocks, thighs, upper arms, and neck. Most of the lesions are large, painful, and cystic and may be characterized by abscesses and scarring. Males are affected more frequently than females. The disease, which usually begins between the ages of 18 and 30 years, often continues for many years, resulting in severe disfigurement (Ref. 4).

c. *Acne fulminans*. Also termed "acute febrile ulcerative conglobate acne with polyarthralgia," acne fulminans is a

rare, severe form of acne. The main lesions are nodules that become ulcerated. Systemic effects include fever, anemia, and painful, swollen joints (Ref. 5).

d. *Acne tropicalis*. This type of acne occurs when a susceptible person is exposed to excessive heat and humidity. It resembles severe acne conglobata and is unchanged as long as the patient remains in a tropical climate, but clears completely when the patient returns to a cool, dry climate (Ref. 1). Military personnel that are stationed in tropical climates are particularly at risk for developing this type of acne.

e. *Infantile acne*. This is an acne-like rash of unknown cause. Comedones and papules usually occur on the cheeks of male infants under 1 year of age, but the disease generally subsides completely in 2 to 3 years (Ref. 4).

f. *Premenstrual flares of acne*. Many women suffer from premenstrual flares of acne characterized by the rapid appearance of papulo-pustules. The precise cause is still unknown, but is presumed to be related to cyclical hormone fluctuation (Ref. 1).

g. *Gram-negative acne or folliculitis*. This type of acne usually occurs during long-term treatment of acne with antibiotics which specifically act on gram-positive bacteria, thereby permitting gram-negative bacteria to flourish. The invading organisms are usually *Enterobacter*, *Klebsiella*, or *Proteus*. A change in the characteristics of the facial acne of a previously well-controlled case of acne may be a sign of gram-negative acne (Ref. 1).

h. *Acne venenata or acne caused by external contactants*. Topical agents or exposure to certain chemicals can cause this type of acne (Ref. 5). "Acne cosmetica" is a mild eruption mainly consisting of closed comedones. It is usually caused by facial creams and is seen in women beyond the age of adolescence (Ref. 1). "Pomade acne" is caused by greases and oils applied to the scalp or face. The lesions are usually small, closed comedones concentrated on the forehead and temples (Ref. 5). "Acne detergentica" is a mild form of acne consisting of closed comedones, apparently induced by excessive scrubbing and washing with certain soaps (Ref. 1).

The most extensive cases of acne venenata are caused by industrially used compounds such as chlorinated hydrocarbons, cutting oils, petroleum oil, coal tars, and pitches. This condition is often referred to as "chloracne." The initial treatment in all forms of acne venenata is to stop the exposure to the causative agent (Ref. 5).

i. *Acne caused by radiation*. Both ultraviolet light and ionizing radiation may be associated with the development of special types of acne. Excessive exposure to the sun may induce comedones, usually large blackheads, around the eyes and cheeks of elderly people. Ionizing radiation, such as cobalt and X-rays, can cause a comedonal acne. *Acne aestivalis* (mallorca acne) is a rare seasonal acne which flares up in the summer months and regresses in winter. It usually affects women beyond adolescence, with papules developing on the lower back. These forms of acne generally subside when the causative agent is eliminated (Ref. 5).

j. *Acne mechanica*. Aggravation of existing acne can develop from localized pressure or friction. For example, resting the chin on the hand can aggravate acne on the chin (Ref. 1).

2. *Drug-induced acne*. Drug-induced acne is not a true acne, but an acne-like eruption caused by drugs. The eruption subsides when the drug is discontinued. The lesions are generally papules and pustules. The condition is usually characterized by a sudden onset after adolescence and an unusual localization (forearm, buttock). Systemic signs of drug toxicity may also be present (Ref. 1). The drugs that are often involved in these kinds of eruptions include steroids, certain anticonvulsants (phenobarbital, phenytoin, and trimethadione), and certain halogenated drugs. Isoniazid, a drug used in long-term therapy of tuberculosis, may also be involved in some acne-like conditions (Refs. 4 and 5).

References

- (1) Kligman, A. M., "Classification of Acne," *CUTIS: Cutaneous Medicine for the Practitioner*, 17:520-522, 1976.
- (2) Moschella, S. L., D. M. Pillsbury, and H. J. Hurley, Jr., "Dermatology," Volume II, W. B. Saunders, Co., Philadelphia, pp. 1129-1131, 1975.
- (3) Shalita, A., et al., "Acne," *Journal of Investigative Dermatology*, 73:434-442, 1979.
- (4) Cunliffe, W. J., and J. A. Cotterill, "The Acnes: Clinical Features, Pathogenesis and Treatment," Edited by A. Rook, W. B. Saunders Co. Ltd., London, pp. 25-28, 33-35, and 38-40, 1975.
- (5) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, pp. 106, 196-198, 226, 230, 233, 238-239, and 257, 1975.

D. Development of Acne

Acne generally begins at puberty when substantial androgen secretion takes place. Androgen is the male sex hormone and comes mainly from the testes in the male and from the ovaries and adrenal glands in the female. Although male adrenals also produce

androgens, they play only a small role in acne. The most potent androgen is testosterone, the circulating androgen. Testosterone is converted in the skin by the enzyme 5- α -reductase to dihydrotestosterone, the tissue-active androgen (Ref. 1).

Dihydrotestosterone stimulates the cells of the sebaceous glands to increase protein synthesis and accelerate cell division and cell turnover. Thus the sebaceous glands become larger until they surround and completely dominate the hair follicles. Sebaceous follicles (pilosebaceous units) like these produce large amounts of sebum which cause the characteristic oily skin of acne (Ref. 1). Acne usually occurs on the face, upper chest, and back because there are more pilosebaceous units there than on other areas of the body (Ref. 2).

The size of the sebaceous gland usually varies inversely with the size of the hair follicle associated with it (Ref. 3). The kind of hair in the follicle can also affect the development of acne. A thin, small hair may be unable to keep the duct open and the hair is trapped in the plug. However, heavier facial or scalp hair may push the plug to the surface of the skin and prevent a comedo from forming (Ref. 2).

People with acne have larger sebaceous follicles than those without acne (Ref. 3). Studies have shown a correlation between the severity of acne (as measured by the degree of inflammation) and the rate of sebum excretion (Refs. 4, 5, and 6). In general, from the studies one can conclude that people with acne produce more sebum than those without acne.

Kligman and Katz (Ref. 7) conducted tests on the ears of albino rabbits and demonstrated that sebum can induce comedones. The components of sebum that have been shown to be most comedogenic are squalene and free fatty acids (Ref. 8). Because subjects with acne produce more sebum than subjects with no acne (controls), it is possible that excessive sebum production is the initiating event in comedogenesis. Research has been done on changes that apparently involve increased turnover of the cells that are shed into the canal of the follicle (Ref. 9). The resulting increased cohesiveness of the cells could explain the formation of a comedo. Although the factors involved in the initiation of this abnormality are not entirely known, one factor appears to be sebum.

Because the sebaceous gland is clearly an androgen-sensitive organ, several investigators have searched for differences in circulating levels of testosterone in acne patients. These

studies showed no significant differences in testosterone in males with or without acne and suggest that females with acne may have somewhat elevated levels (Refs. 10, 11, and 12). However, these studies were conducted when there were no techniques for assessing free versus bound testosterone, and little attention was paid to the possibility of excessive production of adrenal androgens.

Lee's studies (Ref. 13) offer another possibility. In a small group of patients, those who developed acne demonstrated an early onset of testosterone production, suggesting that a "hormone abnormality" may exist. The current evidence favors the conclusion that acne patients do not suffer from excessive production of androgens, but have a hypersensitivity of the end-organ sebaceous gland to normal circulating levels of androgens (Ref. 14).

Certain species of microorganisms including *Staphylococcus*, *Propionibacterium acnes* (*P. acnes*), and *Pityrosporum* produce lipases (fat-splitting enzymes). These microorganisms live on the surface of the skin and in the horny layer. They also accumulate in the sebum within the opening and the neck of the sebaceous follicles. *P. acnes* appears to be the most important of these microorganisms in the development of acne (Refs. 15 and 16).

P. acnes produces cellular products other than lipases which may play some part in the pathogenesis of acne. These products include esterases, proteases, and hyaluronidase. However, the action of lipases is best known. The bacteria produce lipases. The lipases break down triglycerides contained in the sebum into free fatty acids and glycerol, which the bacteria may then use as nutrients. Some researchers believe that the free fatty acids are the irritating, inflammatory, and comedogenic components of sebum (Refs. 8 and 16).

The evidence implicating *P. acnes* in the pathogenesis of inflammation includes the following:

(1) Increasing numbers of *P. acnes* are seen at the light and electron microscopic level with the onset of abnormal keratinization characteristics of acne (Refs. 17 and 18).

(2) Significantly higher densities of *P. acnes* are recoverable from the skin of teenage acne patients than from age-matched controls (Ref. 19).

(3) Successful suppression of *P. acnes* by systemic or topical antibiotics or antimicrobials is accompanied by clinical improvement (Refs. 16 and 20).

(4) *P. acnes* antibody titers tend to parallel the clinical severity of acne (Ref. 21).

(5) Intradermal injection of *P. acnes* produces intense inflammation in subjects with acne and minimal reactions in control subjects who do not have acne (Ref. 22).

(6) Injection of *P. acnes* attracts polymorphonuclear leukocytes to the follicle and results in the release of hydrolase (Ref. 23).

The significance of free fatty acids has been questioned because of the minimal inflammation which develops after a single intradermal injection of amounts of fatty acid comparable to those found in single sebaceous follicles. However, repeated intradermal injections through ruptured follicles can reasonably be expected to contribute to the inflammatory response (Ref. 9).

Some studies suggest that free fatty acids are not the only inflammatory agents in acne. According to Puhvel and Sakamoto (Ref. 22), "the effect of antibiotics in acne is more likely to depend on direct suppression of *P. acnes* as inflammatory agents rather than on indirect reduction of intrafollicular lipase, as the free fatty acid theory of acne therapy had previously supposed."

It is thought that *P. acnes* produces substances that are chemotactic for polymorphonuclear leukocytes (Ref. 24). Chemotactic refers to inducing movement of cells or organisms.

These authors also found that accumulations of polymorphonuclear leukocytes along the periphery of the walls of closed comedones may be the first change marking the transition from noninflamed lesions into inflammatory ones. Furthermore, lipids within comedones have demonstrated chemotactic activity for polymorphonuclear leukocytes (Ref. 24).

More recent studies by the same authors have demonstrated differences in the cytotoxic activity of the same microbial strain grown in different media. This varied movement and arrangement, called cytotoxicity, may explain why comedones may differ in inflammatory potential (Ref. 25).

Another possible triggering or aggravating factor in acne that should be mentioned is stress. Shalita (Ref. 8) reported that acne becomes worse in many people during times of emotional stress. However, controlled studies to support this view are lacking because of the difficulty in designing studies that can accurately measure these effects.

References

(1) Shalita, A. R., "Acne Vulgaris: Current Concepts in Pathogenesis and Treatment,"

International Journal of Dermatology, 15:182-187, 1976.

(2) "Stubborn and Vexing, That's Acne," *FDA Consumer*, 14:14-17, 1980.

(3) Cunliffe, W. J., and J. A. Cotterill, "The Acnes: Clinical Features, Pathogenesis and Treatment," W. B. Saunders Co., London, pp. 62, 66-67, 1975.

(4) Pochi, P. E., and J. S. Strauss, "Sebum Production, Casual Sebum Levels, Titratable Acidity of Sebum, and Urinary Fractional 17-Ketosteroid Excretion in Males with Acne," *Journal of Investigative Dermatology*, 43:383-388, 1964.

(5) Burton, J. L., and S. Shuster, "The Relationship Between Seborrhoea and Acne Vulgaris," *British Journal of Dermatology*, 84:600-602, 1971.

(6) Cunliffe, W. J., and S. Shuster, "Pathogenesis of Acne," *Lancet*, 1:685-687, 1969.

(7) Kligman, A. M., and A. G. Katz, "Pathogenesis of Acne Vulgaris. I. Comedogenic Properties of Human Sebum in the External Ear Canal of the Rabbit," *Archives of Dermatology*, 98:53-57, 1968.

(8) Kligman, A. M., V. R. Wheatley, and O. H. Mills, Jr., "Comedogenicity of Human Sebum," *Archives of Dermatology*, 102:267-275, 1970.

(9) Shalita, A. R., "Acne Vulgaris: Not Curable but Treatable," *Modern Medicine*, 43:66-76, 1975.

(10) Pochi, P. E., et al., "Plasma Testosterone and Estrogen Levels, Urine Testosterone Excretion, and Sebum Production in Males with Acne Vulgaris," *Journal of Clinical Endocrinology and Metabolism*, 25:1660-1664, 1965.

(11) Forstrom, L., et al., "Plasma Testosterone Levels and Acne," *Acta Dermato Venereologica*, 54:369-371, 1974.

(12) Mauvais-Jarvis, P., G. Charransol, and F. Bobas-Masson, "Simultaneous Determination of Urinary Androstenediol and Testosterone as an Evaluation of Human Androgenicity," *Journal of Clinical Endocrinology and Metabolism*, 36:452-459, 1973.

(13) Lee, P. A., "Acne and Serum Androgens During Puberty," *Archives of Dermatology*, 112:482-484, 1976.

(14) Sansone, G., and R. M. Reisner, "Differential Rates of Conversion of Testosterone to Dihydrotestosterone in Acne and in Normal Human Skin—A Possible Pathogenic Factor in Acne," *Journal of Investigative Dermatology*, 56:366-372, 1971.

(15) Marples, R. R., D. T. Downing, and A. M. Kligman, "Control of Free Fatty Acids in Human Surface Lipids by *Corynebacterium Acnes*," *Journal of Investigative Dermatology*, 56:127-131, 1971.

(16) Mills, O. H., Jr., R. R. Marples, and A. M. Kligman, "Acne Vulgaris. Oral Therapy with Tetracycline and Topical Therapy with Vitamin A," *Archives of Dermatology*, 106:200-203, 1972.

(17) Kligman, A. M., "An Overview of Acne," *Journal of Investigative Dermatology*, 62:268-287, 1974.

(18) Knutson, D. D., "Ultrastructural Observations in Acne Vulgaris: The Normal Sebaceous Follicle and Acne Lesions,"

Journal of Investigative Dermatology, 62:288-307, 1974.

(19) Leyden, J. J., et al., "Propionibacterium Levels in Patients With and Without Acne Vulgaris," *Journal of Investigative Dermatology*, 65:382-384, 1975.

(20) Marples, R. R., and A. M. Kligman, "Ecological Effects of Oral Antibiotics on the Microflora of Human Skin," *Archives of Dermatology*, 103:148-153, 1971.

(21) Puhvel, S. M., et al., "Study of Antibody Levels to *Corynebacterium Acnes*," *Archives of Dermatology*, 90:421-427, 1964.

(22) Puhvel, S. M., and M. Sakamoto, "An In Vivo Evaluation of the Inflammatory Effect of Purified Comedonal Components in Human Skin," *Journal of Investigative Dermatology*, 69:401-406, 1977.

(23) Webster, G. F., et al., "Polymorphonuclear Leukocyte Lysosomal Release in Response to *Propionibacterium Acnes* In Vitro and Its Enhancement by Sera from Inflammatory Acne Patients," *Journal of Investigative Dermatology*, 74:398-401, 1980.

(24) Puhvel, S. M., and M. Sakamoto, "The Chemoattractant Properties of Comedonal Components," *Journal of Investigative Dermatology*, 71:324-329, 1978.

(25) Puhvel, S. M., and M. Sakamoto, "Cytotaxin Production by Comedonal Bacteria (*Propionibacterium acnes*, *Propionibacterium granulosum* and *Staphylococcus epidermidis*)," *Journal of Investigative Dermatology*, 74:36-39, 1980.

E. Classifying the Severity of Acne

The lack of an internationally accepted method of classifying or grading the severity of acne has long been a source of confusion and controversy. For many years, morphologists had classified skin disorders according to the predominant lesion. With acne the lesions included comedones, papules, pustules, and nodules. But simply using these words served little purpose except to indicate the extent of the disease process. Consequently, dermatologists have established many different systems in an attempt to classify acne (Ref. 1). The biggest problem with so many different systems is that data originating in different places cannot be easily compared because the criteria may differ widely (Ref. 2).

One classification system has evolved that grades acne according to the number of lesions. For example, Grade I comedonal acne would be defined as less than 10 comedones on one side of the face (Ref. 2). Acne is often classified by using the terms "mild," "moderate," or "severe." Acne that is primarily comedonal is considered mild; papular and pustular, moderate; and nodular, severe (Ref. 2).

Frank (Ref. 3) classified acne into seven types but using no grading scale. Examples of these types are noninflammatory comedonal acne,

inflammatory comedonal acne, and mild papular acne of early adolescence.

Recently a clinical system was devised that uses photographic standards to grade acne on a scale of 0 to 8 (Ref. 4).

Another system, the Pillsbury grading scale, is described here in some detail because it has been widely used by dermatologists. Many studies described later in this document have used this system of classification. Pillsbury (Ref. 5) developed a method of classifying acne by using Roman numerals to grade the severity of the condition. The scale begins with Grade I acne, the mildest type, and ends with Grade IV acne, which is most severe and requires the most aggressive treatment plan. This grading scale is used primarily for acne vulgaris. Other types of acne are generally not graded.

In Grade I acne, comedones are the main lesions with only an occasional small, inflamed pustule. In Grade II acne the inflammatory state becomes more evident. Papules and pustules are more numerous than in Grade I, but the lesions generally remain confined to the face. Grade III acne is a moderately severe acne manifested by numerous small pustules and an occasional larger lesion and usually affects the upper shoulders, back, and chest as well as the face. Grade IV acne is the most severe and is usually called acne conglobata (Ref. 5). (For more details on acne conglobata, see part II, paragraph C.1.b. above—Acne conglobata.)

One problem with Pillsbury's classification is that it does not take into account the number of acne lesions. Most dermatologists would consider a person with hundreds of comedones as having a more severe case of acne compared to an individual with only three or four pustules. Using Pillsbury's classification, the person with the comedones would be considered as having a less severe case of acne. For this reason, other systems of classification have been developed.

Because of the numerous classification systems that have evolved and the various types of lesions present in acne, the Panel believes it is essential that the system used for grading acne in clinical trials be clearly defined.

References

- (1) Witkowski, J. A., and L. C. Parish, "Acne: A New Emphasis," *International Journal of Dermatology*, 14:425-426, 1975.
- (2) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, pp. 162-163, 1975.
- (3) Frank, S. B., "An Update on Acne Vulgaris," *International Journal of Dermatology*, 16:409-412, 1977.

(4) Cook, C., R. L. Centner, and S. E. Michaels, "An Acne Grading Method Using Photographic Standard," *Archives of Dermatology*, 115:571-575, 1979.

(5) Pillsbury, D. M., "A Manual of Dermatology," W. B. Saunders Co., Philadelphia, pp. 173-174, 1971.

F. Treatment of Acne

Acne cannot be cured, but it can be treated successfully. The Panel believes that more than three-fourths of the people suffering from acne can be effectively treated, with visible improvement even in the most severe case. However, treatment may be long and costly in severe cases because many effective medications are available only by prescription and require a physician's supervision. Treatment must be adapted to the individual because no single ideal treatment exists for all types of acne.

Dermatologists generally believe that early treatment can reduce the severity of the disease and, to some degree, also reduce scarring. Nevertheless, many people with severe acne do not see a doctor because they believe there is no satisfactory treatment available or because they cannot afford prescription treatment. Conversely, dermatologists sometimes see patients who are convinced they have acne even though it is barely visible or almost nonexistent.

There is no evidence that any treatment program prevents the onset of acne. However, the Panel believes that the aim of acne therapy is not only to clear up existing acne lesions but also to prevent the formation of new acne lesions. Clinical studies show that individual papules and pustules will resolve without treatment within 14 days (Refs. 1 and 2). Studies reviewed by the Panel have used a conservative estimate of 4 weeks as the natural resolution time of acne pimples (Ref. 3). Using this estimate, any acne therapy that significantly reduces lesion counts over the first 4 weeks of treatment is effective in treating existing lesions. Any treatment that continues to reduce lesion counts beyond 4 weeks is actually preventing the development of new acne lesions. A person who has not been treated for acne will have a natural cyclical rise and fall in the number of acne lesions over this time period.

The Panel has reviewed several studies showing that both benzoyl peroxide and sulfur reduce lesion counts over 8 to 12 weeks. (See part III, paragraph A.1.a. below—Benzoyl peroxide and part III, paragraph A.1.b. below—Sulfur.) The Panel concludes that any ingredient that is shown to be effective in treating acne, by reducing lesion counts over at least 8 weeks, will

also be effective in preventing the development of new acne lesions.

The effect of both mild and severe acne can be significant. The active lesions and resulting scarring may produce emotional distress and social withdrawal. Adolescents suffering from acne may have a particularly difficult time because they are trying to cope with other physical and emotional changes along with the added problem of acne. Cohen and Nadelson (Ref. 4) wrote the following on this subject.

Physicians are often perplexed by the adolescent's paradoxical behavior. The child who appears most preoccupied with his skin may manipulate his lesions, disregard sensible personal hygiene, or apply harmful medication, in spite of his physician's instructions. At other times, he may impose on himself ascetic, and equally self-destructive, programs of abstinence from foods, overzealous washing, or overuse of prescribed medication. These extremes are at times related to the normal drives in adolescence, painfully magnified by the skin disease. Also, just as eczema may deflect parental attention from other family problems, the child with acne may use his blemishes as an excuse for avoiding social situations which arouse anxiety.

Some of the various available treatments (OTC and prescription) are as follows:

1. *Topical OTC products.*
 - a. Benzoyl peroxide 2.5 to 10 percent.
 - b. Salicylic acid 0.5 to 5 percent.
 - c. Abrasives—soaps, granules; epidermabrasion—polyester fiber sponges.
 - d. Sulfur-resorcinol combinations.
 - e. Sulfurated lime topical solution (Vleminkx' solution).
 - f. Sulfur 3 to 10 percent.
 - g. Povidone-iodine 7.5 percent.
2. *Topical prescription products.*
 - a. Benzoyl peroxide 2.5 to 10 percent.
 - b. Tretinoin (vitamin A acid) 0.05 to 0.1 percent.
 - c. Antibiotics—clindamycin, erythromycin, tetracycline.
 - d. Aluminum chloride 6.25 percent.
 - e. Benzoyl peroxide and sulfur combinations.
3. *Systemic prescription products.*
 - a. Antibiotics by mouth (tetracycline, erythromycin, minocycline).
 - b. Corticosteroids.
 - c. Estrogens.
 - d. Investigational drugs, including 13-cis-retinoic acid and cimetidine.
4. *Local therapies.*
 - a. Cryotherapy, carbon dioxide solid or slush, liquid nitrogen.
 - b. Acne surgery, especially for comedones.
 - c. Intralesional steroids for cysts.
 - d. Dermabrasion.
 - e. Fibrin injections for scars.

References

- (1) Kilgman, A. M., "An Overview of Acne," *Journal of Investigative Dermatology*, 62:268-287, 1974.
- (2) Orentreich, N., and N. P. Durr, "The Natural Evolution of Comedones into Inflammatory Papules and Pustules," *Journal of Investigative Dermatology*, 62:316-320, 1974.
- (3) OTC Volume 070280.
- (4) Cohen, D. J., and T. Nadelson, "The Impact of Skin Disease on the Person," in "Dermatology in General Medicine," McGraw-Hill Book Co., New York, pp. 5-8, 1962.

G. Use of Oral Zinc in the Treatment of Acne

Although oral zinc was not submitted to the Panel for review, the Panel chose to include a discussion of this ingredient because of its increasing popularity and current availability as an OTC medication in pharmacies and health food stores. The Panel did not include oral zinc under the ingredient statements in this document because the Panel's review was officially limited to topical products. However, the Panel considered it appropriate to bring this use of oral zinc to the agency's attention.

Zinc is a trace element with an atomic weight of 65.38; thus zinc sulfate 220 milligrams (mg) corresponds to 50 mg elemental zinc (Zn^{+2}). It is an essential nutrient required by animals and humans. The recommended dietary allowance is set at 15 mg and can be supplied by dietary solids containing 25 parts per million (ppm) (Ref. 1).

The rate at which zinc is absorbed from the small intestine is influenced by the level of zinc in the blood. There is a wide margin of safety between the required intake and the toxic dose. Laboratory animals can tolerate up to 2,000 ppm in the diet. Above this level, growth depression and anemia result. The anemia appears to result from an induced copper deficiency, but the growth depression results from reduced food intake (Ref. 2). Toxic levels must be defined cautiously because the levels of other metals greatly influence zinc toxicity. For instance, if copper is present in a limited concentration, zinc is toxic at lower levels. The effects of zinc on copper and iron metabolism can be found in a review of metal toxicities (Ref. 3). Zinc does not appear to accumulate when administered orally (Ref. 2).

The maximum recommended dose for zinc deficiency is 220 mg zinc sulfate three times daily. Nausea may be a problem, but it may be avoided by taking zinc sulfate in capsules after meals (Ref. 4). The emetic dose of zinc sulfate is 1 to 2 grams (g) or 225 to 450

mg zinc. The usual symptoms of toxicity are fever, nausea, vomiting, stomach cramps, and diarrhea (Ref. 2). An adult died from an oral dose of 28 g zinc sulfate (Ref. 5).

Zinc sulfate has been administered therapeutically for leg ulcers and acne in oral doses of 200 mg taken three times daily. This regimen generally caused the serum zinc level to increase by about 25 to 30 percent above the normal range of 70 to 125 micrograms per 100 milliliters ($\mu g/100\text{ mL}$). The serum level reached a plateau within 10 weeks (Refs. 6 and 7).

A 4-month study of 27 patients (Ref. 8) and a 3-month study of 21 patients (Ref. 9) showed no adverse effects from the use of oral zinc. Greaves and Skillen (Ref. 10), however, reported nausea in 3 out of 18 patients in a 4-month study, but hematology studies were normal.

Weimer et al. (Ref. 11) conducted a 12-week study on 28 patients and noted that half of the patients receiving 220 mg zinc sulfate had nausea, vomiting, or diarrhea. Six of these patients could not tolerate the nausea and had to withdraw from the study. In another 12-week study, 5 out of 20 patients reported side effects after treatment with 200 mg zinc sulfate (Ref. 12).

There are reports of gastric bleeding after the ingestion of zinc sulfate monohydrate capsules (Refs. 13 and 14). These studies suggest that the salt form may be an important factor. The studies described earlier, in which no ill effects were reported, used the heptahydrate (citrate) salt dissolved in water (effervescent dosage form) before ingestion.

Zinc oxide ointment has been used extensively without adverse effects (Ref. 2). Considering the poor absorption of metals from the skin, topical use of zinc salts can be considered safe. However, ingesting amounts higher than the recommended dietary allowance may cause adverse effects and should not be encouraged unless supervised by a physician. Furthermore, the consequences of long-term administration of zinc salts are unknown.

Metabolically, zinc is important in many essential enzyme systems, in protein synthesis, and in the stabilization of membranes and macromolecules. Zinc depletion has been observed in malnutrition and malabsorption states. It may also be induced by diets that depend on food grown in soil that is poor in minerals (Ref. 4). In the skin, zinc deficiency has been associated with poor wound healing (Ref. 15), inflammation of the skin of the hands or feet (Ref. 16), and acrodermatitis enteropathica, a severe

gastrointestinal and skin disease of early childhood (Ref. 17). The relationship between acne and zinc deficiency remains uncertain (Ref. 18).

A possible connection between zinc deficiency and acne vulgaris was observed in a patient with acne and acrodermatitis enteropathica. When this patient was treated with oral zinc, the acne cleared "almost completely" (Ref. 19).

Baer et al. (Ref. 20) reported that a zinc depletion diet (0.2 mg elemental zinc daily) in six young men resulted in the development of acne in four of the men. An acute exacerbation of cystic acne developed in one man after 22 days of zinc depletion, when his serum zinc level had decreased from 78 to 28 μ g per 100 mL. Most of the acne lesions disappeared within 4 days of restarting 44 mg elemental zinc (as zinc sulfate) in the diet. Milder acne appeared in other subjects who were on the zinc-depletion diet, but whose serum zinc levels remained normal. The researchers believed that serum zinc levels probably did not reflect the tissue zinc levels of these patients in the early stages of zinc depletion.

This echoed the feeling of Fitzherbert (Ref. 21), who postulated that acne might be associated with deficiencies of zinc not detectable in serum, and that plasma zinc levels were "of little use in assessing whether anyone with acne vulgaris can benefit from zinc replacement therapy." Fitzherbert suggested that zinc levels in hair would be a more accurate method of investigating zinc levels in the skin. He also pointed out that zinc deficiency in rats produces abnormal keratinization of skin and hypertrophy of sebaceous gland cells, causing the sebaceous glands to become more prominent. He further postulated that reversal of these histopathological changes might require administration of daily zinc over periods of 3 to 4 months or longer (Ref. 22). Fitzherbert suggested a dosage of zinc sulfate of 100 mg/day to be taken by teenagers at night, to meet their daily requirement of zinc (Ref. 23).

Several double-blind, controlled studies comparing oral zinc to other medications in the treatment of acne have had conflicting results. Michaelsson, Juhlin, and Ljunghall (Ref. 24) compared oral zinc sulfate 200 mg with oral tetracycline, a well-accepted drug in the treatment of acne, in a 12-week study. No difference was seen between the two drugs in 37 patients with moderate and severe acne. The acne score of each group of patients decreased an average of 70 percent. Serum zinc levels were measured before treatment and after 12 weeks of

treatment. There was no correlation between serum zinc levels and clinical response. Although the investigators felt that zinc was more effective than oral tetracycline in treating papular and pustular acne and less effective on comedones, this was not confirmed statistically.

In 64 patients, the same group of investigators also compared the effects of effervescent tablets of zinc sulfate 200 mg three times daily, with placebo, vitamin A 300,000 to 400,000 International Units per day (I.U./day), or a combination of the same doses of zinc and vitamin A (Ref. 19).

After 12 weeks of treatment the total "acne score" in patients treated with zinc was reduced from 100 percent to 13 percent. The pustules and papules had disappeared in most patients after 8 to 12 weeks, and comedones had decreased to 44 percent. The improvement was about the same in patients given zinc and vitamin A. After only 4 weeks of treatment, the two groups receiving zinc showed a mean decrease of 100 percent to 35 percent, but the placebo and vitamin A groups only decreased from 100 percent to 75 percent and 70 percent, respectively. Then zinc was added to the treatment of all but two patients in both the placebo and vitamin A groups. The researchers switched the medication for "ethical" reasons, based on their belief that most patients' acne improved within 4 weeks and that they could not justify placebo treatment for longer than 4 weeks. Their study was later criticized for this position (Ref. 25). The authors concluded that the effect of zinc plus vitamin A was no better than treatment with zinc alone (Ref. 19).

Goransson, Liden, and Odsell (Ref. 26) conducted a randomized, double-blind investigation of 200 mg oral zinc sulfate three times daily versus effervescent placebo tablets in 54 patients with acne. The trial was performed between October and the end of April to minimize natural ultraviolet radiation and included a 6-week active treatment period. Patients were examined and photographed before treatment, after 3 weeks of treatment, and again 6 weeks after treatment. Each type of lesion was counted and multiplied by a "severity index," so that the sums of all lesion types yielded a score of overall "acne load." After both zinc and placebo treatment, a statistically significant reduction in numbers of lesions was evident. Lesion reduction continued during both the first and second 3-week treatment periods in the zinc treatment group, but no statistically significant reduction occurred in the placebo group after the first 3 weeks of treatment. Zinc

sulfate therapy was statistically significantly better than placebo, when patients showing 25 percent improvement were compared ($p < 0.01$). No statistically significant difference was found when the patients in each group who showed 50 percent improvement were compared.

Overall, the authors concluded that the acne improved "about one-third" after 6 weeks of treatment with zinc. They speculated that the treatment period was probably not long enough to see the full effect of zinc therapy, and that a trial period of 3 months would have been more desirable. According to Fitzherbert (Ref. 23), even 12 weeks is too short a time to see maximal biological changes induced by zinc, as structural changes in the swollen hypertrophic cells of sebaceous glands are only slowly reversed.

A randomized, double-blind trial of 39 patients showed that zinc was not superior to placebo in the treatment of acne (Ref. 12). Patients with papular and pustular acne were given either oral zinc sulfate effervescent tablets 200 mg three times daily or placebo effervescent tablets. Only 25 patients were treated for 12 weeks; the remaining 14 were treated for either 4 or 8 weeks. There was a significant reduction in papules and pustules in both groups, but no statistically significant difference between the groups. Serum zinc levels, which were originally normal in both groups, rose considerably in both groups, although the increase in the zinc group was significantly higher than the placebo group. The researchers thought that the increased zinc levels were possibly caused by seasonal variations in zinc metabolism. They concluded that the negative therapeutic results might have been attributed to the small number of patients or to natural seasonal improvement in acne, as the study was conducted in the spring.

Another double-blind study compared zinc sulfate monohydrate capsules (137 mg three times daily) to placebo (Ref. 7). The use of the monohydrate salt was unique to this study and accounts for the lower dosage. Twelve patients were included in the active treatment group and 10 patients in the placebo group. Patients were evaluated by lesion counts. After 8 weeks of treatment, both groups had decreases in the mean values of papules, pustules, and closed comedones; open comedones remained about the same in the zinc group. No statistically significant differences were seen between the groups in any type of acne lesion. Positive zinc absorption was well documented by rises in zinc levels in serum and urine. The

investigators speculated that the divergent results in their study might have reflected differences in characteristics of their patient population.

In a randomized, double-blind trial involving 40 patients, zinc sulfate capsules (220 mg three times daily) were compared with placebo (Ref. 11). During the 12-week treatment period, patients were seen at 0, 2, 4, 6, 8, and 12 weeks and evaluated with lesion counts. After 12 weeks there was a 37-percent decrease in the pustule counts of the group receiving zinc compared to no change in the placebo group. Comedones and papules decreased 47 percent in the zinc group compared to 37 to 38 percent in the placebo group. This difference was not significant. The researchers concluded that zinc "appeared to have a slightly beneficial effect on pustules after at least 6 weeks of treatment" but was not helpful for comedones or papules.

From these studies zinc appears to be valuable in the treatment of papular and pustular acne. However, the Panel is concerned that there seems to be unexplained wide variation in the results of double-blind studies with zinc conducted in different geographical areas. Investigators in Sweden believe that zinc is valuable in the treatment of acne (Refs. 19, 24, and 26), but investigators in Denmark (Ref. 12) and the United States (Refs. 7 and 11) remain unconvinced of its efficacy. In general, the Swedish studies, done by three different groups of investigators, involved larger numbers of patients than the other studies and the use of an effervescent dosage form. These patients, because they had fewer gastrointestinal side effects, also appeared to tolerate the zinc better than other groups of patients. The contrasting results between studies from various countries suggest to the Panel that environmental factors such as seasonal variation in ultraviolet light exposure, the amount of zinc in the natural diet, and the dosage form may have influenced the studies.

The Panel concludes that more double-blind, controlled trials could be useful in establishing the effectiveness of zinc sulfate in treating acne. As stated earlier, the Panel is not recommending the OTC use of oral zinc in the treatment of acne, but has included it in this document only for discussion.

References

(1) National Nutrition Consortium, Inc., "Vitamin-Mineral Safety, Toxicity, and Misuse," The American Dietetic Association, Chicago, pp. 34-35, 1978.

(2) Van Reen, R., "Zinc Toxicity in Man and Experimental Species," in "Zinc Metabolism," Edited by A. S. Prasad, Charles C. Thomas, Springfield, IL, pp. 411-425, 1966.

(3) Bremner, I., "Heavy Metal Toxicities," *Quarterly Reviews of Biophysics*, 7:75-124, 1974.

(4) Hartoma, R., "Zinc Deficiency—A Disease With Diverse Symptoms," *International Medicine*, 1:9-11, 1979.

(5) Cowan, G. A. B., "Unusual Case of Poisoning by Zinc Sulphate," *British Medical Journal*, 1:451-452, 1947.

(6) Halsted, J. A., J. C. Smith, Jr., and M. I. Irwin, "A Conspectus of Research on Zinc Requirements of Man," *Journal of Nutrition*, 104:347-378, 1974.

(7) Orris, L., et al., "Oral Zinc Therapy of Acne. Absorption and Clinical Effect," *Archives of Dermatology*, 114:1018-1020, 1978.

(8) Hallbook, T., and E. Lanner, "Serum Zinc and Healing of Venous Leg Ulcers," *Lancet*, 2:780-782, 1972.

(9) Vahlquist, A., G. Michaelsson, and L. Juhlin, "Acne Treatment with Oral Zinc and Vitamin A: Effects on the Serum Levels of Zinc and Retinol Binding Protein (RBP)," *Acta Dermato Venereologica*, 58:437-442, 1978.

(10) Greaves, M. W., and A. W. Skillen, "Effects of Long-Continued Ingestion of Zinc Sulfate in Patients with Venous Leg Ulceration," *Lancet*, 2:889-891, 1970.

(11) Weimar, V. M., et al., "Zinc Sulfate in Acne Vulgaris," *Archives of Dermatology*, 114:1776-1778, 1978.

(12) Weismann, K., S. Wadskov, and J. Sondergaard, "Oral Zinc Sulphate Therapy for Acne Vulgaris," *Acta Dermato Venereologica*, 57:357-360, 1977.

(13) Cunliffe, W. J., "Unacceptable Side-Effects of Oral Zinc Sulphate in the Treatment of Acne Vulgaris," *British Journal of Dermatology*, 101:363, 1979.

(14) Moore, R., "Bleeding Gastric Erosion after Oral Zinc Sulphate," *British Medical Journal*, 1:754, 1978.

(15) Pories, W. J., et al., "Acceleration of Healing with Zinc Sulfate," *Annals of Surgery*, 165:432-436, 1967.

(16) Weismann, K., et al., "Acquired Zinc Deficiency Dermatitis in Man," *Archives of Dermatology*, 114:1509-1511, 1978.

(17) Moynahan, E. J., "Acrodermatitis Enteropathica: A Lethal Inherited Human Zinc-Deficiency Disorder," *Lancet*, 1:399-400, 1974.

(18) "Zinc Again," unsigned editorial, *British Medical Journal*, 1:1493, 1977.

(19) Michaelsson, G., L. Juhlin, and A. Vahlquist, "Effects of Oral Zinc and Vitamin A in Acne," *Archives of Dermatology*, 113:31-36, 1977.

(20) Baer, M. T., et al., "Acne in Zinc Deficiency," *Archives of Dermatology*, 114:1093, 1978.

(21) Fitzherbert, J. C., "Acne Vulgaris—Zinc Deficiency?", *Medical Journal of Australia*, 2:273, 1976.

(22) Fitzherbert, J. C., "Acne Vulgaris—Zinc Deficiency?", *Medical Journal of Australia*, 1:848, 1976.

(23) Fitzherbert, J. C., "Zinc Deficiency in Acne Vulgaris," *Medical Journal of Australia*, 2:685-686, 1977.

(24) Michaelsson, G., L. Juhlin, and K. Ljunghall, "A Double-Blind Study of the Effect of Zinc and Oxytetracycline in Acne Vulgaris," *British Journal of Dermatology*, 97:561-566, 1977.

(25) Glover, S. C., and M. I. White, "Zinc Again," *British Medical Journal*, 2:640-641, 1977.

(26) Goransson, K., S. Liden, and L. Odsell, "Oral Zinc in Acne Vulgaris: A Clinical and Methodological Study," *Acta Dermato Venereologica*, 58:443-448, 1978.

H. Abrasive Scrubs

The Panel realizes that some consumers may prefer acne products that are formulated as abrasive scrubs. For this reason, even though the Panel believes it unlikely that superficial epidermabrasion will remove the tightly adherent comedo, the Panel has included the following discussion on physical abrasives.

Saperstein (Ref. 1) reported on a 10-year study of 1,000 acne patients who were treated with abrasives along with other forms of topical and systemic treatment for acne. Saperstein found that fused synthetic aluminum oxide in a soap paste was the most effective abradant of all that were tested. However, no lesion counts were included in this report. According to this researcher, the purpose of epidermabrasion is to keep the sebum washed off the skin and to keep the pores open. Saperstein noted that during this treatment the patients stopped picking and squeezing their acne lesions, "for the abrasion routine apparently replaces the emotional need to scrutinize and express each lesion."

Mills and Kligman (Ref. 2) also studied abrasives for the treatment of acne. They wrote that abrasives "are popular with patients, possibly because the patient is lead (sic) to believe that conscientious scrubbing will clean out 'clogged pores' and that his deliverance is therefore in his own hands." These researchers studied five abrasives including one containing aluminum oxide and one containing polyethylene granules to see whether they were effective in helping to remove comedones. Each test group consisted of 10 patients with "moderate acne and conspicuous comedones." Treatment was twice daily for 8 weeks; no other medication was used during this time. Global clinical assessments were done biweekly. Lesion counts were taken before the study and at the end of the study. Mills and Kligman found that "none of the test materials had a clinically significant effect in eliminating comedones." Open comedones were reduced no more than 20 percent; closed comedones were not reduced at all.

Early in the study, all of the treatments reduced the number of papules and pustules to some extent, but in some patients the reduction was followed by an increase in the number of papules and pustules.

Mills and Kligman (Ref. 2) concluded that there was no evidence showing that abrasives could effectively remove comedones. They stated that, because skin affected by acne is vulnerable to chemical and physical trauma, they "do not advise the use of abrasives as adjuncts in acne treatment."

An unpublished report discussed a half-face study in which 53 subjects were treated either with a combination of polyethylene, 2 percent sulfur, and 1.5 percent salicylic acid or a combination of sulfur and salicylic acid without polyethylene (Ref. 3). Both treatments significantly decreased open comedones, closed comedones, and papules. However, neither formulation decreased pustules significantly over baseline. There was no difference in the results between the combination with polyethylene and the one without polyethylene.

The Panel concludes that aluminum oxide and polyethylene do not have an effect on acne lesions and therefore considers them inactive ingredients.

References

- (1) Saperstein, R. B., "Treatment of Acne with Long-Term Continuous Graded Abrasion," *Archives of Dermatology*, 81:601, 1960.
- (2) Mills, O. H., Jr., and A. M. Kligman, "Evaluation of Abrasives in Acne Therapy," *CUTIS: Cutaneous Medicine for the Practitioner*, 23:704-705, 1979.
- (3) OTC Volume 070268.

I. Evaluation of Safety and Effectiveness

1. *Criteria for evaluating safety.* The Panel has developed flexible criteria for assessing the safety of the many chemical agents used in acne treatment products. This flexibility was needed to accommodate the differences between chemical agents. It should be noted that although some data did not meet all of these criteria, the Panel considered other assessments adequate to allow a safety evaluation for a particular ingredient. Some products had been marketed long before this review began. The Panel's evaluation in those instances was based on limited historical data, new data obtained from various sources, and the Panel's own knowledge and judgment.

Influencing factors in the data assessment were the surface area and the site of application, the frequency and length of application, and the vehicle. The degree of occlusion from clothing was also considered because

acne may affect the upper torso as well as the face. The Panel also recognizes that because of acne the stratum corneum may not be intact and inflammation may be severe. These conditions could greatly influence the degree of absorption through the skin.

To avoid needless repetition, these safety evaluation criteria are detailed later in this document. (See part III, paragraph E.1. below—Safety guidelines.)

After the Panel evaluated the safety of an ingredient, it placed that ingredient in Category I, II, or III. When an ingredient was classified Category III for safety, the Panel concluded that the data base was inadequate to fully assess safety. In these cases the safety guidelines discussed below could be used by a manufacturer to move an ingredient from Category III to Category I by generating data where there are none or where existing data are inadequate.

The actual criteria for the movement to Category I are obviously judgmental and have to be examined in their totality. Although in such cases a benefit-to-risk concept may seem desirable, the Panel attempted to assess safety per se rather than by benefit-to-risk.

The Panel is concerned about the safety of certain ingredients or combinations of ingredients when the single ingredient or combination product has a keratolytic or "peeling" effect on the skin. It has long been known that the stratum corneum protects underlying skin areas against irritants and damage from ultraviolet radiation. Research on the effect of reducing the thickness of the stratum corneum by the use of keratolytic agents has not resolved the Panel's concerns, particularly on absorption, irritation, sensitization, or the possibility of carcinoma from exposure to ultraviolet light.

2. *Criteria for evaluating effectiveness.* The Panel required each ingredient to have at least one well-designed clinical trial demonstrating its effectiveness in the treatment of acne in order to be classified as Category I. In evaluating data, the Panel also considered the study design and how it conformed to the following description of a well-designed trial.

The trial should be a multi-center study involving more than one investigator using the same protocol in different geographic locations, thus helping to eliminate geographic influence and investigator bias. The trial should be double-blind, i.e., the investigators and patients should not know the identity of the drugs. The drugs should be randomly assigned. The trial should also be controlled, with the

control being the vehicle minus the active ingredient or ingredients. The vehicle may be modified or altered if needed to ensure blinding. No additional treatment other than soap and water should be allowed. The investigators should state which calendar months were included in the study because acne lesions generally clear up somewhat in the summer. A well-designed study should last at least 8 to 12 weeks. Patients should be evaluated once before treatment and at least twice during the study, including the final examination.

The Panel preferred lesion counts, grouped by type of lesion, as a method of evaluating acne ingredients. A lesion count is usually taken before treatment, during treatment, and after treatment. The final results show the percentage of reduction in the number of each type of lesion after treatment, compared to before treatment. Global assessments were also considered acceptable as long as they were on a numbered scale (such as 1 to 6) with a rigidly defined numerical system that could be reliably reproduced.

Active ingredients should be significantly more effective in reducing lesion count than the vehicle. Results should be statistically analyzed.

Studies that showed a statistically significant decrease in free fatty acid content or sebum excretion rate as proof of effectiveness were not acceptable as sole evidence of effectiveness. Studies in induced or experimental acne were similarly not considered as proof of effectiveness. The Panel did not evaluate adjunctive therapies. An ingredient was not considered unless it actually treated acne, i.e., actually reduced lesion count. The Panel did not consider ingredients that reduce inflammation but do not act on the comedone, such as, topical steroids.

If a clinical trial did not meet all of the Panel's criteria, some other supporting evidence was necessary to place an ingredient in Category I. However, the Panel did not intend to be too rigid in setting up criteria for proof of effectiveness. The Panel recognized that not all studies would meet each criterion for a single "best study." Each submission and ingredient was analyzed according to the above criteria, but the final categorization depended upon the total information available at the time.

Ingredients were placed in Category II if there was no rational explanation of their mode of action, no substantial scientific evidence to suggest effectiveness, no general acceptance by the consultant "acne experts," and no supportive evidence of effectiveness in

the medical literature on acne. All of these factors were considered in the Panel's decision on final categorization. The ultimate decision did not rest on any single one of them but on the Panel's general recognition of effectiveness of the ingredient.

3. *Vehicles.* The Panel believes that a proper vehicle is one that will deliver the drug to the site of action at a rate that will allow maximum benefit without causing or allowing toxic effects. However, the Panel recognizes that choosing an appropriate vehicle for adequate drug delivery without contributing to the whole acne problem can be quite difficult. Many drug delivery systems are used today in OTC preparations, ranging from solutions, gels, lotions, and creams, to solid sticks, mascara-like creams, and cosmetic touch-up type formulations. The Panel was unable to accurately assess the influence of such a variety of vehicles on the effectiveness of the therapeutic ingredient.

III. Acne Drug Products

A. Category I Conditions

These are conditions under which OTC acne drug products are generally recognized as safe and effective and are not misbranded. The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the Federal Register.

1. Category I active ingredients.

Benzoyl peroxide
Sulfur

a. *Benzoyl peroxide.* The Panel concludes that benzoyl peroxide is safe and effective for OTC topical use in the treatment of acne.

(1) *Safety.* The stability of a given preparation of benzoyl peroxide is especially dependent upon the vehicle (Ref. 1). The potential for irritation or other toxic manifestations are undoubtedly affected by stability.

The intraperitoneal LD₅₀ of benzoyl peroxide in mice has been reported to be from 75 to 210 milligrams per kilogram (mg/kg) (Refs. 2 through 5). Because most deaths following intraperitoneal administration occur after 24 hours, it is important to note that the 75-mg/kg value was calculated after a 7-day observation (Ref. 2). Several factors may account for differences in the LD₅₀ values reported, including vehicle, the length of observation, and the strain of mouse. One study reported the intraperitoneal LD₅₀ in mice as 17.1 plus or minus 2.1 micromoles (μ mol) or 180 mg/kg per mouse. According to this study, 26 μ mol

per mouse will result in 100 percent mortality (Ref. 4).

Although benzoyl peroxide is much less toxic orally than intraperitoneally, death occurs faster by the oral route following a lethal dose. To illustrate, the oral LD₅₀ in mice in one study was reported as 2,127 mg/kg, but a lethal oral dose caused central nervous system depression and death within hours (Ref. 5). Following oral administration to Swiss mice (7-day observation), an LD₅₀ of 1.4 g/kg was calculated (Ref. 6). The animals were lethargic and prostrate, and exhibited labored respiration prior to death.

In another study a lotion containing 10 percent benzoyl peroxide was administered orally to male rats at a dose of 3 g/kg. During the following 2-week observation period there were no deaths. No effects on appearance, behavior, or weight gain were noted (Ref. 6). In rats the LD₅₀ is reported as 373 mg/kg intraperitoneally and 6,400 mg/kg orally (Ref. 5).

The difference in intraperitoneal versus oral LD₅₀ values suggests that orally administered benzoyl peroxide is not readily absorbed. In fact, the cause of death could be due to the metabolite benzoic acid because the oral LD₅₀'s of the two compounds are nearly identical in the mouse. There is, however, indirect evidence to suggest that benzoyl peroxide can be absorbed by the gut. Oral administration in mice produces central nervous system depression (Ref. 5), which is not characteristic of benzoic acid.

There is some evidence that benzoyl peroxide can be absorbed following dermal application to guinea pigs. When benzoyl peroxide was applied to the shaved backs of guinea pigs at doses up to 1 g/kg and occluded for 24 hours, a dose-related weight loss was observed (Ref. 7). This was probably an effect of the metabolite rather than the parent compound.

Holzmann, Morsches, and Benes (Ref. 8) reported the plasma levels at benzoic acid in 20 patients on benzoyl peroxide therapy. The level peaked 3 days after application of 20 percent benzoyl peroxide lotion and was never higher than 610 micrograms per liter (μ g/L). These investigators measured benzoic acid on the assumption that benzoyl peroxide itself does not penetrate the skin.

Two other studies also suggest that benzoyl peroxide does not penetrate the skin. One study consisted of applying benzoyl peroxide to human forearms, waiting 4 hours, then washing the arm with chloroform. Both benzoyl peroxide and benzoic acid were recovered in the chloroform wash in a ratio of 1.5 to 1,

indicating conversion to benzoic acid (Ref. 9).

Nacht et al. (Refs. 10 and 11) reported on an in vitro study in which excised human skin was used to measure penetration of C¹⁴-benzoyl peroxide. After 8 hours, 1.9 percent of the labeled drug was recovered as benzoic acid on the dermal side. Extraction from the skin itself yielded 2.6 percent of the labeled drug, half benzoyl peroxide and half benzoic acid.

These investigators also applied C¹⁴-benzoyl peroxide to the forearms of monkeys and measured radioactivity in the urine. The output peaked between 6 and 30 hours. Forty-five percent of the administered dose was recovered, 98 percent of which was benzoate. Nacht et al. (Ref. 11) concluded that benzoyl peroxide penetrates the skin layers where it is converted to benzoic acid and then absorbed into the systemic circulation. They also concluded that benzoic acid was quickly eliminated through the kidneys without passing through the liver. In the liver, benzoic acid would have conjugated with glycine and formed hippuric acid, but no hippuric acid was recovered in the urine.

In a subchronic study in rats, benzoyl peroxide was administered intragastrically five times weekly for 3 months (Ref. 2). Two control groups of 10 animals, male and female, were used. One group was given the vehicle, 0.1 percent polysorbate 80; the other group was given 2 g/kg benzoic acid. Two other groups were treated with benzoyl peroxide. These groups consisted of 40 animals each, male and female, dosed with either 0.5 or 2 g/kg benzoyl peroxide. The benzoic acid-treated group was removed from the study after 1 week because most of the group developed aspiration pneumonia. During the experiment a hematologic evaluation was done monthly. Gross and histological examination of tissues was done at the end of 3 months.

The following signs were observed near the end of the experiment in the group that was given 2 g/kg benzoyl peroxide: poor appetite, weakness, weight loss (prominent in males), urinary incontinence, intermittent irritability, and transient twisting of the muscles. One striking pathological change was bladder distension due to blockage of the urinary passage by cartilaginous material. Localized lymphangitis (inflammation of the lymph vessels) of the salivary gland was also noted. The urinary effect was most frequent in the high dose group, whereas the lymphangitis occurred in the control group as well. In the high dose group,

tubular destruction was noted in the kidneys.

Feeding studies were conducted in mice, rats, and dogs (Ref. 12 and 13). These studies used flour treated with benzoyl peroxide and are of little value, because benzoyl peroxide is converted to benzoic acid in flour (Ref. 12).

Benzoyl peroxide is not considered to be carcinogen (a cancer-producing substance). In one study in rats and mice, benzoyl peroxide was given orally, painted on the skin, or injected subcutaneously without evidence of carcinogenicity (Ref. 12). In another study, Swiss mice painted three times weekly with 100 mg benzoyl peroxide did not have a tumor index greater than the controls which had been painted with a solvent (Ref. 14). A report by Heuper (Ref. 15) further supports benzoyl peroxide's lack of carcinogenicity.

Benzoyl peroxide was found to be negative in the dominant lethal assay in the mouse when tested at 62 mg/kg intraperitoneally (Ref. 16). The dominant lethal assay is a frequently used method of testing the effect of a chemical substance on spermatogenesis (the maturation of sperm). In another study, benzoyl peroxide was extensively screened for mutagenicity (Ref. 17). The screen consisted of three *Salmonella* mutants and one strain of yeast and was carried out with and without metabolic activation systems. A 0.37-percent concentration of benzoyl peroxide, the highest dose used in the mutagenicity tests, gave 50 percent survival of the test organisms. Results were clearly negative in all tested strains.

A number of subchronic studies have been conducted in rabbits using dermal application of benzoyl peroxide. In one of these, a 10-percent benzoyl peroxide gel was applied to the ears of four rabbits five times weekly for 2 weeks (Ref. 1). The observed irritation in the animals consisted of desquamation and erythema. None of the animals was visibly sick.

A 30-day controlled study was conducted on 16 rabbits, divided into two groups of 8 rabbits each (Ref. 18). The skin was abraded in four rabbits in each group. A lotion containing 5 percent benzoyl peroxide was applied to one group of rabbits five times weekly. The area of application was about 10 percent of the total body surface. Based on the information that 4 to 5 g of lotion was applied, the calculated dose averaged 98 mg/kg. No effects could be detected on body weight, hematology, organ weight, gross pathology, or histopathology. One treated rabbit died from respiratory infection before the end of the study.

A similar study was conducted for 43 days with both 5 and 10 percent benzoyl peroxide lotion (Ref. 6). A group consisted of five rabbits with half of the shaved area abraded on each animal. Based on estimated application, the two test doses were 120 and 240 mg/kg. No effects of benzoyl peroxide were detected other than some reddening of the skin, particularly following application of the 10-percent lotion.

A 12-week study using an ointment containing 10 percent benzoyl peroxide was conducted on rabbits of both sexes (Ref. 2). No adverse effects were noted. Another report contains results of a 3-month study in which 1.9 g of ointment was applied to rabbits five times a week (83 mg/kg estimated dose). The only adverse effect was a slight reddening of the skin during the first few weeks which lessened as the study progressed.

Primary skin irritation was assessed by patch tests on intact and abraded rabbit skin (Ref. 6). The exposure period was 4 hours, after which the reaction was graded immediately and at 24 and 48 hours. Slight erythema was noted only at 4 hours on 5 of 12 sites with 10 percent benzoyl peroxide and 3 of 12 sites with 5 percent benzoyl peroxide. Application of 5 or 10 percent benzoyl peroxide to rabbit eyes produced only a mild, transient erythema (Refs. 6 and 18).

Some irritation occurs when benzoyl peroxide is applied to human skin. This consists of mild burning and itching in most subjects and moderate drying and peeling in all subjects (Refs. 1, 2, and 18).

Complete hematological studies and urinalysis were conducted on 20 out of 147 patients following topical therapy with 5.5 percent benzoyl peroxide (Ref. 19). Results showed no evidence of systemic effects. Also, no sign of sensitivity was noted in any of the 147 patients treated with benzoyl peroxide.

The Panel is particularly interested in the cutaneous toxicity (irritation and contact sensitization) of benzoyl peroxide on human skin. This is important because the effectiveness of benzoyl peroxide is partly due to its mild peeling action on the skin during the early phase of treatment, and peeling may enhance irritation and sensitization.

The sensitization of the skin to this ingredient is well known among physicians (Ref. 20). Sensitization may be related to the genetic makeup of the individual. Certain types of complexion are highly sensitive to environmental factors as well as topical drugs. People who have an atopic background (an inherited tendency to develop allergy) and who have allergies will be more

easily irritated by certain topical preparations. In general, the concentration of the medicine, the vehicle, and the degree of occlusion should be considered in determining sensitization rates. The skin type, individual immunologic background, and other variables should also be considered.

Repeated patch tests with benzoyl peroxide may produce an experimental contact dermatitis (Ref. 21). However, in clinical use sensitization is low, usually between 1 and 2 percent of users (Ref. 22).

Benzoyl peroxide will produce a primary irritant dermatitis in a person with sensitive skin. Light-complexioned individuals may be easily irritated by a benzoyl peroxide preparation as well as other medications. Skin dryness also makes skin vulnerable to irritations. It is well known to the Panel that skin type (ruddy compared with olive) relates to the ease with which the skin is irritated.

There is evidence that the higher the concentration of benzoyl peroxide, the greater the irritation. For that reason, ideally the lowest effective concentration of benzoyl peroxide should be used in the management of acne.

The Panel appreciates that an increase in concentration and the use of drying vehicles may produce more irritation and desquamation in some people but does not believe this represents a substantial hazard. The Panel concludes that benzoyl peroxide in concentrations of 2.5 to 10 percent is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Benzoyl peroxide has antimicrobial properties attributed to its capacity to slowly release oxygen. The oxygen acts on certain kinds of bacteria, called anaerobes, which do not live in its presence. *P. acnes* is an anaerobic bacteria.

Another action of benzoyl peroxide is as an exfoliant, i.e., it causes peeling of the outer layers of the skin. Benzoyl peroxide is formed by the reaction of alkaline sodium hydrogen peroxide with benzoyl chloride in water. Benzoyl peroxide has been used since the 1920's for ulcers and burns. Concentrations of benzoyl peroxide in submissions reviewed by the Panel ranged from 2.5 to 10 percent.

The mechanism of action of benzoyl peroxide was studied by using a 5-percent benzoyl peroxide gel applied twice daily. This preparation was associated with a significant depression of the surface bacterial count and a decrease in the concentration of fatty acid formation. The researchers

theorized that the antibacterial activity of benzoyl peroxide reduced the population of *C. acnes* (*P. acnes*) with a subsequent decrease in free fatty acids. The investigators also believed that benzoyl peroxide is a mild keratolytic, but this was not firmly established (Ref. 23). Although benzoyl peroxide has antibacterial activity, none of the antibacterial studies on this ingredient have met the Panel's *in vivo* criteria. (See part III, paragraph E.2.c. below—*In vivo* testing of acne ingredients.)

Vasarinsh (Ref. 24) studied the effects of 5 percent and 10 percent benzoyl peroxide lotions on epidermis and dermis. He was unable to find any microscopic epidermal changes when there was no peeling. Biopsies showed that dermal changes, however, were common in all patients regardless of whether they had clinical signs of erythema and desquamation. These changes mainly consisted of mild dilatation (expansion) of the blood vessels in the upper portions of the dermis and lymphocytes (white blood cells) surrounding the blood vessels, the hair follicles, and the small lobules of the sebaceous glands. Vasarinsh was unable to quantify any keratolytic effect.

Ede (Ref. 19) studied the effectiveness of 5.5 percent benzoyl peroxide in a randomized, controlled, double-blind trial of 196 patients. Patients who entered the study had Grade II or III acne (system of classification unspecified). Four treatment groups were used. One group consisted of 48 patients treated with 5.5 percent benzoyl peroxide. Another group consisted of 54 patients treated with 5.5 percent benzoyl peroxide-0.25 percent chlorhydroxyquinoline. In the third group, 45 patients were treated with 5.5 percent benzoyl peroxide-0.25 percent chlorhydroxyquinoline-0.5 percent hydrocortisone. In the fourth group, 49 patients were treated with the vehicle as a control.

Frequency of application varied from one to four times daily depending upon "therapeutic response and upon the extent of skin peeling and erythema." At least one of the daily applications was made under direct medical supervision. The patients used soap before each application, but no other therapy was allowed. They were evaluated by lesion counts at 0, 14, and 28 days. Statistical analysis showed no statistically significant differences in the number of patients in the groups or in the distribution of patients with regard to sex, age, complexion, skin type (normal, dry, oily), pores, (normal or enlarged), grade of acne, or frequency of application.

After 4 weeks of treatment, the lesion count of patients treated with benzoyl peroxide alone decreased from 10.5 to 6.6. The count increased in the vehicle group from 10.4 to 11.1. Statistical analysis of results showed that all three active treatments were significantly more effective than the vehicle in reducing lesion counts at 2 and 4 weeks ($p < 0.001$).

Clinical evaluation showed that 65 percent of the patients treated with benzoyl peroxide improved; 29 percent remained the same; and 6 percent were worse. In the vehicle group, 33 percent improved; 37 percent were the same; and 30 percent became worse. Benzoyl peroxide (along and in combination) was found to be significantly more effective than vehicle when overall clinical response was evaluated.

In another double-blind, controlled, randomized study, 28 patients were treated with 5 percent benzoyl peroxide lotion, and 27 patients were treated with the vehicle used as a control (Ref. 25). Patients entered the study only if they had Grade II or III acne based on Pillsbury's classification (Ref. 26). Patients were treated two or three times daily depending upon the evaluator's initial appraisal of the severity of the acne. Comparison of the makeup of the groups showed no significant differences between age, sex, frequency of therapy, or severity of acne.

Patients were evaluated by lesion counts and global impressions before treatment and after 6 weeks of treatment. The benzoyl peroxide group had a 39.7-percent improvement in lesion counts compared to 7.7 percent improvement for the vehicle group. This difference was statistically significant ($p < 0.001$). The investigator rated 68 percent of the patients treated with benzoyl peroxide as excellent or good, 18 percent fair, and 14 percent poor at the conclusion of the study. In the vehicle group, no patients were rated as excellent or good; 30 percent were considered fair; and 70 percent poor. The investigator found treatment with benzoyl peroxide superior to vehicle when evaluated by global impression ($p < 0.001$).

Another randomized, controlled, and double-blind study was done on 92 patients to determine the effectiveness of benzoyl peroxide (Ref. 27). Patients were treated twice daily with either 5 percent benzoyl peroxide, 3 percent sulfur, a combination of 10 percent benzoyl peroxide and 3 percent sulfur, or vehicle. Soap and water was the only other treatment allowed. Treatment lasted 12 weeks. Patients were

evaluated by lesion counts and clinical impression.

Patients were given a satisfactory rating if continued improvement in lesion counts was noted over 12 weeks or if they were discharged in less than 12 weeks with greater than 50 percent improvement in lesion counts. In the benzoyl peroxide group, 41.7 percent (10 patients) were satisfactory and 58 percent (14 patients) were unsatisfactory at the end of the treatment period. Ten percent of the vehicle group (20 patients total) were rated satisfactory and 90 percent unsatisfactory. For the benzoyl peroxide-treated patients rated as satisfactory, treatment averaged 6.8 weeks with a decrease in lesion count of 71.2 percent.

Good and excellent results in clinical impressions were seen in 58.3 percent of patients treated with the benzoyl peroxide-sulfur combination; 41.7 percent of the benzoyl peroxide group; 29.1 percent of the sulfur group; and 10 percent of the vehicle group.

Although a statistical analysis of results was not presented, the researchers stated that the three active preparations were "demonstrably more effective than the placebo." They also stated that the 5-percent benzoyl peroxide treatment "produced the greatest improvement of acne symptoms in the shortest period of time," but that the benzoyl peroxide-sulfur combination "proved somewhat better than the other formulae."

Two unpublished, randomized, double-blind trials comparing 5 and 10 percent benzoyl peroxide followed nearly identical protocols (Refs. 26 and 28). Each treatment group contained 25 patients with Grade II or III acne (Pillsbury classification). The patients had had no systemic therapy for 1 month before entering the study and no topical therapy for 2 weeks. Each patient was treated one to three times daily, depending upon the severity of acne and tolerance to benzoyl peroxide. No vehicle controls were used. The patients were evaluated by lesion counts and global impression when the study began and at intervals of 2 to 4 weeks for the next 12 weeks. The results were expressed as follows: excellent was 75 to 100 percent improvement; good was 50 to 75 percent improvement; fair was 25 to 50 percent improvement; poor was less than 25 percent improvement.

In one study, good to excellent results were reported in 36 percent of the patients who had used 5 percent benzoyl peroxide and 56 percent of the patients who had used the 10-percent

lotion. The second study showed good to excellent results in 54 percent of the group treated with 5 percent benzoyl peroxide and in 72 percent of the group treated with 10 percent benzoyl peroxide. This report also gave the results of the lesion counts. Overall, 5 percent benzoyl peroxide reduced the count from 17.7 to 11.2, and 10 percent benzoyl peroxide decreased the count from 28.0 to 17.9. Although it appears that 10 percent benzoyl peroxide may be more effective than 5 percent benzoyl peroxide in reducing the number of acne lesions, no statistical analysis of the results was presented.

Belknap (Ref. 29) conducted a parallel comparison of 5 percent benzoyl peroxide gel and 0.05 percent retinoic acid cream. (Retinoic acid, also known as tretinoin or vitamin A acid, is a prescription drug for acne.) Patients with Grade II and Grade III acne (Pillsbury classification) were randomly assigned to treatment with either of the active drugs. They had had no topical or systemic medications for 2 weeks before entering the study. The benzoyl peroxide group (29 patients) was treated twice daily and the retinoic acid group (31 patients) was treated once daily. No topical or systemic therapy was allowed other than soap and water. Length of treatment was 8 weeks. Patients were evaluated with lesion counts grouped by type (papules, open comedones, etc.). Results were considered excellent if improvement was greater than 75 percent.

When overall ratings of the two treatment groups were compared, 16 patients who had used benzoyl peroxide showed excellent results compared to 8 patients who had used retinoic acid. This difference was significant ($p < 0.025$).

Both drugs were "extremely effective" for all lesion types, but Belknap (Ref. 29) stated that "it appears that the benzoyl peroxide gel produced a more rapid effect on inflammatory lesions (papules and pustules) than did the vitamin A acid." Both treatments also significantly reduced the number of open and closed comedones after 2 weeks of treatment, although Belknap again reported that "the extent of reduction was greater in the benzoyl peroxide group." The Panel has stated that a Category I acne treatment should be effective against all types of acne lesions and believes this study gives evidence of that effectiveness for benzoyl peroxide.

Several investigators have studied 2.5 percent benzoyl peroxide for effectiveness. One investigator treated 10 males with a 2.5-percent benzoyl peroxide water-based gel twice daily for 28 days (Ref. 30). Ten males were

treated with the control. No other significant topical or systemic therapy was allowed. *P. acnes* and free fatty acid/triglyceride ratios were measured. In the group treated with 2.5 percent benzoyl peroxide, the pretreatment level of *P. acnes* (in millions/square centimeter (cm^2)) was 6.0. On the 28th day of treatment the *P. acnes* level was 4.2. In the control group the pretreatment level of *P. acnes* was 5.9; on the 28th day of treatment the level was 5.7. The free fatty acid/triglyceride ratio in the control group was 0.75. On the 28th day the ratio was 0.71. In the group treated with benzoyl peroxide the pretreatment ratio was 0.88. On the 28th day the ratio was 0.36. Reduction of *P. acnes* and the free fatty acid/triglyceride ratio was significantly greater with 2.5 percent benzoyl peroxide than with the control.

In another unpublished study, 50 acne patients were treated with either 2.5 percent or 10 percent benzoyl peroxide twice daily for 8 weeks (Ref. 31). This study was randomized and double-blind, but not controlled. Patients were examined biweekly. Evaluation was made by measuring the reduction in the number of specific lesion types and in the total of these lesion types. Patients were also evaluated by global impression.

At 8 weeks, the percent reduction of total lesions from baseline was 46.7 percent for 2.5 percent benzoyl peroxide and 44.3 percent for 10 percent benzoyl peroxide. Statistical analysis showed that there was no significant difference between the effectiveness of the two concentrations. Also, both treatments significantly decreased the total number of papules and pustules ($p < 0.001$). No difference was noted between the two treatments in global evaluation. Good to fair results were noted in 46 percent of patients in each treatment group. In this study, side effects from 2.5 percent benzoyl peroxide were found to be less severe and occurred less frequently than with the 10-percent benzoyl peroxide.

Yong (Ref. 32) conducted an open clinical trial with 2.5 percent and 5 percent benzoyl peroxide gel. He treated 200 patients twice daily. Each concentration was given to 100 patients. No significant other topical or systemic therapy was permitted except soap and water. Treatment lasted 4 to 18 weeks. If the lesion count decreased by greater than 75 percent, improvement was considered excellent. Forty-six patients who had been treated with 5 percent gel compared to 36 patients who had been treated with 2.5 percent gel were rated as excellent. Twenty-eight patients in each group were given a good rating (lesions decreased by 50 to 75 percent). Yong concluded that there was no

significant difference in effectiveness between the two different strengths of benzoyl peroxide gel.

Numerous adequately controlled, double-blind, and randomized studies have documented the effectiveness of benzoyl peroxide. The Panel recognizes that acne represents a spectrum of severity ranging from comedones to nodules and pustules. No one concentration of benzoyl peroxide or any other ingredient will be suitable for the wide range of this disease even when the frequency of application is varied. The Panel feels that higher concentrations of benzoyl peroxide may be suitable for severe acne or for mila acne lesions that have not responded to lower concentrations. The Panel concludes that benzoyl peroxide 2.5 to 10 percent is effective for OTC use in the treatment of acne.

(3) *Dosage*—(i) *Concentration*. Benzoyl peroxide 2.5 to 10 percent.

(ii) *Directions for use*. See part III, paragraph A.2. below—Category I labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for OTC products used in the treatment of acne and in the prevention of new acne lesions. (See part III, paragraph A.2. below—Category I labeling.)

References

- (1) OTC Volume 070207.
- (2) OTC Volume 070168.
- (3) Horgan, V. J., et al., "Toxicity of Autoxidized Squalene and Linoleic Acid, and of Simpler Peroxides, in Relation to Toxicity of Radiation," *Biochemical Journal*, 67:551-558, 1957.
- (4) Philpot, J., and D. B. Roodyn, "A Comparison between the Effects in Mice of Injected Organic Peroxides and of Whole-Body X-Irradiation," *International Journal of Radiation Biology*, 4:372-382, 1959.
- (5) Antonyuk, O. K., "Experimental Data on Toxicity of Benzoyl Peroxide and Triphenyl Phosphate," *Gigiena Primeneniya Polimernykh Materialov i Izdelii iz Nkh*, 1:311-313, 1969.
- (6) OTC Volume 070199.
- (7) Sharp, R. L., Eastman Kodak Co., letter to Richard Daily, Informatics, Inc., December 14, 1977, included in OTC Volume 070294.
- (8) Holzmann, H., B. Morsches, and P. Benes, "The Absorption of Benzoyl Peroxide from Leg Ulcers," *Arzneimittel-Forschung*, 29:1180-1183, 1979.
- (9) OTC Volume 070097.
- (10) Nacht, S., et al., "Benzoyl Peroxide: In Vitro and Vivo Skin Penetration and Metabolic Disposition," *Clinical Research*, 27:533A, 1979.
- (11) Nacht, S., et al., "Benzoyl Peroxide: Percutaneous Penetration and Metabolic Disposition," draft of unpublished paper, included in OTC Volume 070264.
- (12) Sharratt, M., A. C. Frazer, and O. C. Forbes, "Study on the Biological Effects of

Benzoyl Peroxide," *Food and Cosmetics Toxicology*, 2:527-538, 1964.

(13) Radomski, J. L., G. Woodward, and A. J. Lehman, "The Toxicity of Flours Treated with Various 'Improving' Agents," *Journal of Nutrition*, 36:15-25, 1948.

(14) Van Duuren, B. L., et al., "Carcinogenicity of Epoxides, Lactones, and Peroxy Compounds," *Journal of the National Cancer Institute*, 31:41-55, 1963.

(15) Hueper, W. C., "Cancer Induction by Polyurethane and Polysilicone Plastics," *Journal of the National Cancer Institute*, 33:1005-1022, 1964.

(16) Epstein, S. S., et al., "Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse," *Toxicology and Applied Pharmacology*, 23:288-325, 1972.

(17) Litton Bionetics, Mutagenic Evaluation of Benzoyl Peroxide, submitted to FDA, June 1975, included in OTC Volume 070294.

(18) OTC Volume 070048.

(19) Ede, M., "A Double-Blind, Comparative Study of Benzoyl Peroxide, Benzoyl Peroxide-Chlorhydroxyquinoline, Benzoyl Peroxide-Chlorhydroxyquinoline-Hydrocortisone, and Placebo Lotions in Acne," *Current Therapeutic Research*, 15:624-629, 1973.

(20) Eaglstein, W. H., "Allergic Contact Dermatitis to Benzoyl Peroxide," *Archives of Dermatology*, 97:527, 1968.

(21) Poole, R. L., J. F. Griffith, and F. S. K. MacMillan, "Experimental Contact Sensitization with Benzoyl Peroxide," *Archives of Dermatology*, 102:635-639, 1970.

(22) Leyden, J. J., and A. M. Kligman, "Contact Sensitization to Benzoyl Peroxide," *Contact Dermatitis*, 3:273-275, 1977.

(23) Fulton, J. E., Jr., A. Farzad-Bakshandeh, and S. Bradley, "Studies on the Mechanism of Action of Topical Benzoyl Peroxide and Vitamin A Acid in Acne Vulgaris," *Journal of Cutaneous Pathology*, 1:191-200, 1974.

(24) Vasarinsh, P., "Benzoyl Peroxide-Sulfur Lotions. A Histological Study," *Archives of Dermatology*, 98:183-187, 1968.

(25) OTC Volume 070098.

(26) Pillsbury, D. M., "A Manual of Dermatology," W. B. Saunders Co., Philadelphia, pp. 173-174, 1971.

(27) OTC Volume 070099.

(28) OTC Volume 070238.

(29) Belknap, B. S., "Treatment of Acne with 5 Percent Benzoyl Peroxide Gel or 0.05 Percent Retinoic Acid Cream," *CUTIS; Cutaneous Medicine for the Practitioner*, 23:856-859, 1979.

(30) OTC Volume 070263.

(31) OTC Volume 070270.

(32) Yong, C. C., "Benzoyl Peroxide Gel Therapy in Acne in Singapore," *International Journal of Dermatology*, 18:485-488, 1979.

b. *Sulfur*. The Panel concludes that sulfur is safe and effective for OTC topical use in the treatment of acne.

(1) *Safety*. The Panel reviewed the toxicology of sulfur in its recommendations on topical antifungal drug products published elsewhere in this issue of the *Federal Register*.

Although the studies usually conducted to establish a toxicological profile were not done on sulfur, the Panel concluded that sulfur is safe for use in antifungal

preparations because of its long history of oral and topical use without serious toxic effects.

Sulfur has been used in acne preparations in concentrations ranging from 2 to 10 percent. Although as much as 50 percent of the body surface area could be exposed to sulfur, there is no indication that absorption occurs, at least not to an extent that could approximate oral doses which have been administered to humans. For this reason, the Panel has focused its attention on the local effects of topically applied sulfur.

Scott (Ref. 1) reported that radioactive sulfur was absorbed by normal skin in 8 hours and disappeared from the dermis within 24 hours. The extent of absorption and the chemical form of the absorbed drug were not discussed. In acne patients, the rate of penetration through the epidermis was the same as for normal skin, but the accumulation of radioactive sulfur in the undischarged contents of the sebaceous glands was 10 times greater than in normal skin and remained in high concentrations for up to 3 weeks.

An unspecified number of rabbits were studied after applications of either a 10-percent sulfur ointment (vehicle not specified) or a combination of 2.5 percent sulfur and 10 percent benzoyl peroxide for a period of 12 weeks (Ref. 2). The only reaction was a redness attributed to mild irritation of the skin. This occurred during the first 3 weeks of the study. No signs of toxicity were noted in the hematological examination, urinalysis, or organ analysis.

Another experiment used a 20-percent sulfur cream or a 20-percent sulfur-20 percent benzoyl peroxide cream on the shaved backs of rabbits for a 2-hour exposure period. No reactions to these materials were noted (Ref. 3).

Sulfur can cause slight skin irritation and irritates the eyes if allowed to remain in them. Neither irritation is serious, however. Also, the Panel is unaware of any systemic toxicity from topically applied sulfur. For these reasons the Panel concludes that sulfur is safe for the treatment of acne. The Panel recommends an upper limit of 10 percent. Although sulfur is safe at higher concentrations, 10 percent is the highest concentration contained in currently marketed acne products. The Panel notes that even though sulfur is a safe, mild, peeling agent for the skin, some data suggested that sulfur may enhance the sensitization potential of benzoyl peroxide. (See part III, paragraph D. below—Combination Products Used in the Treatment of Acne.)

(2) *Effectiveness*. Sulfur has been used medically for centuries and although the

rationale for its use in acne is presumed to be its keratolytic and antibacterial effects, the exact mechanism of action remains unknown. There are no studies available on this ingredient that meet the Panel's in vivo criteria for antibacterial claims. (See part III, paragraph E.2.c. below—In vivo testing of acne ingredients.) Strakosch (Ref. 3) indicated that the keratolytic action of sulfur was actually due to its conversion to hydrogen sulfide when in contact with tissue. The degree of tissue conversion of sulfur to hydrogen sulfide is unknown, and there are no additional data available on this subject.

One study showed that sulfur may have a comedogenic effect. Mills and Kligman (Ref. 4) were able to induce comedones in rabbits after applying concentrations of sulfur from 2 to 8 percent to the external ear canal. They also induced comedones in humans by applying from 2.5 to 5 percent concentrations of sulfur in a closed patch test. Strauss et al. (Ref. 5), however, were unable to reproduce these results. They used identical methods in 52 patients who were treated with 5 percent sulfur in either octoxynol 9 or a carbomer 934P base. Either the octoxynol 9 vehicle or a dry patch was used as a control. The researchers used multiple biopsies of the test sites which were sectioned serially to detect the presence of comedones. Only the octoxynol 9 vehicle was associated with the production of comedones.

A single-blind, half-face evaluation of the effectiveness of a 10-percent sulfur lotion was conducted on 29 patients who had Pillsbury Grade II to III acne (Ref. 6). They had had no topical therapy for 2 weeks before the study and no systemic therapy for 4 weeks before the study. Each patient used a soap control on half of the face. The other half of the face was treated with an aluminum oxide scrub and the sulfur lotion at night, and a soap washing followed by the sulfur lotion in the morning. Treatment lasted for 6 weeks with evaluation by lesion counts at 0, 2, 4, and 6 weeks. Both total lesion and specific lesion counts were reduced by treatment with sulfur and aluminum oxide. However, open comedones were the only specific lesion count significantly reduced more by sulfur and aluminum oxide than by the soap treatment.

Sulfur is frequently combined with resorcinol in acne preparations. Numerous studies have established the effectiveness of this combination. (See part III, paragraph D. below—Combination Products Used in the Treatment of Acne.)

In a double-blind, randomized trial (Ref. 7), 92 patients were treated twice daily with one of the following treatments: (1) 3 percent sulfur, (2) 5 percent benzoyl peroxide, (3) 3 percent sulfur-10 percent benzoyl peroxide, or (4) vehicle lotion. Clinical response was evaluated after 2 weeks by lesion counts and clinical evaluation. In order to merit a satisfactory rating, the patients must have had a 50-percent or greater decrease in lesions if treated for less than 12 weeks or have shown continued improvement over a 12-week period.

Of the 24 patients treated with sulfur, 33 percent were rated as satisfactory. This compared to satisfactory ratings of 54 percent for the sulfur-benzoyl peroxide combination, 41.7 percent for benzoyl peroxide, and 10 percent for the vehicle. Clinical assessment of patients treated with sulfur showed 29.2 percent good to excellent, 50 percent fair to no change, and 20.8 percent worse. This compared to vehicle results of 10 percent good to excellent, 45 percent fair to no change, and 45 percent worse. Although the results were not analyzed statistically, it was concluded that the active treatments (sulfur, benzoyl peroxide, and the sulfur-benzoyl peroxide combination) were "demonstrably more effective" than vehicle.

One submission contained a compilation of five half-face studies conducted by different investigators using the same protocol (Ref. 2). The studies were randomized and double-blind. Patients were treated for 8 weeks and evaluated by lesion counts. Treatment consisted of a base cream on one side of the face. On the other side of the face, a cream containing 5 percent sulfur or 10 percent benzoyl peroxide or a combination of the two ingredients was applied.

Treatment results on the 42 patients treated with sulfur showed a 42.8-percent decrease in comedones and a 36.3-percent decrease in other lesions. For the 123 patients using the vehicle the reduction was 28 percent for comedones and 18.3 percent for other lesions. Overall results showed a reduction in lesions of 52 percent for benzoyl peroxide-sulfur combination; 41 percent for sulfur; 40 percent for benzoyl peroxide; and 25 percent for vehicle.

Not all of the studies were statistically analyzed. Some researchers found the combination of benzoyl peroxide and sulfur superior to either ingredient used alone. In other studies, no significant difference was seen between sulfur, benzoyl peroxide, or the combination of sulfur and benzoyl peroxide.

The Panel concludes that sulfur is effective for OTC use in the treatment of acne.

(3) *Dosage*—(i) *Concentration*. Sulfur 3 to 10 percent.

(ii) *Directions for use*. See part III, paragraph A.2. below—Category I labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for OTC products used in the treatment of acne and in the prevention of new acne lesions. (See part III, paragraph A.2. below—Category I labeling.)

References

- (1) Scott, A., "The Behaviour of Radioactive Sulphur After its External Application to the Skin," *British Journal of Dermatology*, 69:39-49, 1957.
- (2) OTC Volume 070168.
- (3) Strakosch, E. A., "Studies on Ointments. III. Ointments Containing Sulphur," *Archives of Dermatology and Syphilology*, 47:216-225, 1943.
- (4) Mills, O. H., and A. M. Kligman, "Is Sulphur Helpful or Harmful in Acne Vulgaris?", *British Journal of Dermatology*, 86:620-627, 1972.
- (5) Strauss, J. S., et al., "A Re-examination of the Potential Comedogenicity of Sulfur," *Archives of Dermatology*, 114:1340-1342, 1978.
- (6) OTC Volume 070126.
- (7) OTC Volume 070099.

2. *Category I labeling*. The Panel reviewed all submitted labels of preparations used for the treatment of acne and recommends the following labeling. The Panel realizes that there may be many similar phrases and terms that can be used in labeling to convey the same information to consumers. However, to ensure conformity to required standards, variations from the labeling recommended below must be obtained through the procedures to amend the monograph in § 330.10(a)(12) (21 CFR 330.10(a)(12)).

a. *Acne treatment labeling*. The Panel recommends that one or a combination of the following phrases be used as labeling for products effective in the treatment of acne.

- (1) "For the management of acne."
- (2) "For the treatment of acne."
- (3) "Anti-acne formula."
- (4) "Anti-acne medication."
- (5) "Anti-acne formulation."
- (6) "Dries and clears acne blemishes."
- (7) "Dries and clears acne pimples."
- (8) "Dries acne blemishes and allows skin to heal."
- (9) "Dries acne pimples and allows skin to heal."
- (10) "Dries up acne pimples."
- (11) "Helps clear acne pimples."
- (12) "Clears up most acne pimples."
- (13) "Clears up most acne blemishes."

(14) "Reduces the number of acne lesions."

(15) "Reduces the severity of acne lesions."

(16) "Reduces blackheads."

(17) "Clears up most blackheads."

(18) "Loosens blackheads."

(19) "Helps clear up blackheads."

(20) "Helps clear up acne pimples."

(21) "Helps remove blackheads."

(22) "Helps remove acne pimples."

(23) "Dries up blackheads."

(24) "Dries up acne blemishes."

(25) "Unclogs pores to help clear acne."

(26) "Unplugs pores to help clear acne."

(27) "Penetrates follicles to eliminate most blackheads and acne pimples."

(28) "Penetrates pores to eliminate most blackheads and acne pimples."

(29) "Penetrates follicles to control blackheads and acne pimples."

(30) "Penetrates pores to control blackheads and acne pimples."

(31) "Penetrates follicles to clear most blackheads and acne pimples."

(32) "Penetrates pores to clear most blackheads and acne pimples."

(33) "Penetrates follicles to reduce blackheads or acne pimples."

(34) "Penetrates pores to reduce blackheads or acne pimples."

b. *Acne prevention labeling*. Acne prevention labeling may be used in addition to acne treatment labeling for acne drug products that are effective in preventing the development of new acne lesions. These products should not be used to prevent acne in the person who has never had acne. The Panel believes that ingredients that are effective in treating acne are also effective in preventing new lesions. (See part II, paragraph F. above—Treatment of Acne.) The Panel recommends that one of a combination of the following phrases be used as labeling for products effective in the prevention of new acne lesions.

(1) "Helps keep skin clear of new acne lesions."

(2) "Helps keep skin clear of new acne pimples."

(3) "Helps prevent new blackheads or acne pimples."

(4) "Helps prevent new acne pimples."

(5) "Helps prevent new acne pimples from forming."

(6) "Helps prevent new acne lesions."

(7) "Helps prevent the development of new acne lesions."

(8) "Helps prevent new acne blemishes from forming."

Prevention labeling is to be used only in conjunction with treatment labeling. Examples of acceptable labeling are:

"Clears up most acne pimples and reduces blackheads. Helps prevent new acne blemishes from forming."

"Dries and clears acne blemishes and reduces blackheads. Helps prevent the development of new acne lesions."

c. *Antibacterial claims.* Products containing ingredients which are in Category I for the treatment of acne may also be labeled with one or more of the following antibacterial claims, provided that the product as formulated meets the in vivo effectiveness testing criteria recommended by the Panel. (See part III, paragraph E.2.c. below—In vivo testing of acne ingredients.)

- (1) "Antibacterial."
- (2) "Kills acne bacteria."
- (3) "Kills the bacteria that can cause acne."
- (4) "Kills acne bacteria on the skin."
- (5) "Kills acne bacteria in the skin."
- (6) "Kills acne bacteria and helps clear acne pimples."
- (7) "Works to kill bacteria that may cause pimple redness to spread."
- (8) "Works to kill bacteria that may cause inflammation to spread."
- (9) "Penetrates follicles to kill bacteria associated with acne."
- (10) "Penetrates pores to kill bacteria associated with acne."
- (11) "Penetrates follicles to reduce bacteria associated with acne."
- (12) "Penetrates pores to reduce bacteria associated with acne."
- (13) "Reduces *P. acnes*, bacteria associated with acne."
- (14) "Reduces the bacterial products associated with the inflammation of acne."
- (15) "Reduces the bacterial products associated with the irritation of acne."

d. *Product attributes.* The Panel accepts the use of terms describing certain physical and chemical qualities of OTC topical acne drug products, as long as these terms do not imply any therapeutic effect and are distinctly separated from labeling indications.

These product attributes pertain to the inherent characteristics or the pharmaceutical elegance of the formulation. These properties are usually due to specific inactive, and in some cases active, ingredients included in the final product formulation. Product characteristics appear in the labeling for consumer information or product appeal and involve terms relating to the product's color, odor, and feel. The Panel considers the following list and similar terms acceptable:

- (1) "Greaseless."
- (2) "Nonstaining."
- (3) "Odorless."
- (4) "Colorless."
- (5) "Nontinted."
- (6) "Blends easily with skin."

- (7) "Disappearing foam."
- (8) "Drying."
- (9) "Dries excess skin oils."
- (10) "Skin-softening."
- (11) "Cools and comforts hot, irritated skin areas."
- (12) "Cleans the skin and helps to remove oil."

e. *Warnings.*—(1) *For all acne products.* (i) "For external use only." (ii) "Other topical acne medications should not be used at the same time as this medication."

(2) *For products containing benzoyl peroxide.* "Do not use this medication if you have very sensitive skin or if you are sensitive to benzoyl peroxide. This product may cause irritation, characterized by redness, burning, itching, peeling, or possibly swelling. More frequent use or higher concentrations may aggravate such irritation. Mild irritation may be reduced by using the product less frequently or in a lower concentration. If irritation becomes severe, discontinue use; if irritation still continues, consult a doctor or pharmacist. Keep away from eyes, lips, mouth, and sensitive areas of the neck. This product may bleach hair or dyed fabrics."

(3) *For products containing sulfur.* "Do not get into eyes. If excessive skin irritation develops or increases, discontinue use and consult a doctor or pharmacist."

(4) *For sulfur-resorcinol products.* "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body."

f. *Directions for use.* The Panel suggests the following directions for acne products that are applied and left on the skin:

"Cleanse the skin thoroughly before applying medication. Cover the entire affected area with a thin layer one to three times daily. Because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or as directed by a doctor."

Other products, such as soaps or masks, may be applied and removed and should have appropriate directions.

B. Category II Conditions

These are conditions under which OTC acne drug products are not generally recognized as safe and effective or are misbranded. The Panel recommends that the Category II conditions be eliminated from OTC acne drug products effective 6 months after the date of publication of the final monograph in the Federal Register.

1. Category II active ingredients.

Alkyl isoquinolinium bromide

Aluminum salts
Alcloxa
Aluminum chlorohydrate
Aluminum hydroxide
Magnesium aluminum silicate
Benzocaine
Benzoic acid
Borates
Boric acid
Sodium borate
Calcium polysulfide
Calcium thiosulfate
Camphor
Chlorhydroxyquinoline
Chloroxylenol
Coal tar
Dibenzothiophene
Estrone
Magnesium sulfate
Phenolates
Phenol
Phenolate sodium
Phenyl salicylate
Pyrimidine maleate
Resorcinol and resorcinol monoacetate (as single ingredients)
Sodium thiosulfate
Tetracaine hydrochloride
Thymol
Vitamin E
Zinc salts
Zinc oxide
Zinc stearate
Zinc sulfide

a. *Alkyl isoquinolinium bromide.* The Panel concludes that alkyl isoquinolinium bromide is not effective and that there are insufficient data available to permit final classification of its safety for OTC topical use in the treatment of acne.

(1) *Safety.* Alkyl isoquinolinium bromide is a surface-acting agent and is active against bacteria, molds, and fungi (Ref. 1).

The oral LD₅₀ is 230 mg/kg in rats and 200 mg/kg in guinea pigs. Rats that were fed 12.5 mg/kg for 2 years continued to grow normally. Guinea pigs tolerated 1:5,000 alkyl isoquinolinium bromide in drinking water for 6 months (Ref. 2). Normal skin showed no irritation or sensitization from the use of 0.1 percent solutions of this ingredient. Solutions of 0.5 percent can be considered safe for use where accidental contact with the eye may occur (Ref. 1).

The Panel has found the safety data on alkyl isoquinolinium bromide insufficient and therefore considers this ingredient of questionable safety when used topically for the treatment of acne.

(2) *Effectiveness.* Alkyl isoquinolinium bromide is contained in only one product submission reviewed by the Panel (Ref. 1). No data on the effectiveness of this ingredient in the treatment of acne are available in the submission or in the medical literature. For this reason the Panel concludes that alkyl isoquinolinium bromide is not

effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed alkyl isoquinolinium bromide in category II because there are no data available on the effectiveness of this ingredient in the treatment of acne.

References

- (1) OTC Volume 070009.
- (2) Gloxhuber, C., "Review Articles. Toxicological Properties of Surfactants," *Archives of Toxicology*, 32:245-270, 1974.

b. *Aluminum salts (alcloxa, aluminum chlorohydrate, aluminum hydroxide, and magnesium aluminum silicate).* The panel concludes that the aluminum salts (alcloxa, aluminum chlorohydrate, aluminum hydroxide, and magnesium aluminum silicate) are safe but are not effective for OTC use in the treatment of acne.

(1) *Safety.* The Panel determined alcloxa to be safe for topical use in concentrations of 0.25 to 10 percent as described in its recommendations on topical antifungal drug products published elsewhere in this issue of the Federal Register. The Panel has reviewed additional data (Refs. 1, 2, and 3) which support this finding.

Aluminum chlorohydrate was found safe at concentrations up to 25 percent for topical use in nonaerosol formulations in a report by the Advisory Review Panel on OTC Antiperspirant Drug Products published in the Federal Register on October 10, 1978 (43 FR 46719). Although intradermal injections of aluminum chlorohydrate produced granulomas in guinea pigs (Ref. 4), the Panel believes that this ingredient is safe for topical use, particularly because it is a protein precipitant. With protein precipitants, absorption through the skin is probably minimal.

Aluminum hydroxide and magnesium aluminum silicate are widely used antacids and were found safe for that use by the Advisory Review Panel on OTC Antacid Drug Products in a report published on April 4, 1973 (37 FR 8717). Aluminum hydroxide, like aluminum chlorohydrate, produced granulomas in guinea pigs following intradermal injection (Ref. 4), but again the Panel sees no problem when it is used topically. Patch test and primary skin irritation studies showed that magnesium aluminum silicate does not irritate or sensitize the skin (Ref. 5). The Panel concludes that the four aluminum salts discussed above are safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Alcloxa apparently works by dissociating into allantoin and aluminum chloride at skin pH. Its mechanism of action in the treatment of acne is presumed to depend upon the

astringency of the aluminum chloride as well as the soothing and healing properties of the allantoin. Alcloxa has been used for over 50 years for the treatment of a wide variety of skin problems, such as eczema, sunburn, itching, athlete's foot, impetigo, acne, diaper rash, and psoriasis. Its reputation is based upon "skin softening and tissue-building actions" (Ref. 2).

Submissions reviewed by the Panel (Refs. 1, 2, 3, and 6) contained no clinical trials on alcloxa in the treatment of acne, and there is no information in the general medical literature on the effectiveness of this ingredient in treating acne.

Warsaw (Ref. 7) studied an aqueous solution of 20 percent aluminum chlorohydrate on 66 acne patients. She believed the aluminum preparation inhibits sweating and decreases overactivity of the sebaceous gland. All patients in this study were treated with a combination of sulfur and resorcinol. Half of the subjects also used the aluminum chlorohydrate solution. Treatment time varied from 3 weeks to 6 months. The author reported that 32 of the 33 patients treated with aluminum chlorohydrate showed decreased comedones, pustules, and oiliness. The group treated only with sulfur and resorcinol showed "less rapid improvement" and the improvement was not as well maintained.

This study was not randomized, vehicle-controlled, or double-blind. The Panel cannot draw conclusions from this study on the effectiveness of aluminum chlorohydrate as a single ingredient because it was used with the sulfur-resorcinol combination.

Several randomized, blinded, and controlled trials have been conducted on a combination of aluminum chlorohydrate and sulfur (Ref. 8). No statistically significant differences were found between the aluminum chlorohydrate combination, a sulfur-resorcinol combination, and placebo. However, because these studies did not use aluminum chlorohydrate as a single ingredient, they will not be discussed in detail.

The Panel has seen no data in the submissions or in the medical literature to support the use of aluminum hydroxide in acne.

The Panel has received one submission on magnesium aluminum silicate which states that this ingredient is metabolically inert. Magnesium aluminum silicate works by absorbing oils and superficially debriding the skin (Ref. 5).

In an unpublished study of 12 patients, half of the face was treated with magnesium aluminum silicate and the

other half of the face served as the control. After 1 month of treatment, "there appeared to be an improvement in the treated area vs. the control in the clearing of comedones" in six subjects. No change was noted in the other six patients (Ref. 5).

In another unpublished study, 55 patients applied magnesium aluminum silicate nightly for 1 week and then twice weekly for the next 3 to 5 weeks. Controls were not used, and criteria for evaluation were not explained. At the end of the study, 45 patients were considered improved, 8 were unchanged, and 2 were worse (Ref. 5).

Neither of the above two studies meets the Panel's criteria for effectiveness and neither study particularly supports the effectiveness of magnesium aluminum silicate. (See part II, paragraph 1.2. above—Criteria for evaluating effectiveness.)

The Panel concludes that the aluminum salts are not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel believes that the aluminum salts are not effective ingredients for the treatment of acne. Either no effectiveness data were available on the single active ingredients, or the available studies did not support the effectiveness of aluminum salts.

References

- (1) OTC Volume 070030.
- (2) OTC Volume 070100.
- (3) OTC Volume 070124.
- (4) Turk, J. L., and D. Parker, "Granuloma Formation in Normal Guinea Pigs Injected Intradermally with Aluminum and Zirconium Compounds," *Journal of Investigative Dermatology*, 68:336-340, 1977.
- (5) OTC Volume 070172.
- (6) OTC Volume 070230.
- (7) Warsaw, T. G., "A New Approach to the Control of Acne Vulgaris," *New York State Journal of Medicine*, 57:3999-4000, 1957.
- (8) OTC Volume 070053.

c. *Benzocaine.* The Panel concludes that benzocaine is not safe and is not effective for OTC use in the treatment of acne.

(1) *Safety.* Benzocaine has been used widely as a local anesthetic, especially in ointments and dusting powders for wounds, burns, and ulcers. The range of concentrations used is from 5 percent to 50 percent. It has been injected subcutaneously once a week in 3 percent solutions and is said to be almost devoid of local irritant action (Ref. 1).

The Canadian government listed the maximum single oral dose limits for an adult at 195 mg and the maximum oral daily intake at 585 mg. It also limits benzocaine to 8 percent concentrations

in pharmaceuticals for external use (Ref. 2). Dreisbach (Ref. 3) lists the maximum amount safe for surface use as 5,000 mg or 25 mL of a 20-percent solution. Gosselin et al. (Ref. 4) report that benzocaine is a local anesthetic of low toxicity. Despite its low water solubility and its reportedly poor absorption from many sites, there are instances of severe methemoglobinemia in infants from the use of either a benzocaine ointment or suppository.

Benzocaine is a common sensitizing agent which can produce allergic contact dermatitis. Approximately one-fourth of the people who are sensitive to benzocaine react when *para*-phenylenediamine, a component of hair dyes, comes in contact with their skin. Cross-reactivity is also noted with the sulfonamides and with sunscreens that contain *para*-aminobenzoic acid or its esters or both. Benzocaine-sensitive patients may also cross-react with injectable local anesthetics, such as procaine and tetracaine (Ref. 5).

Fisher, Pelzig, and Kanof (Ref. 6) studied the ability of *para*-phenylenediamine to act as a sensitizer on the skin to produce an allergic edematous contact type of dermatitis. The authors noted that allergic hypersensitivity to benzocaine and *para*-phenylenediamine may happen repeatedly even years after the initial sensitization. They found that in a group of 50 patients sensitive to *para*-phenylenediamine, 46 were still sensitive when tested 3 to 10 years later. Of these 46 patients, 18 were found to be sensitive to benzocaine. In a separate study, they also found that 10 of 24 patients sensitized to benzocaine were also sensitive to *para*-phenylenediamine.

In a similar study, Gaul (Ref. 7) used a patch test and found that, in a group of 580 dermatologic patients, 50 were sensitive to *para*-phenylenediamine, and 16 were sensitive to benzocaine. Of the benzocaine-sensitive patients, 3 were sensitive only to benzocaine. The rest were sensitive to other drugs such as *para*-phenylenediamine, procaine, and penicillin in addition to benzocaine. The Panel notes that benzocaine is chemically dissimilar from *para*-phenylenediamine.

In the North American Contact Dermatitis Group's study (Ref. 8), the incidence of allergic sensitivity to benzocaine was 5 percent, equal to some other commonly used drugs, and less than the more frequent sensitizers such as neomycin. This study was on 1,200 patients seeking treatment for skin diseases. These patients were considered high risks for developing allergy.

The routine topical patch test does not reveal immediate sensitivity, such as an urticarial reaction (hives), to benzocaine. Nasal testing, eye testing, scratch tests, or intradermal testing can be used to screen patients for hypersensitivity (Ref. 9). However, there is concern that scratch testing and intradermal skin testing to detect this type of hypersensitivity may give false-negative results.

Benzocaine is a moderate sensitizer when applied topically over a long period to normal or diseased skin. When used for short periods on noninfected skin, it is only a weak sensitizer. The use of benzocaine should be avoided by people known to be sensitive and by those with skin infections.

(2) *Effectiveness.* Benzocaine is a local anesthetic which may alleviate itching, burning, and pain.

Currently marketed OTC acne products contain benzocaine in a concentration of 0.5 percent. A concentration of 5 to 10 percent is considered useful in relieving itching (Ref. 1). Ointments containing less than 5 percent benzocaine and acidic preparations of benzocaine are generally ineffective (Ref. 10).

No effectiveness data are available on benzocaine in the treatment of acne. The Panel sees no need for including a local anesthetic in an acne remedy. The Panel concludes that the use of benzocaine is irrational in acne therapy.

(3) *Evaluation.* The Panel has placed benzocaine in Category II for the treatment of acne because this ingredient's sensitizing potential and because there is no acceptable rationale for the use of this ingredient in treating acne.

References

- (1) Osol, A., and R. Pratt, "United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 186, 1973.
- (2) OTC Volume 070138.
- (3) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 8th Ed., Lange Medical Publications, Los Altos, CA, p. 274, 1974.
- (4) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, p. 142, 1976.
- (5) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, pp. 42 and 312-313, 1973.
- (6) Fisher, A. A., A. Pelzig, and N. B. Kanof, "The Persistence of Allergic Exzematous Sensitivity and the Cross-Sensitivity Pattern to Paraphenylenediamine," *Journal of Investigative Dermatology*, 30:9-12, 1958.
- (7) Gaul, L. E., "Types of Sensitization Disclosed by Positive Patch Testing to Paraphenylenediamine and Benzocaine," *Annals of Allergy*, 18:738-745, 1960.
- (8) North American Contact Dermatitis Group, "Epidemiology of Contact Dermatitis in North America: 1972," *Archives of Dermatology*, 108:537-540, 1973.
- (9) Eyre, J., and F. Nally, "Nasal Test for Hypersensitivity, Including a Positive Reaction to Lignocaine," *Lancet*, 1:264-265, 1971.
- (10) "AMA Drug Evaluations," 3d Ed., Publishing Sciences Group, Inc., Littleton, MA, p. 269, 1977.

d. *Benzoic acid.* The Panel concludes that benzoic acid is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Free and combined forms of benzoic acid occur in nature. Most berries contain appreciable amounts of this acid.

The acute toxicity of benzoic acid is similar in all species. The oral LD₅₀ is 2.53 g/kg in the rat, 2.37 g/kg in the mouse, and 2 g/kg in the cat, dog, and rabbit. Benzoic acid given by other routes yielded these LD₅₀'s: 1.46 g/kg intraperitoneally in mice; 2 g/kg subcutaneously in rabbits; and 1.71 g/kg intravenously in rats (Refs. 1 and 2). After the intravenous injection, rats had tremors and convulsions before death. The surviving rats had excessive salivation, vomiting, and diarrhea (Ref. 2).

Benzoic acid is rapidly absorbed, conjugated with glycine, and excreted in the urine as hippuric acid (Ref. 3). In most species, the liver is the primary site of conjugation. Because there is no accumulation, symptoms of chronic administration are like those seen in acute studies. When rats were fed benzoic acid for 28 days, animals fed 5 percent in the diet died within 2 weeks, showing hyperexcitability, urinary incontinence, and convulsions. Males fed 2 percent benzoic acid exhibited a decrease in body weight (Ref. 4). Dogs can be fed up to 1 g/kg for long periods without effect, but epileptic convulsions and death occur above this amount (Ref. 3).

Benzoic acid was once administered as a 6-g oral dose or a 2-g intravenous dose in humans in a liver function test (Ref. 3). Within 6 hours, 80 percent of the dose is usually eliminated, the remainder being eliminated within 14 hours. Ingestion of 4 to 6 g benzoic acid produces only mild gastric irritation (Ref. 5). "Large oral doses" cause severe gastric pain, nausea, and vomiting (Ref. 6).

Benzoic acid 6 percent is contained in Whitfield's ointment, which has been used as a topical antifungal agent for many years. In view of the use of this ointment for over 50 years without toxic manifestations, the Panel concludes that

benzoic acid is safe for topical use in the treatment of acne.

(2) *Effectiveness.* Benzoic acid is generally considered to be an antifungal agent. It is also widely used as a food preservative. But the Panel has seen only one study (Ref. 7) on the use of benzoic acid in acne treatment and this was not as a single ingredient.

(3) *Evaluation.* The Panel has placed benzoic acid in Category II because it is not generally recognized as an anti-acne agent and because there are no controlled studies on benzoic acid as a single ingredient for the treatment of acne.

References

- (1) Fairchild, E. J., "Registry of Toxic Effects of Chemical Substances," Vol. II, U.S. Department of Health, Education, and Welfare, Cincinnati, p. 179, 1977.
- (2) Hager, G. P., C. W. Chapman, and E. B. Starkey, "The Toxicity of Benzoic Acid for White Rats," *Journal of the American Pharmaceutical Association (Scientific Edition)*, 31:253-255, 1942.
- (3) "Toxicological Evaluation of Some Food Additives Including Anticaking Agents, Antimicrobials, Antioxidants, Emulsifiers and Thickening Agents," 17th Report of the Joint Food and Agriculture Organization of the United Nations/World Health Organization, Expert Committee on Food Additives, World Health Organization, Geneva, Switzerland, pp. 34-42, 1974.
- (4) Fanelli, G. M., and S. L. Halliday, "Relative Toxicity of Chlorotetracycline and Sodium Benzoate after Oral Administration to Rats," *Archives Internationales de Pharmacodynamie et de Therapie*, 144:120-125, 1963.
- (5) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasitides," in "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 994 and 1012, 1975.
- (6) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins Co., Baltimore, p. 137, 1976.
- (7) Milberg, I. L. "Clinical Evaluation of an Antiseptic Medicated Cream in the Treatment of Acne Vulgaris," *New York State Medical Journal*, 58:2674-2675, 1958.

e. Borates (boric acid and sodium borates). The Panel concludes that borates (boric acid and sodium borate) are safe but are not effective for OTC topical use in the treatment of acne.

(1) *Safety.* The toxicology of borates was summarized by this Panel in its recommendations on topical antifungal drug products published elsewhere in this issue of the *Federal Register*. The Panel concluded that borates were safe in concentrations of 5 percent or less. Rather than repeat that data here, the Panel will summarize only the data it has received since completing its

recommendations on antifungal drug products.

One preparation used for acne contains boric acid in a concentration of just over 12 percent. For sodium borate, all of the submitted acne preparations contain less than 5 percent except for one which contains 50 percent sodium borate. However, because this preparation is a scrub, which is rinsed off a few minutes after application, exposure time would be relatively short.

In the antifungal recommendations mentioned above, the greatest concern about the use of sodium borate was its irritation potential because so little data had been submitted on this potential. However, two submissions to the acne review added information on irritation potential (Refs. 1 and 2). Both of these submissions suggest that 50 percent sodium borate preparations are irritating to the eye and have recommended warnings to this effect on the label.

Single applications to normal and abraded rabbit skin have shown different results, but most of the evidence shows that 50 percent sodium borate preparations are mildly irritating. Repeated applications over a period of 2 to 3 weeks, however, are severely irritating (Refs. 1 and 2). When used according to labeled directions (i.e., "wet skin with water, apply, and rinse off after 60 seconds,") over a 20-day period, the 50-percent preparation did not irritate either normal or abraded rabbit skin. Blood levels of boron in the treated group were not significantly different from the controls.

In a 30-day study, however, twice-daily application under the same conditions resulted in such severe skin reactions that the study was ended after 8 days. Although the blood boron levels of the treated group were about five times as high at the end of the study, they were still within the normal values for rabbits. Within 4 or 5 days after the study was discontinued, the rabbits' skin returned to normal (Ref. 1).

In a separate study (Ref. 1) a combination product containing 98 percent borax (sodium borate) was used to evaluate percutaneous absorption and irritation potential in rabbits. Doses of 1.0 g/kg and 5.0 g/kg of the product were used after adding enough saline to form a paste. Sodium borate was applied 5 days a week for 3 weeks with daily exposures of 6 hours to both normal and abraded skin. The treated area was covered with polyethylene wrap.

No rabbits died as a result of the treatment. However, weight gain in the test animals was less than in the control animals. Mild to moderate redness, edema, and mild fissuring indicated

irritation. The skin also became slightly to noticeably leathery. There were no significant differences from controls in hematologic values, urinalysis findings, organ/body weight ratios, or gross pathological tissue changes.

In a similar experiment using mostly the same conditions, the rabbits treated with 5.0 g/kg sodium borate showed emaciation, depressed righting reflex, and impaired muscular coordination (Ref. 1). Several animals also developed acne-like lesions during the latter part of the application period.

The Panel recognizes that this kind of experiment does not approximate the labeled directions for use of the 50-percent sodium borate product. Such data, however, indicate potentially serious problems when high concentrations of sodium borate preparations remain on the skin for long periods and may be under occlusion.

Contrasted with these results, a 4-hour patch test using a 50-percent sodium borate suspension resulted in no primary irritation (Ref. 1).

A study by Weir and Fisher (Ref. 3) was very helpful in calculating the risk of topical applications of 12 percent boric acid if certain assumptions are made. In this study, definite signs of toxicity were noted when 1,170 ppm boron equivalent was fed to rats or dogs. For example, rats that were fed 1,170 ppm boron equivalent of either boric acid or sodium borate became sterile. Dogs that were fed 1,750 ppm boron equivalent developed atrophy of the testicles. In rats, degeneration of the gonads occurred as well as desquamation of the skin on the paws and tail.

If 1,170 ppm boron equivalent is converted, this would represent 6,685 ppm boric acid in the diet and 10,300 ppm sodium borate in the diet. At the 1,750 ppm boron equivalent level of feeding, this would convert to 10,000 ppm boric acid and 15,400 ppm sodium borate in the diet.

If the average mongrel dog weighs 30 lb or 13.6 kg and consumes 500 g of dry food daily (Ref. 4), it can be calculated that the total daily intake in this experiment would have been 5 g boric acid or 7.5 g sodium borate. The average blood volume of a dog is 35.4 mL per lb body weight (Ref. 4). Therefore, a 30-lb dog would have a blood volume of approximately 1 L. If 5 g boric acid were instantaneously distributed in 1 L of blood, there would be a blood concentration of 5,000 ppm. In a similar calculation, the blood sodium borate concentration would be 7,500 ppm. These concentrations of 1,170 ppm and 1,750 ppm boron equivalent are toxic

levels. About one-fourth of this dose, or 350 ppm, was found to be a "no effect" level by this test. This would amount to 2,500 ppm boric acid or 3,850 ppm sodium borate as the "no effect" level. These calculations were derived from the paper by Weir and Fisher (Ref. 3), but it should be noted that assumptions were made that are probably not the actual case.

If one makes the same assumptions about topical absorption in humans, one can approximate a safety evaluation. Assuming a worst-case type of application of the 12-percent boric acid product to the upper torso of a human and again assuming total rapid absorption into the blood, one arrives at a blood concentration similar to that assumed for the dog above. If 15 g of the 12-percent preparation were applied to the back and chest area twice daily, there would be 3.6 g boric acid available for absorption. If this were distributed into 7 L of blood (the blood volume of a person), the blood concentration would be 0.0005 g/mL or 500 ppm. This blood concentration is below the 2,500 ppm calculated above as the possible "no effect" level in dogs.

Although the Panel believes that high concentrations of borates may be irritating to abraded skin, it concludes that boric acid and sodium borate are safe for OTC topical use in concentrations up to 5 percent.

(2) *Effectiveness.* The Panel has found only one study (Ref. 1) evaluating the effectiveness of borates as single ingredients in the treatment of acne. In this clinical trial, 22 patients (13 females and 9 males) with acne and oily skin were treated with 50 percent sodium borate in a vehicle of soapless cleansers. The sodium borate was present as small abrasive particles that dissolved after 30 to 60 seconds of gentle rubbing on the skin. The rationale for its use was oil removal (the soapless cleansers) and gentle abrasion of the skin (the abrasive particles).

The patients were treated one to four times daily with this gritty scrub. They were also given other topical and systemic agents, including antibiotics and prednisone. At the beginning of the study, 18.2 percent of the patients had mild acne, 72.7 percent had moderate acne, and 9.1 percent had severe acne. After 4 weeks of treatment, half of the patients had mild acne and half had moderate acne.

At the final examination (8 weeks), the results were as follows: no acne in 4.8 percent, very mild acne in 14.3 percent, mild acne in 57.1 percent, and moderate acne in 23.8 percent. The oiliness of the patients' skin was also evaluated. Before treatment, oiliness

was mild in 31.8 percent and moderate in 68.2 percent. At the conclusion of the trial, oiliness was absent in 27.8 percent, very mild in 5.6 percent, mild in 50.0 percent, and moderate in 16.7 percent.

The Panel notes that the study was not controlled or double-blind. Lesion counts were not used as a method of evaluation. Concomitant therapy was given. Statistical analysis of results was not presented.

The Panel concludes that borates have not been conclusively shown to be effective in treating acne. Sodium borate may act as a mild physical abrasive to remove superficial pustules, but it probably does not effectively remove the primary lesions of acne (blackheads and whiteheads) because they are deeply rooted in the follicles.

(3) *Evaluation.* Because there is no controlled clinical trial evaluating the effectiveness of boric acid and sodium borate in the treatment of acne, the Panel has placed these ingredients in Category II.

References

- (1) OTC Volume 070206.
- (2) OTC Volume 070218.
- (3) Weir, R. J., Jr., and R. S. Fisher, "Toxicological Studies on Borax and Boric Acid," *Toxicology and Applied Pharmacology*, 23:351-364, 1972.
- (4) Siegmund, O. H., "The Merck Veterinary Manual," 4th Ed., Merck and Co., Rahway, NJ, pp 35 and 1270, 1973.

f. *Calcium polysulfide.* The Panel concludes that calcium polysulfide is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Calcium polysulfide releases hydrogen sulfide and elemental sulfur when placed in contact with water (Ref. 1), such as might be present on the skin. The amount of hydrogen sulfide released is unknown but is thought to be below toxic levels when sulfide compounds are used externally. Neither of the submissions to the Panel (Refs. 2 and 3) contained any toxicity data on calcium polysulfide. However, because the Panel considers calcium polysulfide to be essentially elemental sulfur, it does not consider that the external use of this ingredient would present any systemic toxicological hazard. (See part III, paragraph A.1.b. above—Sulfur.) Also, local effects of calcium polysulfide would probably be the same as for elemental sulfur. The Panel concludes that calcium polysulfide is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Calcium polysulfide is one of the components of a sulfurated lime solution (Vleminkx' solution) which has been used for about 100 years (Ref. 4). In the past, there was no

standardized definition of sulfurated lime solution, but it always contained high concentrations of sulfides and sulfates (25 to 35 percent) (Refs. 2 and 3). According to the "United States Pharmacopeia," sulfurated lime solution contains 25 percent sublimed sulfur and 16.5 percent lime (calcium oxide) (Ref. 5).

The product described in the submissions to the Panel (Refs. 2 and 3) contains calcium thiosulfate along with calcium polysulfide. Four mL of this combination added to 1 pint of water produces a sulfurated lime solution for use as a wet dressing. When used as directed, a substantial amount of hydrogen sulfide is liberated, giving off an obnoxious odor. Drying of the skin is also quite pronounced with sulfurated lime solution.

No controlled clinical trials on effectiveness are contained in the submissions and Panel is not aware of such studies in the medical literature. In addition, the Panel does not believe that calcium polysulfide is intended to be used as a single active ingredient.

The Panel concludes that calcium polysulfide is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* Although calcium polysulfide has been used for many years for the treatment of acne, in the absence of controlled clinical trials demonstrating effectiveness, the Panel concludes that it is not effective for this use.

References

- (1) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 9th Ed., Lange Medical Publications, Los Altos, CA, p. 246, 1977.
- (2) OTC Volume 070248.
- (3) OTC Volume 070250.
- (4) Schmitt, C. L., "Topical Agents Used in Treatment of Acne," *Clinical Medicine*, 70:1473-1476, 1963.
- (5) "United States Pharmacopeia," 20th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 450, 1980.

g. *Calcium thiosulfate.* The Panel concludes that calcium thiosulfate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* No safety data on this ingredient were contained in the submissions (Refs. 1 and 2). But calcium thiosulfate or calcium hyposulfite (CaS_2O_3) decomposes to elemental sulfur and therefore presents the same safety considerations as sulfur. (See part III, paragraph A.1.b. above—Sulfur.) The Panel concludes that calcium thiosulfate is safe for OTC topical use.

(2) *Effectiveness.* No controlled clinical trials demonstrating effectiveness in acne are available on

this ingredient. Calcium thiosulfate is a component of sulfurated lime solution, which also contains calcium polysulfide. (See part III, paragraph B.1.f. above—Calcium polysulfide.)

The Panel concludes that calcium thiosulfate is not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel has placed calcium thiosulfate in Category II because there are no clinical studies demonstrating that this ingredient is effective in the treatment of acne.

References

- (1) OTC Volume 070248
- (2) OTC Volume 070250.

h. *Camphor.* The Panel concludes that camphor is safe but is not effective for OTC topical use in the treatment of acne. The Panel also concludes that at concentrations less than or equal to 0.2 percent, camphor is an inactive ingredient that can be used in formulations for product identification.

(1) *Safety.* The Panel considers camphor to be safe as discussed in its recommendations on topical antifungal drug products published elsewhere in this issue of the *Federal Register*.

(2) *Effectiveness.* Camphor has been submitted for the treatment of acne in concentrations of 2 to about 11 percent. No effectiveness data were contained in any of the submissions (Refs. 1, 2, and 3), nor is such data available in the medical literature. Depending on the concentration, camphor is considered either a local anesthetic to relieve itching (up to 3 percent) or a counterirritant (3 to 11 percent). The Panel sees no rationale for the use of such an ingredient in treating acne and concludes that this ingredient is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed camphor in Category II because there are no clinical studies available demonstrating effectiveness. Also there is no rationale for the use of this ingredient in treating acne.

References

- (1) OTC Volume 070247.
- (2) OTC Volume 070249.
- (3) OTC Volume 070004.

i. *Chlorhydroxyquinoline.* The Panel concludes that chlorhydroxyquinoline is not safe and is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Chlorhydroxyquinoline (5-chloro-8-hydroxyquinoline) is an antifungal agent structurally similar to oxyquinoline (8-hydroxyquinoline) (Ref. 1). The latter compound was evaluated by this Panel in its recommendations on topical antifungal drug products published elsewhere in this issue of the

Federal Register and further studies were recommended to define the safety of oxyquinoline. There is even less information available on the toxicology of chlorhydroxyquinoline. Available data on the carcinogenicity of quinoline and oxyquinoline (Refs. 2 through 5), coupled with the mutagenicity of quinoline, 8-hydroxyquinoline, and 5-hydroxyquinoline in the Ames test (Refs. 6 and 7) make carcinogenicity tests on chlorhydroxyquinoline imperative. These tests should be carried out in a system using a tumor-promoting agent as well.

The Panel conclude that chlorhydroxyquinoline is not safe because there are no safety data available on this ingredient.

(2) *Effectiveness.* The Panel found only one study that evaluated chlorhydroxyquinoline as a single ingredient in the treatment of acne. Witkowski and Parish (Ref. 8) treated 100 patients with Grade II acne (Pillsbury's classification) with either 5 percent benzoyl peroxide-0.25 percent chlorhydroxyquinoline lotion (50 patients) or 0.25 percent chlorhydroxyquinoline lotion (50 patients). Patients were randomly assigned to either treatment group. They were instructed to wash the affected areas daily with "a commercially available soap used at home." Frequency of application was not explicitly defined but apparently varied from patient to patient and with the patient's response to therapy. No other systemic or local therapy was allowed. Patients were examined at 2-week intervals using lesion counts to evaluate responses.

The results shown as percentage of reduction in lesion count after 6 weeks of treatment are as follows: 75 to 100 percent in 4 patients treated with chlorhydroxyquinoline and 10 treated with chlorhydroxyquinoline-benzoyl peroxide; 50 to 74.9 percent in 4 patients treated with chlorhydroxyquinoline and 17 treated with the combination; 25 to 49.9 percent in 5 patients treated with chlorhydroxyquinoline and 3 treated with the combination; 0 to 24.9 percent in 11 patients treated with chlorhydroxyquinoline and 9 treated with the combination. Eleven patients in the chlorhydroxyquinoline-benzoyl peroxide group became worse compared to 26 patients in the chlorhydroxyquinoline group. The combination product was found to be more effective than chlorhydroxyquinoline used alone ($p < 0.0005$). Chlorhydroxyquinoline does not appear to be effective in the treatment of acne, but it is difficult to draw

conclusions because the trial was not vehicle controlled.

Chlorhydroxyquinoline is generally combined with benzoyl peroxide in marketed OTC products. The Panel believes that chlorhydroxyquinoline is not intended to be used as the sole active ingredient for the OTC topical treatment of acne. Because there is no vehicle-controlled trial evaluating the effectiveness of chlorhydroxyquinoline, the Panel concludes that this ingredient is not effective in the treatment of acne.

(3) *Evaluation.* The Panel has placed chlorhydroxyquinoline in Category II because there are no safety data available, particularly carcinogenicity studies. Also, there is not vehicle-controlled clinical trial evaluating the effectiveness of chlorhydroxyquinoline as a single ingredient for the treatment of acne.

References

- (1) Windholz, M., "The Merck Index," (9th Ed., Merck and Co., Rahway, NJ, p. 276, 1976.
- (2) Yamamoto, R. S., et al., "8-Hydroxyquinoline: Chronic Toxicity and Inhibitory Effect on the Carcinogenicity of N-2-Fluorenylaceticamide," *Toxicology and Applied Pharmacology*, 19:687-698, 1971.
- (3) Hirao, K., et al., "Carcinogenic Activity of Quinoline on Rat Liver," *Cancer Research*, 36:329-335, 1976.
- (4) Hueper, E. C., "Experimental Studies on 8-Hydroxyquinoline in Rats and Mice," *Archives of Pathology*, 79:245-250, 1965.
- (5) "World Health Organization, International Agency for Research on Cancer Monographs of Evaluation of Carcinogenic Risk of Chemicals to Man," Vol. 13, World Health Organization, Lyons, France, pp. 101-112, 1976.
- (6) Talcott, R., M. Hollstein, and E. Wei, "Mutagenicity of 8-Hydroxyquinoline and Related Compounds in the *Salmonella Typhimurium* Bioassay," *Biochemical Pharmacology*, 25:1323-1328, 1976.
- (7) Hollstein, M., R. Talcott, and E. Wei, "Quinoline: Conversion to a Mutagen by Human and Rodent Liver," *Journal of the National Cancer Institute*, 60:405-410, 1977.
- (8) Witkowski, J. A., and L. C. Parish, "Chlorhydroxyquin-Benzoyl Peroxide Lotion in the Treatment of Acne—An Objective Evaluation," *CUTIS: Cutaneous Medicine for the Practitioner*, 5:1481-1484, 1969.

j. *Chloroxylenol.* The Panel concludes that chloroxylenol is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* The Panel considers chloroxylenol to be safe in concentrations up to 3.75 percent as discussed in its recommendations on topical antifungal drug products published elsewhere in this issue of the *Federal Register*.

(2) *Effectiveness.* Chloroxylenol is active in vitro against fungi and gram-positive and gram-negative bacteria.

The Panel has received one submission on 2 percent chloroxylenol (Ref. 1) which did not contain any clinical studies on effectiveness. To the Panel's knowledge, this ingredient has not been clinically studied for effectiveness in treating acne. Standard dermatology reference texts do not list chloroxylenol as an active ingredient for the treatment of acne. The Panel concludes that chloroxylenol is not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel has placed chloroxylenol in Category II because no controlled clinical trials are available evaluating the effectiveness of this ingredient.

Reference

- (1) OTC Volume 070060.

k. *Coal tar.* The Panel concludes that coal tar is not safe and not effective for OTC topical use in the treatment of acne.

(1) *Safety.* The Panel thoroughly reviewed the toxicology of coal tar in its recommendations on topical antifungal drug products published elsewhere in this issue of the Federal Register. Coal tar was placed in Category II because of substantial data indicating that it has a carcinogenic potential. Since that time, no other safety data were submitted to the Panel.

The Panel concludes that coal tar is not safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Crude coal tar 0.4 percent in an alcohol base was submitted as an active ingredient in one combination product used to treat acne (Ref. 1). The submission stated that coal tar USP "is a local irritant used topically in lotions and ointments in a range of 1 to 20% concentrations," but no data were included pertaining to the rationale for including the 0.4-percent concentration.

In its earlier review of crude coal tar for use in fungal infections, the Panel found references stating that coal tar 0.1 percent is astringent (Ref. 2); 2 to 4 percent is antipruritic; and 6 to 20 percent is keratoplastic, causing thickening of the upper layers of the skin (epidermis and stratum corneum) (Ref. 3). The Panel is unaware of any studies documenting the effect of 0.4 percent coal tar on skin.

In a letter referring to a presentation before the Panel on coal tar, Cullen (Ref. 4) stated: "There is no evidence in the medical literature that topical tar is of any value in the therapy of pruritus, chafing, tinea pedis, acne vulgaris, or soft corns."

The Panel was able to find only one other mention of the use of coal tar in acne in a book by Plewig and Kligman

(Ref. 5). They wrote that "virtual cures (of acne) have been claimed for the combination of ultraviolet light and crude coal tar. The latter is a potent acneigen; moreover, its capacity to induce comedones is enhanced by sunlight."

The ability of coal tar to photosensitize the skin is well known. It is used therapeutically in the Goeckerman treatment of psoriasis and other skin diseases (Ref. 6).

The principal photosensitizing ingredients of coal tar are the acridine compounds in the anthracene oil fraction. Presumably, after absorption by the cells of the epidermis, these compounds become intimately associated with oxidizable substances in the cell. They are then activated by capture of a quantum (a unit of energy) of radiant energy of a specific wave length and react with oxygen, causing damage to the cell structure. The resulting oxygen deficiency then retards the development of keratin in the epidermis (Ref. 6).

Although exposure to sunlight alone is sometimes beneficial in treating acne, and photosensitization caused by coal tar might be theoretically beneficial in increasing the effects of sun exposure, no evidence of this is known to the Panel. On the contrary, Plewig and Kligman (Ref. 5) state that phototoxic reactions induced by coal tar may complicate acne in workers exposed to coal tar.

The Panel is aware of many reports stating that coal tar can induce acne and is a "potent comedogenic agent" (Ref. 5). Occupational "tar acne" is a common skin problem in road builders, roofers, and conduit makers exposed to coal tar, heavy coal tar distillates, or coal tar pitch (Ref. 7). Such workers develop extensive eruptions, comedones, and small yellowish cysts, which are most prominent on skin surfaces touched by soiled clothing. Hyperpigmentation of skin is also marked on the sun-exposed skin areas of these workers. Tar acne is probably caused by hydrocarbons, especially chloronaphthalene, deposited in the skin. The lesions resolve slowly, probably due to high tissue concentrations of the insoluble acnegenic substances (Ref. 5).

Coal tar induces hyperkeratosis in all keratinizing epithelia, including the upper part of the pilosebaceous duct, which is usually not involved in comedo formation (Ref. 8). The first comedones which become visible in tar acne are of the open type, as the pilosebaceous canal orifice becomes distended with retained keratin (Ref. 9). The follicular horny papules are often black and surrounded by erythema (Ref. 10), and

there is usually uniform involvement of most of the follicles within a certain area of the skin (Ref. 11). The tar comedones usually do not rupture to create papulopustules typical of acne vulgaris. The tar comedones also differ from the comedones of acne vulgaris by the virtual absence of *P. acnes* bacteria, probably due to bacteriostatic substances in the tar. The absence of inflammation in the tar comedones may be due to the lack of bacteria, which are thought to produce follicular irritation (Ref. 9).

A human model of coal tar acne was developed by Kaidbey and Kligman (Ref. 9) using a continuous occlusive application of crude coal tar to the backs of young adult males. A 25-percent concentration of coal tar distillate regularly induced an acneiform eruption after 3 weeks, but a 10-percent concentration produced only a mild follicular thickening in a few subjects.

The Panel concludes that coal tar is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel concludes that coal tar should be placed in Category II for the following reasons: (i) There are no clinical studies supporting the effectiveness of coal tar for the treatment of acne. (ii) Coal tar has been observed to induce acne in human models and in people exposed to it in their occupations. (iii) There are abundant data demonstrating a carcinogenic potential of crude coal tar and preparations derived from crude coal tar containing aromatic hydrocarbons.

References

- (1) OTC Volume 070004.
- (2) Combes, F. C., "The Use of Coal Tar in the Treatment of Skin Diseases," *New England Journal of Medicine*, 228:384-386, 1943.
- (3) Pusey, W. A., "The Principles and Practice of Dermatology Designed for Students and Practitioners," 4th Ed., D. Appleton and Co., New York, pp. 132-135, 1924.
- (4) Letter from Cullen, S. I. to A. M. Welch, Summary of proposed presentation to the Panel, included in OTC Volume 07BPA3.
- (5) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, pp. 59, 239, and 276, 1975.
- (6) Cole, H. N., Jr., "Goeckerman Therapy in the Management of Common Dermatoses," *Archives of Dermatology and Syphilology*, 80:788-791, 1959.
- (7) Ormsby, O. S., and H. Montgomery, "Diseases of the Skin," 7th Ed., Lea and Febiger, Philadelphia, p. 1330, 1948.
- (8) Cunliffe, W. J., and J. A. Cotterill, "The Acne: Clinical Features, Pathogenesis and Treatment," W. B. Saunders and Co., Philadelphia, p. 82, 1975.

(9) Kaidbey, K. H., and A. M. Kligman, "A Human Model of Coal Tar Acne," *Archives of Dermatology*, 109: 21-215, 1974.

(10) Dornik, A. N., "Andrews' Diseases of the Skin," 6th Ed., W. B. Saunders Co., Philadelphia, p. 88, 1971.

(11) Rook, A., D. S. Wilkinson, and F. J. G. Ebling, "Textbook of Dermatology," Vol. II, F. A. Davis Co., Philadelphia, pp. 1350-1351, 1968.

1. *Dibenzothiophene*. The Panel concludes that dibenzothiophene is not safe and that there are insufficient data available to permit final classification of its effectiveness for OTC topical use in the treatment of acne.

(1) *Safety*. Very little safety data are available on dibenzothiophene. The Panel received only one submission (Ref. 1) which contained two animal studies.

Acute oral toxicity was tested in rats using dibenzothiophene suspended in olive oil. Twelve dose levels ranging from 0.25 to 4.0 g/kg were included in the study. Although there were 32 animals in the study, many dose groups consisted of only one animal. The "approximate" LD₅₀ was 0.5 g/kg. All deaths were delayed, and some animals remained comatose for several days. Other signs of toxicity were a rough coat, weakness, diarrhea, and a red crust above the eyes.

From this study, a level of 0.05 g/kg/day was chosen for administration to dogs in a chronic study. Four male beagles were dosed five times a week for 3 months. None of the dogs exhibited any signs of toxicity, including gross pathology and histopathology.

The Panel notes that derivatives of benzothiophene are highly toxic and many are carcinogenic. Because there are not enough toxicity data available to evaluate this ingredient, the Panel concludes that dibenzothiophene is not safe for OTC topical use in the treatment of acne.

(2) *Effectiveness*. The mechanism of action of dibenzothiophene is thought to be the liberation of organic sulfur (Ref. 1), although this has not been well studied. In vitro testing of dibenzothiophene was done using the plate diffusion method (cup plate) with *Staphylococcus aureus* (*S. aureus*) and "a casual mixed culture or organisms found inhabiting normal skin" (Ref. 1). The site was not specified. Falcon plastic assay spiders were inserted into cups filled with 5.0 percent dibenzothiophene cream or lotion and then placed in wells in sterile agar. After 24 hours' incubation at 37° C, the zone of inhibition was measured. The zone of inhibition against *S. aureus* was 22 millimeters (mm) for the lotion and 21 mm for the cream. With the mixed

culture, the zone was 40 mm for the lotion and 32 mm for the cream.

There are several unpublished clinical trials on the effectiveness of dibenzothiophene. One study of 82 patients used 5 percent dibenzothiophene in 10 different creams and lotions (Ref. 1). Some also contained hexachlorophene, sulfur, neomycin, and a cosmetic pigment. Twelve patients had excellent results; 57 had fair results and 13 had results rated as "minimal." However, this study did not meet the Panel's criteria. The specifics of the study were not given. The study was not double-blind or controlled. No definitions of how acne was measured or of treatment results were included. In addition, patients used many other treatments including soaps, systemic antibiotics, "something to relieve premenstrual tension and irregularity," superficial X-ray therapy, ultraviolet light, and staphylococcal vaccine. The length of time necessary to achieve the results was also not specified.

In another study (Ref. 1), 16 patients with Grade I to III acne (based on number of acne lesions) were treated with 5 percent dibenzothiophene cream and lotion. The patients were given no other therapy and used the cream or lotion three or four times daily. Results showed nine patients excellent, three much improved, three improved, and one worse. There was no control in this trial. Also, it was not clear how long it took to achieve the results.

A study on 51 patients treated with 5 percent dibenzothiophene for 3 months showed the following results: 13 excellent, 20 good, 8 fair, and 9 poor. No explanation was given for the one patient who apparently dropped out of the study. Some patients with cystic acne were treated concurrently with superficial X-ray therapy and vaccines. No specific information was given on frequency of application or definition of results (Ref. 1).

Another unpublished study was conducted on over 100 patients treated with 5 percent dibenzothiophene cream or lotion (Ref. 1). No details were given on the frequency of application, other medications used, or the length of the trial. Although no specific results were given, the investigators noted "it is an effective topical agent with good patient acceptance."

Although dibenzothiophene appears useful in the treatment of acne, there are no controlled clinical trials that meet the effectiveness criteria established by the Panel. The Panel concludes that this ingredient is of questionable effectiveness for OTC use in the treatment of acne.

(3) *Evaluation*. Dibenzothiophene has been placed in Category II because the safety data are quite limited. The compound was fairly toxic when given in an acute study. There was no suggestion of a mechanism of action. Also, the Panel considered the only chronic study poorly designed (only four dogs, no controls). The Panel is also concerned about toxicity because many derivatives of benzothiophene are highly toxic.

Reference

(1) OTC Volume 070096.

m. *Estrone*. The Panel concludes that estrone is not safe and is not effective for OTC topical use in the treatment of acne.

(1) *Safety*. Estrone is a metabolite of estradiol, an ovarian hormone. Generally the estrogens used in therapy are readily absorbed through the skin and can have systemic effects. During enterohepatic circulation, they are gradually oxidized and conjugated to less active products. Normally, up to 100 µg of estrogens are excreted daily by females at the midcycle ovulating maximum, up to 25 µg per day by males, and 30 mg per day in pregnant females who are near term. The usual prescription dose of oral estrone given for various uses is 5 mg. Nausea is the most frequent symptom associated with oral estrogen therapy. In addition, it has been suggested that there is an increased risk of thromboembolism and cancer as a result of long-term estrogen therapy (Ref. 1).

The use of creams containing estrone 2.5 mg/g, which results in a daily dose of 5 mg, had not caused obvious side effects (Refs. 2, 3, and 4). However, it is generally agreed that, to achieve local efficacy, estrone must be absorbed in sufficient quantity to cause systemic effects (Refs. 5 and 6). The Panel notes that these studies were not looking specifically for side effects. The studies were short term and included small numbers of patients. The panel concludes that estrone is not safe for OTC topical use in the treatment of acne.

(2) *Effectiveness*. Estrogens were first reported as being used topically in the treatment of acne in the late 1940's. Acne was thought to be primarily caused by an endocrine disturbance affecting the pilosebaceous unit (Refs. 2, 3, and 7). Acne patients were shown to have an increased ratio of androgens to estrogens, the androgens being responsible for pilosebaceous gland activity. It was believed that topical application of estrogens would result in a more normal androgen-estrogen ratio.

resulting in reduction of sebum secretion and subsequent reduction of acne lesions. The substance most commonly used in these studies was a water-soluble, conjugated equine estrogen, sodium estrone sulfate. One mg estrone is equal to 10,000 I.U.

Shapiro (Ref. 7) treated 30 patients with acne that had not responded to the usual treatments with 2.5 to 5 mg estrone applied two to four times daily. Within 6 weeks he noticed improvement shown by a decrease in papules, pustules, and oiliness. The applications were then gradually reduced to once daily or once every other day. After 16 weeks of treatment, Shapiro reported that 20 of the 30 patients showed a satisfactory clinical remission. He stated that treatment with estrone offered "a promising approach to therapy-resistant acne vulgaris." The Panel notes that Shapiro expressed the patients' comedones during the treatment period. (The word "express," as used in dermatology, means to remove contents by squeezing or pressing.) The Panel considers this study not well controlled because expression is also a type of therapy.

In a later study, Shapiro (Ref. 3) tested the effectiveness of estrone in 25 patients. Again he chose patients who had not responded to the methods of treatment usually used then, including X-ray therapy, ultraviolet irradiation, dietary regimens, and various peeling agents. The total daily application of estrone was 5 mg. Treatment was continued for 1 to 7 months (average 4 months). The estimated total amount of estrogenic substances applied in this time ranged from 150 to 700 mg.

As in the previous study by Shapiro (Ref. 7), lesions were not counted. Evaluation was based on clinical judgment, i.e., whether there was an apparent decrease in skin oiliness or a reduction of pustules, papules, comedones, and cysts. Shapiro reported that excellent results were obtained in 15 patients (60 percent). Results were good in four patients and fair in three. Three patients could not tolerate the cream and were dropped from the study.

Shapiro (Ref. 3) also monitored changes in menstrual cycle, breasts, and libido to determine any systemic effects. He found no adverse effects from the use of estrone.

Sawicky, Danto, and Maddin (Ref. 2) evaluated the effectiveness of estrone in a half-face study of 26 patients. Half of the face was treated with 2.5 mg estrone daily. The vehicle control was applied to the other half of the face. The patients were unaware of which side of the face received the active treatment. Patients were treated for 2 to 16 weeks with the

total amount of hormone applied ranging from 38 to 204 mg.

The investigators found estrone to be more effective on cystic lesions than on papules and pustules. Three male patients with cystic acne showed great improvement on the side of the face treated with estrone. Patients with papules and pustules were reported to have moderate, slight, or no improvement.

The clinical data from several researchers (Refs. 8, 9, and 10) indicate that perhaps males benefit more from topical estrogen therapy than females. For example, Whitelaw (Ref. 8) used a cream containing 0.625 mg estrone/g and found that 55 percent of his male patients (76 patients) were much improved after treatment for 6 months or more, but that only 21 percent of the female cases (23 patients) responded satisfactorily.

Using diethylstilbestrol dilaurate (a synthetic estrogen) lotion on 84 patients, Philip (Ref. 9) came to a similar conclusion. Patients applied 3.5 to 7 mg diethylstilbestrol daily. The dosage was gradually reduced after 6 weeks of treatment. The length of treatment, however, is unclear. Of the 36 males in the study, 33 (92 percent) showed good or excellent improvement. Ten (21 percent) of the 48 females were reported as good or excellent at the conclusion of the trial. Philip concluded that estrogen therapy "appears to be effective and desirable only in the management of acne vulgaris in the adolescent male."

Peck, Klarmann, and Spoor (Ref. 10) reported good or excellent results in 55 of 69 patients treated with a lotion containing estrone. The lotion also contained numerous other ingredients including zinc oxide, zinc sulfide, sulfur, salicylic acid, aluminum hydroxide, and oxyquinoline. The authors believed the lotion to be somewhat more effective in males than in females. They stated that natural estrone was more satisfactory than synthetic estrogenic hormones such as diethylstilbestrol.

The researchers also stated that the optimal concentration of estrone is 50,000 I.U./ounce (5 mg/ounce). This is considerably lower than the concentrations used in the studies described above (150,000 to 600,000 I.U./ounce). Concentrations above 50,000 I.U. would produce undesirable systemic effects. Peck, Klarmann, and Spoor (Ref. 10) found no effect of topical estrogen on blood estrogen level, menstrual cycle, or vaginal cornification after 1 month of applications to 12 subjects.

Estrone was contained in only one product submission to the Panel (Ref. 11). The concentration of estrone in this

product is quite low—0.333/mg ounce (3,333 I.U./ounce).

Damrau (Ref. 12) tested the estrone cream described above (which also contains salicylic acid) on 45 subjects. He reported that the action of the cream is hyperemizing, meaning that it causes an increased blood flow to a part of the body. It is keratolytic and "produces an unusual degree of absorption and effectiveness of estrone."

A control group of 16 subjects used a "leading acne product" (ingredients not specified). Both groups were instructed to apply a thin layer of cream over the affected area of the face twice daily. The total amount was one-half teaspoonful. After 5 minutes the cream was washed off with soap and water.

The total amount of estrogenic hormone applied in 1 month was under 2 mg (20,000 I.U.). Length of treatment was 6 months in the estrone group and 3 months in the control group.

The results showed 80 percent of the estrone-treated patients improved after 1 month, with 2 percent of the patients completely cleared. After 6 months, 73 percent of the patients were completely cleared, and the remaining patients were improved. In the control group after 3 months, 75 percent were improved and the rest showed no change.

Overall acne counts decreased from 6.2 to 0.6 in the treated group and from 6.2 to 4.8 in the controls. The acne count was not specified as to lesion type. Although the results were not analyzed statistically, Damrau (Ref. 12) concluded that the estrone cream was a superior product.

Most of the studies reviewed by the Panel reported favorable results for estrone in the treatment of acne. Several authors in medical journals (Refs. 13, 14, and 15), however, held that local estrogen therapy was of limited value.

It is apparent from the review of the literature that there has been little work done in the last 20 years to indicate that topically applied estrogen is an effective ingredient to treat acne. None of the studies reviewed met the standards the Panel has recommended to determine effectiveness. None of the studies were randomized or double-blind and most did not use a vehicle control. Methods of evaluating patients were not rigidly defined and in some cases were difficult to determine. Results were not statistically analyzed.

The effectiveness of topical estrogens in acne is not attributed to a local effect on the skin (Ref. 16). Theoretically, estrogens may affect the sebaceous glands by inhibiting androgen

production. The Panel believes, however, that very high concentrations of estrone would have to be applied topically for sufficient amounts to be absorbed systemically to produce this effect.

The Panel notes that in the only submission on estrone, this ingredient occurs in such a small concentration (3,333 I.U./ounce) that a systemic effect is unlikely. The panel concludes the estrone is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed estrone in Category II because it is toxic at the high concentrations needed to produce an effect on acne lesions.

References

- (1) Murad, F., and A. G. Gilman, "Estrogens and Progestins," in "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 1423-1450, 1975.
- (2) Sawicky, H. H., J. L. Danto, and W. S. Maddin, "Clinical Evaluation of Topically Applied Estrogen Cream in Acne Vulgaris," *Archives of Dermatology and Syphilology*, 68:17-20, 1953.
- (3) Shapiro, I., "Estrogens by Local Application in Treatment of Acne Vulgaris," *Archives of Dermatology and Syphilology*, 63:224-227, 1951.
- (4) Holbrook, A. A., "The Treatment of Acne Vulgaris in Teen-age Males with Oral and Topical Administration of Estrogenic Hormone," *Wisconsin Medical Journal*, 52:425-428, 1953.
- (5) Cunliffe, W. J., and J. A. Cotterill, "The Acne: Clinical Features, Pathogenesis and Treatment," W. B. Saunders Co., Philadelphia, p. 226, 1975.
- (6) Dickerson, J., et al., "Efficacy of Estradiol Vaginal Cream in Postmenopausal Women," *Clinical Pharmacology and Therapeutics*, 28:502-507, 1979.
- (7) Shapiro, I., "Estrogenic Treatment of Acne Vulgaris. A Preliminary Report," *Journal of the Medical Society of New Jersey*, 46:128-129, 1949.
- (8) Whitelaw, M. J., "The Treatment of Adolescent Acne with Topical Application of Estrogens," *Journal of Clinical Endocrinology and Metabolism*, 11:487-491, 1951.
- (9) Philip, A. J., "Tropical Estrogens in Acne Vulgaris," *New York State Journal of Medicine*, 51:1313-1314, 1950.
- (10) Peck, S. M., E. G. Klarmann, and H. J. Spoor, "Treatment of Acne Vulgaris with Estrone," *Archives of Dermatology*, 70:452-467, 1954.
- (11) OTC Volume 070108.
- (12) Damrau, F., "Acne Vulgaris (Evaluation of a New Estrogenic Cream)," *Medical Record and Annals*, 54:219-220, 1961.
- (13) Kline, P. R., "Modern Treatment of Acne Vulgaris," *Journal of the Medical Society of New Jersey*, 51:97-101, 1954.
- (14) "Acne Vulgaris," unsigned reply to letter to the editor, *Journal of the American Medical Association*, 155:1547-1548, 1954.
- (15) "Oestrogen Ointment and Acne," unsigned reply to letter to the editor, *British Medical Journal*, 1:1450, 1954.
- (16) Pochi, P. E., and J. S. Strauss, "Sebaceous Gland Suppression with Ethinyl Estradiol and Diethylstilbestrol," *Archives of Dermatology*, 108:210-214, 1973.

n. *Magnesium sulfate.* The Panel concludes that magnesium sulfate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Magnesium sulfate is also known as epsom salts. One gram is equivalent to 4.06 millimoles or 8.12 milliequivalents (meq) of magnesium (Ref. 1). The primary use of this salt is as a cathartic, where the usual dose is 15 g. Although the mechanism of action may be fluid retention due to an osmotic gradient, absorption of up to 20 percent does occur and can result in symptoms of magnesium intoxication in persons with kidney failure (Ref. 2). A study of five patients with kidney insufficiency who received high doses of magnesium described symptoms of hypermagnesemia (an abnormally large magnesium content in the blood plasma) as nausea, vomiting, malaise, hypotension, and drowsiness (Ref. 3).

In evaluating magnesium sulfate for OTC use as a laxative, one Panel suggested that a warning label for people with kidney disease be included on products in which a daily dose would be more than 50 meq (40 FR 12910). In evaluating this drug as an antacid, the Advisory Review Panel on OTC Antacid Drug Products suggested a similar warning in its recommendations published in the *Federal Register* on April 5, 1973 (38 FR 8719).

Other therapeutic uses of magnesium sulfate include treatment of eclampsia (convulsions and coma occurring in pregnancy or after childbirth) and hypomagnesemia (an abnormally low magnesium content in the blood plasma). For eclampsia magnesium sulfate can be given intramuscularly or intravenously. Magnesium sulfate functions as a sedative and anticonvulsant (Ref. 4). For treatment of hypomagnesemia, magnesium sulfate can be given as intramuscular doses of 2 g four times daily, or as intravenous doses of 2 to 4 g daily (Ref. 1).

Magnesium sulfate has also been extensively used topically to alleviate local inflammatory conditions. No adverse effects were noted (Ref. 5). Because magnesium is poorly absorbed through the skin (Ref. 6), it is unlikely that, even in patients with impaired kidney function, topical use could result in absorption of magnesium in sufficient quantities to cause systemic toxicity. The Panel concludes that magnesium sulfate is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* The Panel received one product submission containing

magnesium sulfate at concentrations of 40 to 43 percent (Ref. 7). The Panel notes that this ingredient is formulated in a hydrophilic ointment base, a known comedolytic agent. According to the submission (Ref. 7), the mechanism of action of magnesium sulfate is "drawing inflammation to the surface of the skin by osmotic pressure." Another submission included a report of a study in which magnesium sulfate was used to treat a dermatological condition (Ref. 8). However, no information on the use of magnesium sulfate in the treatment of acne was included.

There are no studies in the submission or in the medical literature indicating that magnesium sulfate is of value in treating acne. The Panel concludes that magnesium sulfate is not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel has placed magnesium sulfate in Category II because there are no studies that demonstrate that this ingredient is effective in the treatment of acne.

References

- (1) Peach, M. J., "Cations: Calcium, Magnesium, Barium, Lithium, and Ammonium," in "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 790-791, 1975.
- (2) Fingl, E., "Laxatives and Cathartics," in "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, p. 980, 1975.
- (3) Randall, R. E., Jr., et al., "Hypermagnesemia in Renal Failure. Etiology and Toxic Manifestations," *Annals of Internal Medicine*, 61:73-88, 1964.
- (4) Taylor, E. S., "Beck's Obstetrical Practice and Fetal Medicine," 10th Ed., Williams and Wilkins Co., Baltimore, pp. 369-371, 1976.
- (5) Chernick, W. S., "The Ions: Potassium, Calcium, Magnesium, Fluoride, Iodide, and Others" in "Drill's Pharmacology in Medicine," Edited by J. DiPalma, McGraw-Hill, New York, p. 948, 1971.
- (6) Birmingham, D. J., "Cutaneous Absorption and Systemic Toxicity," in "Cutaneous Toxicity," Edited by V. A. Drill and P. Lazar, Academic Press, New York, p. 53, 1977.
- (7) OTC Volume 070245.
- (8) OTC Volume 070276.

o. *Phenolates (phenol and phenolate sodium).* The Panel concludes that the phenolates (phenol and phenolate sodium) are not effective and that there are insufficient data available to permit final classification of their safety in concentrations of 1.5 percent or less for OTC topical use in the treatment of acne.

The Panel considers phenol and phenolate sodium as a single ingredient when both are contained in a product

formulation. The total level of phenol equals the sum of the phenol and phenolate sodium concentrations.

(1) *Safety.* The potential toxicity of phenol in concentrations greater than 1.5 percent was described by the Advisory Review Panel on OTC Antimicrobial I Drug Products elsewhere in the Federal Register (39 FR 33121) published September 13, 1974. This Panel agreed with that assessment and further described the toxicity of phenol in its recommendations on topical antifungal drug products published elsewhere in this issue of the Federal Register. Phenol was considered of questionable safety for OTC topical use in concentrations less than 1.5 percent. The Panel has received no new data that leads it to change this evaluation.

The Panel concludes that there are insufficient data to adequately determine the safety of phenol in concentrations less than or equal to 1.5 percent. The reason for this decision is the lack of controlled studies evaluating (1) the absorption from small areas of application to either broken or intact skin, (2) the local effects on wound healing, and (3) the potential for hypersensitivity or idiosyncratic reactions.

(2) *Effectiveness.* Phenol has anesthetic, bactericidal, and fungicidal properties (Ref. 1). Apparently, the anesthetic effect of phenol is the reason for its inclusion in acne products.

Phenol has been studied in a variety of inflammatory diseases, athlete's foot, and infected eczema (Refs. 1, 2, and 3). However the Panel could find no clinical trials examining the effectiveness of phenol in treating acne.

Plewig and Kligman (Ref. 4) state that most "traditional exfoliants turned out to be surprisingly weak or ineffective: phenol, resorcinol, beta-naphthol, sulfur, Vlemminckx's solution and sodium thiosulfate. Hence, only a few agents which cause peeling are in fact comedolytic. The probable explanation is that most 'peelers' affect only the epidermis and not the follicular infundibulum."

The Panel concludes that there are no data to show that the phenolates are clinically effective in the treatment of acne.

(3) *Evaluation.* In the absence of clinical trials demonstrating effectiveness in the treatment of acne, the Panel has placed phenolates (phenol and phenolate sodium) in Category II.

References

- (1) Freeman, C. W., J. G. Gathings, and T. Gopinathan, "Evaluation of Chloraderm as a Dermatologic Agent. A Study of Bacteriologic, Fungicidal and Antipruritic

Properties," *Medical Annals of the District of Columbia*, 30:213-215, 1960.

(2) OTC Volume 070101.

(3) OTC Volume 070247.

(4) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, p. 278, 1975.

p. Phenyl salicylate. The Panel concludes that phenyl salicylate is not effective and that there are insufficient data available to permit final classification of its safety for OTC topical use in the treatment of acne.

(1) *Safety.* The Panel reviewed the safety of phenyl salicylate in its recommendations on topical antifungal drug products published elsewhere in this issue of the Federal Register. Since the Panel made those recommendations, no additional safety data were submitted. In the absence of data on irritation, sensitization, and effects on broken skin, the Panel concludes that phenyl salicylate is of questionable safety for topical use in the treatment of acne.

(2) *Effectiveness.* The Panel received only one product submission on phenyl salicylate (Ref. 1). This submission contained no data and the Panel could not find mention in the medical literature of phenyl salicylate for the treatment of acne. The Panel concludes that phenyl salicylate is not effective in the OTC topical treatment of acne.

(3) *Evaluation.* The Panel has placed phenyl salicylate in Category II because there are no effectiveness data available. The Panel believes there is no rationale for the use of this ingredient in the treatment of acne.

Reference

- (1) OTC Volume 070004.

q. Pyrilamine maleate. The Panel concludes that pyrilamine maleate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Pyrilamine maleate is a widely used antihistamine. The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products reviewed pyrilamine for that use and considered it safe in its recommendations published in the Federal Register of September 9, 1976 (41 FR 38391). The recommended oral dose is 25 to 50 mg three to four times daily.

Submissions to the Panel indicated no toxic effects or irritation from the topical use of pyrilamine maleate (Refs. 1 and 2). Patch tests on a combination product containing 1 percent pyrilamine maleate showed no cutaneous sensitivity (Refs. 1 and 2), although this ingredient is known to be a mild sensitizer when used topically.

In the Panel's view, pyrilamine maleate is safe for topical use.

(2) *Effectiveness.* The Panel is not aware of any clinical trials demonstrating the effectiveness of pyrilamine maleate in treating acne. According to the submissions received by the Panel (Refs. 1 and 2), pyrilamine maleate is used in acne treatment products as an antipruritic and is effective in treating wheals which are flat or raised lesions that may itch or burn and are typical of hives. The Panel believes it is irrational to use an antihistamine or antipruritic to treat acne. The Panel concludes that pyrilamine maleate is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed pyrilamine maleate in Category II because there is no rationale for the inclusion of an antihistamine in acne treatment products.

References

- (1) OTC Volume 070046.

- (2) OTC Volume 070047.

r. Resorcinol and resorcinol monoacetate. The Panel concludes that resorcinol and resorcinol monoacetate are safe but are not effective as single ingredients for OTC topical use in the treatment of acne.

(1) *Safety.* Resorcinol is a phenolic compound which was reviewed by this Panel in its recommendations on topical antifungal drug products published elsewhere in this issue of the Federal Register. The Panel considered resorcinol in high concentrations (10 percent) to be unsafe for topical use. As discussed in the publication mentioned above, resorcinol resembles phenol in its systemic actions but causes more prominent central stimulation. Acne preparations contain up to 2 percent resorcinol or 3 percent resorcinol monoacetate.

Patty (Ref. 1) reported that the cutaneous application of solutions, or salves containing from 3 to 25 percent resorcinol could result in local toxicity including edema, itching, dermatitis, or peeling. Systemic toxicity could also occur. Some signs of systemic toxicity include restlessness, methemoglobinemia, convulsions, or death. The Panel recognizes that the severity of the signs would be related to the dose.

Patty also noted that ingestion of 4 g resorcinol caused dizziness and sleepiness in a 4-year-old child. In another case after ingestion of 8 g resorcinol the signs and symptoms included fall in blood pressure and low

body temperature. Both patients recovered.

A combination of 8 percent sulfur and 1 percent resorcinol was used in an eye irritation study conducted in rabbits. This study confirmed the potential for irritation if the sulfur-resorcinol combination was allowed to remain in the eye. Washing the eyes after 30 seconds of exposure greatly reduced the irritation (Refs. 2 and 3).

Acute dermal irritation studies in rabbits confirmed the mild irritation potential of this combination (Refs. 2 and 3).

Subacute studies (Refs. 2 and 3) of the above combination were conducted in rabbits on both normal and abraded skin. Some of the studies were done over 20-day periods and others over 30-day periods. Dose levels of 0.1, 0.3, and 1.0 g/kg body weight were applied daily to the shaved backs of rabbits (both males and females). At the end of these studies, hematology studies, urinalysis, gross pathology, and histopathological evaluations were done. In general, all values within normal limits, except that skin changes of an irritant nature were noted for the higher dose levels.

Although these studies appeared to be comprehensive, well-controlled, and well-conducted, the Panel noted several deficiencies. For example, in the dermal exposure of rabbits about 6 to 7 percent of the body surface area was exposed to the sulfur-resorcinol combination. However, in actual human use for acne, the area of application includes the face, shoulders, chest, and back and represents about one-half of the body surface area. In addition, the study indicated the material was applied once daily. But in the treatment of acne in humans the recommended application is three times daily. Also, at the highest dose used, 1 g/kg/day, the total exposure of the rabbit to resorcinol amounted to 20 mg/kg/day with a limited surface area for absorption. This study did not address the Panel's major concern about the absorption potential when large amounts of resorcinol are applied to large surface areas, particularly when it is applied three times daily.

In subchronic studies, resorcinol used alone was administered by various routes to rats and rabbits. The only noteworthy toxicological finding was an increase in the weight of the thyroid. In the rat a no-effect level was reported as 154 mg/kg given twice daily subcutaneously for up to 38 days (Ref. 4).

The results of the micronucleus test in rats and a modified Ames test using *Salmonella typhimurium* showed that resorcinol was not mutagenic (Refs. 5

and 6). Following application to the skin of mice for 368 days or to the skin of the rabbit ear for up to 160 weeks, resorcinol was not found to be carcinogenic (Refs. 7 and 8).

The Panel also received limited data on human exposure to airborne resorcinol in the work place. Workers were exposed for 10 years or longer to an "inhaled threshold limit value" of 10 ppm. This equals a total inhaled dose of about 6.43 mg/kg/day. Workers did not complain of irritations or discomfort, nor did they display abnormal clinical signs referable to the thyroid gland, central nervous system, or hematological system. Blood determinations for thyroid-stimulating hormone (TSH) and thyroid hormone (T₄) showed that values were within the normal range (Refs. 9 and 10).

In vitro skin penetration studies were done using excised human skin to determine the percutaneous absorption of resorcinol applied as a 2-percent resorcinol-8 percent sulfur cream (Ref. 11). Data indicated a lag time of about 3 hours followed by a maximum rate of skin penetration of 6.1 µg/cm²/h. This would yield a pharmacokinetically calculated steady-state blood level of resorcinol of 19 µg/100 mL in persons with acne. (Pharmacokinetics is the study of the action of a drug over a period of time. Steady state refers to the point at which the amount of drug absorbed is equal to the amount eliminated.) This level is reported to be 1/161 to 1/653 of the blood levels estimated to have been reached in leg-ulcer subjects who had systemic toxicity (ref. 11).

Plasma, tissue distribution, and excretion data indicated that resorcinol (containing trace amounts of ¹⁴C-resorcinol) was rapidly eliminated from the rat following a single subcutaneous injection of 10, 50, or 100 mg/kg (Ref. 12). Resorcinol was also rapidly eliminated after repeated dosing with a total daily dose of 100 mg/kg given daily over 14 days. The amount of the resorcinol dose eliminated in the urine was 85.7 percent in about 3 hours and 93.6 percent in 24 hours. Between 1 hour and 24 hours following injection, plasma levels decreased from 0.32 percent to 0.01 percent of the administered dose. One hour after administration, the amount of the administered dose contained in potential target organs was 0.005 percent in the thyroid, 0.02 percent in the brain, and 0.03 percent in the spleen. Plasma half-life was determined using doses of 50 and 100 mg/kg. The half-life was 0.5 hour during the first 2 hours after treatment and about 4 hours thereafter. No significant difference in plasma elimination rates were observed

between the single dose and the repeated doses of resorcinol. Organ disposition data showed that vital and potential target organs did not accumulate resorcinol during the time in which plasma levels were declining (Ref. 12).

Resorcinol excreted in rat urine was about 75 percent glucuronide and 25 percent sulfate ester. No free resorcinol was detected (Ref. 12).

The percutaneous absorption and metabolic disposition of resorcinol were investigated in three human volunteers. Resorcinol 2 percent in a hydroalcoholic vehicle was applied to the face, neck, shoulders, back, and chest (about 30 percent of the available skin area). Blood samples were collected 1 week after this first drug application and weekly for 3 more weeks. No resorcinol was detected at the limit of the assay (0.5 µg/mL).

After 2 weeks of continuous application (800 mg/subject/day), an average of 1.64 percent of the administered dose was excreted in the urine at 24 hours. The excreted resorcinol was in the form of either the glucuronide or the sulfate ester. Thyroid function was assessed at 2, 3, and 4 weeks and found to be normal. Blood chemistries were also normal in all subjects throughout the study (Ref. 12).

The Panel concludes that 2 percent resorcinol or 3 percent resorcinol monoacetate is safe for OTC topical use in the treatment of acne. However, the Panel is concerned about the potentially large surface area of the body that could be available for absorption if an acne preparation were applied to the entire upper torso (about 1 square meter of absorption area through broken skin). For this reason the Panel recommends the following warning for acne combinations containing resorcinol: "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body." (See part III, paragraph A.2. above—Category I labeling.)

(2) *Effectiveness.* The concentration of resorcinol generally used in acne products is 1 to 2 percent. Resorcinol monoacetate 3 percent is equivalent to 2 percent resorcinol. Resorcinol has antibacterial, antifungal, and mild keratolytic activity. Resorcinol monoacetate slowly liberates resorcinol, producing a milder, but longer-lasting effect (Ref. 13).

As mentioned above, sulfur and resorcinol are often used together in the treatment of acne, but it is difficult to document the historical origin of this combination. The precise mechanism of action of these combinations has never

been proven, but may depend on keratolysis or on the ingredients' ability to produce erythema and desquamation with enhanced resolution of comedones, papules, and pustules. (For a review of sulfur-resorcinol combinations, see part III, paragraph D.1. below—Category I combination product—sulfur-resorcinol.)

No study has examined the effectiveness of resorcinol used as a single ingredient in the treatment of naturally occurring acne. The Panel concludes that resorcinol is not effective for OTC topical use as a single ingredient in the treatment of acne.

(3) *Evaluation.* In the absence of data documenting the effectiveness of resorcinol and resorcinol monoacetate used alone in the treatment of acne, the Panel has placed these ingredients in Category II.

References

- (1) Patty, F., "Industrial Hygiene and Toxicology," 2d Ed., Vol. 2, Interscience Publishing Co., New York, p. 1379, 1963.
- (2) OTC Volume 070234.
- (3) OTC Volume 070235.
- (4) OTC Volume 070284.
- (5) Hossack, D. J. N., and J. C. Richardson, "Examination of the Potential Mutagenicity of Hair Dye Constituents Using the Micronucleus Test," *Experientia*, 33:377-378, 1977.
- (6) McCann, J., et al., "Detection of Carcinogens as Mutagens in the *Salmonella*/Microsome Test: Assay of 300 Chemicals," *Proceedings of the National Academy of Sciences*, 71:5135-5139, 1975.
- (7) Van Duuren, B. L., and B. M. Goldschmidt, "Carcinogenic and Tumor-Promoting Agents in Tobacco Carcinogenesis," *Journal of the National Cancer Institute*, 56:1237-1242, 1976.
- (8) Stenback, F., "Local and Systemic Effects of Commonly Used Cutaneous Agents: Lifetime Studies of 16 Compounds in Mice and Rabbits," *Acta Pharmacologica et Toxicologica*, 41:417-431, 1977.
- (9) OTC Volume 070287.
- (10) OTC Volume 070288.
- (11) OTC Volume 070271.
- (12) OTC Volume 070290.
- (13) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasitides," in "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, p. 991, 1975.

s. *Sodium thiosulfate.* The Panel concludes that sodium thiosulfate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Sodium thiosulfate, $\text{Na}_2\text{O}_3\text{S}_2$, is a water-soluble reducing agent used in veterinary medicine to treat ringworm and mange (Ref. 1). It has also been used extensively as an antidote for cyanide poisoning in humans (Ref. 2). In this treatment, the stomach contents are washed out with a solution of 5 percent sodium thiosulfate,

leaving 10 g of the solution in the stomach.

The lowest subcutaneous dose known to cause death in the rabbit is reported as 4 g/kg (Ref. 3). The intravenous LD_{50} in the rat is greater than 2.5 g/kg (Ref. 1). One study used oral gavage and determined the minimal lethal dose in the rat to be greater than 5 g/kg (Ref. 4). At this dose, labored breathing and panting were the only symptoms observed. Sodium thiosulfate at concentrations up to 22 percent was found to be nonirritating to intact or abraded rabbit skin occluded for 24 hours and read at 24 and 72 hours (Ref. 4).

The Panel concludes that sodium thiosulfate is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Sodium thiosulfate is contained in marketed acne products in concentrations of 2 to 8 percent. The apparent rationale for the use of this ingredient is a potential keratolytic and antibacterial activity either by sodium thiosulfate itself or by sulfur that is liberated when the compound comes in contact with the skin.

Numerous unpublished studies have evaluated the effectiveness of sodium thiosulfate (Ref. 4). However, none of these studies met the effectiveness criteria set by the Panel. All involved a combination product containing sodium thiosulfate, resorcinol, and salicylic acid. None used a vehicle control. The method of patient evaluation and treatment results were usually not explained. In one study, the combination product mentioned above was tested on 74 patients with acne vulgaris. The results were as follows: 46 percent very good, 39 percent good, 8 percent "medium," and 7 percent poor. No other details were given.

In an uncontrolled clinical trial, Sewell (Ref. 5) evaluated 224 patients who had mild to severe acne. No mention was made of randomization or blinding. A sodium thiosulfate combination product was applied four times daily for 2 to 50 weeks. The patients also washed with a soap containing salicylic acid and sulfur. Of the 28 subjects using a 2-percent sodium thiosulfate-1 percent salicylic acid-1 percent resorcinol lotion, 64.3 percent showed marked improvement and the rest were improved by the end of the study. The other 196 patients applied an 8-percent sodium thiosulfate-2 percent salicylic acid-2 percent resorcinol lotion. Of these patients, 33.7 percent were improved and 65.8 percent were markedly improved. Sewell concluded that the sodium thiosulfate combinations were effective in the treatment of acne, although it is difficult

to determine the contribution made by sodium thiosulfate as a single ingredient.

Hall and Lupton (Ref. 6) studied 44 patients with acne in a double-blind, half-face trial. One-half of each patient's face was treated with 8 percent sodium thiosulfate-2 percent salicylic acid-2 percent resorcinol. An alcohol-water vehicle was applied to the other half of the face. Treatment was twice daily for 8 weeks. Patients were allowed to continue medications they were previously using including abrasive cleansers and tetracycline. At the final evaluation, the researchers determined which side of the face showed greater improvement. In 19 patients, the treated side showed more improvement. Five patients were more improved on the placebo side. In the remaining patients, no difference was noted between the combination product and the placebo.

Although the effectiveness of sodium thiosulfate has been studied extensively, none of the studies have evaluated sodium thiosulfate as a single active ingredient. For this reason the Panel concludes that sodium thiosulfate is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* In the absence of data demonstrating effectiveness as a single ingredient in the treatment of acne, the Panel has placed this ingredient in Category II.

References

- (1) Windholz, M., et al., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 1122-1123, 1976.
- (2) Thienes, C. H., and T. J. Haley, "Clinical Toxicology," 5th Ed., Lea and Febiger, Philadelphia, p. 205, 1972.
- (3) Fairchild, E., "Registry of Toxic Effects of Chemical Substances," Vol. II, United States Department of Health, Education, and Welfare, Cincinnati, p. 907, 1977.
- (4) OTC Volume 070088.
- (5) Sewell, J. W., Jr., "Therapeutic and Cosmetic Advantages of a Nonpigmented Acne Lotion," *CUTIS: Cutaneous Medicine for the Practitioner*, 1:473-476, 1965.
- (6) Hall, J. H., and E. S. Lupton, "Topical Acne Therapy: A Double-Blind Study," *CUTIS: Cutaneous Medicine for the Practitioner*, 9:545-547, 1972.

t. *Tetracaine hydrochloride.* The Panel concludes that tetracaine hydrochloride is not safe and is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Tetracaine hydrochloride is a derivative of *p*-aminobenzoic acid similar to benzocaine. (For a discussion of benzocaine, see part III, paragraph B.1.c. above—Benzocaine.)

The aminobenzoic acid derivatives are known to cause allergic sensitivity reactions. Also, cross-sensitivity

between members of this group is frequently reported. Sensitivity tests such as skin, conjunctival, and patch tests are not considered reliable for predicting the possibility of allergic reactions (Ref. 1).

Tetracaine hydrochloride is used as a 0.5-percent solution for the topical anesthesia of the eye. On mucous membranes of the nose and throat, a 2-percent solution is used (Ref. 2). However, considering the large surface area of application and the possibility of long-term use in acne, the Panel concludes that tetracaine hydrochloride is not safe for OTC topical use in the treatment of acne because of the potential for sensitization.

(2) *Effectiveness.* According to a submission to the Panel, tetracaine hydrochloride, a local anesthetic, is included in acne preparations to help "relieve the irritation and discomfort usually associated with acne vulgaris" (Ref. 3).

Tetracaine hydrochloride was found to be one of the most effective and longest lasting drugs in a series of topical anesthetics studied by Adriani and Zepernick (Ref. 4). These researchers reported the maximum effective concentration as 1 percent. The concentration of tetracaine hydrochloride currently marketed in acne products is 0.25 percent.

There are no clinical trials establishing the effectiveness of tetracaine hydrochloride in treating acne. The Panel believes the use of a local anesthetic in acne treatment is irrational therapy and concludes that tetracaine hydrochloride is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed tetracaine hydrochloride in Category II because it is a recognized sensitizer and there is no rationale for the use of a local anesthetic in the treatment of acne.

References

- (1) Swinyard, E. A., "Local Anesthetics," in "Remington's Pharmaceutical Sciences," 15th Ed., Edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, pp. 986-987, 1975.
- (2) Ritchie, J. M., and P. J. Cohen, "Cocaine; Procaine and Other Synthetic Local Anesthetics," in "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 379-400, 1975.
- (3) OTC Volume 070046.
- (4) Adriani, J., and R. Zepernick, "Clinical Effectiveness of Drugs Used for Topical Anesthesia," *Journal of the American Medical Association*, 188:711-716, 1964.

u. *Thymol.* The Panel concludes that thymol is not effective and that there are insufficient data available to determine

its safety for OTC topical use in the treatment of acne.

(1) *Safety.* The toxicology of thymol was discussed in the Panel's recommendations on topical antifungal drug products published elsewhere in this issue of the Federal Register. The Panel determined that this ingredient is of questionable safety because of inadequate data evaluating the absorption of thymol from small areas of application to intact and broken skin. Data on the local effects of thymol on wound healing and thymol's irritation potential were also lacking. Acne submissions on thymol (Refs. 1 and 2) were reviewed and found to contain no new information. The Panel concludes that thymol is of questionable safety for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Thymol, an ingredient with antibacterial and antifungal properties, is used in acne preparations in concentrations of about 0.16 to 0.5 percent. At these low concentrations thymol has questionable antibacterial activity.

Several effectiveness studies (Ref. 3) have been reviewed by the Panel, but none evaluated thymol against a vehicle control. In one study, 60 subjects applied a 0.16-percent thymol scrub once or twice daily for 3 months. The patients were evaluated on a scale of 0 to 4 for comedones, papules, pustules, and oiliness at the pretreatment examination and at the conclusion of the study. Results showed that the subjects had significantly fewer acne lesions and less oiliness after 3 months than at the beginning of the trial ($p < 0.01$).

Thymol was also evaluated in an 8-week trial of 139 patients (Ref. 3). Forty-seven subjects applied a thymol gel; 44 subjects used a thymol lotion. The remaining patients used soap and water. Again, acne lesions were not counted. Evaluation of blackheads, whiteheads, papules, pustules, and oiliness was based on a severity scale (1 to 5). Analysis of results showed that the thymol gel and lotion were significantly more effective than soap and water in the overall evaluation at 8 weeks ($p < 0.05$ and 0.01 , respectively). Treatment with soap only, however, also showed a statistically significant improvement over the initial examination ($p < 0.01$).

The Panel doubts that thymol is effective as a single active ingredient for treating acne. This ingredient has little or no antibacterial activity in the concentrations currently used in OTC acne products. To the Panel's knowledge, the effectiveness of this ingredient for treating acne has never been established in a vehicle-controlled clinical trial. Thymol is not listed in

standard medical texts as beneficial in acne therapy. The Panel concludes that thymol is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* In the absence of data evaluating the effectiveness of thymol in a vehicle-controlled study for the treatment of acne, the Panel has placed thymol in Category II for effectiveness.

References

- (1) OTC Volume 070002.
- (2) OTC Volume 070155.
- (3) OTC Volume 070156.

v. *Vitamin E.* The Panel concludes that vitamin E is not effective and that there are insufficient data available to determine its safety for OTC topical use in the treatment of acne.

(1) *Safety.* Vitamin E (alpha-tocopherol acetate) is a naturally occurring oil found primarily in plant materials (Ref. 1). The highest concentrations are found in wheat germ, sunflower seeds, soybean oils, and other plant sources. Deficiency of this vitamin in animals results in symptoms which closely resemble various conditions in the human that allegedly benefit from vitamin E therapy. These include disorders of the reproductive, muscular, cardiovascular, and hematopoietic systems (Ref. 2). (Hematopoietic refers to the production of blood cells.)

There are no notable pharmacological or toxicological effects of oral vitamin E, nor any explanation of its mode of action. Presumably, it exerts its effect by virtue of its properties as an antioxidant (Ref. 2). This concept is supported by observations on the protective effect of vitamin E against the lethality of carbon tetrachloride, mediated by lipid peroxidation (Ref. 3).

Vitamin E is absorbed like other fat-soluble vitamins, entering the blood stream by way of the lymph, and is distributed to all tissues. It is excreted primarily by the liver. Some metabolic derivatives, though, are found in the urine (Ref. 2). Numerous experiments indicate that high dietary intakes of vitamin E are apparently without toxic side effects (Ref. 4). Up to 800 I.U. (about 600 mg) per day for 3 years has been consumed in these studies.

Topical vitamin E is rated 0 to 1 as an irritant and 3 to 4 as a sensitizer. According to Fisher (Ref. 5), vitamin E was a sensitizer when used in an antiperspirant. Sensitization is more of a problem when the ingredient is occluded but also occurs when vitamin E is applied to the face. The risk of sensitization increases when vitamin E is used with a second preparation which causes peeling.

Because this vitamin accumulates in the body, has an unknown mechanism of action, and has some potential for sensitization, the Panel concludes that vitamin E used topically is of questionable safety.

(2) *Effectiveness.* The effectiveness of vitamin E used as a single ingredient in treating acne has never been established in a well-controlled clinical trial.

Nikolowski (Ref. 6) stated that acne vulgaris responds to combined vitamin E and vitamin A treatment. However, he was referring to systemic and not topical use of these drugs. In a later publication, Nikolowski (Ref. 7) stated that "alone and in combination with vitamin A and nicotinamide (vitamin E) is helpful in treating kraurosis, purpura, roentgen therapy, acne vulgaris * * *"

Schuppener (Ref. 8) successfully treated 93 acne patients with a combination of 0.1 percent vitamin E, 1 percent sulfur, 0.003 percent estradiol, 0.3 percent prednisolone, and vitamin A 50,000 I.U./100 mL in an ointment base. It is not clear which of the ingredients in the combination was responsible for the results.

The Panel believes there is no rationale for using vitamin E in topical acne therapy. The Panel concludes that vitamin E is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed vitamin E in Category II because the effectiveness of this ingredient in acne has not been demonstrated in a controlled clinical trial.

References

- (1) Windholz, M., et al., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1290, 1976.
- (2) Cohn, V. H., "Fat Soluble Vitamins: Vitamin K and Vitamin E," in "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 1595-1598, 1975.
- (3) Plaa, G. L., "Toxicology of the Liver," in "Toxicology: The Basic Science of Poisons," Edited by L. J. Casarett and J. Doull, MacMillan Publishing Co., New York, p. 181, 1975.
- (4) Scott, M. L., "Vitamin E," in "The Fat-Soluble Vitamins," Edited by H. DeLuca, Plenum Press, New York, p. 195, 1978.
- (5) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, p. 419, 1973.
- (6) Nikolowski, W., "Vitamin E in Dermatology and Related Fields," *Parfumerie und Kosmetik*, 37:65-68, 1956.
- (7) Nikolowski, W., "Vitamin E and its Indication for the Treatment of Skin Disease," *Medizinische Klinik*, 55:415-418, 1960.
- (8) Schuppener, H. J., "On the Clinical Aspects and Modern Therapy of Acne. Experience with a New Anti-Acne Agent,"

Deutsches Medizinisches Journal, 17:711-714, 1966.

v. Zinc salts (zinc oxide, zinc stearate, and zinc sulfide). The Panel concludes that the zinc salts (zinc oxide, zinc stearate, and zinc sulfide) are safe but are not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Zinc oxide, zinc stearate, and zinc sulfide are insoluble compounds of zinc. It is recognized that a small amount of zinc sulfide may be converted into the soluble zinc sulfate.

Several submissions were reviewed by the Panel, but none contained any toxicity data on the zinc compounds. It has long been recognized that the soluble zinc salts (zinc sulfate and zinc chloride) can cause toxicity when ingested and are somewhat corrosive on the skin. These salts have not been used topically in acne treatment and will not be discussed here. Oral zinc was discussed earlier in this document. (See part II, paragraph G. above—Use of Oral Zinc in the Treatment of Acne.)

Zinc stearate has a relatively long history of use in baby powders. Upon ingestion, it has "a low order of toxicity" (Ref. 1). Topically, salts of zinc have been used as astringents and mild "antiseptics," probably through the precipitation of protein by the zinc ion. Zinc salts have been incorporated into ointments, powders, and pastes and used as absorbents and protectives on epithelial surfaces, ulcers, and wounds (Ref. 2).

Gosselin et al. (Ref. 3) gave the insoluble zinc salts an estimated toxicity rating of 3, meaning that they are "moderately toxic" with a probable oral lethal dose of 0.5 to 5 g/kg. However, this was only an estimate, because, according to Gosselin et al., acute oral toxicity data could not be located. Aspiration of zinc stearate powder has produced fatal pneumonitis in infants. Powdered zinc oxide, however, does not cause a pulmonary reaction. Heat volatilization of zinc produces fine airborne particles of zinc oxide. Inhalation of freshly formed fumes may cause "fume fever," an influenza-like illness (Ref. 3).

McNally (Ref. 4), in a review on zinc toxicity, pointed out that zinc is normally found in the tissues of the human body and plants as well as being a common constituent in many foods. As much as 200 mg zinc was excreted by a human who had been fed a zinc-enriched meal the previous day.

Zinc sulfide lotion, an official topical preparation in Great Britain for many years, has been used in acne treatment (Ref. 5). This lotion is a mixture of various zinc sulfides, including

polysulfides, and probably exerts its action on the skin as an astringent zinc salt. Zinc sulfide is reported to liberate hydrogen sulfide and elemental sulfur when placed in contact with water such as might be present on the skin (Ref. 6). The amount of hydrogen sulfide released is unknown but is thought to be below toxic levels. The Panel views this compound as elemental sulfur and considers it safe. (See part III, paragraph A.1.b. above—Sulfur.)

Despite the scarcity of toxicity data on zinc compounds, their long history of topical use without reported ill effect has led the Panel to conclude that these ingredients are safe for the treatment of acne.

(2) *Effectiveness.* The zinc salts have been used as astringents, protectives, and antiseptics.

In the past, white lotion (lotio alba) containing zinc sulfate, sulfated potash, and water was frequently prescribed for the treatment of mild acne (Ref. 7). This lotion should be freshly compounded because it is unstable. It has an unpleasant odor and may cause excessive drying and redness of the skin.

It appears that any beneficial effect of white lotion in dermatologic conditions results primarily from the sulfur content of the lotion. Guth and Mansour (Ref. 8) stated that when it was freshly prepared, white lotion contained zinc monosulfide, zinc polysulfide, zinc hydroxide, and free sulfur suspended in a solution of sulfate, thiosulfate, and potassium ions. Exposure of the lotion to ultraviolet light or sunlight resulted in the formation of hydrogen peroxide which oxidized sulfides to sulfates and sulfates. When the lotion ages, there is a marked increase in free sulfur in its contents.

No effectiveness data on zinc salts were contained in the submissions to the Panel. To the Panel's knowledge, these ingredients have never been studied in a clinical setting for the treatment of acne.

The Panel concludes that there are no data to show that zinc salts are effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed the zinc salts (zinc oxide, zinc stearate, and zinc sulfide) in Category II because the effectiveness of these ingredients in treating acne has not been established in a controlled clinical trial.

References

- (1) Deichmann, W. B., and H. W. Gerarde, "Toxicology of Drugs and Chemicals," Academic Press, New York, p. 639, 1969.
- (2) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th

Ed., MacMillan Publishing Co., New York, pp. 948 and 1000-1001, 1975.

(3) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, pp. 69-70 and 99, 1976.

(4) McNally, W. D., "Medical Jurisprudence and Toxicology," W. B. Saunders Co., Philadelphia, pp. 192-196, 1939.

(5) Blacow, N. W., "Martindale, The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, p. 455, 1972.

(6) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 9th Ed., Lange Medical Publications, Los Altos, CA, p. 246, 1977.

(7) Lubowe, I. L., "Modern Drugs in Dermatology," *Clinical Medicine*, 78:31-35, 1971.

(8) Guth, E. P., and Z. Mansour, "Photochemical Formation of Hydrogen Peroxide in White Lotion U.S.P.," *Journal of Pharmaceutical Sciences*, 56:376-379, 1967.

2. Category II labeling. The Panel concludes that certain labeling claims related to safety or effectiveness of an ingredient are unsupported by scientific data or, in some instances, by sound theoretical reasoning. The Panel therefore concludes that such labeling should be removed from the market.

Many claims from current labels have been placed in Category II either because they are vague, too broad, incomplete, modified incorrectly, or do not specifically indicate that the product effectively treats acne. Such labels mislead the lay person.

Many claims would appear to be acceptable; however, certain modifying words can make these claims unclear or even imprecise. For this reason, modifiers such as "fast" are not allowed. Examples of labels with vague modifiers include the following:

"Clears up more pimples faster."
"Fights blemishes fast."
"Works fast against surface pimples."
"Clinically proven for prompt effective relief of acne."
"Instantly active medicated cream for acne pimples."
"Speeds up gentle, natural peeling of acne pimples."

Because the following labeling claims do not specifically indicate that the product effectively treats acne or imply that the product treats conditions other than acne, the Panel considers them misleading to the lay person:

"Helps prevent skin infections."
"Degerming."
"For temporary relief of minor soreness, irritations, and itching."
"Anesthetic."
"Pain-relieving antiseptic for the skin."
"Designed to protect against infection while it relieves local soreness, irritations, and dryness."

"Temporary relief of surface pain and discomfort."

"Helps clear up complexion problems."

"It not only goes to work drying out your pimples and blackheads, it does much more."

"Promotes healing."

"Aids healing."

"Helps heal acne and other minor skin conditions."

"Helps clear acne and related skin blemishes."

"Makes externally caused skin flare-ups look better while they're getting better."

The Panel believes that the following labeling claims are either inaccurate or not clear or may be meaningless to the consumer:

"Helps pull loosened oils from pores."

"Helps prevent the reinfection of pimples."

"Minimizes redness and itching."

"Aids in removing greasy oils from your skin. This can prevent the pores from becoming clogged again."

"Hypoallergenic."

"Bactericide."

"Hypoacnegenic."

"An effective antimicrobial against a wide variety of both gram positive and gram negative bacteria and fungi."

"Scientific treatment (or formula)."

"Vitaminized."

"Antiseptic."

"Special ingredients help dry the acne pimple."

"Special medicated skin cleanser."

"Erases worn out cells."

"Dermatologist-tested."

"Dries quickly to give long-term medication."

"Helps heal and clear acne by molecular action."

"100% medication, not a cosmetic."

"Continues to work over a longer period of time."

"Fights acne pimples."

"Kills facial germs."

"Kills germs commonly associated with acne."

"Strips away oils and waxy buildup that can lead to pimples and blackheads."

"Drinks up excess oils."

"Benefits oily and acne-blemished skin."

"Aids in the removal of superficial dry skin."

"Produces a soft, light peeling of the skin."

"Allows healthy new skin to grow."

"Helps normalize underlying tissue."

"Minimizes scarring."

"Anti-irritant."

"Helps involute inflamed pustules."

"Promoted involution of acne lesions and stimulates healing of the underlying

tissues after effectively debriding any necrotic tissue which may be present."

"Bacteriostatic action, especially against Staph bacteria usually present in cases of infected acne lesions."

"Combines the same type of medications prescribed by many leading skin specialists for external application to pimples and blemishes associated with acne."

"Contains time-proved ingredients."

"For mild acne or maintenance therapy."

"Unique base keeps the medication in close contact to the skin all day long."

C. Category III Conditions

These are conditions for which the available data are insufficient to permit final classification at this time.

The safety and efficacy of the following ingredients were classified on the basis of activity and use as ingredients for the treatment of acne. Ingredients for which no acne claim is made, including ingredients that have been reviewed by the Panel and are ultimately placed in Category II for efficacy, may still be included in formulations for purposes other than the treatment of acne providing these ingredients are safe at the concentrations used.

1. Category III active ingredients.

Povidone-iodine
Salicylic acid

a. Povidone-iodine. The Panel concludes that povidone-iodine is safe but that there are insufficient data available to determine its effectiveness for OTC topical use in the treatment of acne.

(1) **Safety.** Povidone-iodine is a complex of iodine with a carrier agent, povidone (polyvinylpyrrolidone), which liberates free iodine in solution. The Panel reviewed the safety of povidone-iodine in its recommendations on topical antifungal drug products published elsewhere in this issue of the *Federal Register*. Povidone-iodine is considered safe for topical antifungal use in concentrations up to 10 percent. However, because the Panel concluded that in some instances iodine may be an irritant or sensitizer, particularly with long-term use and under occlusion, a caution label was recommended.

Povidone-iodine was submitted for the treatment of acne at a concentration of 7.5 percent in a detergent vehicle. The Panel concludes that povidone-iodine is safe for OTC topical use in the treatment of acne. Again, a caution on irritation is recommended.

(2) **Effectiveness.** Povidone-iodine is an antimicrobial agent that has been

widely used on wounds, burns, and abrasions to treat or prevent surface infection. It has also been used as a scrub before and after surgery. Povidone-iodine contains about 10 percent available iodine.

Millikan (Ref. 1) evaluated the effectiveness of 7.5 percent povidone-iodine in two studies on acne patients. In the first study, povidone-iodine was compared to its vehicle control in a double-blind fashion. Patients with mild acne washed two or three times daily with one of the treatments for 3 to 4 months. Evaluation was based on global impression. At the time of the study, 9 of the 10 patients using povidone-iodine were considered improved or much improved. In the control group, three out of seven patients were rated as improved.

Millikan (Ref. 1) also studied 27 patients with Grade II to IV acne (grading system based on type and location of lesions). Povidone-iodine was compared to the vehicle control, but in this study all patients also received systemic tetracycline concomitantly. There was no significant difference in effectiveness between the vehicle and povidone-iodine. The author concluded that the oral tetracycline was responsible for this result.

Brown (Ref. 2) used a 7.5-percent povidone-iodine foam to treat 32 patients who had mild to moderate acne. The patients used the preparation twice daily for at least 6 months. Methods of evaluating patients were not defined. Of the 10 subjects using only povidone-iodine, 8 were good or fair at the conclusion of the trial. The remaining 22 patients used concomitant therapy including oral tetracycline, oral contraceptives, topical agents, and ultraviolet light. In this group, 19 patients showed a favorable response, but it is impossible to determine which ingredient produced this result.

In an uncontrolled study, Hudson (Ref. 3) evaluated the effectiveness of 7.5 percent povidone-iodine in 500 patients with moderate to severe acne. Patients washed with povidone-iodine one to three times daily for 3 months to more than 1 year. Tetracycline and sulfur lotions were used in addition to povidone-iodine. Hudson reported that the skin looked and felt less oily and that patient reaction was not defined and specific treatment results were not reported.

In an unpublished study (Ref. 4), 10 patients with Grade III acne (grading system was not defined) were treated twice daily with 7.5 percent povidone-iodine. A vehicle control was not used in this study. Patients were assessed by global impression 2 weeks after

treatment and 4 weeks after treatment. All patients showed good or fair improvement. Lesion counts at the final visit compared to baseline showed decreases of 79 percent for pustules, 28 percent for open comedones, 18 percent for closed comedones, and 20 percent for papules.

The studies described above indicate that povidone-iodine may be an effective acne treatment; however, none of the studies met the Panel's effectiveness criteria. Deficiencies in study design included one or more of the following: (1) Lack of vehicle control, (2) concomitant therapy used, and (3) method of evaluating patients and treatment results not well defined. Also, none of the studies included a statistical analysis of results. Other studies were reviewed by the Panel (Ref. 4), but are not detailed here because they were not controlled and included concomitant therapy. The Panel concludes that povidone-iodine is of questionable effectiveness in the treatment of acne.

(3) *Proposed dosage*—(i) *Concentration*. Povidone-iodine 7.5 percent.

(ii) *Directions for use*. See part III, paragraph A.2. above—Category I labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for products used in the treatment of acne. (See part III, paragraph A.2. above—Category I labeling.)

Cautions should include the following statement: "If redness or itching occurs or persists, discontinue use and consult a doctor or pharmacist."

(5) *Evaluation*. The Panel recommends that studies be conducted to determine the stability of povidone-iodine and availability of elemental iodine from the complex. The Panel also recommends one double-blinded, vehicle-controlled clinical trial to determine the effectiveness of povidone-iodine in the treatment of acne. These studies should be conducted in accordance with the guidelines set forth below for OTC topical acne ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Millikan, L. E., "A Double-Blind Study of Betadine Skin Cleanser in Acne Vulgaris," *CUTIS: Cutaneous Medicine for the Practitioner*, 17:394-398, 1976.
- (2) Brown, E. J., "A Povidone-Iodine Skin Cleanser Foam in the Management of Acne Vulgaris," *British Journal of Clinical Practice*, 31:218-219, 1977.
- (3) Hudson, A. L., "Betadine Skin Cleanser in Acne Vulgaris. Skin pH Determinations," *Clinical Trials Journal*, 10:23-25, 1973.
- (4) OTC Volume 070239.

Salicylic acid. The Panel concludes that salicylic acid is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical use in the treatment of acne.

(1) *Safety*. Salicylic acid and its derivatives are a widely used group of compounds. Whether the salicylates are administered orally, rectally, intravenously, or cutaneously, systemic absorption occurs. Whatever the mode of administration, the toxic effects from overdosage are essentially the same, i.e., nausea, decreased ability to hear, tinnitus (ringing in the ears), confusion, metabolic disturbances, hallucinations, and death. The possible toxic reactions are collectively known as salicylism.

The Panel reviewed the toxicity of salicylic acid in its recommendations on topical antifungal drug products published elsewhere in this issue of the *Federal Register*. Those data will not be repeated here. This discussion will include data dealing with salicylic acid in the treatment of acne or data received by the Panel since it completed its recommendations on topical antifungal drug products.

The major difference in the use of salicylic acid in acne as opposed to its use in fungal infections of the foot or groin is the very large surface area over which acne may be involved. In fact, roughly half of the body surface could be afflicted with acne. In adult humans, this would amount to close to 1 square meter of absorptive surface area.

Salicylic acid has been applied to relatively small areas of skin or in concentrations of less than 10 percent without apparent ill effects as a keratolytic agent in the treatment of various skin disorders. Salicylic acid for topical use on acne will be considered in concentrations ranging from 0.5 to 5 percent.

Most of the reports submitted for the use of salicylic acid in acne evaluated combination ingredient products. However, the following new data on salicylic acid as a single ingredient were contained in two submissions (Refs. 1 and 2). The acute oral LD₅₀ of salicylic acid in male Sprague-Dawley rats was 800 mg/kg. When concentrations of 0.5 to 2 percent were applied to either normal or abraded skin of rabbits, salicylic acid was judged to be a mild irritant.

A lotion containing salicylic acid 2 percent was applied to normal and abraded rabbit skin at a rate of 2 mL/kg and held under occlusion for 24 hours (Ref. 3). If a rabbit weighed 2 kg, then it received 4 mL of the 2-percent lotion, amounting to a total of 80 mg salicylic

acid. There were no signs of acute toxicity in any of the test animals.

When an undiluted 2-percent salicylic acid lotion was applied to the eyes of rabbits and allowed to remain in the eye, the lotion was found to be an eye irritant. When the lotion was immediately washed out after application, there was no irritation (Ref. 3).

Five mL/kg of the lotion administered by oral gavage to female rats caused no toxic symptoms (total salicylic acid dose, 100 mg per 200 g rat). In mice the acute oral LD₅₀ of the lotion was 32 mL/kg, or a total dose of approximately 666 mg/kg (Ref. 3).

In humans, a blood concentration of 30 to 50 mg salicylic acid per 100 mL is considered to be toxic (Ref. 4). If a human applied 15 g of a 5-percent salicylic acid preparation to the entire upper torso, the amount of salicylic acid available for absorption would be 750 mg. If all of this were instantly absorbed and distributed into 7 L of blood, the blood concentration would be approximately 10 mg/100 mL. Blood concentrations of 6.5 mg to 15 mg/100 mL have been reported to be nontoxic (Refs. 4 and 5). Based on this calculation and the data submitted, the Panel concludes that preparations containing up to 5 percent concentrations of salicylic acid would be safe for use in treating acne.

(2) *Effectiveness.* Salicylic acid has been used for over 100 years in the treatment of acne and various keratinizing diseases. It is used alone or often in combination with sulfur or resorcinol. Despite its long history of use, the exact mechanism of action has never been determined and, in fact, no study has documented the efficacy of salicylic acid used as a single ingredient in the therapy of acne.

An extensive review of the medicinal uses and pharmacologic properties of salicylic acid was published in a series of three articles co-authored by Weirich, Longauer, and Kirkwood (Refs. 6, 7, and 8). Weirich and his associates described 10 specific pharmacological properties of salicylic acid and offered many reference sources to document their viewpoints. These properties included action such as germicidal, photoprotector, astringent, antipruritic, and anti-inflammatory. Other properties discussed were a deep keratolytic action at concentrations greater than 5 percent, a superficial surface keratolytic action at 1 to 4 percent, and an acidifying effect at 0.1 percent and above. The ability to produce an increase in penetration of topical drugs was also described. It is not certain which, if any, of these qualities is responsible for the clinical

responses noted in acne. It is usually assumed, however, that salicylic acid is working as a keratolytic agent and possibly as a substance which promotes the penetration of other active ingredients. Shalita (Ref. 9), Leyden (Ref. 10), and Plewig and Kligman (Ref. 11) believe that salicylic acid, in addition to its keratolytic and anti-inflammatory action, has a comedolytic effect; that is, it causes an increased turnover of follicular epithelial cells and an apparent decrease in the cohesiveness of these cells when they are shed into the cavity of the follicle.

A commercial product containing 2 percent sulfur and 2 percent salicylic acid in a cream base has been studied in numerous investigations (Refs. 12, 13, and 14). One study was conducted to show the effectiveness of this preparation in seborrhea associated with acne. Robinson (Ref. 12) treated 120 patients using either a cake or cream containing 2 percent sulfur and 2 percent salicylic acid. Although the specific details of the study were not given, the investigator noted, " * * * (the) cake and cream quickly dried the skin and were particularly helpful in cleansing comedones."

In another study, Riley (Ref. 13) treated 150 acne patients with a salicylic acid-sulfur combination. Depending upon the severity of the acne condition, the treatment also included a restricted diet, ultraviolet light, acne surgery, astringents, colloidal sulfur, oral vitamin A, oral antibiotics, or X-ray therapy. All patients were instructed to wash their faces with ordinary soap for the first 2 weeks. At the end of the 2-week preliminary phase, patients showing little improvement were continued on the same therapeutic routine except for washing with a 2-percent salicylic acid-2 percent sulfur cream or cake instead of soap. The patients used the salicylic acid-sulfur combination one to four times daily for 4 to 12 months. The method of evaluating patients was not explained. Results showed a good response in 147 patients. The salicylic acid-sulfur combination was helpful in one patient, but two others had a poor response. Riley concluded that the cream or cake containing salicylic acid and sulfur did contribute to the improvement of acne vulgaris. However, the study made no mention of blinding or randomization, and the results were not evaluated statistically.

Baird (Ref. 14) treated 371 patients with acne vulgaris, with 133 cases classified as severe and 238 as moderate. All patients followed a simple, restricted diet, washed their faces with the 2-percent salicylic acid-2 percent sulfur cream, and were treated

with acne surgery. In addition, the severe cases may have been treated with X-rays, oral antibiotics, staphylococcus vaccines, or estrogenic hormones. In conclusion, the investigator stated that the simplified treatment plan improved all the mild to moderate cases of acne. In the severe cases, the author believed that scrubbing with the cream shortened the course of therapy. However, the study made no mention of vehicle control, blinding, randomization, or statistical analysis.

In another study, using a randomized but not blinded method, 109 patients were treated once or twice daily with a 2-percent salicylic acid lotion or a commercially available soap (Ref. 3). Patients included in the study had mild to moderate acne. They were evaluated by global assessment after 4, 7, and 14 days. After 14 days the lotion proved to be significantly superior to the soap for reducing blackheads ($p = 0.029$). There were no statistically significant differences between the two products in the frequency of "breaking out" in acne blemishes, in improvement in overall condition, or in reduction of blemishes (inflammatory lesions). The researchers considered 14 days inadequate to evaluate the frequency of "breaking out." Consequently, a somewhat similar study of 117 patients with mild to very severe acne was conducted for 3 months. The study was blinded.

In this 3-month study, patients were untreated for 2 weeks before enrollment in the study (Ref. 3). After evaluation, they were randomly assigned to the 2-percent salicylic acid lotion (57 patients) or the commercially available soap (60 patients). Patients were treated once or twice daily depending upon the severity of their acne and the oiliness of their skin. The severity of blackheads, pimples, and oiliness was measured as 0=absent, 1=mild, 2=moderate, 3=severe, and 4=very severe. The overall clinical evaluation showed good to excellent results in 72.2 percent of the patients treated with salicylic acid compared with 10.5 percent of those who had used the soap. The group using the salicylic acid lotion had a statistically significant greater improvement than the group using the soap ($p < 0.001$). More importantly, fewer blackheads and pimples were observed in the lotion-treated group. The average reduction in "severity units" at 3 months compared with baseline for salicylic acid was 1.28 for blackheads and 1.41 for pimples. For soap the average reduction was 0.37 for blackheads and 0.19 for pimples. These results were statistically significant at

the $p < 0.001$ level. This was a well-designed study; however, lesion counts were not used and the control was not the vehicle used in the 2-percent salicylic acid lotion.

Another study was conducted using a lotion containing 2.2 percent salicylic acid and 2.2 percent resorcinol in an ethyl alcohol vehicle (Ref. 15). Sixteen patients were treated for 2 months using a twice-daily regimen. Evaluation was by lesion counts. After 2 months, reduction in lesion counts was 42.9 percent for blackheads, 43.8 percent for whiteheads, 66.2 percent for pustules, and 31.0 percent for cysts. Slight to marked improvement was noted in 81 percent of the patients. However, there were no controls or randomization and the study was not blinded.

In another study (Ref. 16), 44 adolescent males with mild to moderate acne were treated twice daily for 2 weeks with a preparation containing 0.5 percent salicylic acid. There was no mention of other treatments, how the evaluations were done, whether the study was blinded, or whether a vehicle control was used. At the end of the study, 57 percent of the patients showed improvement in overall severity of acne. A decrease in facial oiliness was noted in 77 percent. Seventy-three percent of the patients showed a decrease in the amount of pressure needed to express comedones. The investigator concluded that 0.5 percent salicylic acid was effective in the treatment of mild acne.

The effectiveness of 0.5 percent salicylic acid was also evaluated in an unpublished, single-blind trial of 120 patients. Patients with mild to moderate acne were treated with either 0.5 percent salicylic acid, a commercial product containing 6 percent sulfur and 1.5 percent resorcinol, or soap. Application was made twice daily for 3 weeks. No other topical or systemic treatment was allowed. Patients were evaluated by global impression. At the end of the trial, the two active treatments were found to be significantly more effective than soap in effecting overall improvement, decreasing oiliness, and making it easier to express comedones ($p < 0.01$) (Ref. 17).

In a single-blind study, patients with Grade I to III acne (grading system was not specified) were treated with either 0.25 or 0.5 percent salicylic acid. Each treatment group contained 50 patients. Patients applied the solutions once daily for 6 weeks. The method of patient evaluation was not described. At the end of the study, improvement was noted in 70 percent of the group receiving the 0.5-percent concentration. Fifty-four percent of the patients treated with 0.25 percent salicylic acid were

reported as improved. Although the results were not statistically analyzed, the investigator concluded that the 0.5-percent solution was superior to the 0.25-percent solution (Ref. 18).

In a study of 95 patients, treatment with 0.5 percent salicylic acid lasted for 1 to 8 months. Patients entered into the study had Grade I to III acne (grading system based on type of lesion). Controls were not used and methods of evaluation were undefined. Results showed good to excellent improvement in 25 percent, satisfactory improvement in 38 percent, and no improvement in 37 percent (Ref. 18).

In a double-blind, randomized trial, 49 patients with Pillsbury Grade I to II acne were studied. A medicated pad containing 0.5 percent salicylic acid in an alcoholic detergent solution was compared with placebo (pads soaked in buffered water). No systemic therapy was used, and soap and water was the only other topical treatment.

Patients were evaluated before treatment and at 4, 8, and 12 weeks by lesion counts and global evaluation. After 12 weeks, inflammatory lesions were reduced by 54 percent in the salicylic acid group and 29 percent in the placebo group. This difference was significant ($p = 0.005$). Salicylic acid also reduced open comedones by 39 percent compared with placebo, 28 percent ($p < 0.05$). There was no significant difference between treatments on closed comedones (Ref. 19). The Panel notes that this study did not use a vehicle control.

A 0.5-percent salicylic acid solution has been evaluated in five other trials involving 282 patients with mild to moderate acne (Ref. 18). Vehicle controls were not used in any of these studies. Although none of the studies included a statistical analysis of results, all indicated that 0.5 percent salicylic acid reduces the severity of acne and oiliness of the skin. Also, comedones were easier to express.

Various other submissions discussed combinations of salicylic acid but none provided any specific data; however, the general medical literature contains several pertinent articles. Kaidbey and Kligman (Ref. 20) used 50 percent crude coal tar with plastic occlusion to induce the formation of comedones on 12 subjects' backs. Comedones produced this way remain evident on the skin for months. Therefore, any reduction of comedones is considered attributable to the peeling agents and not to time.

After 2 to 4 weeks of applying the crude coal tar followed by 2 weeks of no application, the patients were treated with a wide variety of peeling agents. The comparative comedolytic activity in

order of decreasing effectiveness was 0.1 percent tretinoin, 15 percent salicylic acid, 10 percent benzoyl peroxide, and 15 percent trichloroacetic acid. Neither the ethanol control nor a combination of 5 percent sulfur and 2 percent resorcinol showed comedolytic activity. A 15-percent salicylic acid preparation applied topically twice daily for 6 weeks resulted in a greater than 50 percent reduction in the number of comedones. This model is valuable only for comparing agents that are capable of dislodging or reducing the size of the comedones.

Davies and Marks (Ref. 21) studied the effects of varying concentrations of salicylic acid on normal skin of the thigh or the forearm. The strengths applied were between 2 and 12 percent in either a water-washable base or in white paraffin. Vehicle controls were applied to the opposite thigh and forearm. The patients were treated twice a day for 1 week and then biopsied. No changes were apparent except when the electron microscope was used to examine the biopsies. Using this technique, Davies and Marks noted "striking differences" in the outer layer of the skin which had been treated with 6 to 12 percent concentrations of salicylic acid. This study was undertaken in the hope of determining the exact action of salicylic acid on the skin. The authors' theory was that salicylic acid preparations enhance the shedding of the outer layer of skin by dissolving the material which holds the cells together.

The Panel concludes that salicylic acid is of questionable effectiveness as a single ingredient in the treatment of acne. Although considerable clinical experience as well as uncontrolled studies suggest that salicylic acid is an effective ingredient, there has been no vehicle-controlled, double-blind study to confirm salicylic acid's effectiveness in the treatment of acne.

(3) *Proposed dosage*—(i) *Concentration*. Salicylic acid 0.5 to 5 percent.

(ii) *Directions for use*. See part III, paragraph A.2. above—Category I labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for products used in the treatment of acne. (See part III, paragraph A.2. above—Category I labeling.)

(5) *Evaluation*. The Panel recommends one double-blind, vehicle-controlled clinical trial to determine the effectiveness of salicylic acid in the treatment of acne. This study should be conducted in accordance with the guidelines set forth below for OTC topical acne ingredients. (See part III.

paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) OTC Volume 070088.
- (2) OTC Volume 070090.
- (3) OTC Volume 070188.
- (4) Sautter, R. D., J. A. Buckwalter, and S. E. Ziffren, "Chemicals and Enzymes in Debridement of Thermal Burns," *American Medical Association Archives of Surgery*, 76:744-748, 1958.
- (5) Von Weiss, J. F., and W. F. Lever, "Percutaneous Salicylic Acid Intoxication in Psoriasis," *Archives of Dermatology*, 90:614-619, 1964.
- (6) Weirich, E. G., "Dermatopharmacology of Salicylic Acid. I. Range of Dermatotherapeutic Effects of Salicylic Acid," *Dermatologica*, 151:268-273, 1975.
- (7) Weirich, E. G., J. K. Longauer, and A. H. Kirkwood, "Dermatopharmacology of Salicylic Acid. II. Epidermal Antihyperplastic Effect of Salicylic Acid in Animals," *Dermatologica*, 151:321-332, 1975.
- (8) Weirich, E. G., J. K. Longauer, and A. H. Kirkwood, "Dermatopharmacology of Salicylic Acid. III. Topical Contra-Inflammatory Effect of Salicylic Acid and Other Drugs in Animal Experiments," *Dermatologica*, 152:87-89, 1976.
- (9) Shalita, A., et al., "Acne," *Journal of Investigative Dermatology*, 73:434-442, 1979.
- (10) Leyden, J. J., "Human Comedolytic Assay," unpublished study, included in OTC Volume 070242.
- (11) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, pp. 277-278, 1975.
- (12) Robinson, A. M., "A New Treatment for Seborrhea and Allied Skin Conditions (Fostex)," *Journal of the South Carolina Medical Association*, 52:253-254, 1952.
- (13) Riley, K. A., "Therapeutic Skin Washing in Seborrhea and Acne Vulgaris," *Medical Times*, 86:973-977, 1958.
- (14) Baird, J. W., "Acne. A New Approach to an Old Problem," *Journal of Pediatrics*, 52:152-157, 1958.
- (15) OTC Volume 070191.
- (16) OTC Volume 070083.
- (17) OTC Volume 070181.
- (18) OTC Volume 070242.
- (19) OTC Volume 070286.
- (20) Kaidbey, K. H., and A. M. Kligman, "Effectiveness of Peeling Agents on Experimental Open Comedones," *CUTIS; Cutaneous Medicine for the Practitioner*, 16:53-56, 1975.
- (21) Davies, M., and R. Marks, "Studies on the Effect of Salicylic Acid on Normal Skin," *British Journal of Dermatology*, 95:187-192, 1976.

2. Category III Labeling. None.

D. Combination Products Used in the Treatment of Acne

The Panel concurs with the rationale expressed in the OTC drug combination policy regulation (21 CFR 330.10(a)(4)(iv)) as follows:

An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective

when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety of effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel concludes that combination products for the treatment of acne should contain the minimal number of active ingredients necessary to achieve effectiveness. In general, the fewer the ingredients, the safer and more rational the therapy. Consumer interests are best served by exposure to the fewest ingredients possible at the lowest possible dosage regimen that is consistent with a satisfactory level of effectiveness.

In the past, combinations of ingredients were based largely on personal experience and testimonials. The Panel believes, however, that combinations should be based on clinical trials. In order to achieve the goal of efficacy consistent with exposure to the least number of ingredients, the Panel considered only those studies that demonstrated each ingredient's contribution to the efficacy of the complete combination. The Panel realizes that such a clinical trial for Category III combinations to move to Category I will require a substantial effort. The study should be designed so that each single active ingredient makes a statistically significant contribution to the efficacy of the combination, and the combination itself should be more effective than the vehicle control.

1. *Category I combination drug product—Sulfur resorcinol.* The Panel concludes that a combination of 8 percent sulfur with either 2 percent resorcinol or 3 percent resorcinol monoacetate is safe and effective for OTC use in the treatment of acne. Sulfur and resorcinol are often used together in the treatment of acne, but it is difficult to document the historical origin of this combination. The precise mechanism of action of these combinations has never been proven, but it may depend on keratolysis or the ability to produce erythema and desquamation with enhanced resolution of comedones, papules, and pustules.

A half-face study was conducted on 25 males (Ref. 1). After washing the entire face with soap and water, the patients applied a cream containing 8 percent sulfur and 2 percent resorcinol to half of the face three times daily for 3 weeks. No other therapy was allowed. The weekly evaluation was based on clinical impression with acne rated as

slight, moderate, or severe. The sulfur-resorcinol combination was found to significantly improve acne at 1 and 2 weeks when compared to no treatment ($p < 0.001$).

In a single-blind, half-face trial, the effectiveness of 8 percent sulfur-2 percent resorcinol cream was studied in 28 subjects (Ref. 1). The patients applied the combination to one side of the face and a placebo lotion to the other side twice daily. The only other therapy allowed during the 8-week treatment period was soap and water. Patients were evaluated by global impression. After 8 weeks, the side of the face treated with the sulfur-resorcinol cream was improved in 75 percent of the cases. Improvement on the placebo side was noted in 46.4 percent of the patients. Sulfur-resorcinol was concluded to be effective in the treatment of acne.

Another single-blind study was conducted on 79 patients with Pillsbury Grade II or III acne (Ref. 1). Patients used no topical therapy for 2 weeks and no systemic therapy for 1 month before entering the study. They were divided into three treatment groups: (1) 8 percent sulfur-2 percent resorcinol cream, (2) "phosphate-stabilized" sulfur-resorcinol cream, and (3) no treatment. The patients applied the active medications twice daily. At regular intervals during the 12-week study they were evaluated by lesion counts and global impressions.

At the end of the treatment period, good to excellent results were reported for 44 percent of the group treated with sulfur-resorcinol, 38.5 percent of the group who had used the stabilized cream, and 17.4 percent of the no-treatment group. The investigators concluded that the sulfur-resorcinol formulations gave significantly better results than no treatment in reducing the overall severity of acne. No difference was noted between the three groups in reduction of comedones. The two active treatments showed significantly better results than no treatment in reducing inflammatory lesions.

In a half-face study of 25 patients with mild to moderate acne, 8 percent sulfur-2 percent resorcinol cream was compared to a placebo cream (Ref. 2). This study was randomized and single-blind. Before treatment there was a 4-week washout period during which no systemic or topical therapy was given. The patients were evaluated weekly with lesion counts and global assessments.

After 8 weeks of treatment, 12 patients were improved on the side of the face treated with sulfur-resorcinol and 1 patient improved on the side treated with the placebo. One patient

was worse on the side of the face treated with the placebo but had no change on the side treated with the combination. Seven patients had no change on either side of the face and four patients were worse on both sides.

Inflammatory lesions decreased 30.5 percent in the group treated with sulfur-resorcinol; in the control group the lesions increased 4 percent. Open comedones decreased 20.7 percent in the combination group and 1.8 percent in the control group. The statistical analysis showed that sulfur-resorcinol significantly decreased open comedones ($p < 0.05$), papules ($p < 0.001$), and pustules ($p < 0.005$) compared to placebo. There was no significant difference between the two groups for closed comedones, which actually increased during the course of the trial.

Another study evaluating the effectiveness of sulfur-resorcinol used four treatment groups of about 60 subjects each. The groups were as follows: (1) 2.66 percent sulfur-1 percent resorcinol, (2) 8 percent sulfur-2 percent resorcinol, (3) 2.66 percent sulfur, and (4) placebo. The patients included in the study had mild to moderate acne and were randomly assigned to a treatment group. No concurrent topical or systemic therapy was allowed. The creams were applied three times daily for 8 weeks. The patients were evaluated at 0, 2, 4, 6, and 8 weeks. Lesion counts were not used, but global assessment was based on the number of blackheads, whiteheads, papules, pustules, and on oiliness and overall complexion.

Results after 8 weeks showed that the two sulfur-resorcinol creams were equivalent and superior to the placebo and to sulfur alone in reducing papules and whiteheads. No differences in blackheads, pustules, oiliness, or overall complexion were noted between the four treatment groups. Also, there was no statistically significant difference between sulfur alone and the placebo in any category (Ref. 3).

Sulfur-resorcinol cream was compared to benzoyl peroxide in a half-face, single-blind study (Ref. 2). The vehicle of the benzoyl peroxide cream served as a control. The study included 50 institutionalized male patients with Pillsbury Grade II to III acne. The patients were allowed no other topical or systemic therapy. All medications were applied by dispensary personnel. Twenty-four patients had half of the face treated with 5 percent benzoyl peroxide and the other half treated with 8 percent sulfur-2 percent resorcinol. In the remaining patients, one side of the face was treated with benzoyl peroxide and the other side with the vehicle. Assignment of treatment and side of

application were randomized. Treatment was twice daily for 8 weeks. The patients were evaluated weekly by lesion counts and global assessments.

Final results showed that there was no significant difference between sulfur-resorcinol and benzoyl peroxide. Both sulfur-resorcinol and benzoyl peroxide were more effective than the vehicle in the reduction of pustules, open comedones, the closed comedones ($p < 0.01$ to $p < 0.001$).

A double-blind, randomized, multicenter trial was conducted in three European countries (Ref. 2). Patients were admitted to the study with Pillsbury Grade II to III acne. There was a 4-week washout period during which no therapy was allowed. Fifty-four patients were treated with 8 percent sulfur-2 percent resorcinol; 53 patients were treated with a sulfur-resorcinol combination plus 0.1 percent triclosan, an antibacterial agent.

The medications were applied twice daily for 8 weeks. Patients were evaluated by lesion counts every 4 weeks. Both treatments showed a statistically significant decrease in open comedones, closed comedones, total number of comedones, and inflamed lesions when the washout period was compared to the treatment period ($p < 0.05$ to $p < 0.01$).

Although resorcinol has been placed in Category II as a single ingredient because it is not effective, the Panel believes that resorcinol enhances the activity of sulfur. The Panel concludes that a combination of 8 percent sulfur with either 2 percent resorcinol or 3 percent resorcinol monoacetate is safe and effective in the treatment of acne but recommends that products containing this combination not be used on broken skin or over large areas of the body. The Panel recommends that sulfur-resorcinol combination products contain the following warning: "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body."

The Panel recommends that Category I combinations be labeled according to the Category I labeling for products used in the treatment of acne, as outlined elsewhere in this document. (See part III, paragraph A.2. below—Category I labeling.)

References

- (1) OTC Volume 070039.
- (2) OTC Volume 070236.
- (3) OTC Volume 070256.

2. *Category II combination drug product—Benzoyl peroxide-sulfur.* A combination is classified by the Panel as a Category II drug product, i.e., one that is not generally recognized as safe or

effective, if it contains any ingredient that is listed elsewhere in this document as a Category II ingredient for safety reasons. Although benzoyl peroxide and sulfur are Category I as single ingredients for OTC use in the treatment of acne, the Panel recommends that the benzoyl peroxide-sulfur combination be Category II because of the possibility of sensitization.

Combinations of benzoyl peroxide and sulfur are currently available by prescription only and the Panel does not recommend that these combinations be switched to OTC. However, a combination of 7.5 percent benzoyl peroxide and 5 percent sulfur was submitted for review. The Panel concludes that this combination is effective but is not safe for OTC topical use in the treatment of acne. Other concentrations of these two ingredients are used in prescription acne preparations and were submitted, but the effectiveness of these combinations has not been adequately studied in a clinical trial which meets the Panel's criteria.

a. *Safety.* Because benzoyl peroxide and sulfur are safe as single ingredients, in considering the safety of the combination one need be concerned only with the possible effect one chemical might have on the potential toxicity of the other. One such possibility is increased absorption of benzoyl peroxide due to irritation by sulfur. There is evidence, however, that benzoyl peroxide is not absorbed from rabbit skin even in the presence of 5 percent sulfur (Ref. 1). Topical studies on rabbits with a formulation containing 7.5 percent benzoyl peroxide and 5 percent sulfur showed no systemic effects (Ref. 2).

The primary concern regarding the safety of benzoyl peroxide is direct cutaneous toxicity. There is evidence that this is enhanced by the presence of sulfur. Poole, Griffith, and MacMillan (Ref. 3) demonstrated a 40-percent rate of hypersensitivity to benzoyl peroxide in guinea pigs and humans who were given a patch test with an ointment containing 10 percent benzoyl peroxide and 1 percent sulfur. In the study on guinea pigs it was clearly demonstrated that sulfur was needed in addition to benzoyl peroxide to produce sensitization. Guinea pigs tested with benzoyl peroxide alone, sulfur alone, or the vehicle showed no reaction (Ref. 3). Histological alterations, particularly dermal changes, produced by benzoyl peroxide are also enhanced by sulfur (Ref. 4). In the rabbit ear assay, greater irritation was observed from the combination than from either

ingredients along (Ref. 5). Using the Draize-Shelanski test (Re. 1), true allergic responses to benzoyl peroxide-sulfur lotion were demonstrated in 19 out of 221 people, which is a higher rate than expected with benzoyl peroxide alone.

It is difficult to understand why sulfur would enhance the sensitization potential of benzoyl peroxide. Perhaps an oxidation product of sulfur is formed and this product is irritating. Because the possibility of sensitization increases when sulfur is combined with benzoyl peroxide, the Panel recommends that this combination remain available by prescription only.

b. *Effectiveness.* A double-blind, controlled, randomized trial was conducted on 80 males with moderate acne (Ref. 2). The patients applied creams containing no benzoyl peroxide or containing benzoyl peroxide in concentrations of 2.5, 5, 7.5, or 10 percent either with or without 5 percent sulfur. Half of the group was treated for 2 weeks; the other half was treated for 8 weeks. The patients were assessed by lesion counts. The statistical analysis of results showed that the most effective formulation contained 7.5 percent benzoyl peroxide and 5 percent sulfur. This combination was effective against all types of acne lesions (comedones, papules, pustules, and all lesions combined). The duration of treatment did not affect the results.

One submission contained a compilation of five half-face and five full-face studies using 10 percent benzoyl peroxide, 5 percent sulfur, a combination of these two ingredients, or a placebo base (Ref. 2). These studies were randomized and blinded. Treatment lasted 8 weeks with evaluation by lesion counts. The results of the half-face studies showed that improvement in comedones was 58.3 percent for the combination, 42.8 percent for sulfur, 49.1 percent for benzoyl peroxide, and 28 percent for the base. For inflammatory lesions the improvement was 40 percent for the combination, 36.3 percent for sulfur, 23.7 percent for benzoyl peroxide, and 18.3 percent for the base.

Most of the studies were not analyzed. However, analysis of one study showed that the benzoyl peroxide-sulfur combination was more effective than benzoyl peroxide alone ($p < 0.05$).

In the full-face studies, one investigator found the combination product to be superior to sulfur used alone ($p < 0.05$). Another researcher, however, reported no significant differences between active treatments (Ref. 2).

In a double-blind, randomized study, 48 patients were treated with either a

combination containing 7.5 percent benzoyl peroxide and 5 percent sulfur, 7.5 percent benzoyl peroxide, or the placebo (Ref. 2). The patients applied the lotions twice daily for 8 weeks. They were evaluated by lesion counts at 0, 2, and 8 weeks, but the numerical results of these counts were not reported. However, using a "means of slope estimate" (rate of lesion decrease) for the three treatments, the researchers found the combination product to be superior to the placebo in the treatment of comedones and in all lesions combined ($p < 0.05$ and $p < 0.025$). In treating inflammatory lesions, no significant difference was noted between the combination and the placebo. Also, no significant difference was seen between benzoyl peroxide and placebo for any lesion type.

In a double-blind, randomized, half-face study (Ref. 2), 48 patients applied a combination of 7.5 percent benzoyl peroxide and 5 percent sulfur to one side of the face. On the other side of the face, they used benzoyl peroxide alone. Treatment was twice daily for 7 weeks. The patients were examined by global assessment and lesion counts at 0, 2, and 7 weeks. Both treatments reduced lesion counts, but by this method of evaluation no significant difference was noted between treatments. Analysis of global results showed that the combination product was superior to benzoyl peroxide in the treatment of comedones at 2 weeks ($p < 0.05$) and in the treatment of inflammatory lesions at 7 weeks ($p < 0.05$).

In a multiple-center trial (Ref. 2), three investigators treated 156 patients with acne. The study was double-blind and randomized. The patients applied either a combination of 7.5 percent benzoyl peroxide and 5 percent sulfur, a placebo cream, or a commercially available cream containing sulfur and resorcinol. Treatment was twice daily. No concurrent therapy was allowed. The patients were evaluated at 0, 2, 8, and 12 weeks by lesion count.

The results of each investigator's work were statistically analyzed. One researcher reported greater improvement with the combination than with the other two treatments, but the difference was not significant. Another investigator found no significant difference between the three preparations in reducing comedones. However, benzoyl peroxide-sulfur combination was superior to sulfur-resorcinol and the placebo in reducing inflammatory lesions ($p < 0.001$). The third investigator found benzoyl peroxide-sulfur combination to be superior to the placebo for all lesion types ($p < 0.05$).

c. *Evaluation.* The Panel concludes that 7.5 percent benzoyl peroxide and 5 percent sulfur is an effective combination for topical use in the treatment of acne. However, the Panel does not recommend that this combination be made available OTC because of the potential for sensitization.

References

- (1) OTC Volume 070259.
- (2) OTC Volume 070168.
- (3) Poole, R. L., J. F. Griffith, and P. S. K. Macmillan, "Experimental Contact Sensitization with Benzoyl Peroxide," *Archives of Dermatology*, 102:635-639, 1970.
- (4) Vasarinsh, P., "Benzoyl Peroxide-Sulfur Lotions, A Histological Study," *Archives of Dermatology*, 98:183-187, 1968.
- (5) OTC Volume 070207.

3. *Category III combination drug products.* A combination is classified as a Category III product if one of the following apply:

- (1) The combination contains one or more ingredients listed elsewhere in this document as a Category III ingredient.
- (2) The combination contains one or more ingredients listed elsewhere in this document as a Category II ingredient for effectiveness only. (An exception is sulfur-resorcinol combinations where resorcinol enhances the activity of sulfur.)

(3) The effectiveness of the combination has not been shown in a controlled clinical trial.

a. *Calcium polysulfide-calcium thiosulfate.* Calcium polysulfide and calcium thiosulfate the active ingredients in sulfurated lime topical solution (Vlieminckx' solution). This solution is most frequently used as a scabicide (Ref. 1). It has also been used in the treatment of severe pustular or cystic acne. Although sulfurated lime topical solution has been used in dermatology for over 100 years, there are no clinical trials establishing its effectiveness in treating acne.

Sulfurated lime topical solution works as a peeling agent. Plewig and Kligman (Ref. 2) stated that "only a few agents which cause peeling are in fact comedolytic." They listed sulfurated lime topical solution as one of the traditional exfoliants which is "surprisingly weak or ineffective."

Only one submission contained a clinical trial testing the effectiveness of calcium polysulfide-calcium thiosulfate combination (Ref. 3). In this double-blind, randomized study, 59 patients used either the medicated facial mask or a nonmedicated mask (vehicle). The masks were applied once every other day and rinsed off after 15 minutes. Patients were evaluated by lesion

counts and global assessment at the initial visit and at 2, 4, 7, and 10 weeks. At each visit the patients using the combination showed a significant decrease in comedones compared to baseline ($p < 0.001$). In the vehicle group the decrease in comedones was significant only at 2 and 4 weeks ($p < 0.05$). The reduction of papules, however, was significant at each visit for both treatments when compared to baseline ($p < 0.01$). Both groups also showed a significant decrease in the pustule counts over the 10-week course of treatment ($p < 0.025$).

The Panel notes that a calcium polysulfide-calcium thiosulfate combination is generally used by dermatologists to treat severe acne that does not respond to other treatments. In this study, however, the combination was no more effective than the vehicle on papules and pustules. Although the combination was more effective than the vehicle in reducing comedones, effectiveness should be shown against all lesion types. The Panel concludes that a combination of calcium polysulfide and calcium thiosulfate is of questionable effectiveness for OTC use in the treatment of acne.

References

- (1) Osol, A., and J. E. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1180, 1975.
- (2) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, p. 278, 1975.
- (3) OTC Volume 070291.

b. *Sulfur-aluminum chlorohydrate*. The Panel concludes that a combination of 5 percent sulfur and 10 percent aluminum chlorohydrate is safe but that there are insufficient data available to permit final classification of the effectiveness of this combination.

The Panel reviewed two double-blind, randomized, and controlled studies that compared the combination to the individual active components and to the vehicle (Ref. 1). However, because there was no washout period between the cross-over segments of these trials, the results were difficult to interpret.

Another study on this combination was also double-blind, randomized, and controlled. Forty-five patients with Pillsbury Grade I to III acne completed the 8 weeks of treatment. They were treated twice daily with either 5 percent sulfur-10 percent aluminum chlorohydrate, 5 percent sulfur, or the vehicle. No other treatment was allowed. Patients were evaluated by lesion counts and global assessments.

Results of global assessments showed that the combination was significantly more effective than sulfur or vehicle.

Sulfur-aluminum chlorohydrate was also significantly better than sulfur and vehicle in reducing the lesion counts of papules and pustules ($p < 0.05$). Reduction in the number of open comedones and cysts was greater for the combination than for the other two preparations but this was not a statistically significant difference. None of the treatments had an appreciable effect on closed comedones, difficult lesions to treat (Ref. 1).

The only side effect noted was excessive dryness. In the first 2 weeks of treatment, there were significantly more reports of this side effect with the combination product than with sulfur. At that time, the amount of drug and the frequency of administration were adjusted.

There was only one report of excessive dryness from the combination in the next 6 weeks of the trial (Ref. 1).

The Panel concludes that 5 percent sulfur-10 percent aluminum chlorohydrate is safe, but that its overall effectiveness is questionable because of its lack of effect on comedones. The Panel has stated previously that acne treatments should be effective against all lesion types to be considered as Category I. Although this combination was significantly more effective on papules and pustules, it did not have a statistically significant effect on other kinds of lesions, particularly open comedones.

Reference

- (1) OTC Volume 070283.

c. *Other Category III combination products*. The Panel is unaware of any clinical trials on the following combinations which compared the combination to the individual active ingredients and to the vehicle. Although studies were submitted and reviewed by the Panel for some of these combinations, none of them met the Panel's criteria.

The Panel concludes that the following combinations are of questionable effectiveness because of inadequate data. One of these combinations contains an ingredient on which there are inadequate safety data (thymol). The safety of this ingredient must be established before the combination can move from Category III to I.

- (1) Sulfur-resorcinol-alcloxa.
- (2) Sulfur-resorcinol-thymol-zinc oxide.
- (3) Sulfur-salicylic acid.
- (4) Salicylic acid-resorcinol.
- (5) Salicylic acid-resorcinol-alcloxa.
- (6) Salicylic acid-resorcinol-sodium thiosulfate.

(7) Benzoic acid-boric acid-zinc oxide-zinc stearate.

E. Guidelines for Safety and Effectiveness Studies

The following guidelines are for studies that the Panel recommends be conducted in order to move a Category III topical acne drug product into Category I. These guidelines are in accord with the present state of the art but do not preclude the use of any future advances or improved technology.

The Panel's approach has been to completely study the potential toxicity of active ingredients used in topical acne products. Even though these ingredients are to be used topically, their oral toxicity should be studied first to identify the target organ or system and then to determine the safety factor which permits safe use when absorption and systemic toxicity occur.

1. *Safety guidelines*. The Panel recommends that the following studies be performed as appropriate to evaluate topical acne ingredients classified in Category III because of inadequate safety data.

a. *Acute studies in animals*. (1) Determine the acute oral toxicity of the total formulation in an appropriate species to define the response curve and allow determination of the LD_{50} , LD_{50} , and LD_{50} . Short-term topical toxicity tests on the total formulation should be done on both intact and abraded skin.

(2) Conduct an appropriate rabbit skin irritation study on intact and abraded skin on the vehicle and total formulation.

(3) Conduct an appropriate rabbit eye irritation study on the vehicle and total formulation.

b. *In vitro screening for carcinogenic potential*. (1) A bacterial mutagenesis assay would be a logical first step in screening for carcinogenic potential. One of the assays using the *Salmonella* histidine auxotroph back mutation, such as that described by Ames (Ref. 1) or Frantz and Mallin (Ref. 2), would be suitable. Because the compounds in question are likely to be antibacterial, parallel dose-response curves for viability must be done. Where obvious antibacterial activity occurs, other cellular testing procedures should be used.

(2) Depending on the properties of the chemical tested and the results of the bacterial mutagenesis assay, other *in vitro* tests could be conducted for clarification. These tests should use a mammalian cell culture system designed to test either mutagenicity or transformation. Strategies for selecting

tests in this rapidly developing field can be found in current literature.

c. *Subchronic studies in animals.* (1) Conduct a 28-day dermal toxicity study in the rabbit or other appropriate species on abraded skin at suitable dose levels to ensure adequate exaggeration of normal "use" levels. At the conclusion of this study, conduct a full pathological assessment on vital organs and skin. It would be desirable to evaluate the direct effects on the skin following application for a longer period of time, but the Panel is not aware of a suitable model for such a study.

(2) Conduct a subchronic (90 days or longer) feeding study with the total formulation. Determine blood levels and conduct full pathology at termination of the study. This study should attempt to determine the "no effect" blood level of the total formulation. Determine the target organ(s) for toxic effects.

d. *Chronic studies in animals.* (1) Conduct a 1-year chronic feeding study with at least two dose levels. Monitor blood levels at 3-month intervals. Conduct a full pathology evaluation at conclusion of study.

(2) A carcinogenicity evaluation following dermal application will be necessary only if the appropriate *in vitro* screening assays are positive or have yielded questionable results. For example, acne agents may have antibacterial activity which can cause false-negative or misleading results in the *Salmonella* mutagenicity test because the assay procedure involves bacterial enumeration.

e. *Studies in humans.* (1) Determine the irritation potential of the vehicle and total formulation using the best current procedures.

(2) Conduct an appropriate sensitization potential study on the total formulation using the most reliable procedure for identifying both potent and weak sensitization potential(s).

(3) Because absorption studies in animals do not necessarily parallel those in humans, appropriate transepidermal studies should be conducted in humans. These studies should be conducted only where the safety of the ingredient has been adequately established in animals.

References

- (1) Ames, B. N., J. McCann, and E. Yamasaki, "Methods for Detecting Carcinogens and Mutagens with the *Salmonella*/Mammalian-Microsome Mutagenicity Test," *Mutation Research*, 31:347-364, 1975.
- (2) Frantz, C. N., and H. V. Malling, "The Quantitative Microsomal Mutagenesis Assay Method," *Mutation Research*, 31:365-380, 1975.

2. Effectiveness guidelines—a.

Guidelines for clinical trials. To move a Category III ingredient into Category I, the ingredient must be shown to be effective in the treatment of acne in a well-designed clinical trial that meets the following criteria:

(1) The trial should involve a sufficient number of subjects established by using accepted statistical procedures.

(2) An objective measure of the severity of acne should be decided before the study. This method should be precisely defined.

(3) Patients should be randomly assigned to total formulation or control group. The control is the vehicle (total formulation minus the active ingredient (s)). When comparing total formulation to vehicle, the use of parallel groups of patients is preferable to half-face comparisons. The comparability of groups should be established by analyzing pertinent variables, such as age, sex, severity of acne.

(4) The study should be double-blind.

(5) No concomitant therapy (other than soap and water) should be allowed.

(6) The trial should last at least 8 weeks. The investigators should state which calendar months were included in the study because acne lesions generally clear up somewhat in the summer.

(7) The patients should be evaluated at least three times: before treatment, at final examination, and at one other time. The method of evaluation should be lesion counts grouped by type of lesion (closed comedones, open comedones, papules, pustules, and total lesions). A global assessment of patients may also be helpful. Local adverse effects and patient compliance should be noted and systematically recorded.

(8) Results should be statistically evaluated. The total formulation should be significantly more effective than the placebo in reducing lesion counts.

b. *In vitro testing of acne ingredients*—(1) *Background.*

The Panel has included an optional *in vitro* testing procedure. Before a manufacturer tests an ingredient for clinical effectiveness in acne or determines *in vivo* activity for an antibacterial claim, it would be helpful to determine activity against *P. acnes* in an *in vitro* test. With *in vitro* testing the minimal inhibitory concentration (MIC) of an ingredient can be determined against *P. acnes*. With this information one can determine whether the ingredient has antibacterial activity under these testing conditions. MIC determination can also be used to compare different ingredients tested against the same pure culture under the same conditions. Another use is to find whether antibacterial activity varies

when an ingredient is tested against various strains of bacteria.

Ingredients often show activity *in vitro* which cannot be shown *in vivo*. Although the reverse is not so often true, it can happen when the conditions of the MIC test differ significantly from the availability of the antibacterial agent *in vivo*. *In vitro* antibacterial activity may also be affected by the interaction of the antibacterial ingredients or other components in the formulation with one of the components of the medium used to determine the MIC. Obviously this will not affect the *in vivo* activity.

Because the *in vitro* availability of the ingredient may be altered in formulation, it is often advisable to determine the MIC for the formulation as well as for the ingredient alone. The optimal multiple of the MIC of an ingredient in a topical dosage form is often very high, ranging from a hundred times to thousands of times the MIC. This high multiple is often necessary because of formulation binding, partition of the ingredients on the skin, and differential absorption into the skin. Absorption into the follicle is critical in formulations for acne treatment.

Therefore, the information derived from *in vitro* data may be helpful in trying to make the most effective formulations or in reaching a decision about whether to proceed with testing. Although the *in vivo* data ultimately determine the validity of the antibacterial claim, the MIC test is a helpful guide to potential activity and availability. In some cases it can also be useful in quality control. The following discussion illustrates how the MIC data can be used.

The MIC of benzoyl peroxide was reported as approximately 78 µg/mL against *P. acnes*. The minimal bactericidal concentration (MBC) was reported as approximately 156 µg/mL.

If these figures are applied to actual use of a formulation on the skin and some assumptions are made, useful information can be derived. The amount of drug material applied is 2 mg/cm² or 2,000 µg/cm². If an average lotion or cream product contains 10 percent benzoyl peroxide, then the amount applied could be in the range of 200 µg/cm².

If an average volume of a single follicle is assumed to be 2 microliters (µL) and it is estimated that there are 200 follicles/cm², then the total follicular volume could be estimated at 400 µL (0.4 mL) for each cm² of involved epidermis. Based on this estimate and assuming complete and uniform follicular penetration, the concentration of benzoyl peroxide at the site of the

organism would be 200 µg/0.4 mL or 500 µg/mL benzoyl peroxide. To obtain the multiples, the estimated concentration of benzoyl peroxide at the site is derived using the MIC or the MBC. The multiples for various concentrations of benzoyl peroxide would be as follows:

Concentration of benzoyl peroxide (percent)	MIC	MBC
10	6×	3×
7	4×	2×
5	3×	1.5×
2.5	1.5×	.75×

These data and calculations suggest that appropriate availability of the benzoyl peroxide from 2.5 percent formulations will be important to their effectiveness.

(2) *Testing procedures.* The Panel suggests the following procedures for testing ingredients in vitro for possible bactericidal or bacteriostatic activity against *P. acnes* (although other procedures may be used): (i)

Materials—(a) Double-strength brain-heart infusion agar, containing 104 g/L.

(b) Single-strength brain-heart infusion agar, containing 52 g/L.

(c) Double-strength brain-heart infusion broth, containing 74 g/L.

(d) Single-strength brain-heart infusion broth, containing 37 g/L.

The brain-heart infusion agar and broth are commercial preparations to which double-distilled water is added to make the working preparations.

(ii) *Basic P. acnes culture.* An ATCC *P. acnes*-type culture or a well-characterized *P. acnes* facial isolate is reconstituted and then grown anaerobically under hydrogen/carbon dioxide or equivalent, in brain-heart infusion or a similar broth at pH 7, for 5 to 7 days, until good growth is obtained as evidenced by turbidity.

(iii) *Determination of the minimal inhibitory concentration for agents insoluble in water by the agar dilution method.* The agar dilution test is used for products that are insoluble or precipitate in broth, rendering culture media cloudy and making turbidimetric measurements of microbial growth difficult.

The test is run in duplicate. The following should be prepared and sterilized: 2 test tubes (18 mm × 150 mm) with 5 mL of double-strength brain-heart infusion agar, 22 test tubes containing 5 mL of single-strength brain-heart infusion agar, and 2 test tubes containing 9 mL of brain-heart infusion broth. The agar in these test tubes is melted and kept in a 45° C water bath to prevent solidification during the test. Next, 5 mL of the concentrated test ingredient is placed into the test tubes

containing the double-strength brain-heart infusion agar and mixed well for 10 seconds. Then the tubes are returned to the water bath. (This is a 1:2 dilution.)

Five mL from each one of these tubes is transferred into each of two of the single-strength brain-heart infusion agar tubes, mixed, and returned to the water bath. (This is a 1:4 dilution.) This procedure is continued until a 1:1,024 dilution has been prepared. From the last dilution tube, 5 mL is discarded so that all tubes contain a total of 5 mL of agar. The last two agar tubes will be kept undiluted and uninoculated as negative controls. The contents of each tube are mixed well and poured into 25 mm × 10 mm petri dishes. The agar is allowed to solidify.

Two serial tenfold dilutions from the *P. acnes* broth culture are made using the two brain-heart infusion broth tubes. The 1:100 dilution constitutes the inoculum. The duplicate set of plates (from the 1:2 dilution to 1:1,024 dilution) is seeded with one drop of the diluted *P. acnes* culture. Two plates with inoculated brain-heart infusion agar, two plates containing a 1:2 dilution of the sample but no inoculum seeding, and two uninoculated brain-heart infusion plates serve as controls. The plates are incubated anaerobically at 35° C for 1 week and examined for growth. The end point of bacteriostatic activity is between the last plate with no growth and the first plate with growth. The titer is the dilution of the last clear plate before the first plate growth.

A piece of the agar from the plates showing no growth is subcultured in brain-heart infusion broth tubes to determine the bactericidal titer of the antimicrobial agent. An effective neutralizer should be included.

The MIC is calculated from the titer and the original concentration of the test compound in the suspending agent.

(iv) *Determination of the minimal inhibitory concentration for agents soluble in water by the broth dilution method.* The test is run in duplicate. Twenty-four test tubes (18 mm × 150 mm) are set up. Into the first four test tubes, 5 mL of a double-strength brain-heart infusion broth is pipetted. Five mL of the single-strength broth is placed into each of the other tubes.

Next, 5 mL of sterile saline is pipetted into each of the first two test tubes of double-strength broth and mixed. These will be the positive control tubes. Five mL is removed from each of these control tubes and discarded, leaving a total volume of 5 mL in each tube.

A known amount of the acne ingredient is mixed in a suspending medium and 5 mL of this dispersion is pipetted into each of the next two test

tubes and mixed for 10 seconds. This is a 1:2 dilution.

Five mL of the content of each 1:2 dilution tube is transferred into the next two test tubes and mixed for 10 seconds. This is a 1:4 dilution.

This procedure is continued until a 1:1,024 dilution is obtained. Five mL from each test tube with the highest dilution is discarded, leaving a 5 mL total volume in each of the test tubes. The last two tubes will not be diluted or inoculated and will serve as negative controls. The culture of *P. acnes* in brain-heart infusion broth is mixed well to suspend the cells evenly and 1 mL is added to 9 mL of single-strength broth and mixed well. This is a 1:10 dilution.

One mL from this 1:10 dilution is added to 9 mL of single-strength brain-heart infusion broth to obtain a 1:100 dilution. This dilution constitutes the inoculum.

One-tenth mL of the inoculum is added to each of the sample dilutions and to the positive control tubes. All tubes are incubated at 35° C anaerobically for 1 week and then examined for growth.

(v) *Interpretation of the results.* The more concentrated suspensions of the test agent should completely inhibit the growth of *P. acnes*, and the broth should be clear. At higher dilutions the concentration of the active agent will be too low to completely inhibit the growth of the organism. These tubes should be turbid. The end point of activity is between the last clear and the first turbid adjacent tube. The titer is the dilution of the last clear tube.

When the test is concluded, a loopful of broth from each tube not showing turbidity should be streaked on brain-heart infusion agar plates and incubated at 35° C anaerobically for 1 week to determine whether the test compound is bacteriostatic or bactericidal at a given concentration. An effective neutralizer should be included. Knowing the titer (bacteriostatic and bactericidal) and the initial concentration of the dispersion tested, an MIC for this ingredient can be calculated by the following formula:

$$\text{Minimal inhibitory concentration } (\mu\text{g/mL}) \\ = \frac{\text{Initial concentration } (\mu\text{g/mL}) \times 1}{\text{Bacteriostatic titer}}$$

c. *In vivo testing of acne ingredients.* The Panel recommends the following testing guidelines to determine antimicrobial activity in an in vivo test. Ingredients which demonstrate in vivo activity and meet the criteria may use antibacterial claims in their labeling.

(1) *Study design.* Either parallel or half-face groups may be used. The half-

face design is permitted for drugs that are not sufficiently absorbed to result in antibacterial effects. When a drug is absorbed to a degree that systemic activity occurs, the untreated side of the face may be affected, thus invalidating the test. Reliability and extent of application are particularly important in a half-face test. For this reason, technicians should apply the drug when this study design is used. If translocation of the medication is known to occur, the half-face design should not be used.

All studies should be double-blind with the formulation containing the active ingredient compared with the vehicle control.

(2) *Subjects.* A minimum of 15 subjects for a half-face study and 30 for a parallel group study should be used. The groups should include males and females 15 years of age or older. The subjects may or may not have active acne, but they must have significant follicular fluorescence indicating an adequate density of *P. acnes* on the skin. The subjects must have a *P. acnes* baseline count of 1×10^5 to 1×10^6 organisms per cm^2 .

(3) *Treatment.* The forehead and cheeks should be used as treatment sites. The method of application should be that specified in directions for use. The drug should be applied twice daily. The duration of treatment should usually be 4 weeks unless the study is intended to show that a product can meet the criteria in a shorter time. In that case the treatment time may be shortened.

(4) *Measurements.* The sample site should be specified by the investigator. To reduce error the same sample site should be used on each individual each time. The *P. acnes* count should be determined using the Williamson and Kligman scrub technique (Ref. 1). The Panel believes that the Williamson and Kligman scrub technique is the best method presently available to determine *P. acnes* counts. However, if other methods that are equivalent or superior to the Williamson and Kligman scrub technique are developed, they may be used after the agency has approved a petition to amend the monograph.

Three separate determinations of the baseline *P. acnes* count should be made. The values may be averaged to obtain a single baseline value for each subject. Measurements to determine reduction should be made weekly thereafter.

The free fatty acids determination is an optional confirmatory test. However, if it is used, the free fatty acids concentration should be carefully assessed by thin-layer chromatography,

such as the method described by Downing (Ref. 2).

(5) *Criteria.* For an ingredient to be considered effective in demonstrating antibacterial activity against *P. acnes*, the following criterion must be met:

A reduction in *P. acnes* counts of 0.75 log must be shown. This reduction should be statistically significant at the $p < 0.1$ level. Therefore, the hypothesis test should be framed to test whether there is a 0.75-log reduction from baseline.

If it is desirable to show that the reduction is significant at the $p < 0.05$ level, the number of subjects should be increased appropriately.

To confirm antibacterial activity, an optional test to show reduction of free fatty acids may also be done. A 30-percent reduction in free fatty acids on the skin surface should be shown. The reduction should be statistically significant at the $p < 0.1$ level. The free fatty acid determination is included to ensure that the antimicrobial agent has penetrated and is acting at the follicular level.

(6) *Methodology*—(i) Microbiological sampling of the skin should be by the Williamson and Kligman detergent scrub technique or an equivalent technique. The following culture techniques should be observed:

a. Brain-heart infusion medium should be used to culture *P. acnes*. If another medium is developed that is shown to be equivalent or superior to brain-heart infusion, it may be used.

b. The sample retrieved from the scrub technique should be vortexed for 10 seconds prior to enumeration.

c. Anaerobic incubation should be at 35°C for 7 days.

d. A neutralizer adequate for the antimicrobial ingredient being tested should be added to the scrubbing fluid. The toxicity of the neutralizer must be determined for *P. acnes*. The presence of any residual antimicrobial agent in the sampling fluid must be investigated using adequate microbiological tests.

(ii) *Free fatty acids determination.* Samples of skin lipids should be obtained by swabbing the area with a hexane-saturated sponge (Ref. 3). Lipid analysis should be performed using a thin-layer chromatography technique, such as the one described by Downing (Ref. 2). Another method of lipid analysis that may be used is infrared spectroscopy, described by Anderson and Fulton (Ref. 4).

References

- (1) Williamson, P., and A. M. Kligman, "A New Method for the Quantitative Investigation of Cutaneous Bacteria," *Journal*

of Investigative Dermatology, 45:498-503, 1965.

(2) Downing, D. T., "Photodensitometry in the Thin-Layer Chromatographic Analysis of Neutral Lipids," *Journal of Chromatography*, 38:91-99, 1968.

(3) Yeung, D., and W. Smith, "Method for the In Vivo Collection of Skin Lipids," memorandum to S. Nacht, June 4, 1980, OTC Volume 070279.

(4) Anderson, A. S., and J. E. Fulton, Jr., "Sebum: Analysis by Infrared Spectroscopy," *Journal of Investigative Dermatology*, 60:115-120, 1973.

PART 333—TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), under the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11, (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding in Part 333, a new Subpart D, to read as follows:

Subpart D—Topical Acne Drug Products

- Sec.
- 333.301 Scope.
 - 333.303 Definitions.
 - 333.310 Acne active ingredients.
 - 333.320 Permitted combinations of active ingredients.
 - 333.340 Testing procedures to determine antibacterial activity of acne active ingredients.
 - 333.350 Labeling of acne drug products.
- Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart D—Topical Acne Drug Products

§ 333.301 Scope.

(a) An over-the-counter acne drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart and each general condition established in § 330.1.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 333.303 Definitions.

As used in this part:

(a) *Acne*. An inflammatory skin disease involving the oil glands and hair follicles of the skin.

(b) *Acne drug product*. A drug product used to reduce the number of acne lesions.

(c) *Blackhead*. An acne lesion characterized by a black tip.

(d) *Follicle*. A minute cavity with an opening on the surface of the skin.

(e) *Lesion*. A characteristic area of a skin condition. Lesions in acne include blackheads and pimples.

(f) *Pimple*. A small, prominent inflamed elevation of the skin.

§ 333.310 Acne active ingredients.

The active ingredients of the product consist of any of the following when labeled according to § 333.350.

(a) Benzoyl peroxide 2.5 to 10 percent.

(b) Resorcinol 2 percent when combined in accordance with § 333.320.

(c) Resorcinol monoacetate 3 percent when combined in accordance with § 333.320.

(d) Sulfur 3 to 10 percent.

(e) Sulfur 8 percent when combined in accordance with § 333.320 (a) and (b).

§ 333.320 Permitted combinations of active ingredients.

(a) Resorcinol identified in § 333.310(b) when combined with sulfur identified in § 333.310(e) provided the product is labeled according to § 333.350.

(b) Resorcinol monoacetate identified in § 333.310(c) when combined with sulfur identified in § 333.310(e) provided the product is labeled according to § 333.350.

§ 333.340 Testing procedures to determine antibacterial activity of acne active ingredients.

(a) *Study design*. Either parallel or half-face groups may be used. The half-face design is permitted for drugs that are not sufficiently absorbed to result in antibacterial effects. When a drug is absorbed to a degree that systemic activity occurs, the untreated side of the face may be affected, thus invalidating the test. Reliability and extent of application are particularly important in a half-face test. For this reason, technicians should apply the drug when this study design is used. If translocation of the medication is known to occur, the half-face design should not be used. All studies should be double-blind with the formulation containing the active ingredient compared with the vehicle control.

(b) *Subjects*. A minimum of 15 subjects for a half-face study and 30 for

a parallel group study should be used. The groups should include males and females 15 years of age or older. The subjects may or may not have active acne, but they must have significant follicular fluorescence indicating an adequate density of *Propionibacterium acnes* (*P. acnes*) on the skin. The subjects must have a *P. acnes* baseline count of 1×10^5 to 1×10^6 organisms per square centimeter.

(c) *Treatment*. The forehead and cheeks should be used as treatment sites. The method of application should be that specified in directions for use. The drug should be applied twice daily. The duration of treatment should usually be 4 weeks unless the study is intended to show that a product can meet the criteria in a shorter time. In that case the treatment time may be shortened.

(d) *Measurements*. The sample site should be specified by the investigator. To reduce error the same sample site should be used on each individual each time. The *P. acnes* count should be determined using the Williamson and Kligman scrub technique (*Journal of Investigative Dermatology*, 45:498-503, 1965). Other methods of measuring *P. acnes* counts may be used if they are shown to be equivalent or superior to the Williamson and Kligman method. Such methods may be used only after the agency has approved a petition to amend the monograph. Three separate determinations of the baseline *P. acnes* count should be made. The values may be averaged to obtain a single baseline value for each subject. Measurements to determine reduction should be made weekly thereafter. The free fatty acids determination is an optional confirmatory test. However, if it is used, the free fatty acids concentration should be carefully assessed by thin-layer chromatography, such as the method described by Downing (*Journal of Chromatography*, 38:91-99, 1968).

(e) *Criteria*—(1) *Required*. For an ingredient to be considered effective in demonstrating antibacterial activity against *P. acnes*, the following criterion must be met: A reduction in *P. acnes* counts of 0.75 log must be shown. This reduction should be statistically significant at the $p < 0.1$ level. Therefore, the hypothesis test should be framed to test whether there is a 0.75-log reduction from baseline. If it is desirable to show that the reduction is significant at the $p < 0.05$ level, the number of subjects should be increased appropriately.

(2) *Optional*. To confirm antibacterial activity, an optional test to show reduction of free fatty acids may also be done. A 30-percent reduction in free fatty acids on the skin surface should be

shown. The reduction should be statistically significant at the $p < 0.1$ level. The free fatty acid determination is included to assure that the antimicrobial agent has penetrated and is acting at the follicular level.

(f) *Methodology*—(1) Microbiological sampling of the skin should be by the Williamson and Kligman detergent scrub technique or an equivalent technique. The following culture techniques should be observed:

(i) Brain-heart infusion medium should be used to culture *P. acnes*. If another medium is developed that is shown to be equivalent or superior to brain-heart infusion, it may be used.

(ii) The sample retrieved from the scrub technique should be vortexed for 10 seconds prior to enumeration.

(iii) Anaerobic incubation should be at 35° C for 7 days.

(iv) A neutralizer adequate for the antimicrobial ingredient being tested should be added to the scrubbing fluid. The toxicity of the neutralizer must be determined for *P. acnes*. The presence of any residual antimicrobial agent in the sampling fluid must be investigated using adequate microbiological tests.

(2) *Free fatty acids determination*. Samples of skin lipids should be obtained by swabbing the area with a hexane-saturated sponge as in the method by Yeung and Smith (contained in a memorandum to S. Nacht, dated June 4, 1980, in OTC Volume 070279, on file in the Dockets Management Branch, HFA-305, Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857). Lipid analysis should be performed using a thin-layer chromatography technique, such as the one described by Downing (*Journal of Chromatography*, 38:91-99, 1968). Another method of lipid analysis that may be used is infrared spectroscopy, described by Anderson and Fulton (*Journal of Investigative Dermatology*, 60:115-120, 1973).

§ 333.350 Labeling of acne drug products.

(a) *Statement of identity*. The labeling of the product contains the established name of the drug, if any, and identifies the product as an "acne medication."

(b) *Indications*. The labeling of the product contains a statement of the indications under the heading "Indications" and is limited to the following:

(1) *For products containing any ingredient identified in § 333.310 for the treatment for acne*. The indications consist of one or more of the following statements:

- (i) "For the management of acne."
- (ii) "For the treatment of acne."

(iii) "Anti-acne formula."
 (iv) "Anti-acne medication."
 (v) "Anti-acne formulation."
 (vi) "Dries and clears acne blemishes."
 (vii) "Dries and clears acne pimples."
 (viii) "Dries acne blemishes and allows skin to heal."
 (ix) "Dries acne pimples and allows skin to heal."
 (x) "Dries up acne pimples."
 (xi) "Helps clear acne pimples."
 (xii) "Clears up most acne pimples."
 (xiii) "Clears up most acne blemishes."
 (xiv) "Reduces the number of acne lesions."
 (xv) "Reduces the severity of acne lesions."
 (xvi) "Reduces blackheads."
 (xvii) "Clears up most blackheads."
 (xviii) "Loosens blackheads."
 (xix) "Helps clear up blackheads."
 (xx) "Helps clear up acne pimples."
 (xxi) "Helps remove blackheads."
 (xxii) "Helps remove acne pimples."
 (xxiii) "Dries up blackheads."
 (xxiv) "Dries up acne blemishes."
 (xxv) "Unclogs pores to help clear acne."
 (xxvi) "Unplugs pores to help clear acne."
 (xxvii) "Penetrates follicles to eliminate most blackheads and acne pimples."
 (xxviii) "Penetrates pores to eliminate most blackheads and acne pimples."
 (xxix) "Penetrates follicles to control blackheads and acne pimples."
 (xxx) "Penetrates pores to control blackheads and acne pimples."
 (xxxi) "Penetrates follicles to clear most blackheads and acne pimples."
 (xxxii) "Penetrates pores to clear most blackheads and acne pimples."
 (xxxiii) "Penetrates follicles to reduce blackheads or acne pimples."
 (xxxiv) "Penetrates pores to reduce blackheads or acne pimples."
 (2) *For products containing any ingredient identified in § 333.310 for the prevention of new acne lesions.* The indications consist of one or more of the following statements provided that the labeling also contains one or more of the indications identified in § 333.350(b)(1).
 (i) "Helps keep skin clear of new acne lesions."
 (ii) "Helps keep skin clear of new acne pimples."
 (iii) "Helps prevent new blackheads or acne pimples."
 (iv) "Helps prevent new acne pimples."
 (v) "Helps prevent new acne pimples from forming."

(vi) "Helps prevent acne lesions."
 (vii) "Helps prevent the development of new acne lesions."
 (viii) "Helps prevent new acne blemishes from forming."
 (3) *For products that have shown antibacterial activity according to § 333.340.* The indications consist of one or more of the following provided that the labeling also contains one or more of the indications identified in § 333.350(b)(1).
 (i) "Antibacterial."
 (ii) "Kills acne bacteria."
 (iii) "Kills the bacteria that can cause acne."
 (iv) "Kills acne bacteria on the skin."
 (v) "Kills acne bacteria in the skin."
 (vi) "Kills acne bacteria and helps clear acne pimples."
 (vii) "Works to kill bacteria that may cause pimple redness to spread."
 (viii) "Works to kill bacteria that may cause inflammation to spread."
 (ix) "Penetrates follicles to kill bacteria associated with acne."
 (x) "Penetrates pores to kill bacteria associated with acne."
 (xi) "Penetrates follicles to reduce bacteria associated with acne."
 (xii) "Penetrates pores to reduce bacteria associated with acne."
 (xiii) "Reduces *P. acnes*, bacteria associated with acne."
 (xiv) "Reduces the bacterial products associated with the inflammation of acne."
 (xv) "Reduces the bacterial products associated with the irritation of acne."
 (4) *Product attributes.* Terms to describe certain physical and chemical qualities may be used, as long as these terms do not imply any therapeutic effect and are distinctly separated from the indications identified in § 333.350(b)(1), (2), and (3). These terms are intended to provide consumer information and relate to a product's color, odor, or feel.

The following or similar terms may be used:

(i) "Greaseless."
 (ii) "Nonstaining."
 (iii) "Odorless."
 (iv) "Colorless."
 (v) "Nontinted."
 (vi) "Blends easily with skin."
 (vii) "Disappearing foam."
 (viii) "Drying."
 (ix) "Dries excess skin oils."
 (x) "Skin-softening."
 (xi) "Cools and comforts hot, irritated skin areas."
 (xii) "Cleans the skin and helps to remove oil."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredient identified in § 333.310.* (i) "For external use only."

(ii) "Other topical acne medications should not be used at the same time as this medication."

(2) *For products containing benzoyl peroxide identified in § 333.310(a).* "Do not use this medication if you have very sensitive skin or if you are sensitive to benzoyl peroxide. This product may cause irritation, characterized by redness, burning, itching, peeling, or possibly swelling. More frequent use or higher concentrations may aggravate such irritation. Mild irritation may be reduced by using the product less frequently or in a lower concentration. If irritation becomes severe, discontinue use; if irritation still continues, consult a doctor or pharmacist. Keep away from eyes, lips, mouth, and sensitive areas of the neck. This product may bleach hair or dyed fabrics."

(3) *For products containing sulfur identified in § 333.310 (d) and (e).* "Do not get into eyes. If excessive skin irritation develops or increases, discontinue use and consult a doctor or pharmacist."

(4) *For products containing any combination identified in § 333.320.* "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body."

(d) *Directions.* The labeling of the product containing any ingredient identified in § 333.310 contains the following statements under the heading "Directions":

(1) "Cleanse the skin thoroughly before applying medication. Cover the entire affected area with a thin layer one to three times daily. Because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or as directed by a doctor."

(2) The directions described in paragraph (d)(1) of this section are intended for products that are applied and left on the skin. Other products, such as soaps or masks, may be applied and removed and should have appropriate directions.

Interested persons may, on or before June 21, 1982, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance

notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before July 21, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: January 19, 1982.

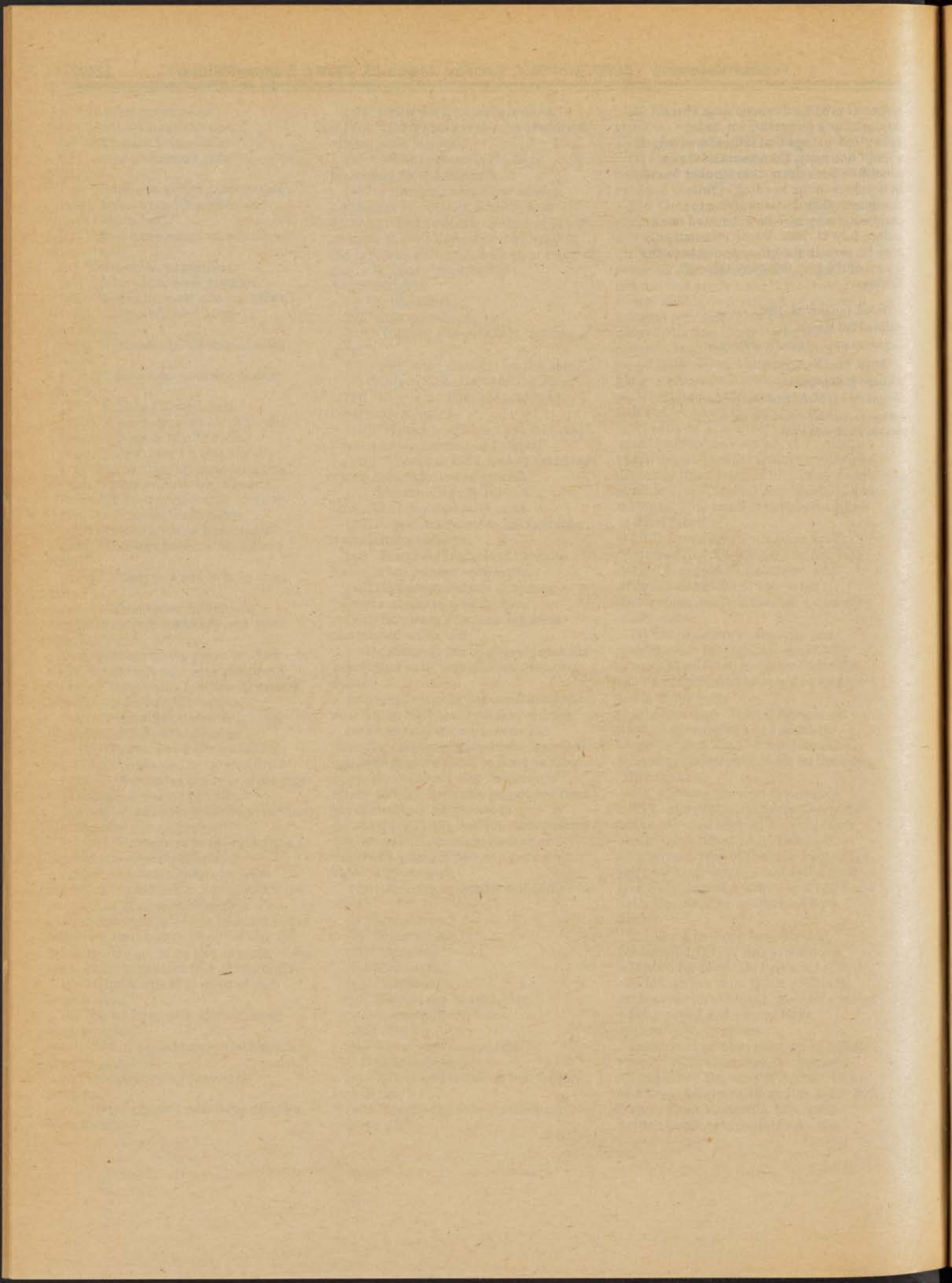
Arthur Hull Hayes, Jr.,
Commissioner of Food and Drugs.

Dated: March 16, 1982.

Richard S. Schweiker,
Secretary of Health and Human Services.

[FR Doc. 82-7683 Filed 3-22-82; 8:45 am]

BILLING CODE 4160-01-M



**Tuesday
March 23, 1982**

First Report

Part III

Department of Health and Human Services

Food and Drug Administration

Topical Antifungal Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Part 333**

[Docket No. 80N-0476]

Topical Antifungal Drug Products for Over-the-Counter Human Use; Establishment of a Monograph**AGENCY:** Food and Drug Administration.**ACTION:** Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of a proposed rulemaking that would establish conditions under which over-the-counter (OTC) topical antifungal drug products are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by June 21, 1982 and reply comments by July 21, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on February 23, 1980, a report of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the *Federal Register* a proposed order containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC topical antifungal drug products are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

FDA is aware of the Panel's recommendation to make the prescription drugs haloprogin 1 percent and miconazole nitrate 2 percent available for OTC use as single ingredients for the treatment of athlete's foot, jock itch, and ringworm. Without addressing the merits of this recommendation, the agency wishes to point out that no final decision will be made without a careful and thorough evaluation of all comments that are submitted in response to the publication of this recommendation. Any persons marketing such OTC drug products before a final monograph is published in the *Federal Register* will do so at their own risk, since the agency may at any time adopt a position requiring relabeling, recall, or other regulatory action, as detailed in § 330.13 (21 CFR 330.13).

FDA is also aware of the Panel's recommendation that the prescription drugs haloprogin 1 percent, miconazole nitrate 2 percent, and nystatin 100,000 U/g as single ingredients be made available OTC for the indications of "treatment of external feminine itching associated with vaginal yeast (candidal) infection" and "treatment of superficial skin infections caused by yeast (*Candida*)." The agency is dissenting from this recommendation at this time. FDA believes that self-treating the symptoms of itching around the vagina without knowing or treating the underlying cause of the itching could create a serious health hazard. Infections caused by *Candida* must be diagnosed in the laboratory; they cannot be self-diagnosed by consumers. Some candidal infections may require both systemic and intravaginal treatment. Furthermore, itching around the vagina can be a symptom of serious systemic disease, such as diabetes, or of a serious gynecological disorder, including trichomoniasis or gonorrhea. Trichomoniasis and gonorrhea must be diagnosed in the laboratory and treated with appropriate systemic medicines,

not with topical nystatin. FDA is soliciting comments on the Panel's recommendations that haloprogin, miconazole nitrate, and nystatin be available OTC for the treatment of candidal infections and particularly invites comments from gynecologists. Under § 330.13 (21 CFR 330.13), haloprogin, miconazole nitrate, and nystatin may not be marketed OTC with anticandidal claims at this time.

FDA is also aware that the Panel recommended that up to three Category I antifungal ingredients may be combined, provided that each ingredient broadens the antifungal spectrum, for the treatment of athlete's foot, jock itch, and ringworm. The agency is not aware of any such Category I combinations currently on the OTC market. At this time, the agency will continue to permit the marketing of combinations of antifungal ingredients already on the OTC market and will permit the reformulation of products to include Category I ingredients except where prescription to OTC switches are involved. However, under § 330.13 (21 CFR 330.13), no new combinations of antifungal ingredients containing an active ingredient limited to prescription use on or after May 11, 1972 may be marketed at this time. The agency invites comments and data on any combination of antifungal ingredients which the Panel recommended for Category I status.

The agency is also aware of the Panel's recommendation that, for the treatment of athlete's foot, jock itch, and ringworm, any single Category I antifungal ingredient, except nystatin, or any combination identified in proposed § 333.220(a) may be combined with any single antiperspirant which is generally recognized as safe and effective in an OTC drug final monograph. The agency is not aware of any combination product currently on the OTC market containing the Category I ingredients recommended by the Panel, nor were such combinations submitted to the Panel. Only two products containing an antiperspirant combined with one or more antifungal ingredients were submitted to the Panel. The agency notes that the Panel stated a belief that drying the affected area will aid in the treatment of athlete's foot. However, the Panel cited no data to support this theory. The agency advises that the Advisory Review Panel on OTC Antiperspirant Drug Products placed antiperspirants for use on the foot in Category III in its report published in the *Federal Register* on October 10, 1978 (43 FR 46727). Data are needed to establish the safety and effectiveness of

combinations of antifungal and antiperspirant ingredients. At this time, the agency will continue to permit the marketing of antifungal-antiperspirant combinations already on the OTC market and will permit the reformulation of products to include Category I ingredients except where prescription to OTC switches are involved. However, under § 330.13 (21 CFR 330.13), no new combinations of antifungal and antiperspirant ingredients containing an active antifungal or antiperspirant ingredient limited to prescription use on or after May 11, 1972 may be marketed at this time. The agency invites comments and data on any combination of antifungal and antiperspirant ingredients.

The agency is also aware that the Panel recommended that, for the treatment of athlete's foot, jock itch, and ringworm, any single Category I antifungal ingredient, except nystatin, or any combination identified in § 333.220(a) may be combined with any single keratolytic agent which is generally recognized as safe and effective in an OTC drug final monograph. The agency is not aware of any combination product currently on the OTC market containing only a keratolytic and the Category I antifungal ingredients recommended by the Panel. The agency points out that a number of currently marketed OTC products, some of which were submitted to the Panel, are combinations of antifungals with salicylic acid as the keratolytic. The agency advises that the Miscellaneous External Panel reviewed salicylic acid as a keratolytic in its report on wart remover drug products published in the Federal Register of October 3, 1980 (45 FR 65609). Although that Panel classified salicylic acid as Category I, it expressed concern regarding the safety of salicylic acid on skin areas other than those being treated and proposed a warning to advise users to keep the product away from surrounding skin while treating warts. In addition, the agency notes that the Antimicrobial II Panel stated that theoretically an effective keratolytic agent could remove the outer layers of the stratum corneum, thus better exposing the infecting fungus to the action of the antifungal ingredients, and cited salicylic acid as an example of such an agent. However, the Panel provided no data to support its recommendation. Further, there was no evidence submitted to the Panel to show that a keratolytic agent would be useful or safe in treating fungus conditions. At this time the agency will continue to permit the marketing of antifungal-keratolytic combinations already on the

OTC market and will permit the reformulation of products to include Category I ingredients except where prescription to OTC switches are involved. However, under § 330.13 (21 CFR 330.13), no new combinations of antifungal and keratolytic ingredients containing an active antifungal or keratolytic ingredient limited to prescription use on or after May 11, 1972 may be marketed at this time. The agency invites comments and data on any combination of antifungal and keratolytic ingredients.

The agency is aware that the Panel also recommended that combinations of up to three Category I antifungal ingredients and hydrocortisone or hydrocortisone acetate 0.5 to 1 percent be available for OTC use for the treatment of athlete's foot, jock itch, and ringworm. The agency is dissenting from this recommendation at this time. The agency recognizes that the Panel reviewed data for two marketed products which are currently available by prescription only. The agency advises that both of these prescription products, containing hydrocortisone combined with either iodochlorhydroxyquin or calcium undecylenate as the antifungal, are currently classified by FDA as lacking adequate evidence of effectiveness. (See 37 FR 12171, June 20, 1972; 37 FR 12856, June 29, 1972; and 39 FR 36365, October 9, 1974.) These products are in various stages of administrative review and remain on the prescription market pending final resolution and review of available data. The agency further points out that the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products recommended that hydrocortisone and hydrocortisone acetate 0.25 to 0.5 percent be allowed OTC as single ingredients, but not in any combination. (See the External Analgesic Drug Products report published in the Federal Register on December 4, 1979 (44 FR 69813)). The agency is currently reviewing that Panel's recommendation and the comments to that report, but has not made a final decision on whether hydrocortisone should be an OTC drug. Under § 330.13 (21 CFR 330.13), no combinations of antifungal ingredients and hydrocortisone or hydrocortisone acetate may be marketed OTC at this time. The agency invites comments and data relating to the Panel's recommendation that these combination products be available OTC. The agency specifically invites comments on adequate directions for use, appropriate

warnings, and duration of use for these products before a physician should be consulted.

After reviewing all comments submitted in response to the agency's statements above and to the Panel's recommendations and conclusions, FDA will issue in the Federal Register a tentative final monograph for OTC topical antifungal drug products as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

In the preamble to this report, the agency comments on a number of the Panel's recommendations. Because of these agency comments, certain prescription to OTC drug switches recommended by the Panel will not be permitted at this time; other such switches will not be permitted. In the case of some combinations, the agency will permit the reformulation of products to include Category I ingredients as long as no prescription to OTC drug switches are involved. This means that one currently marketed OTC ingredient in a combination drug product may be replaced by another currently marketed OTC ingredient. Because these actions do not restrict the previously existing marketing conditions of OTC drug products, the agency has determined that there is no regulatory impact of these actions at this time.

The agency's position on OTC topical antifungal drug products will be stated initially when the tentative final monograph is published in the Federal Register as a notice of proposed rulemaking. In that notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice if referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the Federal Register of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this

rulemaking would have on OTC antifungal drug products. Types of impact may include, but are not limited to, the following: increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC antifungal drug products should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC topical antifungal drug products submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after April 22, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

FDA published in the *Federal Register* of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler v. Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, would need to be done during the OTC drug rulemaking process, before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not

misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the *Federal Register*. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subject to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the *Federal Register* of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the *Federal Register* of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all antimicrobial active ingredients for the treatment and prevention of specific disorders such as seborrhea, dandruff, acne, athlete's foot, vaginitis, and otitis externa (swimmer's ear) was issued in the *Federal Register* of December 16, 1972 (37 FR 26842). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.'")

A subsequent request for data and information on topical antibiotic active ingredients used in OTC drug products for the treatment and prevention of

infections in minor skin wounds was published in the *Federal Register* of September 7, 1973 (38 FR 24391). The Panel's conclusions and recommendations for topical antibiotic drug products were published in the *Federal Register* of April 1, 1977 (42 FR 17642).

Under § 330.10(a) (1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients contained in those products:

Wallace Guess, Ph. D.; Chairman
Frank B. Engley, Jr., Ph. D.
Paul D. Stolley, M.D., M.P.H. (resigned June 1977)
William F. Schorr, M.D. (resigned July 1977)
W. Kenneth Blaylock, M.D.
E. Dorinda Loeffel Shelley, M.D.
Margaret Hitchcock, Ph. D. (resigned September 1974)
David R. Brown, Sc. D. (appointed March 1975, resigned March 1976)
Eula Bingham, Ph. D. (appointed July 1976, resigned June 1977)
James E. Rasmussen, M.D. (appointed October 1976)
George B. Youngstrom, M.D. (appointed June 1977, resigned October 1979)
Anne Tucker, Ph. D. (Panel consultant from July 1978 to March 1979; appointed as a Panel member March 1979)
Zenona Mally, M.D. (appointed October 1979)

The Panel first convened on July 26 and 27, 1974 in an organizational meeting. Working meetings which dealt with the topic in this document were held on January 9, 10, and 11, February 13, 14, and 15, March 12, 13, and 14, June 25, 26, and 27, July 23, 24, and 25, August 20, 21, and 22, October 29, and 30, November 19, 20, and 21, 1976; January 7 and 8, February 18 and 19, April 15 and 16, May 20 and 21, June 24, 25, and 26, August 26 and 27, October 8 and 9, November 18 and 19, 1977; January 13 and 14, February 10 and 11, March 17 and 18, April 14, and 15, August 18 and 19, September 29 and 30, November 10 and 11, 1978; January 19 and 20, March 23 and 24, April 27 and 28, June 8 and 9, July 20, August 17 and 18, October 12 and 13, 1979; January 18 and 19, and February 22 and 23, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address given above).

The following nonvoting consultants assisted the Panel: Brenda M. Brandon,

Sc. M., from October 1977 to June 1979, and Kazuo M. Kimura, M.D., Ph. D., from October 1977 to June 1978.

The following nonvoting liaison representatives served on the Panel: James D. Lawrence, M.D., Ph. D., served as an industry liaison in October 1976. Gavin Hildick-Smith, M.D., nominated by the Cosmetic, Toiletry and Fragrance Association, served as an industry liaison until April 1978. Michael Winrow, Ph. D., nominated by the Proprietary Association, served as an industry liaison until April 1979, followed by Kenneth Johannes until January 1980, followed by C. Elizabeth McKinivan, M.D. Ms. Sarah Newman, nominated by an ad hoc group of consumer organizations, served as the consumer liaison.

The following FDA employees served: Mary K. Bruch served as Executive Secretary; Michael Kennedy served as Panel Administrator in July 1974, followed by Armond M. Welch, R.Ph., until August 1978, followed by Lee Geismar, Melvin Lessing, R.Ph., M.S., served as Drug Information Analyst until October 1974, followed by Joseph Hussion, R.Ph., until July 1976, followed by Anne W. Eggers, R.Ph., M.S., until June 1978, followed by Elaine G. Euchner, R.Ph.

The following individuals were given an opportunity to appear before the Panel to express their views on topical antifungal agents either at their own or at the Panel's request:

A. M. Allen, M.D.
Harvey Blank, M.D.
Eugene A. Conrad, Ph. D.
James D. Cope
David Cram, M.D.
Stanley Cullen, M.D.
R. Sherman Detrick
Eugene Farber, M.D.
Beverly Foster
Kare Gundersen, M.D.
Larry Gundersen, Ph. D.
Dietrich Hoffman, Ph. D.
William Hubregs, Ph. D.
Arthur Isbit, Ph. D.
Herman Jass, Ph. D.
Albert Kligman, M.D., Ph. D.
John Leer, M.D.
Leonard Levy, M.D.
James Leyden, M.D.
Edward Marlowe, Ph. D.
William Merz, M.D.
John Middleton, Ph. D.
Sigrid Muller, M.D.
Gerbert Rebell, M.D.
Robert I. Schattner, D.D.S.
Vithal Shetty, Ph. D.
Donald Smith
David Taplin
Frederick Urbach, M.D.
George Warren, Ph. D.
Peyton Weary, M.D.
Nardo Zaias, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through February 23, 1980, in arriving at its conclusions and recommendations.

In this document the Panel presents its conclusions and recommendations on antifungal drug products used for the treatment of jock itch and ringworm and for the treatment and prevention of athlete's foot. The Panel believes that some of these drug products are also effective in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*). Thus, these indications for use have been included where appropriate.

The Panel's findings for acne drug products will be presented in a future issue of the **Federal Register**.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed OTC topical antifungal drug products with respect to the following three categories:

Category I. Conditions under which OTC topical antifungal drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC topical antifungal drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed 33 active antifungal ingredients. Six ingredients were placed in Category I for use in treating athlete's foot, jock itch, and ringworm. The Panel placed 9 ingredients in Category II and 18 ingredients in Category III for the treatment of athlete's foot, jock itch, and ringworm. One of the six ingredients placed in Category I for the treatment of athlete's foot, jock itch, and ringworm was also placed in Category I for the prevention of athlete's foot. Three of the ingredients placed in Category I for treating athlete's foot, jock itch, and ringworm were also reviewed for treating feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*) and were placed in Category I for these uses.

I. Submission of Data and Information

A. Submissions by Firms

Firms	Marketed products
Ayerst Laboratories, New York, NY 10017.	Enzactin Aerosol, Enzactin Cream, Enzactin Power Pack.
Buckman Laboratories, Inc., Memphis, TN 38108.	Buderma First Aid Ointment.
Chattam Drug and Chemical Co., Chattanooga, TN 37409.	Blis-To-Sol Aerosol Power, Blis-To-Sol Liquid, Blis-To-Sol Medicated Gel, Blis-To-Sol Power.
Ciba-Geigy Corp., Summit, NJ 07901.	Vioform Antiseptic Dusting Power, Vioform Cream, Vioform Ointment, Vioform-Hydrocortisone Cream, Vioform-Hydrocortisone Mild Cream, Vioform-Hydrocortisone Ointment, Vioform-Hydrocortisone Mild Ointment, Vioform-Hydrocortisone Lotion.
Clapp, Otis, and Son, Inc., Cambridge, MA 02139.	Obtundia Antiseptic Swab Pads, Obtundia First Aid Spray, Obtundia Surgical Dressing.
Cramer Products, Inc., Gardner, MA 01930.	Cramer Foot Ointment, Fung-O-Spray.
Gaddy, R. L., Tallahassee, FL 32302.	Ez-It Liquid.
Gillette Medical Evaluation Laboratories, Rockville, MD 20850.	Foot Guard Power, Foot Guard Spray.
Laboratory Robaina, Inc., Hialeah, FL 33010.	Acetolia Robaina.
La Wall and Harrison Research Laboratories, Inc., Philadelphia, PA 19103.	Ecco Medicated Powder.
Magnesia Products, Inc., Dayton, OH 45404.	Sporodyne.
Norwich Pharmacol Co., Norwich, NY 13815.	NP-27 Aerosol, NP-27 Cream, NP-27 Liquid, NP-27 Powder.
Pennwalt Corp., Rochester, NY 14603.	Cruex Medicated Cream, Cruex Medicated Spray-On Powder, Desenex Ointment, Desenex Powder, Desenex Solution, Desenex Spray-On Foot Powder, Ting Antiseptic Medicated Cream.
Plough, Inc., Memphis, TN 38151.	Aftate Antifungal Gel, Aftate Antifungal Powder, Aftate Antifungal Spray Liquid, Aftate Antifungal Spray Powder.
Purdue Frederick Co., Norwalk, CT 06856.	Isodine Athlete's Foot Solution.
Red Foot Products Co., Inc., Detroit, MI 48228.	Red Foot Powder.
Rilox Co., New Orleans, LA 70122.	Geneva Ointment.
Rorer, William H., Inc., Fort Washington, PA 19034.	Carfusin.
Ryslan Co., Inc., Little Falls, NJ 07424.	Prophylin Ointment, Prophylin Powder.
Schattner, R. Co., Washington, D.C. 20016.	Chloraderm.
Schering Corp., Bloomfield, NJ 07003.	Tinactin Cream, Tinactin Powder, Tinactin Powder Aerosol, Tinactin Solution, Tinactin Solution Aerosol.
Scholl, Inc., Chicago, IL 60610.	Solvex Athlete's Foot Liquid, Solvex Athlete's Foot Ointment, Solvex Athlete's Foot Powder, Solvex Athlete's Foot Spray Powder, Solvex Athlete's Foot Spray.
Smith, Kline, and French Laboratories, Philadelphia, PA 19101.	Pragmatar.
Sterling Drug, Inc., New York, NY 10016.	Campho-Phenique Liquid, Campho-Phenique Powder.
Stiefel Laboratories, Inc., Oak Hill, NY 12460.	Salicylic Acid and Sulfur Soap.
Texas Pharmacol Co., San Antonio, TX 78296.	Verdefam Cream, Verdefam Solution.
Upjohn Co., Kalamazoo, MI 49001.	Fluid Salicresin, Medicated Foot Powder.
Wade Chemical Corp., Shreveport, LA 71103.	Jim Wade Foot Powder.

Firms	Marketed products
Westwood Pharmaceuticals, Inc., Buffalo, NY 14213.	Halotex Cream, Halotex Solution.
Wyeth Laboratories, Inc., Philadelphia, PA 19101.	Sopronol Ointment, Sopronol Powder, Sopronol Solution.
Young, W. F., Inc., Springfield, MA 01101.	Absorbine Athlete's Foot Powder, Absorbine Jr.
In addition, the following firms or groups provided related information:	
Carbisulphoil Co., Dallas, TX 75204.	Sulfur.
Clairol Research Laboratories, Stamford, CT 06902.	Resorcinol.
Dermik Laboratories, Inc., Syosset, NY 11791.	Coal tar.
Ferro Corp., Washington, D.C. 20014.	Chloroxylenol.
Givaudan Corp., Clifton, NJ 07014.	Dichlorophen.
Johnson and Johnson, New Brunswick, NJ 08903.	Miconazole nitrate, Miconazole nitrate/hydrocortisone, talc.
Norcliff Thayer, Inc., Tuckahoe, NY 10707.	Tolindate.
Pennwalt Corp., Rochester, NY 14603.	Calcium undecylenate/hydrocortisone, chloroxylenol, fungicidal testing.
Purdue Frederick Co., Norwalk, CT 06856.	Povidone-iodine.
Proprietary Association, Washington, DC 20006.	OTC labeling terminology, use of a guinea pig model in product testing.
Reckitt and Colman, Hull, England.	Chloroxylenol.
Richardson-Merrell, Inc., New Rochelle, NY 10801.	Resorcinol.
Schattner, R. Co., Washington, DC 20016.	Phenol/phenolate sodium.
Schering Corp., Bloomfield, NJ 07003.	Tolnaftate/nystatin, professional labeling.
Schuykill Chemical Co., Philadelphia, PA 19132.	Alcloxa, allantoin.
Sterol Controls Co., East Northport, NY 11731.	Candididin.
U.S. Borax Research, Anaheim, CA 92801.	Boric acid.
Warner-Lambert Co., Morris Plains, NJ 07950.	Methyl salicylate.
Westwood Pharmaceuticals, Inc., Buffalo, NY 14213.	Professional labeling.
Young, W. F., Inc., Springfield, MA 01101.	Chloroxylenol, in vivo guinea pig studies.

B. Ingredients Reviewed by the Panel

1. Labeled ingredients contained in OTC marketed products submitted to the Panel.

Acetone
Alcohol
Aluminum chlorhydroxyallantoinate
Aluminum potassium sulfate
Aluminum sulfate
Aluminum sulphate
Anhydrous ethanol
Aromatic oils
Basic fuchsin
Bentonite
Benzethonium chloride
Benzocaine
Benzoic acid
Benzyl alcohol
Boric acid
Calcium silicate
Calcium undecylenate
Camphor
Cetyl alcohol-coal tar distillate¹
Chlorophyll
Chlorothymol

¹ In this document, this mixture will be considered as two separate ingredients—coal tar and cetyl alcohol.

Chloroxylenol
Chlorthymol
Cinnamaldehyde
Coal tar
Copper undecylenate
Corn starch
Dichlorophene (G-4)
Diethyl sebacate
Diethyl sodium sulfosuccinate
Essential oils
Eucalyptol
Glycerin
Glycerine
Hexadecyl alcohol
Hydroxyquinoline
8-Hydroxyquinoline
8-Hydroxyquinoline benzoate
8-Hydroxyquinoline sulfate
Iodochlorhydroxyquin
Isopropyl alcohol
Magnesium carbonate
Magnesium stearate
Menthol
Meta-cresol
Methylparaben
Methyl salicylate
Oil of pine
Orthochloromercuriphenol
Orthohydroxyphenylmercuric chloride
Oxyquinoline
Oxyquinoline sulfate
Parachlorometaxylenol
Petrolatum
Phenol
Phenyl Salicylate
Polyethylene glycol 400
Polyethylene glycol 4000
Polyvinylpyrrolidone
Polyvinylpyrrolidone-iodine
Potassium sulfate
Propionic acid
n-Propyl alcohol
Propyl alcohol
Propylene glycol
Propylparaben
Resorcinol
Salicylic acid
Secondary amyltricrosols
Sodium borate
Sodium caprylate
Sodium dioctylsulfosuccinate
Sodium phenolate
Sodium propionate
Starch
Sulfur
Sulphur
Talc
Talcum
Tannic acid
Thymol
Tincture benzoin compound
Tolnaftate
Triacetin
Trimethyloctadecadienyl ammonium chloride
Trimethyloctadecenyl ammonium chloride
Undecylenic acid
Wormwood

Zinc caprylate
Zinc oxide
Zinc propionate
Zinc stearate
Zinc undecylenate

2. Other ingredients reviewed by the Panel.

Candididin
Haloprogin
Hydrocortisone
Hydrocortisone acetate
Miconazole nitrate
Nystatin
Tolindate

C. Classification of Ingredients

1. *Ingredients identified by the Panel as active antifungal ingredients.* The Panel has adopted the following nomenclature for the active ingredients reviewed in this document. Where applicable, other nomenclature has been included in parentheses for purposes of clarification.

Aluminum salts
Alcloxa (aluminum chlorhydroxyallantoinate)
Aluminum sulfate (aluminum sulphate)
Potassium alum (aluminum potassium sulfate)
Basic fuchsin
Benzethonium chloride
Benzoic acid
Borates
Boric acid
Sodium borate
Camphor
Candididin
Caprylates
Sodium caprylate
Zinc caprylate
Chlorothymol (chlorthymol)
Chloroxylenol (parachlorometaxylenol)
Coal tar (coal tar distillate)
Cresols
m-Cresol (meta-cresol)
Secondary amyltricrosols
Dichlorophen (dichlorophene (G-4))
Haloprogin
Iodochlorhydroxyquin
Menthol
Miconazole nitrate
Nystatin
Oxyquinolines
Benzoxiquine (8-hydroxyquinoline benzoate)
Oxyquinoline (8-hydroxyquinoline and hydroxyquinoline)
Oxyquinoline sulfate (8-hydroxyquinoline sulfate)
Parabens
Methylparaben
Propylparaben
Phenolates
Phenol
Phenolate sodium (sodium phenolate)

Phenyl salicylate
Povidone iodine
Propionic acid and its salts
Sodium propionate
Zinc propionate

Resorcinol
Salicylic acid
Sulfur (sulphur)
Tannic acid

Thymol
Tolindate
Tolnaftate

Triacetin

Undecylenic acid and its salts

Calcium undecylenate
Copper undecylenate
Zinc undecylenate

2. *Ingredients identified by the Panel as inactive or pharmaceutically necessary ingredients.* The following ingredients have been carefully reviewed by the Panel as possible antifungal agents. Based on the available literature and in some cases based on concentrations reported in a submission, the Panel considers the following to be inactive ingredients when used in products labeled for fungal infections of the foot, body, or groin. In general, most are used as pharmaceutical aids (solvent, vehicle, dispersant, or preservative) or as product identification materials.

Acetone
Alcohol
Aromatic oils
Bentonite
Benzyl alcohol
Calcium silicate
Cetyl alcohol (hexadecyl alcohol)
Chlorophyll
Cinnamaldehyde
Compound benzoin tincture (tincture benzoin compound)
Corn starch (starch)
Dehydrated alcohol (anhydrous ethanol)
Diethyl sebacate
Diethyl sodium sulfosuccinate (sodium dioctylsulfosuccinate)
Essential oils
Eucalyptol
Glycerin (glycerine)
Isopropyl alcohol
Magnesium carbonate
Magnesium stearate
Methyl salicylate
Oil of pine
Petrolatum
Polyethylene glycol 400
Polyethylene glycol 4000
Polyvinylpyrrolidone
Propyl alcohol (*n*-propyl alcohol)
Propylene glycol
Talc (talcum)
Trimethyloctadecadienyl ammonium chloride
Trimethyloctadecenyl ammonium chloride
Wormwood oil (wormwood)

Zinc oxide
Zinc stearates

3. *Nonantifungal ingredients reviewed under combination products.* See part III, paragraph D. below—Combination Products Used in the Treatment of Athlete's Foot, Jock Itch, and Ringworm.

Benzocaine
Hydrocortisone
Hydrocortisone acetate

4. *Ingredient referred to the Advisory Review Panel on OTC Miscellaneous External Drug Products.*

o-Mercufenol chloride (ortho-chloromercuriphenol and ortho-hydroxyphenylmercuric chloride)

5. *Products referred to other advisory review panels.*

Products for the treatment of swimmer's ear were referred for review to the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Products. Products for the intravaginal treatment of vaginitis were referred for review to the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products. Products for the treatment of dandruff and seborrhea were referred for review to the Advisory Review Panel on OTC Miscellaneous External Drug Products.

A notice of transfer of responsibility for the review of OTC drug products for the treatment or prevention of dandruff or seborrhea was published in the Federal Register of March 6, 1979 (44 FR 12271).

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notice published in the Federal Register of December 16, 1972 (37 FR 26842). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after April 22, 1982, in the Docket Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statement and Recommendations

A. Definitions

The Panel adopted the following definitions related to the use of topical antifungal drug products:

1. *Antifungal agent.* An agent which either kills or inhibits the growth and reproduction of fungal cells.

2. *Athlete's foot.* In common usage the term "athlete's foot" is applied to any

chronic, acute, or recurrent rash occurring on the soles of the feet or between the toes, regardless of cause. In this document, however, the term "athlete's foot" is restricted to infections of the feet caused by dermatophytic fungi. The active rash is usually itchy, red, and scaling. Often, the toe webs (spaces between the toes) are white and soggy and painful cracks may occur between the toes. There may be small water blisters and pustules on the soles. The term "jungle rot" is also used to describe athlete's foot, particularly by men who developed the condition during military service in hot, humid climates. Secondary bacterial infections often accompany the underlying fungal infection.

3. *Dermatophytes.* A group of taxonomically related fungi which normally live in soil, where they metabolically decompose organic keratinous debris through the enzymatic digestion of keratin (a fibrous protein also found in cornified epidermis). Many of these fungi cause superficial skin infections including athlete's foot, jock itch, and ringworm in humans and in animals by invading and living in the cornified epidermis or in the hair or nails. These fungi are subdivided and classified according to their usual source of isolation from soil, from animals, or from man.

The dermatophytic fungi most commonly mentioned in this document include *Trichophyton rubrum* (*T. rubrum*), *Trichophyton mentagrophytes* (*T. mentagrophytes*), and *Epidermophyton floccosum* (*E. floccosum*). These organisms are the most frequent causes of human infections in the United States, but other strains may be involved.

4. *Dermatophytosis.* Any superficial infection in humans or animals caused by dermatophytic fungi. In this document, athlete's foot, jock itch, and ringworm represent types of dermatophytosis.

5. *Fungicidal agent.* An agent that kills fungi.

6. *Fungistatic agent.* Traditionally, an agent that inhibits the growth or reproduction of fungal cells, but allows later culturing of viable fungal cells when contact with the agent is removed. However, more modern approaches to the destruction of microbial cells have emphasized that agents described as either fungicidal or fungistatic kill the exposed fungal cells, but at different rates. A fungicidal agent kills the fungal cells more rapidly, whereas a fungistatic agent may permit cell reproduction for several generations before cell death is observed.

7. *Fungus*. The term "fungi" or the plural "fungi" encompasses a diverse group of organisms which includes yeasts and molds. Although the general term is used, this document most often refers to a specific group, the dermatophytic fungi. This group includes yeastlike and moldlike organisms and some with the morphological characteristics of both.

8. *Intertrigo*. An inflammatory skin eruption occurring in any skin-fold area. Intertrigo develops when opposing skin surfaces, such as those of the upper thigh and lower abdomen surrounding the groin, rub against each other and trap moisture, creating a warm, moist environment that favors the proliferation of microorganisms, including bacteria and fungi.

9. *Jock itch*. In common usage the term "jock itch" refers to a chronic and recurrent rash, regardless of cause, which occurs on the upper inner thighs of men and sometimes extends into the groin and pubic areas. Jock itch is usually caused by dermatophytic fungi, and in this document jock itch is limited to dermatophyte infections. This rash may also be referred to as "crotch rot" or "Dhobie itch." When active, the rash is usually red, scaling, and itchy, with a well-defined border along the inner thigh.

Women may develop the same rash, but much less commonly than men. The Panel is not aware of any common designation given to this skin condition in women. The general term "intertrigo" could be used to describe the condition in women, although the use of this term is not strictly limited to the groin area.

10. *Potassium hydroxide (KOH) preparation*. This laboratory test (called KOH preparation) is performed to help confirm a diagnosis of a superficial fungus infection of the skin, including one caused by dermatophytes and other types of fungi, such as *Candida albicans* (*C. albicans*). Although a positive KOH may mean the presence of a dermatophytic fungus, it will not distinguish between different genera or species of dermatophytes. And a negative KOH does not definitely rule out the presence of fungi. In performing the test, skin scrapings from recently formed, enlarging lesions are placed on a glass slide and treated with a few drops of 10 to 20 percent KOH. The slide is then gently heated and microscopically examined for fungal hyphae (threadlike filaments).

11. *Ringworm*. In common usage the term "ringworm" is applied to any ring-shaped lesion on the skin. This document, however, limits the term to skin infections caused by dermatophytic fungi. Such lesions usually have a clear

center and an active border which is red and scaling. Ringworm may also be used generally to describe any superficial fungus infection of the skin, hair, or nails, even when individual skin lesions are not ring shaped. For example, "ringworm of the groin" refers to jock itch. A common misconception is that ringworm involves a "worm" in the skin.

In scientific usage the Latin word "tinea" is generally combined with another Latin word designating the location of the fungal infection, i.e., *tinea capitis*—ringworm of the scalp; *tinea corporis*—ring-shaped or other fungal lesion on the hairless parts of the body; *tinea cruris*—jock itch; *tinea pedis*—athlete's foot.

12. *Wood's light*. This light is used to help detect some fungal and bacterial infections on the skin. It consists of an ultraviolet light source which shines through glass composed mainly of barium silicate with nickel oxide. The transmitted light rays with a wavelength above 3,650 angstrom units cause some microorganisms to fluoresce due to the chemicals they produce. The Wood's light is particularly useful in diagnosing ringworm of the scalp, since hairs infected by the dermatophytic fungi *Microsporum canis* (*M. canis*) and *Microsporum audouinii* (*M. audouinii*) fluoresce a brilliant green because the chemical, pteridine, is formed in the hair.

Ringworm lesions caused by these same organisms on the skin do not fluoresce under the Wood's light. Neither do the fungi that most commonly cause athlete's foot and jock itch. But the Wood's light can detect specific bacteria which induce conditions on the feet and in the groin that mimic athlete's foot and jock itch. The major types of bacteria thus detected include *Pseudomonas aeruginosa* (*P. aeruginosa*), which causes infection in macerated toeweb, and *Corynebacterium minutissimum* (*C. minutissimum*), which causes erythrasma in the toeweb and groin.

B. Types of Fungal Infections

Although all surfaces of the human body can be infected by one or another of the various microorganisms that cause fungal infections of the skin, the Panel has concentrated on fungal infections of the foot and the groin and on ringworm of the body excluding the scalp and nails. Fungal infections of the foot and groin often occur in the same individual.

The names of fungi in mycological literature number more than 200,000, according to Emmons, Binford, and Utz (Ref. 1). Many are earlier names; many others are names that have been given

to minor variations of fungi. For example, other names for *T. mentagrophytes* include *Microsporum mentagrophytes* (*M. mentagrophytes*), *Trichophyton gypseum* (*T. gypseum*), and *Trichophyton interdigitale* (*T. interdigitale*). This document will use the names that appear in the cited references.

The pathogenic fungi that cause athlete's foot are also commonly found in jock itch (Ref. 2). The fungi most commonly isolated from the feet and the groin are *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*. Of these, *T. rubrum* is more prevalent in infections of the feet; *E. floccosum* is more prevalent in the groin. These organisms may vary with a patient's sex, age, ethnic group, or geographic location.

1. *Tinea pedis* (athlete's foot). Athlete's foot usually begins in men between the ages of 15 and 40 years. It is uncommon in children before puberty. Women develop athlete's foot much less commonly than men. The infection may begin in the web spaces of the toes or on the sole. Itching and burning are the common symptoms, but the clinical picture varies from the moist web to the relatively dry soles.

In the toeweb, white scale is common especially between the fourth and fifth toe. Vesicles (blisters) and pustules (pus-filled sweat pores or hair follicles) may also occur. The skin may crack, probably causing the burning sensation.

On the sole, irregularly grouped vesicles and superficial scale are common, but athlete's foot rarely produces the "ringworm" shape that is considered characteristic of fungal infections in other sites. The disease may produce only slight scales and little significant inflammation (vesicles or erythema). With such a variety of lesions, a KOH preparation of skin scrapings is usually necessary to accurately differentiate *tinea pedis* from all the other diseases which mimic it and are sometimes called "athlete's foot." A fungal culture will confirm the presence of fungi and enable identification of the specific fungus.

If the infection persists, the appearance of the lesion can change and the infection may spread to other areas. Chronic athlete's foot usually produces either a superficial scale on both soles or white, scaling lesions in the web spaces. Sometimes both the soles and the web spaces are affected. The toenails are commonly involved, and fungus may invade and destroy the nail plate.

2. *Tinea cruris* (jock itch). Jock itch is most common in young men (ages 18 to 40 years) and is rarely seen in

pubertal children. The initial infection occurs on the upper inner thigh near the genito-crural crease. It spreads downward, to the side, and onto the scrotum. Frequently the result is a semicircle and not a "ring." The expanding margin is slightly raised and scaling; the clearing center is stained a light brown by the resolving inflammation. Vesicles and pustules are uncommon.

3. *Tinea corporis* (ringworm of the body). Ringworm of the body is the most common type of dermatophyte infection before puberty. It is commonly caused by *M. canis*, an organism which can be carried by dogs and cats. Ringworm of the body usually forms ring-shaped lesions, erythema and scaling at the margins, and relatively clear centers.

4. *Tinea capitis* (ringworm of the scalp) and *tinea unguium* (ringworm of the nails). Fungal infections of the scalp and nails tend to be chronic. They respond poorly to topical therapy, partly because of the thickness of the nails and the depth of the hair roots. Both sites of infection provide inaccessible locations for fungi, thus drastically decreasing the penetration of topical antifungals. For this reason, OTC topical antifungals must be labeled that they are not effective for the treatment of ringworm of the scalp or nails.

References

- (1) Emmons, C. W., C. H. Binford, and J. P. Utz, "Medical Mycology," 2d Ed., Lea and Febiger, Philadelphia, pp. 2 and 138, 1970.
- (2) Beare, J. M., J. C. Gentles, and D. W. R. Mackenzie, "Textbook of Dermatology," 2d Ed., Edited by A. Rook, D. S. Wilkinson, and F. J. G. Ebling, Blackwell Scientific Publications, Oxford, Eng., pp. 714-716, 1972.

C. Diseases That May Simulate Athlete's Foot or Jock Itch

There are several less common skin conditions that may affect the feet and the groin and cause symptoms that mimic athlete's foot and jock itch. These conditions may be misdiagnosed as athlete's foot or jock itch. Common examples of such conditions include the following: candidiasis, a yeast infection; allergic contact dermatitis; psoriasis; and hyperhidrosis (excessive perspiring) which may be associated with maceration of the skin and an inflammatory eruption known as dyshidrotic eczema.

1. *Candidiasis* (moniliasis). This infection is caused by *Candida* species, usually *C. albicans*, a yeast which is pathogenic under certain circumstances. The organism thrives on warm, moist areas of the body, such as the toewebs and groin. On the feet, the symptoms of candidiasis are redness, maceration,

and fissuring of the toewebs. In the groin, the infection produces itchy, bright-red, exuding patches with numerous pustules along the outer edge. In men the eruption frequently spreads to involve the scrotum and the skin around the rectum. In women the eruption is similar but is usually associated with extreme itching and with a discharge if the vagina is infected. Candidiasis in the groin is often secondary to proliferation of *C. albicans* in the digestive tract following a disturbance of normal intestinal bacterial flora. Numerous factors predispose the patient to develop candidiasis, including diabetes, pregnancy, obesity, and profuse sweating. Birth control pills, oral corticosteroid drugs, or broad-spectrum antibiotics may also predispose to candidiasis.

The diagnosis of candidiasis is confirmed by finding the organism in a KOH preparation of skin scrapings, where it appears as long pseudohyphae associated with clusters of oval, budding, thin-walled yeast cells. The organism may be easily cultured on Dermatophyte Test Medium (DTM), Mycosel[®], Sabouraud's Glucose Agar, or equivalent media.

2. *Allergic eczematous contact dermatitis*. Allergy to shoes is usually caused by the rubber in the insoles. It can, however, be caused by dyes or tanning agents. The area of dermatitis will correspond to the part of the shoe containing the allergen. For persons who are allergic to the sponge rubber insoles, the usual pattern of dermatitis is on the arch of the foot, with less involvement on the thickly keratinized sole. At this site, there may be erythema, scale, and visible blistering. The toewebs are not involved and unless the disease is severe and longstanding, the toenails will remain normal.

3. *Bacterial infection of the feet*. Bacterial infection of the feet is usually limited to the toewebs. It is a common secondary infection occurring with fungal disease. The bacterial infection may be acutely inflammatory and is usually caused by gram-negative bacteria, such as *Pseudomonas*. Odor, pus, and a yellowish-green color are all suggestive of a gram-negative infection of the toewebs.

4. *Erythrasma*. Erythrasma is a common bacterial infection which causes macerated scale in the toewebs (Ref. 1). It is frequently seen in adolescence and young adulthood, where it tends to involve the third and fourth toewebs bilaterally (Ref. 2). The infection is caused by *Corynebacterium minutissimum*, an aerobic gram-positive diptheroid, or by several other

fluorescent diptheroids. Erythrasma is diagnosed by exposing the foot to a Wood's light and detecting a bright coral-red color, resulting from the fluorescence of porphyrin pigments produced by the bacteria (Ref. 3). Skin scrapings with staining of the scales will reveal gram-positive slender rods, filaments, and coccoid forms.

Erythrasma may also involve the inner thighs, where it is often misdiagnosed as jock itch. The eruption appears as irregular, well-circumscribed, reddish-brown patches with fine scales and slight wrinkling of the skin. Here, too, the diagnosis is confirmed by Wood's light.

5. *Psoriasis*. Psoriasis, a disease of unknown cause, may cause lesions of the feet and groin which closely resemble athlete's foot and jock itch. On the feet, psoriasis usually produces dry, red, scaly plaques which are sharply margined, and symmetrical, and often limited to pressure points. Maceration is sometimes present between the toes. The toenails are likely to be pitted and thickened, and may resemble toenails infected by fungus. In the groin, psoriasis usually produces red plaques which may be either scaly or macerated.

Psoriasis of either the feet or groin can be more readily diagnosed if the typical red, scaly lesions are also found on the knees, elbows, and scalp.

6. *Dyshidrosis*. Dyshidrosis is a recurrent noninflammatory eruption of the palms and soles. Occasionally it may involve only the feet and is difficult to distinguish from athlete's foot. Although most people with dyshidrosis also have hyperhidrosis of the hands and feet, the relationship between dyshidrosis and abnormal functioning of the underlying sweat glands remains unclear. Attacks of dyshidrosis tend to be worse during warm weather and are sometimes precipitated by emotional stress.

Dyshidrosis begins suddenly with crops of itchy, deeply set, clear or white blisters on the palms and soles and on the sides of the fingers and toes. Involvement on the feet is usually symmetrical and favors the high part of the instep. The blisters sometimes merge to form large blisters, which may rupture, ooze fluid, and develop secondary bacterial infection. An attack of dyshidrosis usually subsides spontaneously after 2 to 3 weeks, resolving with peeling.

In contrast to most cases of athlete's foot, dyshidrosis does not cause the sole to become red and scaly. Nevertheless, the presence or absence of fungi in dyshidrosis should be determined with a KOH preparation and fungal culture.

References

- (1) Sarkany, L. D. Taplin, and H. Blank, "Erythrasma—Common Bacterial Infection of the Skin," *Journal of the American Medical Association*, 177:130-132, 1961.
- (2) Munro-Ashman, D., R. S. Wells, and Y. M. Clayton, "Erythrasma in Adolescence," *British Journal of Dermatology*, 75:401-404, 1963.
- (3) Partidge, B. M. and F. L. Jackson, "The Fluorescence of Erythrasma," *British Journal of Dermatology*, 74:326-328, 1962.

D. Factors That May Affect the Development of Fungal Infections

The development of a fungal infection, such as athlete's foot or jock itch, depends on multiple factors that influence susceptibility to these diseases. Primary among these factors is exposure to *T. mentagrophytes*, *T. rubrum*, and *E. floccosum*. These fungi are common in homes, offices, and athletic facilities; yet most adults and children do not have chronic athlete's foot or jock itch. The rate and prevalence of these superficial fungal infections are obviously related to many factors other than exposure to pathogenic organisms. Two important factors are local environmental and climatic conditions and the body's natural immunity.

1. *Environmental factors.* Fungal infections are difficult to establish naturally or experimentally on normal, dry skin. Conversely, skin damage (cracks, blisters, other infections) and increased moisture (from tight shoes, excessive sweating, humid summer weather, tropical climate) contribute to the development and continuation of athlete's foot and jock itch (Ref. 1). Some fungal infections can be prevented and others terminated simply through control of the local environment and improvement in the patient's hygiene.

2. *Natural immunity.* Fungal skin infections can be established in natural or experimental settings when those exposed have never had a fungal skin infection (Ref. 2). Such individuals are called nonimmune or "virgin" in medical parlance. Once a fungal infection has been established in the skin, certain fungal components (antigens) diffuse through the skin where they are exposed to the white blood cells. These antigens sensitize the white blood cells so that further exposure to fungal antigens attracts white blood cells to the site of skin infection.

When the sensitized white blood cells are in the area of fungal infection, they act as "killer cells" to destroy the fungi, producing a spontaneous clinical "cure." The previously infected host is now immune and repeated exposure to fungi results in either no infection or in a very brief inflammatory one (Ref. 2).

Immunity can be detected with the trichophytin (fungal antigen) skin test; a hard, red papule occurs 24 to 48 hours following injection into the skin. Because the immunity is mediated by the white blood cells, it is called cell-mediated immunity.

Not all individuals develop cell-mediated immunity during their first fungal infection so that spontaneous clinical "cures" are rare in this group. Many of these people have asthma, hay fever, or atopic eczema and do not develop 48-hour reactions to injected fungal antigens (Refs. 2 and 3). However, they will develop immediate reaction (wheal and flare) to trichophytin, a reaction which represents the presence of antibodies. Apparently, antibodies are not effective in destroying superficial fungi, possibly because they cannot reach the outer surface of the skin. Such individuals commonly develop chronic athlete's foot or jock itch.

There are other factors, such as circulating inhibitory agents, which influence the host's immunity, but these are not well understood (Ref. 4).

a. *Dermatophytid ("id").* The dermatophytid reaction is a response of the skin to a localized fungal infection caused by dermatophytes. The original concept of the "id" response was that a hapten (partial antigen) moved from the feet through the bloodstream to the skin of the body, causing a skin reaction similar to contact dermatitis. The eruption was free of the fungi noted in the original focal infection. Current data, however, suggest that sensitized T-cells (thymus-influenced lymphocytes sensitized to trichophytin) react to a carrier protein in the skin of the hands which is identical to the protein in the skin of the feet. This reaction results in the release of lymphokinin and the destruction of tissue. To date, trichophytin antigen has not been found in the bloodstream.

Symptoms of an "id" reaction may be fever, malaise, and loss of appetite. Enlarged lymph nodes, enlarged spleen, and an increased white blood cell count are occasionally noted. The skin lesions may be localized or generalized. The most common localized dermatophytid reaction is the vesicular dermatitis noted primarily between the fingers and on the palmar surface of the hands (Ref. 5). When the eruption is widespread, the primary lesions are usually follicular papules (small bumps arising about hair follicles) which may become hard, leathery, and scaly. Other skin lesions may include erythema nodosum (tender, red nodules), urticaria (hives), and erythema annulare centrifugum (a chronic skin eruption in the form of

rings). There may also be migratory superficial thrombophlebitis.

b. *Skin test for tinea infections:* Trichophytin (T). Trichophytin (T), a glycoprotein commercially prepared from the filtrate or broth used to grow several *Trichophyton* species, is used to determine immediate and delayed sensitivity to the *Trichophyton* hapten. Immediate reactions (20 minutes or less) may be noted in certain individuals who have chronic tinea infections. The immediate reaction may also be noted in persons with hives following acute infection, i.e., acute dermatophytosis. The delayed reaction to trichophytin is more common and may be noted in persons who have clinical symptoms and signs of active infection as well as in those without clinical infection. This kind of reaction may be most intense when a person has a kerion (massive acute inflammatory infiltrate in the skin) or a dermatophytid.

The delayed reaction to trichophytin can be used as a tool to evaluate a portion (efferent links) of cell-mediated immunity; it may also be helpful in studies of the epidemiology of tinea infections. But the delayed reaction cannot be used therapeutically to reduce the risk of infections by these organisms.

References

- (1) Allen, A. M., and D. Taplin, "Epidemic *Trichophyton mentagrophytes* Infections in Servicemen. Source of Infection, Role of Environment, Host Factors, and Susceptibility," *Journal of the American Medical Association*, 226:864-867, 1973.
- (2) Jones, H. E., J. H. Reinhardt, and M. G. Rinaldi, "Immunologic Susceptibility to Chronic Dermatophytosis," *Archives of Dermatology*, 110:213-220, 1974.
- (3) Hanifin, J. M., L. E. Ray, and W. C. Lobitz, Jr., "Immunological Reactivity in Dermatophytosis," *British Journal of Dermatology*, 90:1-8, 1974.
- (4) Lorincz, A. L., J. O. Priestley, and P. H. Jacobs, "Evidence for a Humoral Mechanism which Prevents Growth of Dermatophytes," *Journal of Investigative Dermatology*, 31:15-17, 1958.
- (5) Moschella, S. L., D. M. Pillsbury, and H. J. Hurley, Jr., "Dermatology," Vol. 1, W. B. Saunders Co., Philadelphia, pp. 660-661, 1975.

E. Consumer Use of Topical Antifungal Drug Products

The Panel recognizes that safe and effective topical medications for the treatment of athlete's foot, jock itch, and ringworm are useful to the general public and should be available on the OTC market.

To illustrate the scope of the problem of treating athlete's foot, the Panel offers the following quotation by Mitchell (Ref. 1):

It is an interesting fact that some patients have had a macerations [sic] and the fissures about the toes for so many years that they have come to regard the condition as perfectly normal, and will sometimes be somewhat indignant when it is pointed out to them that they have an infection.

Although no information was submitted on factors that influence the consumer's choice of topical antifungal drug products, the Panel suspects that there are several. Among these factors are media advertising, advice of a pharmacist, and suggestions from friends and acquaintances. The Panel also believes that most cases of athlete's foot, jock itch, and ringworm are self-diagnosed and self-treated by the consumer before a physician is consulted. The severity of symptoms, along with physician availability and cost, probably influence the duration of self-medication. Often the symptoms are mild enough to be little more than a nuisance, and the consumer may even accept them as "normal." The Panel suspects that many consumers do not realize that athlete's foot, jock itch, and ringworm are caused by fungi.

The Panel is concerned that many of these antifungal products may be used daily for months or even years with questionable benefit and possibly harmful side effects. For example, prolonged application of medication to chronic, persistent athlete's foot can produce skin sensitization and irritation without eradicating the underlying fungus. Such prolonged use on soggy toeweb or in a macerated groin with areas of broken skin can lead to the absorption and accumulation in tissue of certain ingredients that eventually could produce toxic effects. The Panel is also concerned that some products used to treat jock itch may be applied inappropriately over large areas of skin, thus leading to increased absorption of certain potentially toxic ingredients.

The Panel realizes that consumers' habits of self-medication and personal hygiene vary greatly. For example, some consumers may continue to use a product indefinitely that gives only symptomatic relief instead of looking for a more effective product. Others would probably discontinue any form of medication as soon as the signs and symptoms improve or disappear. Some consumers routinely use a foot powder to decrease sweating and promote drying. Consumers also choose varying types of footwear: some wear heavy shoes and occlusive socks or stockings that increase sweating and favor the development of athlete's foot; others wear lightweight, nonocclusive shoes or

sandals which promote drying of the feet.

The Panel concludes that in order to best serve all consumers, an OTC product must provide more than temporary symptomatic relief of athlete's foot, jock itch, and ringworm. Such products must contain a Category I antifungal ingredient capable of killing the fungus.

Reference

(1) Mitchell, J. H., "Further Studies on Ringworm of the Hand and Feet," *Archives of Dermatology and Syphilology*, 5:174-197, 1922.

F. Availability of Antifungal Agents From Ointments, Creams, Powders, and Aerosol Sprays

Most antifungal materials are active in low concentrations and are usually incorporated into suitable vehicles for convenient application. Vehicle selection depends on many factors including consumer acceptance. But deviations from the theoretical ideal vehicle may tend to decrease the effectiveness of an antifungal agent in vivo. The following discussion, which is included to review the effects of vehicles and possible problems relating to availability of the active antifungal agent, is based on the Panel's general knowledge. Accordingly, there may be exceptions to the statements made, and none of the statements should be interpreted as reflecting adversely on any product which uses the kind of vehicle under discussion. Data on vehicles were not submitted to the Panel. (For a more detailed discussion of drug release from topical preparations, see the report on topical antibiotic products in the *Federal Register* of April 1, 1977 (42 FR 17647).)

Most antifungal agents are designed to be used on broken, denuded, diseased, or infected skin. The objective of any form of treatment is to deliver the antifungal chemical to the fungus in sufficient concentration to exert its antifungal activity. In athlete's foot, jock itch, and ringworm, the skin may be intact, or it may be inflamed, scaly, irritated, or fissured. In general, the most effective way to deliver an antifungal agent is to have the agent solubilized in an appropriate vehicle. Then the only obstacle to reaching an adequate concentration at the site of action is the rate at which the agent moves through the vehicle to reach the site (rate of diffusion). The rate of diffusion of an antifungal agent in solution in a nonviscous (watery) vehicle is fast enough so that there would be no obstacle to reaching an adequate concentration at the site of action.

Other factors, however, must be considered when choosing a vehicle for a given product. For example, an aqueous solution of an antifungal agent would not necessarily be the best for treating jock itch or athlete's foot because it would tend to run off the site of application so rapidly that contact time would be too short and action would be slight. A semisolid (viscous) dosage form, however, tends to hold an antifungal agent at the site somewhat longer than aqueous solutions.

Ointments have been popular vehicles for antifungal agents for many years. The term "ointment" at one time connoted a thick, greasy, water-repellent preparation as typified by white petrolatum. More modern pharmaceutical references to ointments include materials such as polyethylene glycols, which have varying viscosities and are water soluble. Ointments differ in degree of water solubility and miscibility. Petrolatum is water insoluble and immiscible; polyethylene glycols, to a varying degree, are water soluble and miscible. The major similarity between these vehicles is their viscosity. Between these extremes are other preparations with their own solubility and miscibility characteristics.

Vehicle solubility also influences the effectiveness of antifungal agents. Water-insoluble or repellent vehicles may tend to retard the release of medicaments to the skin. Water-insoluble or repellent vehicles may not adhere if the skin is broken and has serum in a fissure or wound. They may also be repelled from intact skin that is moist with sweat. In such vehicles moisture and serum may reduce the intimate contact of the medication with the infected site. Once the product contacts the skin, the antifungal agent must diffuse to the interface between the product and skin. It must then move from the vehicle to the aqueous milieu, where it can exert its antifungal activity.

In contrast, if the vehicle is a water-soluble polyethylene glycol type, both the vehicle and the antifungal agent dissolve in the serum or moisture and no partitioning needs to take place. Then the controlling factor becomes solely the rate of diffusion. Thus water-soluble vehicles may have certain advantages over water-insoluble vehicles in delivering the drug to the site of action. However, considerations such as solubility of the drug in the vehicle, site of application, type of skin condition, patient preference, and other factors also influence the final decision on which vehicle should be used for a given product.

The viscosity of a vehicle may simultaneously be an advantage and a disadvantage. For example, a viscous vehicle may adhere better to the application site, but its viscosity can also slow the diffusion of an antifungal agent through it. As a result, the concentration of drug at the interface with the skin can be rapidly depleted, with the possible result of a reduced concentration of drug at the site of action. With a viscous vehicle which is water soluble as well, diffusion is not such a major problem.

Powder formulations compose a large class of vehicles used in athlete's foot, jock itch, and ringworm products. Despite the wide use of these vehicles, there is little basic research on the bioavailability of drugs from powders, particularly on mixtures of powders.

To varying degrees, most powders used in these preparations are insoluble but wettable. The antifungal agent is usually dispersed uniformly throughout the powder vehicle by thorough mixing so that the antifungal agent is dispersed as a solid in a solid.

When a powder formulation is applied to diseased skin, the powder sticks in a layer. Some adheres to the site or if made to adhere by rubbing onto the site.

One way the antifungal agent can possibly reach intimate contact with the skin and the target fungus is for moisture to penetrate the powder by diffusion through interstitial spaces of the powder, solubilize or leach the antifungal agent, and carry the antifungal agent to the site. This process obviously requires sufficient moisture to effect the solubilization or leaching process. If a powder base is too absorbent, it may retard this process by absorbing too much moisture from the skin into the absorbent powder base. The resulting dry surface of the skin may interrupt diffusion of the antifungal agent from the powder to the skin.

One possible advantage of a powder vehicle stems, however, from this same drying mechanism in that the fungus does not thrive well in a dry environment.

A number of products reviewed by the Panel contain volatile solvents as vehicles for the various antifungal agents. These include aerosol sprays and alcohol-acetone solutions. In general, these solvents evaporate quite rapidly, leaving the antifungal agent in immediate and intimate contact with the skin. Subsequent solubilization of the antifungal agent may then take place in moisture (sweat) or serum at the site. If the antifungal agent is sufficiently solubilized at the action site, it should carry out its designed effect.

G. Labeling

The Panel reviewed and concurs with the labeling requirements for OTC drugs (21 CFR 210.61 (a), (b), and (c)). The Panel also reviewed all submitted labels of preparations used for the treatment of athlete's foot, jock itch, and ringworm and the prevention of athlete's foot. The following general recommendations for labeling are based on these reviews. (For details see part III, paragraph A.2. below—Category I Labeling.)

1. *Pharmacological action.* In order to use the term "antifungal" in its labeling, a product must contain at least one ingredient with specific fungicidal or fungistatic action.

The Panel recognizes that many agents, especially those that promote drying of infected skin, such as alcohols, starch, talc, and acetone, may temporarily relieve symptoms of certain kinds of fungal infection. This is especially true if these ingredients are used on macerated skin. But these drying agents are not true antifungals. Drying alone will not produce clinical cures and negative cultures in most cases of athlete's foot and jock itch.

2. *Indications.* The indications for use should be simply and concisely stated. They should enable the consumer to clearly understand the results that can be anticipated from the use of the product. Any statement on the indications for use should be restricted to the conditions for which the product is recommended. There should be no reference, made or implied, to the relief of any symptoms unrelated to the condition accepted as an indication for use of the product.

For Category I ingredients the indications for use include the treatment of jock itch and ringworm and the treatment and prevention of athlete's foot. The Panel does not recommend the use of antifungal agents for the prevention of jock itch or ringworm. Because the groin is a much more sensitive area than the feet, antifungal agents should not be used indefinitely in the groin. Also, it would be impractical to use an antifungal agent prophylactically over large areas of the body to prevent ringworm of the body. The Panel believes that ingredients proven effective for the treatment of fungal disease may also be effective in the prevention of athlete's foot. But these ingredients may use the prevention labeling only after performing an appropriate clinical trial to demonstrate effectiveness in prevention. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

For some ingredients the indications for use also include the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*).

3. *Ingredients.* Antifungal drug products should contain only active ingredients plus such inactive ingredients as needed for formulation. The label should state the concentration of each active ingredient.

The Panel strongly recommends that all inactive ingredients be listed as such on the label in descending order of quantity. For a variety of reasons, such as allergies and idiosyncratic reactions, the consumer may need to know the product ingredients. The label, however, should not imply or claim that the product's inactive ingredients have a therapeutic benefit.

4. *Directions for use.* The directions for use should be clear and direct. They should provide the user with sufficient information to enable safe and effective use of the product. (See part III, paragraph A.2. below—Category I Labeling.)

Where necessary, the Panel has recommended specific directions under the ingredient statements in later sections of this document.

H. Evaluation of Safety and Effectiveness

1. *Sensitization by topical preparations—Contact dermatitis.* Believing that sensitization is an important consideration when determining the safety of antifungal ingredients, the Panel has reviewed all submitted ingredients for sensitization potential, including those which might ordinarily be classified as weak sensitizers.

Some topical preparations contain ingredients that may sensitize only at low concentrations and only when applied frequently over long periods of time. But even this weak sensitization potential should be identified in ingredients tested for use as topical antifungals. Large numbers of people use these preparations, possibly over long periods of time and on body areas that may be occluded or may easily become sensitized, such as the feet and the groin.

Modified maximization tests or the original Draize test or one of its many modifications are the most commonly used procedures for predicting sensitization to chemicals or formulations applied to the skin (Ref. 1). (The original Draize test does not classify ingredients as weak sensitizers.) Weak sensitizers may easily be missed

in predictive testing. Maximization procedures or an increase in the number of subjects tested will increase the likelihood of identifying less potent or weak sensitizers. Grading an ingredient as a nonsensitizer based on zero positive reactions out of 200 individuals tested is a less reliable procedure than, for example, the Kligman Maximization Test or modifications of it (Ref. 2).

The Advisory Review Panel on OTC Antiperspirant Drug Products concluded that in testing, the following methods of enhancing the accessibility of the allergens to the skin are essential if any degree of predictability is to be attained: (1) stripping, cutting, or abrading the skin; (2) occlusion; (3) exposure to sodium lauryl sulfate or other material; and (4) raising the concentration of the ingredient to be tested (Ref. 3).

When selecting testing procedures for an ingredient, the individual variation in the test subjects must also be considered. Induction of contact dermatitis is influenced by a variety of factors including:

- (1) Genetic predisposition;
- (2) Age and sex;
- (3) Exposure time to antigen;
- (4) Frequency of exposure to antigen;
- (5) Antigen concentration;
- (6) Antigen vehicle or adjuvant;
- (7) Surface area of application on the skin;
- (8) Site of application;
- (9) Type of skin—diseased or healthy;
- (10) Other factors, e.g., irritation.

The use of various maximization procedures that have been described in the literature increases the probability that the tester will identify weak sensitizers and thereby may provide a basis for predicting the number of sensitizations that may occur when the product is marketed.

For example, neomycin and benzocaine are similar in their ability to sensitize the skin of human subjects in circumstances like those of the modified maximization and Draize tests and in restricted populations, such as those in dermatology practices. This level of reaction, however, does not necessarily correlate with the prevalence of contact dermatitis attributed to neomycin and benzocaine in the general population. Likewise, this prediction of a sensitization rate does not necessarily translate to the sensitization rate of normal human skin in the testing of concentrations in predictive tests without maximization techniques or in circumstances of actual consumer use. These maximization tests will allow detection of materials that may not appear to have any risk of sensitization by some tests, but that actually do elicit responses in use situations.

The question of whether human skin can be sensitized with a low concentration of hapten needs further attention. It has been shown in animals that a low concentration of the hapten may induce tolerance. When low concentrations of haptens such as neomycin and benzocaine are applied to normal human skin, one might expect them to be low in sensitization potential. But when they are applied to irritated or inflamed skin, the sensitization potential increases.

The studies of Marzulli and Maibach (Ref. 4) support the concept that the incidence of experimentally induced contact dermatitis is proportionate to the concentration of the hapten in question. Abnormally low concentrations may induce tolerance; excessive concentrations may cause irritation and also induce tolerance. Some haptens may sensitize only at low concentrations and only when applied frequently over prolonged periods of time.

References

- (1) Jordan, W. P., Jr., and S. E. King, "Delayed Hypersensitivity in Females. The Development of Allergic Contact Dermatitis in Females During the Comparison of Two Predictive Patch Tests," *Contact Dermatitis*, 3:19-26, 1977.
- (2) Kligman, A. M., and W. Epstein, "Updating the Maximization Test for Identifying Contact Allergens," *Contact Dermatitis*, 1:231-239, 1975.
- (3) Summary Minutes of the Advisory Review Panel on OTC Antiperspirant Drug Products, 5th Meeting, September 19, 20 and 21, 1974.
- (4) Marzulli, F. N., and H. I. Maibach, "Antimicrobials: Experimental Contact Sensitization in Man," *Journal of the Society of Cosmetic Chemists*, 24:399-421, 1973.

2. *Criteria for evaluating safety.* To assess the safety data of topical antifungal ingredients, the Panel developed a set of flexible guidelines. Flexibility was needed to accommodate difficult chemical agents. Factors influencing the data assessment were the surface area and site of application, frequency and length of application, the vehicle, and the degree of occlusion.

To avoid needless repetition, the safety evaluation criteria are detailed later in this document. (See part III, paragraph E.1. below—Safety guidelines.)

Because many antifungal products had been marketed for extensive periods before this review was begun, the safety evaluation was based on limited historical data, new data obtained from various sources, and the expertise of the Panel.

3. *Criteria for evaluating effectiveness.* In evaluating the data

submitted on antifungal ingredients, the Panel considered *in vitro* data, animal and human models, and clinical trials.

a. *In vitro data.* Antifungal activity should be demonstrated against *T. mentagrophytes*, *T. rubrum*, *E. floccosum*, *M. canis*, and, under certain conditions, *Candida* species. Data should include information on: (1) strains of microorganisms, (2) culture media, (3) neutralizers used, (4) type of inoculation, (5) temperature and time of incubation, (6) identification of isolates, and (7) procedures used.

b. *Animal and human models.* A variety of experimental cutaneous fungal infections can be induced in animals (Refs. 1 through 4) and in humans (Refs. 5, 6, and 7).

The guinea pig is the usual animal studied (Ref. 8). Fungi (usually spores of *T. mentagrophytes*) are applied and then occluded with tape after the animal's hair has been shaved. In a few days the infection is established and will progress until the test animal develops immunity to the fungi (usually 6 to 8 weeks). This is signaled by an increase in inflammation and a halt in peripheral spread. Once the animal is immune, it can no longer be used in the study.

Although the Panel concludes that animal models are important in testing the potential usefulness of topical antifungal agents, it does not accept animal model data as the sole criterion for initial categorization of effectiveness of these agents. Such proof of effectiveness must be derived from appropriate human clinical studies.

The methods of inducing experimental fungal skin infections in humans are similar to those used in animals. Applications of fungal spores under occlusion with plastic wrap produce a spreading infection followed by resolution in a variable period of time. To increase the likelihood that an infection will be induced, the skin may be abraded with chemicals, such as cantharadin which produces blisters, or may be stripped with tape.

Not all fungi can be studied in such models: some require a different environment or host, such as hair. But the animal and human models usually suffice for preliminary study of the pathogens commonly isolated from patients with athlete's foot, jock itch, and ringworm.

c. *Clinical data.* The Panel required each antifungal ingredient to have at least one well-designed clinical trial demonstrating its effectiveness in the treatment of athlete's foot in order to be classified as Category I. The Panel believes that ingredients that are effective in athlete's foot will also be

effective in jock itch and ringworm because the infecting organisms of these conditions are representative of the same groups as the organisms causing athlete's foot and have been shown to be susceptible to the same antifungal drugs.

In evaluating data, the Panel considered each study design and how it conformed to the following description of a well-designed trial. A well-designed clinical trial is usually double-blinded, randomized, and vehicle controlled. Test groups are of adequate size. Patients enter the study based on clinical signs and symptoms, such as redness, cracking, fissuring, scaling, swelling, pain, itching, and burning. Diagnosis of fungal infection is verified by positive KOH preparation and positive culture.

The dosing regimen is standardized. Athlete's foot and ringworm are more difficult to treat than jock itch. For this reason the treatment period should be at least 4 weeks for athlete's foot and ringworm and 2 weeks for jock itch. There should be followup examinations at specified intervals. (For details see part III, paragraph E.2.c. below—Effectiveness standards for labeling indications of antifungal products.) There should also be evidence of compliance of test subjects and statistical analysis of study results.

Antifungal ingredients effective in the treatment of athlete's foot should be equally effective in treating jock itch or ringworm. However, the Panel believes that the groin represents a more sensitive and easily irritated area than the feet and recommends that any antifungal products for the treatment of jock itch have a low potential for irritation.

References

- (1) Weinstein, M. J., E. M. Oden, and E. Moss, "Antifungal Properties of Tolnaftate In Vitro and In Vivo," *Antimicrobial Agents and Chemotherapy*, 36:595-601, 1964.
- (2) Bonk, A. F., I. Friedman, and V. J. Derbes, "Experimental dermatophytosis," *Journal of Investigative Dermatology*, 39:281-286, 1962.
- (3) Tagami, H., W. Watanabe, and S. Ofuji, "Trichophyton Contact Sensitivity in Guinea Pigs with Experimental Dermatophytosis Induced by a New Inoculation Method," *Journal of Investigative Dermatology*, 61:237-241, 1973.
- (4) Greenberg, J. H., et al., "A Quantitative Dermatophyte Infection Model in the Guinea Pig—A Parallel to the Quantitated Human Infection Model," *Journal of Investigative Dermatology*, 67:704-708, 1976.
- (5) Reinhardt, J. H., et al., "Experimental Human Trichophyton Mentagrophytes Infections," *Journal of Investigative Dermatology*, 63:419-422, 1974.
- (6) Jones, H. E., J. H. Reinhardt, and M. G. Rinaldi, "Model Dermatophytosis in

Naturally Infected Subjects," *Archives of Dermatology*, 110:369-374, 1974.

(7) Baer, R., "Studies on Prophylaxis of Experimental Fungal Infections of the Feet." Draft of unpublished study is included in OTC Volume 070157.

(8) Jones, H. E., "Animal Models of Human Dermatophyte Infection," in "Animal Models in Dermatology," Edited by H. Maibach, C. Livingstone, Edinburgh, pp. 166-175, 1975.

III. Topical Antifungal Drug Products

A. Category I Conditions Under Which Topical Antifungal Products Are Generally Recognized as Safe and Effective and Are Not Misbranded. The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the Federal Register.

1. Category I Active Ingredients

Haloprogin
Iodochlorhydroxyquin
Miconazole nitrate
Nystatin
Tolnaftate
Undecylenic acid and its salts
Calcium undecylenate
Copper undecylenate
Zinc undecylenate

a. Haloprogin. The Panel concludes that haloprogin is safe and effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. Haloprogin is also safe and effective in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*).

Haloprogin, 1,2,4-trichloro-5-[(3-iodo-2-propynyl) oxy] benzene, was developed in Japan in 1962. It is a white or yellowish crystalline powder, practically odorless, and freely soluble in acetone and chloroform (Ref. 1). Haloprogin is insoluble in water. It is stable against heat or ultraviolet rays (Ref. 2).

Haloprogin is presently a prescription drug, and the Panel recommends that it be available for OTC use. New Drug Applications for 1 percent haloprogin cream and solution were approved by FDA in August 1971, and both dosage forms have been marketed on a prescription-only basis in the United States since 1972. Haloprogin has been available as an OTC drug in Japan (as tincture and ointment) since 1962 and in Canada (as solution and cream) since 1976.

(1) Safety. The acute toxicity of haloprogin was evaluated in mice, rats, dogs, and rabbits by using aqueous suspensions administered orally and intraperitoneally to determine the median lethal dose (LD_{50}) (Ref. 3). The drug was much less lethal orally than intraperitoneally. The oral LD_{50} in

milligrams per kilogram (mg/kg) was >3,000 in mice, >5,600 in rats, >3,000 in dogs, and 1,825 in rabbits. The intraperitoneal LD_{50} in mg/kg was 183 in mice, 152 in rats, 250 in dogs, and 137 in rabbits. The cause of death after intraperitoneal administration was not apparent, but irritancy was observed. The results suggested poor absorption from the gastrointestinal tract.

In an acute dermal toxicity test (Ref. 3), the fur was clipped from rabbit skin before large doses of haloprogin were applied and held in place for 24 hours. No evidence of systemic toxicity was observed for the 2-week study period. However, dermal irritation was noted. Injected intradermally, 1 percent haloprogin caused irritation. When 1 percent haloprogin was instilled in the rabbit eye both as a solution and as a cream, it was observed that although the cream caused no significant irritation, the solution caused severe irritation because of the alcohol used in the solution vehicle (Ref. 3).

Using C^{14} -labeled haloprogin in both animals and humans, researchers determined that the drug is absorbed into the skin and systemically distributed. (C^{14} is carbon-14, widely used as a tracer in metabolic research.) Using a ratio comparing excretion after topical application to excretion after intravenous administration, it was determined that humans absorb about 15 percent of a 1-percent cream and about 6 percent from a 1-percent topical solution (Ref. 4). Distribution studies in rats also showed that about 4 hours after absorption, 62 percent had been excreted in the urine and by 24 hours, less than 3 percent remained in the tissues. Apparently most of the absorbed haloprogin is metabolized to 2,4,5-trichlorophenol, which is probably excreted as the sulfate salt in the urine (Ref. 3).

A subacute dermal toxicity study of the Draize type (Ref. 3) was conducted on 22 male and 22 female rabbits. A 1-percent haloprogin solution or cream was applied to intact or abraded skin in 0.5, 1.0, or 2.0 milliliters per kilogram (mL/kg) doses 5 days a week for 4 weeks. Appropriate hematologic and urinalysis studies were done. The rabbits were killed in either the fifth or seventh week of the study. Blood and vital organs were microscopically examined, and no distinct changes were noted. The only alterations noted were erythema and edema in intact as well as in abraded skin. Considerable recovery from these effects was noted during the 2 days a week when haloprogin was not applied. This study also included a 2-week "recovery" group, in which the

treated area of skin showed good hair regrowth and skin color.

A 90-day dermal toxicity study (Ref. 3) was also conducted in miniature pigs. Three groups of four male pigs each were treated with either 0.5, 1.0, or 2.0 grams per kilogram (g/kg) per day of 1 percent haloprogin cream applied to about a 25-square centimeter (cm²) area of skin. The area of application was then covered with plastic sheeting and bandages. A fourth group of four pigs served as nonmedicated controls. Hematologic studies, serum chemistry, and urinalysis studies were conducted. After the animals were killed, appropriate tissues were microscopically examined; no significant alterations were noted in the haloprogin-treated groups. No clear or consistent skin changes were noted in the pigs.

The effects on reproduction (Ref. 4) in rats and rabbits were studied after topical application of 1 percent haloprogin cream during days 6 through 15 of presumed gestation. No difference was noted between the litters of the treated and the control animals.

Studies conducted on humans (Ref. 5) used daily application of 1 percent haloprogin under occlusive dressing for 10 or 20 days in adult males. No evidence of significant irritation, allergic contact sensitization, or toxicity was noted. The allergic contact sensitization potential of 1 percent haloprogin cream was evaluated using both the Kligman maximization method (22 subjects) and the Draize-Shelanski method (219 subjects). There was no indication of allergic contact sensitization with either method of evaluation.

Two investigators used a total of 20 subjects to evaluate the phototoxicity potential of haloprogin. Although this number is far too small for the results to be conclusive, no evidence of phototoxicity was noted in these studies (Refs. 4 and 5).

Allergic contact photosensitization was evaluated in 28 patients, and haloprogin was found to have minimal or no potential to induce photosensitization. However, the numbers in this study were also too small to produce conclusive results (Refs. 4 and 5).

Body-inunction studies (Ref. 4) were conducted in 16 persons (eight subjects per dosage form). Fifteen grams of cream of 15 mL of solution (1 percent haloprogin) was applied for 10 days to the entire body excluding the head. No signs of toxicity were noted, and only trace amounts of unchanged haloprogin were recovered in the urine.

The Panel calculated a "safety factor" based on data mentioned above.

Although no studies were performed to support the validity of the calculation below, the Panel suggests that it represents a maximal load or exaggerated use condition. Assuming that 15 percent of an applied dose is absorbed (Ref. 4), the following calculation may be made. If 15 g of a 1-percent cream were applied, then total exposure to the body would be 150 mg. Assuming 15 percent absorption, and assuming rapid, instantaneous absorption, the total amount in systemic circulation would be 22.5 mg. This amount of haloprogin distributed into 7 L of blood results in a maximum blood concentration of about 0.3 mg/100 mL. This blood level is far below any expected acute toxicity level that would result from exaggerated use. Also, elimination studies show little or no accumulation of the drug over 24 hours.

In view of the above summary, the Panel concludes that haloprogin is safe for OTC topical antifungal use.

(2) *Effectiveness.* Seki et al. (Ref. 6) reported the in vitro test results of haloprogin. These investigators concluded that haloprogin has strong antifungal and antibacterial activity "chiefly confined to *Trichophyton*, *diplococci*, *streptococci*, and *staphylococci*."

The in vitro antifungal activity of haloprogin was compared with tolnaftate using the two-fold tube dilution method in Sabouraud's liquid medium (Ref. 4). Tolnaftate was probably selected because it has only antidermatophytic activity, while haloprogin is thought to have a broader spectrum. Several organisms were tested, many of which were fungi totally unrelated to the dermatophytic fungi. For many species haloprogin had a low minimal inhibitory concentration of 0.047 microgram per milliliter ($\mu\text{g/mL}$) or lower. However, for species such as *T. mentagrophytes* the values varied considerably. Tolnaftate showed essentially the same results against this group of organisms. It may be concluded that the minimal inhibitory concentrations are probably low for both drugs. However, a number of details of the testing procedures were not recorded; this could possibly alter the reported values.

The in vitro activity of haloprogin against yeasts was determined using growth comparison techniques (Ref. 4). The minimal inhibitory concentrations were less than 1 $\mu\text{g/mL}$ for haloprogin using a variety of yeasts. For tolnaftate, the minimal inhibitory concentration ranged from $>25 \mu\text{g/mL}$ to $>100 \mu\text{g/mL}$. The minimal fungicidal concentration of haloprogin against *C. albicans* was determined to be 20 to 40 $\mu\text{g/mL}$.

Haloprogin has anticandidal activity in vitro which tolnaftate does not possess.

The minimal inhibitory concentration for several bacteria was determined by tube dilution in soybean-casein digest agar (Ref. 4). This is not considered standard procedure. (Mueller-Hinton is the standard.) Although haloprogin has been considered active in vitro against staphylococci and streptococci, it showed variable activity in this test. Activity was shown against only a few strains of staphylococci and streptococci. It was not active against gram-negative bacteria. Because haloprogin has such a narrow spectrum of antibacterial activity in vitro, it cannot be considered an antibacterial agent.

In 1963, four separate studies (Refs. 2, 7, 8, and 9) published in Japanese journals concluded that 1 percent haloprogin is an effective antifungal ingredient. The Panel reviewed these studies and found that they lacked double-blinding, randomization, or placebo-controlled groups. For this reason these studies will not be reviewed in detail.

Weitgasser (Ref. 1) reported on the success of 1 percent haloprogin in the treatment of various tinea infections in both an "open" study and a double-blind study. The "open" study, by definition, was not blinded, randomized, or placebo controlled, and hence will not be discussed.

Weitgasser's double-blind, randomized study compared 1 percent haloprogin ointment and solution with 1 percent clotrimazole cream and solution in the treatment of 152 subjects with athlete's foot, ringworm of the body, or cutaneous candidiasis. (Clotrimazole is a recognized antifungal agent.) Diagnostic criteria for study inclusion are unclear. Treatment with either haloprogin or clotrimazole continued for "a maximum of four weeks." Outcome criteria included performing KOH preparations. No followup observations were made. Weitgasser concluded that there were no marked differences in the antifungal effectiveness of haloprogin and clotrimazole.

Hermann (Refs. 10 and 11) compiled data from multiple investigators, in addition to the results of other haloprogin effectiveness studies. The reports, both published in December 1972, are similar in content. The author concluded in both instances that the effectiveness of 1 percent haloprogin was substantially greater than a placebo and similar to tolnaftate in the treatment of dermatophytoses.

Olansky (Ref. 12) studied the effectiveness of 1 percent haloprogin cream in treating chronic dermatophytoses other than athlete's foot. Study design included double-blinding, randomization, and two placebo groups. Diagnosis and treatment outcome were based on clinical inspection confirmed by KOH preparations. Treatment continued for 28 days. Of the 31 patients in the study, 10 received the haloprogin cream. Only 5 of these 10 patients were diagnosed as having ringworm of the body or jock itch. Olansky concluded that 1 percent haloprogin cream was "significantly more effective ($p < 0.005$) than placebo." Although the basic study design is sound, the Panel notes the small number of subjects receiving haloprogin. No followup observations were made.

Katz and Cahn (Ref. 13) conducted a double-blind, randomized study comparing the effectiveness of 1 percent haloprogin and 1 percent tolnaftate in the treatment of 74 patients with dermatophytosis (athlete's foot or ringworm of the body). Both the initial diagnosis and the treatment outcome were based on clinical inspection confirmed by KOH preparation. Treatment continued for 14 to 28 days. No followup observations were made.

Table 1 shows that the results obtained with haloprogin are comparable to those obtained with tolnaftate. Haloprogin and tolnaftate proved to be significantly more effective than placebo ($p < 0.05$).

TABLE 1.—RESULTS OF TREATMENT WITH HALOPROGIN, TOLNAFTATE, OR PLACEBO CREAM

Treatment group	Number of patients treated	Treatment outcome			
		Clinically improved (50 pct reduction in pretreatment lesion score)		Positive KOH reversed to negative	
		Number	percent	Number	percent
Haloprogin.....	27	20	(74)	17	(63)
Tolnaftate.....	20	16	(80)	13	(65)
Placebo.....	27	11	(40)	9	(33)

Katz and Cahn (Ref. 13) further analyzed the results of treatment by specific disease, i.e., athlete's foot or ringworm of the body. The investigators noted the greatest clinical improvement occurred in ringworm of the body, regardless of treatment. The 11 patients treated with haloprogin and the 9 treated with tolnaftate improved. In the placebo group 55 percent (5/9) improved. In athlete's foot, however, improvement was noted in only 60 percent (9/15) of the patients treated with haloprogin, 64 percent (7/11) of

those treated with tolnaftate, and 35 percent (6/17) of those who received the placebo.

Van Dersarl and Sheppard (Ref. 14) conducted a double-blind, clinical study comparing the effectiveness of clotrimazole solution with haloprogin solution for the treatment of jock itch. Sixty-six patients with clinical evidence of jock itch confirmed by positive KOH preparation and culture were randomly assigned to either 1 percent clotrimazole (34 patients) or 1 percent haloprogin (32 patients). Treatment continued for 14 days with a 4-week assessment period following treatment. Treatment outcome was based on clinical improvement, KOH preparation, and culture results.

After 2 weeks of treatment, the mycologic evaluation was negative (i.e., negative KOH preparation and negative culture), and the fungal infection was considered cured in 85 percent of the patients treated with clotrimazole as compared to 62 percent of the patients treated with haloprogin. Four weeks after treatment stopped, mycologic evaluation was negative in 57 percent of the clotrimazole group as compared to 31 percent of the haloprogin group.

At the end of the 14-day treatment, there was no statistically significant difference between the number of patients clinically cured with clotrimazole (65 percent) or haloprogin (56 percent). Four weeks later, however, 63 percent of those treated with clotrimazole remained free of disease, whereas only 34 percent of the group treated with haloprogin had no clinical signs of disease. From these data, Van Dersarl and Sheppard (Ref. 14) concluded that clotrimazole was significantly more effective than haloprogin for the treatment of jock itch.

In 1972, Carter (Ref. 15) published the results of a double-blind, clinical study evaluating the effectiveness of three 1 percent haloprogin products and a 1-percent tolnaftate solution in the treatment of 82 patients. All patients had a diagnosis of athlete's foot determined by clinical inspection, KOH preparations, and cultures. Patients were randomly assigned to one of the following four treatment groups: 1 percent haloprogin solution, 1 percent haloprogin cream, 1 percent haloprogin foam, or 1 percent tolnaftate solution. Treatment lasted 27 days. A 8-day post-treatment assessment was also included in the study protocol. Treatment outcome was based on clinical improvement, KOH preparations, and culture results.

Clinical observations revealed no significant differences in the effectiveness of 1 percent haloprogin

and 1 percent tolnaftate. Of the group treated with haloprogin, 92 percent (56/60) were clinically improved after 27 days of treatment and remained improved at the assessment 8 days after treatment. Of the group treated with tolnaftate, 85 percent (17/20) were clinically improved after 27 days of treatment, and 80 percent (16/20) remained improved 8 days later. However, KOH preparations and cultures showed that the patients treated with haloprogin had a significantly greater 27-day cure rate and maintenance of cure 8 days after therapy was discontinued: 90 percent (56/62) of the haloprogin group and 60 percent (12/20) of the tolnaftate group had negative KOH examinations after 27 days of treatment.

One week after treatment, 80 percent (50/62) of the patients treated with haloprogin maintained negative KOH examinations, compared to 25 percent (5/20) of those treated with tolnaftate. This difference is significant at the $p < 0.001$ level. After 4 weeks of treatment, 88 percent (46/52) of the patients treated with haloprogin and 65 percent (11/17) of those treated with tolnaftate had negative cultures.

The 1-week posttherapy culture of these patients showed that 79 percent (41/52) of the patients treated with haloprogin and 41 percent (7/17) of those treated with tolnaftate maintained negative cultures. This difference is significant at the $p < 0.01$ level. Carter concluded that there was no difference between haloprogin and tolnaftate in curing athlete's foot as measured by clinical inspection. KOH preparations and cultures, however, showed a significantly higher cure rate and lower relapse rate with haloprogin than with tolnaftate.

Several studies (Refs. 16, 17, and 18) have reported the use of haloprogin in the treatment of cutaneous candidiasis. In 1973, Montes (Ref. 16) reported a pilot study in which 10 patients with cutaneous candidiasis applied 1 percent haloprogin cream twice daily. The eight patients in this group with common forms of candidiasis had "excellent results," including negative post-treatment cultures (post-treatment time unspecified). Two patients with chronic mucocutaneous candidiasis, a form of fungal infection often resistant to treatment, also experienced a "dramatic response," although *C. albicans* could still be recovered after several weeks of treatment.

In 1974, the use of "megadosage" haloprogin was reported in the treatment of another case of unremitting chronic mucocutaneous candidiasis in a

4-year-old child (Ref. 17). The disease was controlled, although not cured, with 1 percent haloprogin cream and solution applied three times daily over a 3-year period. No toxicity developed from the administration of 12,090 g during seven treatment periods totalling 460 days.

In a double-blind parallel comparison study, 1 percent haloprogin cream was compared with nystatin ointment 100,000 units/gram (U/g) in 68 patients with cutaneous candidiasis (Ref. 18). The treatment period was 13 days, and each product was applied twice daily. Followup KOH preparations and cultures were obtained 1 day after treatment stopped and repeated 2 weeks after treatment was discontinued. The overall cure rate exceeded 80 percent in both groups, with 29 of 35 haloprogin-treated patients responding "satisfactorily."

From this review of the available literature, the Panel concludes that Haloprogin is effective for OTC topical use in the treatment of athlete's foot, jock itch, and ringworm. Haloprogin is also effective in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*).

(3) *Dosage*—(i) *Concentration*. Haloprogin 1.0 percent.

(ii) *Directions for use*. See part III, paragraph A.2. below—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm, and in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*). Category I labeling may also be used for antifungal products with activity against both dermatophytes and yeast. (See part III, paragraph A.2. below—Category I Labeling.)

References

- (1) Weitgasser, H., "Clinical and Mycologic Trials with the Antifungal Medication Haloprogin," *Mykosen*, 20:15-24, 1977.
- (2) Yaguchi, H., and H. Hori, "The Treatment of Trichophytia Eczematosa and Trichophytia Pompholyticiformis with Haloprogin Tincture and Ointment," *Dermatology and Urology*, 25:6-19, 1963.
- (3) Weikel, J. H., and M. J. Bartek, "Toxicological Properties and Metabolic Fate of Haloprogin, and Antifungal Agent," *Toxicology and Applied Pharmacology*, 22:375-386, 1972.
- (4) OTC Volume 070219.
- (5) Hermann, H. W., "Clinical Safety of Haloprogin, a New Topical Antimicrobial," *Clinical Pharmacology and Therapeutics*, 14:100-103, 1973.

(6) Seki, S., et al., "Laboratory Evaluation of M-1028 (2,4,5-Trichlorophenyl-gamma-iodopropargyl ether), A New Antimicrobial Agent," *Antimicrobial Agents and Chemotherapy*, pp. 569-572, 1963.

(7) Ikenaga, M., "Antitrichophytic Effects of Polik (Haloprogin) Solution and Ointment," *Clinical Dermatology*, 25:526-529, 1963.

(8) Yasuda, T., and I. Terayama, "The Clinical Evaluation of Haloprogin Tincture and Ointment (2,4,5-Trichlorophenyl-iodopropargyl ether), A New Synthetic Antifungal Agent in the Treatment of Cutaneous Fungal Infections," *New Remedy and Practice*, 12:20-25, 1963.

(9) Yahata, T., "Topical Treatment of Dermatophytosis with Haloprogin," *Japanese Journal of Dermatology*, 73:151-153, 1963.

(10) Hermann, H. W., "Clinical Evaluation of Haloprogin," *Toxicology and Applied Pharmacology*, 23:598-605, 1972.

(11) Hermann, H. W., "Clinical Efficacy Studies of Haloprogin, A New Topical Antimicrobial Agent," *Archives of Dermatology*, 106:839-842, 1972.

(12) Olansky, S., "Double-Blind Study of a Topical Antifungal Agent in the Treatment of Human Cutaneous Fungal Infections," *CUTIS: Cutaneous Medicine for the Practitioner*, 9:470-472, 1972.

(13) Katz, R., and B. Cahn, "Haloprogin Therapy for Dermatophyte Infections," *Archives of Dermatology*, 106:837-838, 1972.

(14) Van Dersarl, J. V., and R. H. Sheppard, "Clotrimazole vs. Haloprogin Treatment of Tinea Cruris," *Archives of Dermatology*, 113:1233-1235, 1977.

(15) Carter, V. H., "A Controlled Study of Haloprogin and Tolnaftate in Tinea Pedis," *Current Therapeutic Research*, 14:307-310, 1972.

(16) Montes, L. F., and H. W. Hermann, "Topical Use of Haloprogin for Candidiasis," *Archives of Dermatology*, 107:773, 1973.

(17) Hughes, W. T., S. Feldman, and H. W. Hermann, "Safety of Megadosage Haloprogin," *Archives of Dermatology*, 110:926-928, 1974.

(18) Carter, V. H., and S. Olansky, "Haloprogin and Nystatin Therapy for Cutaneous Candidiasis. Comparison of the Efficacy of Haloprogin and Nystatin Therapy," *Archives of Dermatology*, 110:81-82, 1974.

b. *Iodochlorhydroxyquin*. The Panel concludes that iodochlorhydroxyquin is safe and effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Iodochlorhydroxyquin is a yellowish-white or brownish-white powder with a slight characteristic odor. Its chemical formula is 5-chloro-7-iodo-8-quinolinol. It is practically insoluble in water and alcohol, but soluble in hot ethyl acetate and hot glacial acetic acid (Ref. 7).

(1) *Safety*. The acute toxicity of iodochlorhydroxyquin has been reported in the form of oral lethal doses. Female mice appear to be more sensitive than male mice to the lethal effects of iodochlorhydroxyquin. The oral LD₅₀ in mice is reported to be about 1,800 mg/kg in males and 800 mg/kg in females (Ref.

2). The oral LD₅₀ in guinea pigs is 175 mg/kg; in cats it is 400 mg/kg (Refs. 2 and 3).

In a 3-month oral toxicity study of iodochlorhydroxyquin, daily doses of up to 30 mg/kg were administered to rabbits. No adverse effects on the animals' behavior or laboratory chemistry values were noted.

Histopathologic examination of the tissue indicated no treatment-related changes in any tissues. In a followup study, half of the high-dose group was followed for 90 days and observed for delayed toxic effects. There were no behavioral or gait changes that suggested neurologic disorders or any histopathologic changes in tissues (Ref. 3).

In another toxicity study (Ref. 3), beagles were treated with daily oral doses of 100 mg/kg or 300 mg/kg iodochlorhydroxyquin for 4 months. There were no adverse effects noted in the group receiving 100 mg/kg. However, among the six dogs receiving 300 mg/kg iodochlorhydroxyquin, two deaths occurred: a male died on day 6 of treatment and a female died on day 12 of treatment. Autopsy of these two animals revealed acute congestion and diffuse edema of the lungs. Another female dog was killed on day 96 of treatment because of poor general condition. However, the three surviving animals were free of symptoms, and no pathological changes of organs or tissues were noted at autopsy.

In a second 90-day study (Ref. 3) on beagles, iodochlorhydroxyquin was given orally once daily in doses of 30, 100, or 300 mg/kg to groups of six dogs each. A female dog receiving 300 mg/kg was killed because of poor health on the second day of treatment. Cerebral edema with acute neuronal lesions was attributed to anoxia (oxygen deficiency) judged to be unrelated to drug treatment. At autopsy after 90 days of dosing with iodochlorhydroxyquin, two dogs that had received low doses (30 mg/kg) and two that had received high doses (300 mg/kg) showed histological changes in the kidneys. These changes were considered unrelated to treatment. No other changes were noted in any of the tissues.

A third long-term toxicity study (Ref. 3) in beagles was conducted over 24 months using daily doses of 30, 100, or 200 mg/kg iodochlorhydroxyquin. In the high-dose (200 mg/kg) group, five animals died or were killed because of poor physical condition. These five deaths were attributed to nonspecific causes. A female dog in the 100-mg/kg group developed convulsions in the 84th week of the study and was also killed.

No gross or microscopical changes were evident in any tissues. All the other dogs survived the study with no changes which differed remarkably from the controls.

Two separate toxicity studies (Ref. 3) were conducted in monkeys. One study lasted for 6 months, the other, nearly 3 years. In the 6-month study, rhesus monkeys received daily oral doses of 60 or 200 mg/kg iodochlorhydroxyquin. One animal in each group was killed at the end of the first month of the study; the remaining animals were killed at 6 months. Standard laboratory tests revealed no changes in body chemistry either at 1 month or 6 months. At autopsy the only changes noted in any tissues were in the monkeys that had received high doses (200 mg/kg). Tubular dilation and protein casts in the kidneys were noted both after 1 month and after 6 months of dosing. These changes were considered reversible.

In a 33-month study (Ref. 3), cynomolgus monkeys received daily oral doses of 50 or 200 mg/kg iodochlorhydroxyquin. No differences in behavior or motor function were noted between the controls and the treated animals. Autopsy and tissue examination revealed no tissue changes, and no changes were noted in various parts of the nervous system.

The Panel is aware of a serious adverse effect reported with the use of iodochlorhydroxyquin. This effect is called subacute myelo-optic neuropathy (SMON). However, data presented by two groups of investigators led the Panel to conclude that SMON is very unlikely to occur as a result of the topical application of iodochlorhydroxyquin. Tsubaki and Igata (Ref. 4) presented data on oral doses of iodochlorhydroxyquin up to 2,400 mg per day given to humans. No evidence of SMON occurred. In addition, Gholz and Arons (Ref. 5) reported on 4,000 patients taking 250 mg iodochlorhydroxyquin orally three times daily, among whom only 20 (0.5 percent) showed neurological symptoms. These data are further substantiated by long-term studies in monkeys as well as by the absorption data presented below.

Using radioactive tracers, researchers showed that orally administered iodochlorhydroxyquin is rapidly eliminated from the body (Ref. 3). Within 120 hours after oral administration to a rat, 99.6 percent of the dose had been eliminated—15.3 percent in the urine and 84.2 percent in the feces. In the rat, dog, and human, more than 96 percent of the oral dose is eliminated within 72 hours. Distribution studies carried out in rats, rabbits, and dogs demonstrated that neither

iodochlorhydroxyquin nor its metabolites accumulated in any organ or tissue. In humans, after single oral doses of 250 mg, 750 mg, and 1,500 mg, peak plasma levels of 5, 12, and 20 $\mu\text{g/mL}$, respectively, were reached about 4 hours after administration. Plasma half-life was calculated to be about 13 hours (Ref. 3).

In one study, six human volunteers were given oral doses of 500 mg iodochlorhydroxyquin three times daily for 7 days; then 250 mg three times daily for 7 days. During the high-dose week, peak plasma levels reached about 30 $\mu\text{g/mL}$, later falling to 15 $\mu\text{g/mL}$ when the dose was reduced. These results indicate good absorption of iodochlorhydroxyquin from the gut, and rapid elimination following discontinuance of the drug (Ref. 3).

The panel is not aware of any specific data demonstrating the carcinogenicity of iodochlorhydroxyquin, although certain quinolines appear to be carcinogenic (Ref. 6). One unpublished report suggests that iodochlorhydroxyquin has mutagenic potential in *Streptomyces coelicolor* (Ref. 7), but this abstract contains no details. Using Ames' well-known in vitro mutagenesis test, researchers found that iodochlorhydroxyquin was negative at 1 μg per plate (Ref. 8). At concentrations higher than this, toxicity precluded evaluation of mutagenicity. Neither the 24-month study in dogs nor the 33-month study in monkeys revealed a problem with tumorigenesis from the use of this drug (Ref. 3).

In one percutaneous absorption study in two human volunteers, 1 g of cream containing 3 percent iodochlorhydroxyquin and 1 percent hydrocortisone was applied over an area of 200 cm^2 at the rate of 5 mg/cm^2 . Occluding the area for 10 hours resulted in 2 to 3 percent absorption of the topically applied iodochlorhydroxyquin (Ref. 3).

Fischer and Hartvig (Ref. 9) treated four patients with widespread dermatitis with an ointment containing 3 percent iodochlorhydroxyquin and a corticosteroid. Forty percent of the body was treated with 15 to 20 g of the ointment twice daily. Within 4 hours the serum concentration of iodochlorhydroxyquin increased from 0.8 to 1.2 $\mu\text{g/mL}$ and remained constant during treatment. In one patient the daily urinary excretion of iodochlorhydroxyquin amounted to 15 to 20 mg, estimated by the authors to represent a 3- to 4-percent absorption of the applied dose.

The Panel recognizes that in the above two percutaneous experiments, the corticosteroids in the test products

may have interfered with the absorption of iodochlorhydroxyquin. Even though the above data suggest only a 3- to 4-percent absorption of iodochlorhydroxyquin after topical application, the Panel has calculated the following "worst case" situation in order to evaluate possible blood levels in humans following the topical application of iodochlorhydroxyquin to broken skin. The calculation is based on the following assumptions: (1) A 3-percent iodochlorhydroxyquin product is applied to a jock itch or ringworm condition (both of which represent a larger surface area than an athlete's foot condition); (2) a 2-g dose is applied twice a day, and (3) total and rapid absorption occurs after each application.

The highest possible amount of absorbed drug would be 30 mg iodochlorhydroxyquin distributed in 7,000 mL of blood twice a day, resulting in a blood level of approximately 4.5 $\mu\text{g/mL}$. This blood level is well below the reported 15 to 30 $\mu\text{g/mL}$ blood levels obtained during the 2-week oral administration of iodochlorhydroxyquin in which no toxic symptoms were observed (Refs. 3 and 9).

Considering the data summarized above, the Panel concludes that iodochlorhydroxyquin is safe for OTC topical use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* In vitro activity of iodochlorhydroxyquin has been reported against a number of fungi, yeasts, and bacteria (Ref. 10). The average minimal inhibitory concentrations are listed below. (The method was used to determine these values was not given.)

Microorganism	Minimal inhibitory concentration ($\mu\text{g/mL}$)
<i>T. rubrum</i>	10
<i>M. Gypseum</i>	20
<i>C. albicans</i>	10
<i>S. aureus</i>	2
<i>P. aeruginosa</i>	40

In vitro testing indicates that iodochlorhydroxyquin has some antibacterial activity. A series of isolates from patients with various dermatological conditions were tested for susceptibility to iodochlorhydroxyquin. Using gradient plate technique, the researchers tested 818 gram-positive and 263 gram-negative organisms. Soybean-casein digest agar was used, although Mueller-Hinton is the standard medium. Incubation was at 37° C; 32 to 35° C is considered optimal. The minimal inhibitory concentration for

staphylococci (estimated with cumulative percentage) ranged from 40 to 100 µg/mL. Most gram-negative organisms had a minimal inhibitory concentration of 100 µg/mL, but some could not be determined because the levels were not run above 100 µg/mL. The levels recorded with this testing are relatively high for therapeutic activity (Ref. 10).

The minimal inhibitory concentration of iodochlorhydroxyquin was determined by agar dilution in Dermatophyte Sporulation Test Agar (DST) beginning at 128 µg/mL (Ref. 10). In these tests, staphylococci and streptococci were inhibited at 16 to 32 µg/mL. Gram-negative strains generally had minimal inhibitory concentration values of 64 µg/mL (for 100 percent inhibition), but *P. aeruginosa* showed a minimal inhibitory concentration of > 128 µg/mL. Because the levels at which iodochlorhydroxyquin is therapeutically active are high, it can be concluded that this ingredient has little or no antibacterial activity.

Carpenter et al. (Ref. 11) tested the effectiveness of iodochlorhydroxyquin with and without hydrocortisone in 277 patients diagnosed with inflammatory skin diseases associated with secondary bacterial or fungal infections. Seventy-nine patients had primary fungal infections. The study design was randomized and double-blinded. The initial diagnosis was established by cultures, but no KOH preparations were performed. Patients applied one of the following four treatments three times daily: (1) 3 percent iodochlorhydroxyquin and 1 percent hydrocortisone cream, (2) 3 percent iodochlorhydroxyquin cream, (3) 1 percent hydrocortisone cream, or (4) cream base. The authors noted that the distribution of organisms and disease severity did not differ appreciably among the four treatment groups. Patients were seen before treatment, after 2 to 3 days of treatment, and after 7 to 10 days of treatment. Cultures were taken at each visit, and symptomatic response and clinical improvement were evaluated.

At the final visit, cultures were negative in 51 percent (39/77) of the iodochlorhydroxyquin-treated patients as compared to 27 percent (18/68) of the placebo group. Negative cultures were reported in 31 percent (21/68) of the hydrocortisone group and 56 percent (36/64) of the patients receiving the iodochlorhydroxyquin-hydrocortisone combination. The iodochlorhydroxyquin-hydrocortisone combination results were statistically significant when compared to the

placebo base or hydrocortisone alone. Iodochlorhydroxyquin appears much more effective than placebo in the treatment of inflammatory skin diseases, but the investigator did not analyze this statistically.

In a double-blind, placebo-controlled study (Ref. 3) conducted by a large group of dermatologists, the effectiveness of iodochlorhydroxyquin 3 percent used alone or combined with hydrocortisone 1 percent, was compared to hydrocortisone alone and a placebo vehicle base in the treatment of jock itch and ringworm. A total of 354 patients with KOH positive, culture-positive fungal infections were randomly assigned to one of the four previously mentioned treatment groups. The investigators noted that all four treatment groups were comparable in age, sex, isolated organism, and site and severity of infection. Patients were treated twice daily and were seen 2 to 3 days after the study began, and again after 6 to 8 days of treatment.

At the last visit, 65 percent of the patients treated with the iodochlorhydroxyquin-hydrocortisone combination had moderate to complete clearing compared to 46 percent of the patients treated with iodochlorhydroxyquin, 32 percent treated with hydrocortisone, and 25 percent treated with the vehicle. "The cultural conversion rate" (positive to negative culture) was 76 percent in the iodochlorhydroxyquin group, 67 percent for iodochlorhydroxyquin-hydrocortisone, 23 percent for hydrocortisone, and 30 percent for the placebo vehicle. The investigators concluded that iodochlorhydroxyquin was significantly more effective than the placebo vehicle in the treatment of cutaneous fungal infections ($p < 0.05$). Also, the iodochlorhydroxyquin-hydrocortisone combination was found to be significantly more effective than either of its components or the vehicle in the relief of symptoms and in overall clinical response ($p < .01$).

A randomized, double-blind study (Ref. 3) of 94 Texas prison inmates compared the effectiveness of 3 percent iodochlorhydroxyquin to a placebo in the treatment of athlete's foot. Athlete's foot was diagnosed by clinical appearance, positive KOH preparations, and positive cultures. Patients were treated twice daily and seen weekly for 4 weeks; then therapy was discontinued. The patients who remained in the study were reevaluated 2 weeks after therapy. Table 2 shows that iodochlorhydroxyquin was more effective than the placebo in the treatment of athlete's foot at both the 4-

week and the 6-week evaluation. These results are statistically significant at the $p < 0.05$ level.

TABLE 2.—COMPARISON OF IODOCHLORHYDROXYQUIN (ICHQ) AND PLACEBO IN ATHLETE'S FOOT

	[In percentage]			
	Results 4 weeks		Results 2 weeks post-therapy	
	3 percent ICHQ	Placebo	3 percent ICHQ	Placebo
Excellent/good.....	* 23(55)	* 16(31)	* 18(50)	* 10(21)
Fair/no change.....	18(43)	34(65)	18(50)	32(68)
Worse.....	1(2)	2(4)	0(0)	5(11)
Total.....	42(100)	52(100)	36(100)	47(100)

An asterisk indicates $p < 0.05$.

Based on the above review of the literature, the Panel concludes that iodochlorhydroxyquin is effective for OTC topical use in the treatment of athlete's foot, jock itch, and ringworm.

(3) *Dosage*—(i) *Concentration*.

Iodochlorhydroxyquin 3.0 percent.

(ii) *Directions for use*. See part III, paragraph A.2. below—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. below—Category I Labeling.)

References

- (1) Osol, A., and J. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1093, 1975.
- (2) OTC Volume 070068.
- (3) OTC Volume 070193.
- (4) Tsubaki, T., and A. Igata, "Comparative Study on the Pathogenesis of Subacute Myelo-Optico-Neuropathy (S.M.O.N.): A Peculiar Neurological Disease in Japan," World Health Organization Exchange of Research Workers Grant. Final Report.
- (5) Gholz, L. M., and W. L. Arons, "Prophylaxis and Therapy of Amebiasis and Shigellosis with Iodochlorhydroxyquin," *American Journal of Tropical Medicine and Hygiene*, 13:396-401, 1964.
- (6) Hueper, W. C., "Experimental Studies on 8-Hydroxyquinoline in Rats and Mice," *Archives of Pathology*, 79:245-250, 1965.
- (7) Carere, A., et al., "Point Mutations Induced by Pharmaceutical Drugs," *Mutation Research*, 29:235, 1975.
- (8) Hollstein, M., R. Talcott, and E. Wei, "Quinoline Conversion to a Mutagen by Human and Rodent Liver," *Journal of the National Cancer Institute*, 60:405-410, 1977.
- (9) Fischer, T., and P. Hartvig, "Skin Absorption of 8-Hydroxyquinolines," *The Lancet*, March 12, 1977, p. 603.
- (10) OTC Volume 070233.
- (11) Carpenter, C. L., Jr., et al., "Combined Steroid-Antifungal Topical Therapy in Common Dermatoses: A Double-blind, Multi-center Study of Iodochlorhydroxyquin-

Hydrocortisone in 277 Patients," *Current Therapeutic Research*, 15:650-659, 1973.

c. *Miconazole nitrate*. The Panel concludes that miconazole nitrate is safe and effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. Miconazole nitrate is also safe and effective in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (Candida).

Miconazole nitrate is a white, crystalline powder. The chemical name of miconazole nitrate is 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-imidazole mononitrate. It is very slightly soluble in water and very slightly to slightly soluble in most organic solvents (Ref. 1).

A New Drug Application for miconazole nitrate 2 percent cream was approved in January 1974. At present this ingredient is marketed in the United States as a prescription drug for the treatment of fungal infections and cutaneous candidiasis. The Panel recommends that miconazole nitrate be made available for OTC use.

(1) *Safety*. Acute oral toxicity studies have been conducted on miconazole nitrate suspensions in mice, rats, guinea pigs, and dogs. The oral LD₅₀ for mice was 578 mg/kg. All rats survived oral doses up to 640 mg/kg, while the oral LD₅₀ in guinea pigs was reported to be 276 mg/kg. All dogs survived a high oral dose of 160 mg/kg, but four of the six treated animals vomited shortly after receiving the dose. The acute intraperitoneal LD₅₀ in mice from a miconazole suspension was 670 mg/kg (Ref. 2).

Acute oral toxicity studies (Ref. 2) in mice and rats used a 2-percent miconazole nitrate cream formulation with the cream base serving as placebo control. Acute oral LD₅₀ values could not be obtained in mice because the maximum volume the animals could accept was 40 mL/kg (800 mg/kg miconazole). Although two deaths occurred at the 40-mL/kg dose, with symptoms of irregular respiration and general central nervous system depression, deaths were too few to establish an LD₅₀. Acute studies in adult rats were essentially the same as in mice, with no LD₅₀ established because of the limit of 40 mL/kg which the rats could accept.

Subacute oral toxicity studies were conducted on miconazole nitrate suspensions in rats and dogs. In one well-controlled study (Ref. 2), three groups of 20 adult Wistar rats (10 male, 10 female) received 5, 20, or 80 mg/kg miconazole nitrate daily in their diets

for 13 weeks. Hematology, clinical chemistry, urinalysis, and body weight studies were conducted. No abnormal behavior was observed in any of the animals, and all survived the 13-week study.

At the end of the study, all animals were killed and autopsied and selected tissues examined for histological change. There were no significant differences in body weight among any of the animals in the different dosage groups. However, the intermediate dose level (20 mg/kg) group did show a slight, though not significant, decrease in body weight. There were no significant differences in the hematological data or in clinical chemistry data. Urinalysis data for male rats indicated an increase in specific gravity at the 80-mg/kg dose level and a decrease in pH in both the 20- and 80-mg/kg dose level groups. At the 80-mg/kg dose level, the absolute and relative liver weight of both males and females increased. Thymus gland weight decreased in males but increased in females. Spleen weight decreased in both males and females. Pathological evaluation of tissues showed mild variations in the liver and kidney evident only at the 80-mg/kg dose level.

Subacute studies were also conducted over a 13-week period in purebred beagles (Ref. 2). Three groups of six dogs (three male, three female) received oral doses of miconazole nitrate by capsule 6 days per week at dose levels of 2.5, 10, and 40 mg/kg, respectively. Control dogs (three male, three female) received lactose capsules. Both treated and controlled animals exhibited infrequent periodic vomiting, loose or soft stools, and loss of appetite. However, there were no deaths due to toxicity.

Hematological, clinical, urological, and body weight studies were conducted. At autopsy, selected tissues were studied for pathological alterations. There was a slight decrease in body weight in the 10-mg/kg and in the 40-mg/kg dose groups. Hematocrit and hemoglobin showed a decline in the 40-mg/kg dose group, but all other hematological parameters were normal. Only slight changes in clinical chemistry patterns were noted. No significant variations occurred in the urinalysis patterns. Relative and absolute liver weight increases were noted in the 40-mg/kg dose group. Only the livers of animals in the high-dose group showed any cloudy swelling, a pathological alteration considered to be reversible.

Chronic oral toxicity studies (Ref. 2) were conducted in rats and in dogs. Three groups of 60 Wistar rats (30 male, 30 female) received miconazole nitrate at respective dose levels of 10, 40, and

160 mg/kg mixed in their diet for 18 months. A control group of 60 rats received a drug-free diet.

Hematological, clinical chemistry, and urinalysis studies were conducted on all test animals. No dose-related or drug-related effects on health, behavior, or physical appearance were observed. All hematological, clinical chemistry, and urinalysis values were similar for both groups.

At sacrifice, selected tissues were examined for pathological alteration. Mortality rates at 6, 12, and 18 months were considered normal for both the miconazole and control groups. No carcinogenic effects were noted. Organ weights were normal, except for liver weight increases in the 160-mg/kg dose group. Histological examination revealed changes in the liver only where centrilobular cloudy swelling or fatty changes were noted in the high-dose animals. The changes were slightly more pronounced in males and were considered reversible.

Three groups of six purebred beagles (three male, three female) received oral doses of miconazole nitrate by capsule 6 days a week for 52 weeks at respective dose levels of 1.25, 5, and 20 mg/kg. Six control dogs received oral capsules of 250 mg lactose. Hematological, clinical chemistry, and urinalysis studies were conducted. Hematological and urinalysis values for all of the study animals were within normal limits. A persistent increase in serum alkaline phosphatase and a slight increase in serum glutamic pyruvic transaminase values was noted in the 20-mg/kg group. All animals survived the 12-month study. No drug-related or dose-related effect on behavior, health, or appearance was detected. At sacrifice, selected tissues were examined histologically. No pathologic changes were noted in any tissues except a relative increase in liver weight in this group; histological examination failed to show tissue changes in the liver (Ref. 2).

Teratology studies (Ref. 2) were conducted in rats and rabbits after oral administration of miconazole nitrate. Rats received miconazole nitrate in the diet from day 6 to day 15 of pregnancy at levels of 80 or 160 mg/kg. No abnormalities were noted in the cesarean-delivered fetuses of the control or test animals. Rabbits were dosed orally with miconazole nitrate suspended in polyethylene glycol 200 from day 6 to day 18 of presumed gestation at dose levels of 40, 80, or 160 mg/kg. A few fetuses had skeletal abnormalities which were observed in both control and treated litters. In another study using rabbits, pregnant

females were dosed by gavage with miconazole nitrate suspended in 25 percent methylcellulose at levels of 20, 40, or 80 mg/kg from day 7 to day 19 of pregnancy. At the 80-mg/kg dose level there was evidence of maternal and fetal toxicity which could be secondary to maternal nutritional effects. No birth defects were noted, even in the high-dose group.

Several studies (Ref. 2) of the excretion and metabolism of miconazole have been conducted in male rats. In each study, tritium-labeled miconazole nitrate in polyethylene glycol was given in oral doses of 40 mg/kg. In one such study, 90.1 percent of the administered dose was recovered from the feces and 9.4 percent from the urine after 96 hours. Another 96-hour study found 85 percent recovery from the feces and 10 percent recovery from the urine. Because most of the drug is excreted, relatively little absorption from the gut occurs. About 18 percent of the radioactivity excreted in the feces was unchanged miconazole. Most of the miconazole in the urine was the metabolite form, alpha-(2,4-dichlorophenyl)-imidazole-ethanol. Less than 2 percent of the radioactivity was recovered in the brain, lungs, kidneys, and bladder. Peak blood levels, consisting mainly of metabolites, never exceeded 0.4 percent of the administered dose.

After oral dosing of tritiated miconazole in rabbits, the researchers found that absorption did occur and the labeled drug could be found systemically. It could also be found in the eye and in the skin. The amount of radioactivity due to unchanged miconazole was about 15 percent in the plasma, and 20 to 30 percent in the liver, muscle, and eye.

Three-month intravaginal irritation studies were conducted in rabbits and monkeys (Ref. 2). Ten white rabbits received daily intravaginal suppositories of 2 percent miconazole (total dose 20 mg) in a carbowax vehicle for 90 days; 10 control rabbits received placebo suppositories. At sacrifice, the hematological, urological, and clinical chemistry data of test animals and controls were similar. Microscopic examination of the vaginal mucosa indicated more irritation in the test group than in the control group.

In a similar study (Ref. 2), vaginal suppositories of 2 percent miconazole in a carbowax base were inserted daily into four cynomolgus monkeys. Four control monkeys received base suppositories only. All monkeys survived the study and remained in good health. Hematological and clinical chemistry values remained within normal limits for all study animals.

Histological examination of the vaginal wall revealed a slight increase in the thickness of the vaginal squamous epithelium in both test and control animals, which was slightly more pronounced in the test animals.

Vaginal absorption and excretion studies (Ref. 2) were conducted in rabbits and dogs after administration of miconazole either by polyethylene glycol suppositories or a vehicle composed of triglycerides derived from coconut and palm kernel oils. Higher levels of absorption and excretion were noted from the polyethylene glycol and miconazole combination than from the triglyceride and miconazole combination.

Eye irritation studies (Ref. 2) in 12 rabbits using 0.1 mL of 2 percent miconazole cream resulted in negative or low potential to produce eye irritation, in both test cream and placebo.

In an acute topical toxicity study in rabbits (Ref. 2), 2 percent miconazole nitrate cream was evaluated on intact and scarified (artificially scratched) skin under a 24-hour occlusive sleeve. Based on gross observation, hematology, and urology data, there was no evidence of local or systemic toxicity.

Two topical subacute studies (Ref. 2) were conducted on rabbits using both intact and scarified skin. Two percent cream was applied at levels of 0.2, 1.0, or 2.0 g/kg daily for 4 weeks. Except for occasional minimal patchy redness, hyperkeratosis, and loss of skin elasticity, no evidence of skin irritation was observed. Histopathologic examination of tissues revealed no treatment-related lesions. In a similar study conducted over 3 and 6 months, certain minor hematological changes were noted, namely an increased neutrophil level and a decreased lymphocyte count correlating roughly with dosage. A slight tendency for the hemoglobin hematocrit to show depression proportionate with dosage was also observed. Other than local skin irritation occurring in both the test and placebo groups, no changes were noted.

Two separate photosensitivity and phototoxicity studies (Ref. 2) of 2 percent miconazole nitrate cream were conducted in 35 human volunteers using xenon solar-simulating radiation filtered through window glass. It was concluded that the cream did not induce allergic photosensitization or phototoxicity reactions in humans.

Topical application of 1 g of the 2-percent tritiated cream on the forearm under an occlusive bandage was studied in three volunteers. Blood chemistry

indicated absorption was too low for accurate measurement (Ref. 2).

In another study on 50 human subjects (Ref. 2), the 2-percent cream was applied under occlusive patches for 24 hours. No reactions were observed at the 72-hour evaluation period.

Using a modified Draize test to determine the human allergic skin sensitization potential (Ref. 2), the 2-percent cream was used on 220 healthy adult male volunteers between the ages of 21 and 65. The cream was applied to the same site with occlusive strips three times weekly for a total of 10 applications. A 2-week rest period was followed by a final 72-hour challenge application. Irritation occurred in 12 of the 220 subjects. Miconazole cream was not considered a contact sensitizer.

In a double-blind, subtotal incision study, 10 human subjects has 2.5 g miconazole cream applied to the entire back twice daily for 28 days (Ref. 2). Five subjects were given a placebo cream. No skin irritation occurred. Hematology and urinalysis indicated no significant differences.

Oral studies (Ref. 2) were conducted in three humans who were each initially given 50 mg tritiated miconazole nitrate. After 1 week and after 3 weeks, the subjects took a capsule containing 250 mg labeled miconazole and 750 mg unlabeled miconazole. Between day 7 and day 28 they also took 1 g unlabeled miconazole nitrate three times daily. The researchers found that the relative absorption and metabolism were unrelated to the dosage and remained unchanged during chronic treatment. Only 10 to 20 percent of the administered dose could be recovered in the urine, while 40 to 55 percent was recovered in the feces.

In another study (Ref. 2), vaginal instillation of 1 g cream in three women showed total plasma levels of miconazole and its metabolites reached a maximal blood level between 4 and 24 hours after administration. This level never exceeded the detection limit, 30 micrograms per liter ($\mu\text{g/L}$). The researchers reported that miconazole was scarcely absorbed when administered vaginally.

Vaginal instillation of 5 g tritiated miconazole cream in three volunteers resulted in blood levels too low for accurate measurement (Ref. 2).

In an intravenous infusion study (Ref. 2), four patients (three males, one female) were given a single dose of 174 mg of labeled miconazole base equivalent to 200 mg miconazole nitrate over a 1-hour period. Blood, urine, and feces samples were taken periodically. Maximum levels of unchanged

miconazole in plasma of 1.6 µg/mL were reached 1 hour after starting the infusion. The concentration in plasma rapidly diminished over 12 hours, with a half-life of 24 hours. About 14 percent of the total radioactive material was excreted in the urine, with the highest rate of excretion 2 to 8 hours after infusion. Thirteen to 35 percent miconazole was excreted in the feces. The researchers concluded that the excretion of miconazole and its metabolites after intravenous infusion is qualitatively very similar to excretion patterns after oral administration.

The Panel concludes that adequate, well-controlled, animal and human toxicity studies were conducted and that miconazole nitrate exhibits a low order of toxicity. The major indications of toxicity noted in the animal studies were cloudy swelling in the liver and some central nervous system effects. The only deficiency noted in the animal data base for toxicity is the blood levels of miconazole needed to produce these toxic symptoms. But considering the extensive studies presented, the Panel does not consider this to be a serious deficiency.

Even though a few cases of mild irritancy in humans in the modified Draize test have been reported, the Panel concludes that miconazole nitrate is safe for OTC topical antifungal use.

(2) **Effectiveness.** Miconazole is an antifungal agent with activity against fungi responsible for both systemic and superficial infection. It is also effective against gram-positive bacteria in vitro (Ref. 3). Fungicidal action is believed to result from the effect of miconazole on the cell membrane, altering cellular permeability (Ref. 4). At a concentration of 1 µg/mL, miconazole nitrate inhibits the following microorganisms: *T. mentagrophytes*, *T. rubrum*, *E. floccosum*, and *Candida* species (Refs. 2 and 3).

The following studies conducted on human volunteers were random and double-blind (Refs. 5 through 9). Only those subjects with positive KOH preparations and cultures were studied. Each study tested 2 percent miconazole against a placebo (vehicle) in twice-daily applications. Most of the studies also included a 4-week followup examination with cultures and KOH preparations.

A study was conducted on 62 dermatology clinic patients at a military hospital in Mississippi (Ref. 5). On initial examination, all of the patients had a symptomatic infection clinically compatible with diagnoses of jock itch, ringworm of the body, or athlete's foot. The patients ranged in age from 17

through 39 years; the typical one was in his early twenties.

Thirty patients were treated with 2 percent miconazole. The 32 controls were treated only with the vehicle (placebo). Other than the twice-daily application of the cream, no changes were made in the patients' daily activities, work habits, dress, or personal cleanliness. Of the 30 miconazole-treated subjects, 18 were suffering from *T. rubrum* infections, 7 from *T. mentagrophytes*, 2 from *E. floccosum*, 2 from *C. albicans*, and 1 showed no culture growth. Culture results from the 32 controls revealed that 20 had *T. rubrum* infections, 10 had *T. mentagrophytes*, 1 had *E. floccosum*, and 1 had *C. albicans*.

At the end of the second and fourth weeks of therapy, clinical and symptomatic evaluations were repeated. KOH preparations and cultures were repeated only at the fourth-week visit to the clinic. Medication was stopped at least one day before the cultures were performed. At the end of the 4-week therapy, 28 (93.3 percent) of the 30 miconazole-treated patients were reported free of both signs and symptoms of the disease, while in the placebo group, only 6 of 32 patients (18.8 percent) were reported to have similar clearing. Persistence of symptoms (burning, itching, and pain) in the control group paralleled the poor clinical results. Of the miconazole-treated group, 75 percent obtained relief of symptoms within 3 days.

At the end of therapy (28 days), 21 of the 32 in the control group had positive KOH preparations and 23 had positive cultures. Only 2 of the 30 in the miconazole treatment group had positive KOH preparations, and 3 had positive cultures. Four weeks after treatment stopped, followup KOH preparations and cultures were obtained. Only one miconazole-treated patient showed evidence of recurrence of the disease with delayed growth of *T. rubrum* from the 28th-day culture. However, this patient was reported clinically clear and had a negative KOH preparation at followup.

The effectiveness of miconazole against endemic dermatophytosis was tested by Fulton (Ref. 6) on 99 inmates (20 to 29 years old) in a crowded Florida prison. The patients were told to apply either the 2-percent miconazole cream or the control vehicle each morning and night. Of the 49 patients in the miconazole treatment group, 22 had a diagnosis of jock itch, 20 had athlete's foot, 4 had ringworm of the body, and 3 had mixed tinea infections. Of the 50 patients in the placebo group, 26 had a diagnosis of jock itch, 18 had athlete's

foot, 1 had ringworm of the body, and 5 had mixed tinea. Those having jock itch and ringworm of the body were treated for 2 weeks and clinically evaluated each week. Those with athlete's foot were treated for 1 month and evaluated biweekly. The following table summarizes the results:

TABLE 3.—ISOLATION OF PATHOGENS

Pathogen isolated	Patients treated with miconazole		Patients treated with placebo	
	Before	After	Before	After
<i>T. rubrum</i>	39	7	43	33
<i>T. mentagrophytes</i>	1	0	2	2
<i>C. albicans</i>	7	1	4	4
<i>T. rubrum</i> and <i>C. albicans</i>	2	0	1	1
No growth on culture.....	0	41	0	10
Total.....	49	49	50	50

Thirty-six (73.5 percent) of the 49 patients treated with miconazole cream showed symptomatic relief of itching within the first week of therapy compared to 5 (10 percent) of the 50 patients in the placebo group. After therapy was discontinued, 30 of the successfully treated test group subjects were followed up. Only one patient in this group has a recurrence of signs and symptoms of the original condition, with a positive KOH preparation and culture. In addition, *T. rubrum* was isolated from two other patients who were otherwise free of any evidence of infection.

Duncan (Ref. 7) also studied 51 KOH positive and culture-positive patients in a Texas prison for 28 days of treatment plus 28 days of observation. Twenty-one inmates were treated with a 2-percent miconazole cream, and 30 were treated with the vehicle. *T. rubrum* was isolated in 14 of the miconazole-treated group, *T. mentagrophytes* in 6, and *E. floccosum* in 1. Duncan also noted a similar distribution of causative organisms in the control group.

The overall clinical effectiveness, judged by the disappearance of signs and symptoms, was significantly greater in the miconazole group (63 percent) than in the control group (18 percent). After 28 days, 82 percent of the treatment groups had negative KOH preparations. Ninety percent had negative KOH preparations at the end of the followup (56 days). In contrast, 62 percent of the controls were KOH negative after 28 days and 39 percent were KOH negative after 56 days. Patients who had *T. rubrum* infections on admission to the study showed the greatest clinical responses to miconazole with 93 percent obtaining a good to excellent response immediately after therapy (28 days). After the

followup, 64 percent had maintained a good to excellent result. The number of patients with *T. mentagrophytes* infections was not considered large enough for statistical analysis.

A study at the University of Glasgow tested the effectiveness of 2 percent miconazole cream and 2 percent miconazole powder against their vehicles (Ref. 8). The study was done under relatively uncontrolled conditions to test the effectiveness of miconazole in self-treatment. The 45 young male subjects, all of whom had athlete's foot, were university athletes. They regularly trained in the gymnasium and used its showers. The most common dermatophytes isolated were *T. rubrum* in 27 subjects, *T. mentagrophytes* var. *interdigitale* in 10 subjects, and *E. floccosum* in 4 subjects. Twenty subjects received the miconazole and 25 received the placebo. Their instructions were to gently massage the cream onto the affected areas each evening and to use the powder every morning and after bathing.

After the 4-week treatment, 12 of the 20 miconazole-treated subjects were cleared of infection. Of the 25 who received the placebo, 6 had negative cultures. When 16 of the 18 infection-free subjects were examined 4 weeks after treatment, 11 of them remained culture negative. (Seven were on miconazole and four were on the placebo.) The authors report that "it is worth noting that, despite the adverse effects of intensive gymnasium activity in rubber soled shoe, the active preparation succeeded in eliminating the subjective symptoms in 100% and objective symptoms in 80% of cases compared to the placebo group in which they persisted in 47% and 60% of cases respectively."

A study of the effect of 2 percent miconazole cream on dermatophytosis, skin candidiasis, pityriasis versicolor (also called tinea versicolor) and erythrasma revealed definite cures (defined as negative cultures) in 31 patients (93.9 percent) in the miconazole group. Only six patients (21.4 percent) of the placebo group were cured ($p < 0.0005$). The mean time in which the definite cure was obtained was 1.6 weeks in the miconazole group and 1.8 weeks in the placebo group (Ref. 9).

Additional studies have shown the effect of miconazole nitrate on the treatment of mycotic vulvovaginitis. A Belgian study (Ref. 10) reported the results on 230 patients whose ages ranged from 12 to 75 years with a median of 27 years. Most of them had *C. albicans* cultured on the first visit. Altogether, nine different yeasts were

isolated from the patients before treatment. Symptoms included itching.

Of the 230 patients, 194 returned for a post-treatment examination 4 days after the completion of treatment. Of 165 women treated with miconazole, 147 were cured (negative cultures). The most successful treatment appeared to be 2 percent miconazole cream applied intravaginally once daily for 2 weeks; 54 out of 57 women were cured. After this treatment, "all patients who were mycologically cured and most patients treated with miconazole 2 percent from whom yeasts were grown after treatment were free from symptoms * * *". The least effective treatment was 1 percent cream, with only 18 patients out of 25 cured. In comparison, 7 out of 21 women treated with nystatin were cured, and 1 out of the 8 who used only the vehicle was cured.

Between 1974 and 1977, three studies compared miconazole nitrate 2 percent cream with nystatin vaginal tablets in the treatment of vulvovaginal candidiasis (Refs. 11, 12, and 13). (For details of these studies see part III, paragraph A.1.d. below—Nystatin.) Cure rates with miconazole cream were 91.1 percent, 76 percent, and 92.9 percent, respectively, with a pooled patient population of over 300 cases of candidiasis.

In view of these studies, the Panel concludes that miconazole nitrate is effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. Miconazole nitrate is also effective in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*).

(3) *Dosage*—(i) *Concentration*. Miconazole nitrate 2.0 percent.

(ii) *Directions for use*. See part III, paragraph A.2. below—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm; and in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*). Category I labeling may also be used for antifungal products with activity against both dermatophytes and yeast. (See part III, paragraph A.2. below—Category I Labeling.)

References

(1) Van Cutsem, J. M., and D. Thienpont, "Miconazole, a Broad-Spectrum Antimycotic Agent with Antibacterial Activity," *Chemotherapy*, 17:392-404, 1972.

(2) OTC Volume 070204.

(3) Hildick-Smith, G., "Antifungal Agent," *Advances in Biology of the Skin*, 12:303-314, 1972.

(4) Cullen, S. I., "Cutaneous Candidiasis: Treatment with Miconazole Nitrate," *CUTIS: Cutaneous Medicine for the Practitioner*, 19:126-129, 1977.

(5) Mandy, S. J., and T. C. Garrott, "Miconazole treatment for Severe Dermatophytoses," *Journal of the American Medical Association*, 230:72-75, 1974.

(6) Fulton, J. E., Jr., "Miconazole Therapy for Endemic Fungal Disease," *Archives of Dermatology*, 111:596-598, 1975.

(7) Duncan, W. C., "Tinea Pedis: Treatment with Topical Miconazole," *CUTIS: Cutaneous Medicine for the Practitioner*, 16:647-649, 1975.

(8) Gentles, J. C., G. R. Jones, and D. T. Roberts, "Efficacy of Miconazole in the Topical Treatment of Tinea Pedis in Sportsmen," *British Journal of Dermatology*, 93:79-83, 1975.

(9) Stratigos, I., et al., "A Double-Blind Evaluation of Miconazole in Dermatomycoses," *Current Therapeutic Research*, 20:24-31, 1976.

(10) Proost, J. M., et al., "Miconazole in the Treatment of Mycotic Vulvovaginitis," *American Journal of Obstetrics and Gynecology*, 112:688-692, 1972.

(11) Davis, J. E., Prudenfeld, J. H., and J. L. Goddard, "Comparative Evaluation of Monistat and Mycostatin in the Treatment of Vulvovaginal Candidiasis," *Obstetrics and Gynecology*, 44:403-406, 1974.

(12) Wallenburg, H. C. S., and J. W. Wladimiroff, "Recurrence of Vulvovaginal Candidosis during Pregnancy. Comparison of Miconazole vs. Nystatin Treatment," *Obstetrics and Gynecology*, 48:491-494, 1976.

(13) McNellis, D., et al., "Treatment of Vulvovaginal Candidiasis in Pregnancy. A Comparative Study," *Obstetrics and Gynecology*, 50:674-678, 1977.

d. *Nystatin*. The Panel concludes that nystatin is safe and effective for OTC topical antifungal use in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*). The Panel concludes that nystatin is also safe and effective in the treatment of athlete's foot, jock itch, and ringworm, but only in combination with Category I antifungal ingredients. (See part III, paragraph D. below—Combination Products Used in the Treatment of Athlete's Foot, Jock Itch, and Ringworm.)

New Drug Applications for nystatin were approved in February 1957. Nystatin is currently marketed on a prescription-only basis for the treatment of infections caused by *C. albicans* and other *Candida* species. The Panel recommends that this ingredient be made available for OTC use in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections

caused by yeast (*Candida*). The Panel also recommends that nystatin be made available for OTC use in combination with antifungals for the treatment of athlete's foot, jock itch, and ringworm.

Compared with the limited use of nystatin reported in the literature in treating dermatophyte infections, the use of topical, oral, and intravaginal nystatin in the treatment of candidiasis has been extensively reported for over 20 years. Marketing experience revealed that topical nystatin was the most frequently prescribed single-ingredient topical product for candidiasis in 1977 (Ref. 7).

Nystatin is a polyene antibiotic obtained from *Streptomyces noursei* (*S. noursei*), an actinomycete originally found in a dairy farm pasture in Virginia. First isolated in 1949, nystatin was the first antifungal antibiotic to be found. Originally, 1 mg nystatin was arbitrarily assigned an activity value of 1,000 units (U), but later purification methods enabled production of the antibiotic with activity of 2,500 to 3,500 U/mg (Ref. 2).

Nystatin inhibits the growth of yeasts and some other fungi, but has no activity against bacteria and viruses (Ref. 3). It is a yellow to light tan hygroscopic powder with an odor resembling cereal. It is very slightly soluble in water, slightly soluble in alcohol, and insoluble in chloroform, ether, and benzene. Nystatin deteriorates on long exposure to light, heat, and air (Ref. 4), and even in a dry state may lose 25 percent of its microbiologic activity in 6 months (Ref. 5). In neutral solutions at room temperature in ordinary sunlight, nystatin may lose 50 percent of its activity after 2 weeks (Ref. 6).

(1) **Safety.** Nystatin has been used extensively for over 20 years in the treatment of candidal infections of the skin, mucous membranes, vagina, and intestinal tract. Reports of adverse effects are rare. Topical application does not irritate the skin and mucous membranes (Ref. 3).

The intraperitoneal LD₅₀ of nystatin in mice is between 29,450 and 50,040 U/kg. In rats it is 85,068 to 93,440 U/kg. The mouse can tolerate a single oral dose of 12.5×10^6 U/kg without adverse effects (12-day observation). Absorption is negligible by this route, as an oral dose of 2.7×10^6 U/kg yields only 9.8 U/mL in plasma. Rats can tolerate a single oral dose of 8.34×10^6 U/kg (25-day observation). When an oral dose of 450,000 U/kg was administered to a dog, less than 1 percent was recovered in the urine after 24 hours, whereas 23 percent of a 3,200 U/kg intravenous dose could be recovered in the urine, again

demonstrating poor absorption from the gastrointestinal tract (Ref. 7).

When nystatin was applied topically to rats, no reaction was observed on intact skin, but abraded skin showed slight erythema. This preparation was 0.2 to 0.8 percent nystatin in an oleaginous ointment base (1,280 U/mg) (Ref. 7).

Chronic testing of nystatin was carried out in rats by daily oral administration of 121,000 to 810,000 U/kg for 90 days. The only indication of drug intolerance in rats given 202,500 to 540,000 U/kg was a depression in the rate of growth of male rats. At the highest dose (810,000 U/kg), gastrointestinal distress, dehydration, and diarrhea were observed in both male and female rats. A few deaths occurred from pulmonary hemorrhage, but no gross or microscopic pathological lesions were found (Ref. 7).

Dogs tolerated 90,000 to 450,000 U/kg daily for 217 days; the only adverse effect noted were a few cases of vomiting during the first few weeks (Ref. 7).

In humans, daily oral doses of 10×10^6 U nystatin are well tolerated, with only a few cases of a mild, transitory nausea (Ref. 7). The amount of nystatin absorbed from the gastrointestinal tract is negligible. Levels of only 1 to 2.5 µg/mL in plasma were found in persons with normal kidney function (Ref. 3).

Topical application of creams containing 100,000 U/g nystatin are without adverse effect. Nystatin is not absorbed from the skin. Allergic contact dermatitis from nystatin is extremely uncommon, with the first case not reported until 1970, about 15 years after nystatin was introduced for the treatment of *C. albicans* infections (Ref. 2). In this report a woman apparently became sensitized through contact with a cream medication containing nystatin which her husband had used for 2 weeks to treat jock itch. She developed a strongly positive patch test to nystatin 100,000 U/mL in 70 percent ethanol (Ref. 8). Further patch testing in this patient revealed positive tests to nystatin in 10 percent propylene glycol in concentrations as low as 5,000 U/mL ($\frac{1}{20}$ the usual therapeutic concentration). A strongly positive patch test also developed with nystatin 100,000 U/g in petrolatum, although a concentration of 50,000 U/g failed to cause a positive reaction. It was suggested that a commercially available ointment containing 100,000 U/g in a plasticized hydrocarbon gel be used for routine patch testing a nystatin (Ref. 9).

A few other case reports of nystatin sensitivity appeared in 1971. Coskey reported the case of a man who had

chronic itching of the perianal area and who developed positive patch tests to several ingredients, including nystatin. These ingredients were contained in a cream that he had used intermittently for 6 months. He was not rechallenged with the product containing nystatin (Ref. 10). Two later cases reported by Coskey also had positive patch tests to nystatin. One patient developed sensitivity after treating jock itch with a nystatin-containing cream for 30 days. The other patient first developed a widespread skin eruption after using nystatin vaginal suppositories. She later developed dermatitis of the hand after applying a cream containing nystatin (Ref. 11).

The Panel is not aware of any other reports of contact sensitivity to nystatin. It concludes that allergic contact dermatitis caused by nystatin probably is very rare and not a significant hazard to the users.

The Panel concludes that nystatin is safe for OTC topical antifungal use in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*).

(2) **Effectiveness.** Although nystatin inhibits various dermatophytic fungi in vitro, it is particularly active against *C. albicans* and is primarily used for the treatment of candidiasis. The mechanism of action appears to be the ability of nystatin to bind to sterols in the cell membrane, thus rendering the membrane leaky to water and small molecules and ions, such as potassium (Ref. 12). Nystatin induces the formation of microscopic aqueous pores in thin cell membranes containing cholesterol. These pores act as single ionic channels and also induce changes in the electrical conductance of the cell membranes (Ref. 13).

In 1951, Hazen and Brown (Ref. 14) described two antifungal agents which were produced by *Streptomyces*; these agents were nystatin and actidione. They listed the minimal inhibitory concentration of nystatin as 3.12 µg/mL against *C. albicans* and 6.25 µg/mL against *T. mentagrophytes*. They noted that nystatin is strongly fungicidal.

According to Pansy et al. (Ref. 15), the minimal inhibitory concentration of nystatin is 1.1 µg/mL against *C. albicans*, 0.5 µg/mL against *M. canis*, and 2.8 µg/mL against *T. mentagrophytes*.

DiPalma (Ref. 16) lists the following minimal inhibitory concentrations:

Microorganism	Minimal inhibitory concentration (U/ml)
<i>C. albicans</i>	7.8
<i>M. canis</i>	15.6
<i>M. audouinii</i>	15.6
<i>E. floccosum</i>	7.8
<i>T. rubrum</i>	31.2

Shadomy (Ref. 17) studied the in vitro activity of numerous topical antifungals including nystatin. Table 4 shows his findings on nystatin.

TABLE 4.—THE MINIMAL INHIBITORY CONCENTRATION OF NYSTATIN AGAINST MULTIPLE STRAINS OF FUNGI

Microorganism	Number of strains	Mean (μg/ml)	Range (μg/ml)
<i>T. mentagrophytes</i>	3	12.5	3.13 to 25.
<i>T. rubrum</i>	5	1.56	0.39 to 1.56.
<i>M. canis</i>	3	0.78	0.78 to 1.56.
<i>M. gypseum</i>	3	0.78	0.39 to 1.56.
<i>E. floccosum</i>	3	1.56	0.78 to 12.5.

Hashimoto and Blumenthal (Ref. 18) tested the in vitro activity of several antifungal agents including nystatin, clotrimazole, griseofulvin, and miconazone. They studied the survival rates of arthrospores of *T. mentagrophytes* after a 24-hour exposure to the various ingredients. Nystatin proved to be the most effective of the antifungal tested.

Resistance to nystatin has been observed in mutant yeasts which do not contain cholesterol in their cell membranes (Ref. 2). However, such resistance is difficult to induce in the laboratory and, as reported in 1955, repeated efforts had failed to develop strains of *C. albicans* resistant to nystatin by incorporating the antibiotic in agar and broth dilution tubes (Ref. 19). In this same study, preliminary efforts to obtain nystatin-resistant strains of the dermatophytes *M. canis* and *T. mentagrophytes* also failed. In later studies, however, resistance of *Candida* species to nystatin was produced in the laboratory, although such strains are nonpathogenic (unable to cause infection). Significant natural resistance to *C. albicans* has not been observed in clinical isolates (Ref. 2).

Clinical studies using nystatin to treat dermatophytic fungal infections have not been extensive. In 1955, nystatin was used to treat 93 patients with culture-positive dermatophytosis (Ref. 20). Although the types of fungal infections were not specified, cultures revealed 60 cases of *T. rubrum*, 26 cases of *T. gypseum*, 3 cases of *Microsporum lanosum* (*M. lanosum*), and 4 other fungi.

Most patients with *T. rubrum* infections were treated for at least 3 months, after which all but one patient still had positive cultures. The results were rated as excellent in 1, good in 3, fair in 28, and no change in 28. Similar results were reported in patients with *T. gypseum* infections. These results were: 1 excellent, 20 fair, and 5 unchanged; 25 of 26 patients still had positive cultures after treatment. The results were more favorable in the three patients with *M. lanosum* infections, with good to excellent clinical improvement and negative cultures after treatment.

With all of the dermatophytes, clinical improvement generally occurred slowly, but cultures were still positive at the end of the treatment periods, which varied from 1 week to 8 months, with an average of 3 months.

The Panel is aware of only one other study in which nystatin as a single ingredient was used to treat dermatophyte infections (Ref. 21). In this unpublished multicenter study, nystatin cream 100,000 U/g was compared with tolnaftate cream 1 percent and the combination of tolnaftate 1 percent/nystatin 100,000 U/g in cream base. The random, double-blind, controlled study involved 178 patients with jock itch caused by dermatophyte fungi (76 percent) or *C. albicans* (17 percent) or by both (7 percent). Types of dermatophytes were not specified. All patients had a positive KOH preparation or gram stain, and 90 percent had positive fungal cultures at the beginning of the study.

Among 47 patients with dermatophytic infections treated with nystatin cream, 30.4 percent (14/46) had positive KOH preparations and cultures at the end of 1 week. At the end of 2 weeks, 16.7 percent (6/36) were positive. This compared favorably with treatment with tolnaftate cream alone and the combination tolnaftate-nystatin cream. In each of these groups over 75 percent of the patients were either cleared or improved, and about 80 percent had negative KOH preparations and cultures. There were no significant differences between treatment groups in the overall success of treatment.

Nystatin has been used in double-blind, controlled studies to treat candidiasis of the skin in various anatomical areas, including the genital area (Refs. 21 through 24). In a randomized, double-blind study by Alban (Ref. 21), 50 infants (aged 6 days to 20 months) were treated for a variety of skin conditions with either nystatin topical cream (100,000 U/g) or placebo cream. These conditions included diaper rash, intertrigo, paronychia

(inflammation of the folds of tissue around the fingernail), and perleche (inflammation and cracking of the lips). All patients had positive cultures before therapy and were recultured at the end of therapy. The creams were applied either three or four times daily for 2 to 8 days (average 6 days).

In the nystatin group, good to excellent results were seen in 21 of 25 (84 percent) infants compared with 8 of 25 (32 percent) in the placebo group. This difference is statistically significant ($p=0.001$). Positive cultures at the end of therapy were seen in only 8 (32 percent) of the nystatin cases, compared with 21 (84 percent) of the placebo group, a statistically significant difference ($p<0.001$).

Following this study, 18 infants who failed to respond to the placebo cream were treated with nystatin cream, with clinical clearing in 15 (83 percent) and mycologic clearing in 14 (78 percent) (Ref. 21). Alban concluded that nystatin was "a rapid and convincing therapeutic agent for the treatment of cutaneous moniliasis (candidiasis) in infants when applied as a topical cream several times daily for six days."

Nystatin ointment 100,000 U/g was compared with 1 percent haloprogin cream in a double-blind parallel comparison method in 68 patients with cutaneous candidal infections (sites not stated) (Ref. 22). Two institutions in the southeastern United States cooperated in the study. All skin lesions were rated 1 (mild) to 4 (severe) in clinical severity prior to treatment. Except for one child, all patients were adults, and all had positive pretreatment KOH preparations and cultures for *C. albicans*. Each product was applied twice daily for 13 consecutive days. One day later and again 2 weeks after discontinuing treatment, the clinical lesions were scored and followup KOH preparations and fungal cultures were obtained. Clinical improvement was considered to have occurred if lesion scores were reduced by 50 percent or more. Objective improvement was considered confirmed if cultures after therapy were negative for *C. albicans*. There was no significant difference in clinical improvement between the two groups, as 28 of 33 nystatin-treated patients and 29 of 35 haloprogin-treated patients responded satisfactorily to treatment. The overall cure rate exceeded 80 percent in both groups, including clinical and mycologic cures.

Another double-blind study compared nystatin ointment 100,000 U/g with 1 percent clotrimazole cream in a group of 10 patients with cutaneous candidiasis of the toeweb (7 patients) and groin (5

patients). Before therapy all patients had positive KOH preparations and cultures for *C. albicans*. Treatments were applied twice daily.

The patients were reexamined with microscopy and culture after 4 weeks of treatment and again 4 weeks after treatment stopped. Although the numbers of patients in the study were too small to be significant, the preparations seemed to be equally effective. Four weeks after the end of therapy, all three nystatin-treated patients and six of seven clotrimazole-treated patients were clear of infection as judged by cultures (Ref. 23).

A multicenter, double-blind trial compared nystatin cream with nystatin/triamcinolone acetonide combination cream in the treatment of 31 patients with bilateral *Candida* infections of the flexural folds (Ref. 24). (Triamcinolone acetonide is a corticosteroid anti-inflammatory drug.) In this bilateral paired comparison study, the patients (20 males and 11 females) applied nystatin cream on one side and nystatin/triamcinolone acetonide cream on the other side for 14 days. Before treatment all patients had positive cultures for *Candida*.

During the first 7 days of treatment, each patient completed a daily self-assessment form pertaining to symptoms of itching, irritation, and pain. This enabled a preference assessment to be made of the effectiveness and speed of action of the two creams. Both treatments proved equally effective in terms of clinical improvement and mycological cure. Mycological cure occurred in 27 patients on the nystatin-treated side and 26 patients on the nystatin/triamcinolone-treated side. Clinical improvement occurred on both sides in 29 patients.

Although 13 patients had no preference between the two creams, 13 other patients preferred the nystatin/triamcinolone combination and 5 preferred the nystatin alone. Physician assessment of the two creams, based on the rapidity of symptomatic relief, preferred the nystatin/triamcinolone combination 14 times; nystatin alone, 6 times; and no difference, 11 times. Although these numbers were too small to be statistically significant, patients and physicians tended to prefer the nystatin/triamcinolone combination. The study concluded that "the addition of a steroid may be desirable for a more rapid relief of the symptoms while a mycological cure is being achieved."

A series of 76 consecutive cases of vaginitis seen in office practice was reported in 1956 (Ref. 25). *C. albicans* was demonstrated by culture in 59 patients, of whom 31 were pregnant. All

patients complained of itching. Treatment consisted of the insertion of either one or two vaginal tablets containing nystatin 100,000 U at bedtime for either 7 or 14 days. No controls were included in the study. Evaluation was based on clinical improvement and culture results obtained at examinations 1 week later and 2 to 3 months later. Nystatin therapy was successful in 58 of the 59 patients. Vaginitis recurred with symptoms and positive cultures for *C. albicans* in 10 pregnant patients and 4 nonpregnant patients 2 to 5 weeks after therapy stopped. Repeat courses of nystatin gave excellent results in all cases. Itching was relieved within the first 48 hours of nystatin treatment.

Another uncontrolled study in 1956 reported the "successful" use of both oral and vaginal nystatin in combined therapy for candidal vulvovaginitis in 50 patients (Ref. 26). Nystatin was said to be the "treatment of choice." Oral nystatin was used to reduce the candidal population in the gastrointestinal tract, often the source of the candidal infection. The report stated that patients should be warned to expect soreness and pain a day or so after treatment is started. This discomfort is probably caused by the dissolution of the yeast curds in the vagina with resulting raw eroded areas. The intensification of symptoms after treatment is started was said to be "almost diagnostic" of a yeast infection.

A randomized, double-blinded, controlled study in 1973 compared nystatin vaginal cream 100,000 U/g with placebo cream in 50 adult female patients (Ref. 27). All patients had *C. albicans* vaginitis documented by positive KOH preparations and fungal cultures. The creams were applied in 5 g doses twice daily with 14-day treatment in most cases. Followup examinations were made after 4 to 7 days of therapy and 4 to 7 days after completion of therapy. The overall response was significantly better in the nystatin treatment group; 92 percent of these patients had good to excellent clinical results and positive cultures remained in only 26 percent. In contrast, positive cultures remained in 79 percent of the placebo-treated group; 60 percent had good to excellent clinical responses.

Two randomized, double-blinded studies in Europe compared nystatin with clotrimazole in the treatment of candidal vaginitis. In Germany, 120 patients with culture-proven candidal vaginitis were treated with a 7-day course of vaginal tablets containing either nystatin 100,000 U or clotrimazole 100 mg (Ref. 28). None of these patients was pregnant. Followup examinations and cultures were performed 1 week

and 4 weeks after beginning treatment. In the nystatin-treated group, 47 of 60 patients were "cured" at the 4-week followup, whereas 54 of 60 of the clotrimazole-treated group were "cured." A cure was defined as a clinical cure combined with negative cultures. There was no statistically significant difference between the results of the two treatment regimens. However, the symptoms of itching, burning, and vaginal discharge were mentioned much less frequently in the clotrimazole-treated group. Clotrimazole was concluded to be as effective as nystatin in treating vaginal candidiasis (Ref. 28).

In Scotland, 62 pregnant patients were treated with either two vaginal suppositories of nystatin (100,000 U each) or one vaginal suppository of clotrimazole (100 mg) daily for 6 days (Ref. 29). All patients had positive cultures for *Candida* species before beginning the study, and followup cultures were obtained 1 week and 5 weeks after ending therapy. The symptoms including itching. The treatment groups included 29 patients using nystatin and 33 patients using clotrimazole.

Five weeks after the end of therapy, 91 percent of the clotrimazole-treated patients and 32 percent of the nystatin-treated group had negative cultures. This difference between the two therapies was highly significant (<0.005). Both treatments reduced signs and symptoms including itching. Although clotrimazole resulted in a greater reduction of symptoms than nystatin, the researchers report that the difference was significant only in the reduction of vaginal discharge. Neither drug adversely affected the pregnancy, with all infants normal at birth. Clotrimazole was concluded to be superior to nystatin in the local treatment of candidal vaginitis during pregnancy.

Three studies compared nystatin with miconazole nitrate in the treatment of vulvovaginal candidiasis. In 1974, 116 pregnant or nonpregnant women with KOH and culture-positive vulvovaginal candidiasis were randomly assigned to two treatment groups (Ref. 30). In one group of 60 women, treatment was one nystatin vaginal tablet (100,000 U) twice daily for 15 days. In the second group of 56 patients, 2 percent miconazole nitrate cream was inserted vaginally at bedtime for 14 days, with each applicator containing 0.1 g miconazole nitrate.

A "cure" was defined as clearing of signs and symptoms, including itching, as well as negative KOH preparation and fungal culture at least 30 days after

completion of therapy. In the nystatin-treated group, 46 of 60 (76.7 percent) were cured, compared to 51 of 56 (91.6 percent) cured with miconazole. A second course of nystatin treatment given to nine patients who were not cured after the first course resulted in cures in five of these nine patients. This gave an overall cure rate of 85 percent with nystatin.

Although the cure rate with miconazole was significantly higher than with nystatin, the Panel concludes that nystatin was still an effective therapeutic agent, curing over 75 percent of the cases of candidiasis.

A similar study (Ref. 31) compared the nystatin vaginal tablets (100,000 U) and the 2-percent miconazole cream preparations in 94 pregnant patients with vulvovaginal candidiasis. The patients were randomly assigned to treatment groups. Among 42 culture-positive patients treated with nystatin tablets, 31 (75 percent) considered themselves subjectively cured at the end of the treatment period. However, 18 (44 percent) still had positive cultures for *Candida*. In contrast, only 8 of 37 (22 percent) of the miconazole-treated group had positive cultures at the end of treatment, while 34 (91 percent) considered themselves subjectively cured.

Among patients who had negative cultures at the end of treatment and who were followed for up to 16 weeks, the recurrence rate of vulvovaginal candidiasis was 48 percent in the nystatin group and 24 percent in the miconazole group. The recurrence rate was significantly lower in the miconazole-treated group (Ref. 31). The Panel concludes that vulvovaginitis in pregnancy is often persistent and difficult to treat and that a "subjective" cure rate of 75 percent for nystatin would be acceptable for OTC use, despite the persistence of *Candida* on culture in many cases.

Nystatin vaginal tablets and 2 percent miconazole nitrate cream were again compared in pregnant women with vulvovaginal candidiasis in a multicenter comparative randomized study involving 33 investigators using a common protocol (Ref. 32). Nystatin tablets were inserted twice daily for 15 days; miconazole cream was inserted once daily at bedtime for 14 days.

Followup clinical examinations with KOH preparations and cultures were done 8 to 10 days and 30 to 35 days after completion of therapy. A second course of therapy was offered to patients whose first course had failed. After the first course of therapy, 53.3 percent of 244 patients were cured with nystatin, compared with 83.5 percent of patients

treated with miconazole nitrate. After two courses of therapy, the combined cure rate was 66.1 percent for nystatin and 92.9 percent for miconazole. Although the cure rate for nystatin was significantly lower than that of miconazole, the Panel still regards an overall cure rate of 66 percent as acceptable in showing clinical effectiveness of nystatin.

The Panel is particularly interested in the use of nystatin for feminine itching that is usually associated with vaginal yeast infection. This infection is usually caused by *C. albicans*, unlike jock itch in males which usually a dermatophytic infection. In reviewing the efficacy of nystatin, the Panel also carefully reviewed the use of intravaginal nystatin in treating vulvovaginitis. Vaginal discharge is the most common pelvic complaint seen in office practice and is usually associated with vaginal itching (Ref. 25). In vulvovaginitis due to *Candida* infection, the entire vulva may become moist, red, and raw; itching of the vulva may become so intense that the patient must seek emergency medical treatment. There may also be a white vaginal discharge. Of the two microorganisms most often responsible for vaginal itching and discharge, *C. albicans* is far more common than *Trichomonas vaginalis*. In 1956 the ratio of patients seen with *Candida* compared to *Trichomonas* was estimated to be 7:1 in nonpregnant patients and 15:1 in pregnant patients (Ref. 25).

The Panel recognizes that the most successful treatment of vulvovaginitis caused by *Candida* involves combined therapies designed to eradicate the yeast infection from the vulva, vagina, and gastrointestinal tract (Ref. 4). Such ideal therapy includes an appropriate anticandidal medication for each of these three areas, including a cream, lotion, ointment, or powder for the skin and mucous membranes of the vulva; intravaginal creams or tablets for the vagina; and oral tablets for the gastrointestinal tract. The Panel also recognizes, however, that women with *Candida* vulvovaginitis are bothered most by the itching and by the moist, raw, red eruption of the vulva. The Panel believes that this discomfort could be rapidly relieved by the application of OTC nystatin cream or ointment until more definitive treatment with oral and intravaginal anticandidal medications could be obtained from a physician.

The Panel concludes that nystatin is effective for OTC topical antifungal use in the treatment of superficial skin infections caused by species of *Candida*. Nystatin is also effective in the types of athlete's foot and jock itch (in males) caused by yeast infection. However,

because most causes of athlete's foot and jock itch are caused by dermatophytes, the Panel recommends that nystatin not be used alone to treat these conditions. But nystatin would be useful in the treatment of mixed infections (candidal-dermatophytic) of the feet and groin. For this reason the Panel recommends the use of nystatin combined with a Category I antifungal ingredient in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph D. below—Combination Products Used in the Treatment of Athlete's Foot, Jock Itch, and Ringworm.) The Panel also concludes that nystatin is effective for the treatment of external feminine itching associated with vaginal yeast (candidal) infection.

Candidal or yeast infection of the vagina is extremely common and recurrent, and is the most common cause of intense itching and erythema of the vulva associated with a white vaginal discharge. The Panel believes that most women are familiar with this condition, particularly if they have ever been treated for it by a physician. The Panel believes that OTC treatment of the vulva with nystatin cream or ointment will often provide rapid symptomatic relief of itching through eradication of *Candida* on the vulva. The Panel recognizes that this treatment alone is insufficient to "cure" the yeast infection (because it does not eradicate the fungus in the vagina and gastrointestinal tract). For this reason the Panel recommends that labeling for nystatin used as a single ingredient for the treatment of external feminine itching associated with vaginal yeast (candidal) infection include a warning limiting use to 14 days if there is no improvement. Nevertheless, the Panel concludes that the use of topical nystatin is a rational and well-accepted part of the treatment of yeast vulvovaginitis.

(3) *Dosage*—(i) *Concentration*. Nystatin 100,000 µg/g.

(ii) *Directions for use*. See part III, paragraph A.2. below—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*). For nystatin combined with up to two Category I antifungal ingredients, provided these ingredients broaden the spectrum, the Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and

ringworm. For such combinations, Category I labeling may also be used for antifungal products with activity against both dermatophytes and yeast. [See part III, paragraph A.2. below—Category I Labeling.]

References

- (1) OTC Volume 070216.
- (2) Rippon, J. W., "Medical Mycology," W. B. Saunders Co., Philadelphia, pp. 531-534, 1974.
- (3) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., MacMillan Publishing Co., Inc., New York, pp. 1235-1236, 1975.
- (4) Osol, A., and J. E. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1167, 1975.
- (5) Witten, V. H., and S. I. Katz, "Nystatin," *Medical Clinics of North America*, 54:1329-1337, 1970.
- (6) Dutcher, J. D., D. R. Walters, and O. P. Wintersteiner, "Studies of the Chemical Properties and Structure of Nystatin (Mycostatin)," in "Therapy of Fungus Diseases. An International Symposium," edited by T. H. Sternberg and V. D. Newcomer, Little, Brown and Co., Boston, pp. 168-175, 1955.
- (7) Hildick-Smith, G., H. Blank, and I. Sarkany, "Fungus Diseases and Their Treatment," Little, Brown, and Co., Boston, pp. 378-382, 1964.
- (8) Wasilewski, C., Jr., "Allergic Contact Dermatitis From Nystatin," *Archives of Dermatology*, 102:216-217, 1970.
- (9) Wasilewski, C., Jr., "Allergic Contact Dermatitis from Nystatin," *Archives of Dermatology*, 104:437, 1971.
- (10) Coskey, R. J., "Contact Dermatitis Due to Nystatin," *Archives of Dermatology*, 103:228, 1971.
- (11) Coskey, R. J., "Contact Dermatitis Due to Nystatin," *Archives of Dermatology*, 104:437-438, 1971.
- (12) Osol, A., and R. Pratt, "The United States Dispensary," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 800-803, 1973.
- (13) Ermishkin, L. N., Kh. M. Kasumov, and V. M. Potzeluyev, "Single Ionic Channels Induced in Lipid Bilayers by Polyene Antibiotics Amphotericin B and Nystatine," *Nature*, 262:698-699, 1976.
- (14) Hazen, E. L., and R. Brown, "Fungicidin, an Antibiotic Produced by a Soil Actinomycete," *Proceedings of the Society for Environmental Biology and Medicine*, 76:93-97, 1951.
- (15) Pansy, F. E., et al., "Hamycin: In Vitro and In Vivo Studies," *Antimicrobial Agents and Chemotherapy*, 6:399-404, 1967.
- (16) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill Book Co., New York, pp. 1756-1758, 1971.
- (17) Shadomy, S., "In Vitro Antifungal Activity of Clotrimazole (Bay b 5097)," *Infection and Immunity*, 4:143-148, 1971.
- (18) Hashimoto, T., and H. J. Blumenthal, "Survival and Resistance of *Trichophyton Mentagrophytes* Arthrospores," *Applied and Environmental Microbiology*, 35:274-277, 1978.
- (19) Donovan, R., et al., "Some In Vitro Characteristics of Nystatin (Mycostatin)," in "Therapy of Fungus Diseases. An International Symposium," edited by T. H. Sternberg and V. D. Newcomer, Little, Brown and Co., Boston, pp. 176-185, 1955.
- (20) Graham, J. H., et al., "The Use of Nystatin as a Topical Antifungal Agent," in "Therapy of Fungus Diseases. An International Symposium," edited by Sternberg, T. H., and V. D. Newcomer, Little, Brown and Co., Boston, pp. 220-227, 1955.
- (21) Alban, J., "Efficacy of Nystatin Topical Cream in the Management of Cutaneous Candidiasis in Infants," *Current Therapeutic Research*, 14:158-161, 1972.
- (22) Carter, V. H., and S. Olansky, "Haloprogin and Nystatin Therapy for Cutaneous Candidiasis: Comparison of the Efficacy of Haloprogin and Nystatin Therapy," *Archives of Dermatology*, 110:81-82, 1974.
- (23) Comaish, J. S., "Double-blind Comparison of Clotrimazole with Whitfield's and Nystatin Ointments," *Postgraduate Medical Journal*, 50 (Supplement 1):73-75, 1974.
- (24) Beveridge, G. W., et al., "A Comparison of Nystatin Cream with Nystatin/Triamcinolone Acetonide Combination Cream in the Treatment of Candidal Inflammation of the Flexures," *Current Medical Research and Opinion*, 4:584-587, 1977.
- (25) Pace, H. R., and S. I. Schantz, "Nystatin (Mycostatin) in the Treatment of Monilial and Nonmonilial Vaginitis," *Journal of the American Medical Association*, 162:268-271, 1956.
- (26) Jillson, O. F., and J. S. Lyle, "Yeast Vulvovaginitis: Its Successful Treatment with Nystatin (Mycostatin)," *Archives of Dermatology*, 74:489-492, 1956.
- (27) Isaacs, J. H., "Nystatin Vaginal Cream in Monilial Vaginitis," *Illinois Medical Journal*, 143:240-241, 1973.
- (28) Marks, H. J., "A Double-Blind Comparison of Clotrimazole and Nystatin Vaginal Tablets in Candida Vaginitis," *Postgraduate Medical Journal*, 50 (Supplement 1):105-108, 1974.
- (29) Tan, C. G., et al., "A Comparative Trial of Six-Day Therapy with Clotrimazole and Nystatin in Pregnant Patients with Vaginal Candidiasis," *Postgraduate Medical Journal*, 50 (Supplement 1):102-105, 1974.
- (30) Davis, J. E., Frudenfeld, J. H., and J. L. Goddard, "Comparative Evaluation of Monistat and Mycostatin in the Treatment of Vulvovaginal Candidiasis," *Obstetrics and Gynecology*, 44:403-406, 1974.
- (31) Wallenburg, H. C. S., and J. W. Wladimiroff, "Recurrence of Vulvovaginal Candidosis During Pregnancy. Comparison of Miconazole Vs. Nystatin Treatment," *Obstetrics and Gynecology*, 48:491-494, 1976.
- (32) McNellis D., et al., "Treatment of Vulvovaginal Candidiasis in Pregnancy: A Comparative Study," *Obstetrics and Gynecology*, 50:674-678, 1977.

e. *Tolnaftate*. The Panel concludes that tolinaftate is safe and effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm and in the prevention of athlete's foot.

The chemical name of tolinaftate ($C_{19}H_{17}NOS$) is methyl (3-

methylphenyl)-carbamothioic acid 0-2-naphthalenyl ester. Tolinaftate is a fine, white, odorless powder with a melting point of 110° to 113° C. It is practically insoluble in water, slightly soluble in alcohol, and freely soluble in chloroform (Ref. 1).

(1) *Safety*. Acute toxicity studies (Ref. 2) indicate that in rats, dogs, and rabbits, tolinaftate 1 percent displays a good therapeutic index (the ratio between the toxic dose and the therapeutic dose). An oral LD₅₀ could not be obtained in mice, rats, guinea pigs, rabbits, or dogs, even with doses as high as 14 g/kg.

Acute dermal and eye irritation studies in rabbits revealed no changes. Subacute and chronic toxicity studies lasting from 3 weeks to 1 year and performed in a variety of animals showed no toxicity due to tolinaftate. Dosage forms tested included powder, solution, and cream with the highest concentration being a 3-percent solution. A 1-year, chronic dermal study in rats and mice showed no evidence of carcinogenicity or adverse reaction after application of tolinaftate in acetone (Ref. 2).

Reproduction studies were conducted in rabbits, guinea pigs, mice, and rats. The researchers found no teratogenic effects from tolinaftate administered orally, topically, or subcutaneously (Ref. 2).

In humans, some uncontrolled studies of tolinaftate have reported an insignificant incidence of mild dermatitis, including irritation, erythema, and itching (Ref. 2). But numerous other studies confirm an absence of toxicity potential from the use of this ingredient.

Several controlled studies (Refs. 3 through 6) using 1 percent tolinaftate solution or powder showed an absence of toxicity potential. Lubowe and Wexler (Ref. 3) tested tolinaftate solution in 25 patients with athlete's foot and jock itch. The solution was applied two to three times daily for an average of 3.5 weeks. The investigators found "no evidence of primary irritation or secondary sensitization."

Tolinaftate solution was also used by Kurban et al. (Ref. 4) in 49 patients; 27 had ringworm of the body and 22 had tinea versicolor. Treatment was twice daily for 2 to 3 weeks. The researchers reported no local side effects and no apparent hematologic or renal toxicity from tolinaftate.

Charney et al. (Ref. 5) conducted a double-blind, multicenter trial to test tolinaftate powder in the treatment and prevention of athlete's foot. The study population consisted of 635 adults from

four different institutions. During the 12-week treatment period, one-half of the subjects received applications of tolnaftate powder twice daily. The other half received the vehicle. The treatments were given 5 days a week for 12 weeks with one investigator completing the scheduled 60 treatment days over an 8-week period by treating 7 days a week.

The researchers wrote that "there was no documented instance of hypersensitivity to any component of the medication." At one institution, however, two subjects who received the vehicle complained of irritation. Charney et al. believed these side effects were caused by "exacerbation of the disease process."

In a double-blind study, 50 subjects applied tolnaftate powder or vehicle twice daily during the 5-week to 6-week test period (Ref. 6). None of these subjects had any clinical signs or symptoms of irritation due to tolnaftate or the vehicle.

After reviewing the data presented, and considering the area of use of tolnaftate preparations, the Panel concludes that tolnaftate is safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm, and in the prevention of athlete's foot.

(2) *Effectiveness.* Tolnaftate was submitted to the Panel at a concentration of 1 percent in powder, cream, solution, spray powder, and spray solution. Most of the relevant clinical data available pertain to the powder, cream, and solution forms of the drug. Very little information is available on the effectiveness of the spray powder and the spray solution.

The *in vitro* antifungal activity of tolnaftate was tested against 29 strains of fungi grown in Sabouraud's liquid medium (Ref. 7). Using the tube-dilution method, the fungistatic concentration against *T. mentagrophytes* was 0.008 µg/mL, and the fungicidal concentration was 0.08 µg/mL. Tolnaftate was found to be "highly active and specific *in vitro*" against 19 strains of the following genera: *Trichophyton*, *Microsporum*, and *Epidermophyton*. Tolnaftate showed no activity against *C. albicans* (Ref. 7). As stated earlier, the *in vitro* activity of tolnaftate against dermatophytes compared favorably with haloprogin, but tolnaftate did not show anticandidal activity. (See part III, paragraph A.1.a. above—Haloprogin.)

Tolnaftate has been studied in animal models (Ref. 7), in induced human infections (Ref. 8), and in natural human infections (Ref. 4). In guinea pigs, tolnaftate has been shown to be effective in treating superficial fungal infections caused by *T. mentagrophytes*.

Weinstein, Oden, and Moss (Ref. 7) reported on the antifungal properties of tolnaftate in an *in vivo* animal model system. Male guinea pigs were infected with *T. mentagrophytes*. Three days after infection, eight animals were treated with either a 1 percent tolnaftate solution, cream, or powder; 12 were treated with a control vehicle, and 8 were untreated controls. Animals were evaluated on days 1, 3, 7, 9, 11, and 21 after treatment was begun. By day 11, all tolnaftate-treated animals were clear of lesions both on examination and by culture. Conversely, after 21 days of therapy, neither the animals treated with the powder, solution, or cream bases alone nor the untreated animals were free of lesions.

In treating human dermatophytoses, tolnaftate has been shown to be far more effective than the placebo vehicle. In a double-blind controlled trial, Kurban et al. (Ref. 4) studied 88 consecutive patients with superficial mycoses of the skin. Only patients with positive KOH preparations and cultures were included in the study. This discussion pertains to the 43 patients diagnosed with ringworm of the body. These 43 patients were instructed to apply either 1 percent tolnaftate solution or its vehicle twice daily and to use no other medications during the 2- to 3-week treatment. During this time the patients were seen for a weekly or biweekly evaluation including the patient's objective comments, clinical assessment, KOH preparation, and culture.

Twenty-seven patients received tolnaftate; of these patients, 25 (93 percent) had clinical cures and negative cultures. Of 16 patients treated with placebo vehicle, only 1 was cured. The authors concluded that tolnaftate was an effective topical antifungal agent.

Adam and Craig (Ref. 8) in a double-blind, controlled study of 38 patients also illustrated the effectiveness of tolnaftate. The study population consisted of 23 cases of athlete's foot, 12 of jock itch, and 3 of ringworm of the body. KOH preparations were positive in all patients and cultures showed *T. rebrum*, *T. mentagrophytes*, or *E. floccosum*. Patients were treated with 1 percent tolnaftate in a cream base or the cream base alone. Observations were recorded at weekly intervals over a 3-week period and at a reevaluation visit 1 to 4 weeks after treatment was stopped. Lesions were cultured, and KOH preparations were performed at each visit.

Of the 29 patients treated with tolnaftate, 18 (62 percent) were cleared and 3 (10 percent) were failures. Of the 9 patients treated with the placebo, 2 (22

percent) were cleared and 5 (56 percent) were failures. The remaining 10 patients represented partial responses. Drawbacks in the study design include the apparent lack of randomization and failure to match patients and cultures.

Tolnaftate has been used extensively in controlled studies as a standard against which other topical antifungals have been compared and rated. Carter (Ref. 9) compared the effectiveness of tolnaftate and haloprogin in a double-blind, clinical trial. A 1-percent solution of tolnaftate was compared to 1 percent haloprogin in 82 patients with athlete's foot. The diagnosis of cutaneous infection was determined by clinical inspection, KOH preparations, and cultures. Patients were randomly assigned to treatment groups and treated twice daily for 27 consecutive days. Of the 20 tolnaftate-treated patients, 17 (85 percent) showed clinical improvement; 56 (92 percent) of the 81 patients treated with the various forms of haloprogin showed improvement. Eighty percent of the tolnaftate-treated group and 91 percent of haloprogin-treated group maintained or further improved lesion scores 8 days after treatment.

Hermann (Ref. 10) conducted three double-blind studies in which he compared 1 percent tolnaftate cream with 1 percent haloprogin cream in patients with dermatophyte infections. Haloprogin was also compared to its cream vehicle. Only patients with a clinical diagnosis confirmed by a positive culture and KOH preparation were included in the study. Patients applied the drugs twice daily and were observed at 7-day and 14-day intervals with repeated inspection and KOH determinations. These studies were carried out over a 28-day period. Of the 22 patients receiving tolnaftate, 20 (91 percent) improved and 2 (9 percent) did not improve. Of the 18 patients treated with haloprogin, 11 (61 percent) improved and 7 (39 percent) did not improve. From these data the author concluded that tolnaftate and haloprogin were comparable in effectiveness.

A double-blind study compared the effectiveness of 1 percent tolnaftate and 1 percent clotrimazole creams in 54 patients with superficial dermatophytoses (Ref. 11). Each treatment group contained 27 patients, with *E. floccosum* and *T. rubrum* cultured from all patients. Patients applied either tolnaftate or clotrimazole twice daily for 21 days. Clinical, microscopic, and culture examinations were performed at weekly intervals during therapy and at 1, 3, and 5 weeks after completing therapy. At the end of

the treatment period, 19 (70 percent) of the tolnaftate-treated patients were cured, compared to 21 (78 percent) of the clotrimazole-treated patients. This difference was not statistically significant.

Wethered and associates (Ref. 12) conducted a double-blind, paired comparison, clinical trial in 24 patients with athlete's foot caused in most cases by *T. rubrum*. On microscopy, all patients demonstrated fungal elements on both feet. Patients were randomly assigned two tubes of ointment marked for the right or left foot. The tubes contained either 1 percent pecilocin ointment or its ointment base, or 1 percent tolnaftate cream or its base. (Pecilocin is an antifungal antibiotic used in Great Britain.) The ointments were applied twice daily for 28 days. Clinical assessment was made weekly. Seven days after the end of the trials, scrapings were taken from each foot for microscopy and culture. A similar examination was done 3 weeks later. Of the 12 patients in the tolnaftate treatment group, 5 showed greater clinical improvement on the untreated side and 2 showed greater improvement on the treated side. (Both sides were culture positive.) In most cases, the mycological findings were the same on both sides. The results of this study indicated that neither tolnaftate nor pecilocin has a clinical or mycological effect. The Panel considers that the paired-comparison study design is responsible for the lack of evidence of tolnaftate effectiveness.

A double-blind study by Smith and co-workers (Ref. 13) tested both the effectiveness and the prophylactic activity of a 1-percent tolnaftate powder in the treatment and prevention of athlete's foot in a prison population. Before beginning treatment, the feet of all inmates were examined and clinical observations recorded. Scrapings of scale were taken for KOH preparation and for culturing on Sabouraud's media. This study included 317 men, 144 of whom had confirmed athlete's foot.

Of these 144 subjects, 71 were treated with 1 percent tolnaftate powder applied twice daily to the feet and toes. As a control, 49 inmates were treated twice daily with the talc-cornstarch vehicle. Twenty-four subjects were left untreated. No other topical or systemic therapy was given.

At the end of 8 weeks a series of final examinations of the subjects began. At the end of the study, 26 of the 71 subjects treated with tolnaftate had clinical cures and negative cultures. Five of the 49 men using the vehicle alone and 2 of the 24 men in the untreated group had clinical cures and negative

cultures. Tolnaftate powder was shown to be superior both to the vehicle alone and to no treatment at all ($p < 0.01$).

Seventy of the 317 patients had no sign of fungal infection when they began the above study. Twenty-eight of these subjects used tolnaftate powder prophylactically twice daily. At the end of the study period, 23 of these subjects still had normal clinical findings and negative cultures and KOH preparations. Of the 36 subjects who used the vehicle powder prophylactically, 20 remained "normal." Of the six subjects who were untreated, three remained free from the fungal disease at the end of this period. Statistical analysis of the study results revealed that tolnaftate powder was significantly more effective than the vehicle in preventing athlete's foot ($p < 0.05$). There were not enough subjects in the untreated group to permit statistical analysis of the effectiveness of the talc-cornstarch vehicle alone in the prevention of athlete's foot (Ref. 13).

Several other studies (Ref. 5, 6, and 14) have also examined the prophylactic effectiveness of tolnaftate.

An investigator (Ref. 6) conducted a double-blinded study in 50 volunteers to test the prophylactic effectiveness of 1 percent tolnaftate powder in experimentally induced fungal infections of the foot. Preceding treatment, cantharidin was used to induce blisters on the feet of the test subjects before deliberate exposure to masses of *T. mentagrophytes* spores in foot baths. After the foot baths the subjects were instructed to apply either tolnaftate powder or the powder base to both feet twice daily throughout the 5-week to 9-week test period. Half of the subjects received tolnaftate powder, the others received the vehicle control. Of the 25 tolnaftate-treated patients, 20 remained clear of fungal infection throughout the study. Of the 25 vehicle-treated patients, 13 remained free of fungal infection. This difference is statistically significant ($p = 0.035$).

A double-blind, controlled study by Burrill and Nemlick (Ref. 14) tested the prophylactic effectiveness of 1 percent tolnaftate powder in 86 patients for 12 weeks. The patients did not have athlete's foot before treatment. Diagnosis was established by clinical inspection, KOH preparations, and culturing. Response to treatment was evaluated in the same way. Six of the 45 patients treated prophylactically with tolnaftate developed new lesions while under study, although KOH preparations were negative. Of the 41 patients in the placebo group, 21 developed lesions during the treatment period and 16 of the 22 had positive KOH preparations.

The difference between tolnaftate-treated and placebo-treated groups was statistically significant ($p < 0.001$).

In the prophylactic segment of the multicentric study by Charney et al. (Ref. 5) described above, a common protocol was employed at four institutions in California, Mississippi, Puerto Rico, and Texas. A total of 168 subjects entered the study with no evidence of fungal infection based on clinical and mycological examinations. These subjects were distributed among the four institutions with 69 receiving tolnaftate and 99, the vehicle control. They completed 60 prophylactic treatment days. Based on the pooled data, it was reported that 61 (88 percent) of the tolnaftate-treated subjects had no clinical evidence of athlete's foot at the end of the study, as compared to 68 (69 percent) of the vehicle-treated subjects. These results showed tolnaftate powder to be significantly more effective than the vehicle, talc-cornstarch, in preventing athlete's foot ($p < 0.01$).

The Panel reviewed numerous other studies supporting the effectiveness of tolnaftate in the treatment and prevention of superficial fungal infections. These studies were found to be lacking in double-blinding, randomization, or placebo controlling. For this reason they are not presented here in detail.

Tolnaftate has been shown to be an effective drug in the treatment of athlete's foot, jock itch, and ringworm and in the prevention of athlete's foot. Its effectiveness has been demonstrated in both humans and laboratory animals by controlled, blinded studies in which tolnaftate was compared against its vehicle as well as against other known effective topical antifungals (e.g., haloprogin and clotrimazole).

The Panel concludes that tolnaftate may be used in the prevention of athlete's foot, but not in the prevention of jock itch or ringworm. Because the groin is a much more sensitive area than the feet, antifungal agents should not be used indefinitely in the groin. Also, it would be impractical to use an antifungal agent prophylactically over large areas of the body to prevent ringworm of the body.

Based on the foregoing clinical studies, the Panel concludes that tolnaftate is effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm, and in the prevention of athlete's foot.

(3) *Dosage—(i) Concentration.* Tolnaftate 1.0 percent.

(ii) *Directions for use.* See part III, paragraph A.2. below—Category I Labeling.

(4) **Labeling.** The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm and in the prevention of athlete's foot. (See part III, paragraph A.2. below—Category I Labeling.)

References

- (1) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1204, 1973.
- (2) OTC Volume 070010.
- (3) Lubowe, I. L., and L. Wexler, "Comparative Study of Tolnaftate Solution and Compound Undecylenic Acid Ointment N.F. in the Treatment of Epidermophytoses," *Current Therapeutic Research*, 7:401-405, 1965.
- (4) Kurban, A. K. et al., "Clinical Evaluation of Tolnaftate. A Double Blind Study of a Topical Antifungal Agent," *Dermatologica*, 133:482-486, 1966.
- (5) Charney, P., et al., "Tolnaftate as a Prophylactic Agent for Tinea Pedis," *International Journal of Dermatology* 12:179-185, 1973.
- (6) OTC Volume 070157.
- (7) Weinstein, M. J., E. M. Oden, and E. Moss, "Antifungal Properties of Tolnaftate In Vitro and In Vivo," *Antimicrobial Agents and Chemotherapy*, 36:595-601, 1964.
- (8) Adam, J. E., and G. E. Craig, "Tolnaftate (Tinactin), a New Topical Antifungal Agent," *Canadian Medical Association Journal*, 93:1004-1005, 1965.
- (9) Carter, V. H., "A Controlled Study of Haloprogin and Tolnaftate in Tinea Pedis," *Current Therapeutic Research*, 14:307-310, 1972.
- (10) Hermann, H. W., "Clinical Efficacy Studies of Haloprogin, a New Topical Antimicrobial Agent," *Archives of Dermatology*, 106:839-842, 1972.
- (11) Male, O., "A Doubled-blind Comparison of Clotrimazole and Tolnaftate Therapy of Superficial Dermatophytoses," *Postgraduate Medical Journal*, 50:75-76, 1974.
- (12) Wethered, R. R., W. R. Heeler, and R. P. Warin, "Clinical Trials of Tolnaftate and Variofin," *British Journal of Dermatology*, 79:352-356, 1972.
- (13) Smith, E. B., J. E. Dickson, and J. M. Knox, "Tolnaftate Powder in Prophylaxis of Tinea Pedis," *Southern Medical Journal*, 67:776-778, 1974.
- (14) Burrill, B. B., and A. S. Nemlick, "Prophylaxis of Tinea Pedis," *Journal of the Medical Society of New Jersey*, 67:629-631, 1970.

f. **Undecylenic acid and its salts (calcium undecylenate, copper undecylenate, and zinc undecylenate).** The Panel concludes that undecylenic acid and its salts (calcium undecylenate, copper undecylenate, and zinc undecylenate) are safe and effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm when used in a concentration of 10 to 25 percent.

Undecylenic acid is 10-undecenoic acid, an 11-carbon unsaturated fatty acid (Ref. 1) which has been used

topically as an antifungal agent since Peak et al. (Ref. 2) first described its activity in 1939. It is a normal constituent of human sweat. Undecylenic acid is a yellow liquid with a characteristic unpleasant odor. It is almost insoluble in water, but is miscible with alcohol, chloroform, and ether (Ref. 1). Undecylenic acid is most frequently used in combination with its salts (zinc, calcium, and copper). The concentration of undecylenic acid and its salts in marketed products ranges from 1.5 to 25 percent. Undecylenic acid is marketed as a powder, aerosol, ointment, solution, and gel, but is most commonly found as a dusting or aerosol powder, possibly because of its greater patient acceptance in these dosage forms.

(1) **Safety.** Years ago, undecylenic acid was administered by mouth for the treatment of psoriasis. Daily doses from 6 to 14 g produced transient adverse effects including gastrointestinal disturbances, headache, fever, dizziness, hives, folliculitis, and conjunctivitis (Ref. 3).

The LD₅₀ in rats is reported to be between 2 g/kg (Ref. 4) and 2.5 g/kg (Ref. 3). The intraperitoneal LD₅₀ is approximately 888 mg/kg (Ref. 4). Up to 0.4 g/kg undecylenic acid in the diet of rats caused no toxicity even when continued daily for 6 to 9 months (Ref. 5).

Undecylenic acid has a low incidence of topical irritation in humans. In 22 cases treated with undecylenate ointment, two cases of irritation were noted (Ref. 6). Another study of 1,213 men using undecylenate powder prophylactically reported a complete lack of irritation and no adverse reactions (Ref. 7).

A combination of 5 percent undecylenic acid and 20 percent zinc undecylenate in an ointment was applied to intact and abraded rabbit skin at a dose of 25.5 g. The area was occluded under plastic for 24 hours. Slight irritation was noted at the end of 24 hours. After 2 weeks the animals were killed and autopsied, and no evidence of organ toxicity was observed. Using the Draize test in rabbits, this same combination was rated as essentially nonirritating at a dose of 0.5 mL and was found to be slightly irritating to the rabbit's eyes at a dose of 0.1 mL (Ref. 4).

Copper undecylenate-undecylenic acid solution was used topically to treat 28 children with ringworm of the scalp, 56 patients with dermatophytosis of the feet and hands, 6 patients with jock itch, and 5 patients with ringworm of the body. No evidence of toxicity or irritation was observed (Ref. 8). The

Panel notes that this study does not give the dose and does not indicate the degree of copper absorption or retention in the body.

The Panel concludes that undecylenic acid and its salts are safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(2) **Effectiveness.** The minimal inhibitory concentrations of zinc undecylenate and of calcium undecylenate against laboratory strains of dermatophytic fungi were determined by broth dilution and gradient agar plate techniques (Ref. 4). The gradient plate method is less accurate than broth dilution. *Candida* showed a minimal inhibitory concentration of 400 to 500 µg/mL by broth dilution, which should be considered resistant. Undecylenic acid was less active in these tests than the salts, but this could be a somewhat artificial result influenced by the pH of the test medium. The dermatophytes showed average values from 100 to 200 µg/mL. No data were submitted determining the antibacterial activity of the undecylenates.

A group of researchers tested the effectiveness of undecylenic acid-zinc undecylenate powder in 104 patients with athlete's foot verified by positive KOH preparation, positive culture (Sabouraud's agar), and clinical evaluation (Ref. 9). Patients were assigned to one of four treatment groups with no substantial difference among the groups in age, sex, or race. There was also little variation in severity of disease or type of organism isolated. The types of organisms included *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*.

The patients were treated twice daily with either 2 percent undecylenic acid and 20 percent zinc undecylenate; "old undecylenic acid powder," an OTC antifungal preparation with components similar to the undecylenic acid-zinc undecylenate preparation; or the vehicle of the undecylenate combination. A "no treatment" group was also included in the study. The patients were closely monitored for 6 weeks and evaluated with KOH preparations and cultures at 2, 4, and 6 weeks. However, there was no post-treatment examination. Two patients in the undecylenic acid-zinc undecylenate group with what was believed to be primary irritant dermatitis superimposed on allergic dermatitis were dropped from the study.

Fifty-nine percent (16/27) of the undecylenate group and 47 percent (14/30) of the "old undecylenic acid powder" group were clinically and mycologically cured after 6 weeks. This difference was not statistically

significant. However, both of these treatments resulted in a significantly higher cure rate than either the vehicle alone (4 percent) or the "no treatment" group (9 percent) ($p < 0.001$).

In another study (Ref. 7) comparing a 20-percent zinc undecylenate-2.5 percent undecylenic acid powder aerosol with a placebo aerosol, 93 patients with clinical evidence of athlete's foot and positive KOH preparations and cultures were evaluated. Patients were randomly assigned to a treatment group; therapy was given twice daily for 2 weeks. *T. rubrum*, *T. mentagrophytes*, and *C. albicans* were the organisms recovered after culturing. Forty-nine percent (21/43) of the active aerosol group and 26 percent (13/50) of the placebo group were reported as showing greater than 75 percent improvement. This difference is significant at the $p < .022$ level when analysis is based on all patients in the trial. Results were also statistically significant when based on those individuals infected with *T. mentagrophytes* ($p < .012$). But results obtained from patients infected with *C. albicans* and *T. rubrum* were not significantly different from controls.

An unpublished study (Ref. 10) examined the effectiveness of 10 percent calcium undecylenate in a talc aerosol product. Eight-two consecutive patients with jock itch, documented by clinical impression, positive KOH preparation, and positive culture, were observed in this randomized, double-blinded study. No substantial differences in the types of organisms isolated from patients in either of the groups were noted. The aerosols were used twice daily for 2 weeks, and the only other therapy was a daily soap and water wash. Weekly followups on each patient included an examination, KOH preparation, and culture. Results were presented as excellent, good, fair, or poor based on negative KOH, negative culture, and negative clinical examination. Fifty-three percent (23/43) of the patients in the active aerosol group and 5 percent (2/39) of the patients in the placebo control group were rated "excellent" (greater than 75 percent improvement) after therapy. This difference is statistically significant ($p < .001$).

The effectiveness of a 2-percent undecylenic acid-20 percent zinc undecylenate powder was compared with a 20-percent sodium propionate and talc powder in a large study on naval recruits (Ref. 7). Patients were entered into the study after a diagnosis of athlete's foot by clinical examination. The diagnosis was not confirmed by KOH preparation or cultures. Patients received either active drug or placebo

twice daily and were clinically evaluated weekly and at the end of the 10-week testing period. No followup examination after treatment was attempted. Of the 386 patients receiving the undecylenic acid powder, 76 percent (292/386) were cured or improved. A cure was defined as the absence of signs or symptoms. Sodium propionate cured or improved 47 percent (31/66). In the placebo group, 27 percent (80/297) were cured. The investigations concluded that the undecylenic acid powder was superior to the other agents tested.

In the same study, 133 patients with jock itch were treated with the undecylenic acid-zinc undecylenate powder or talc powder (Ref. 7). Once again, neither KOH preparations nor cultures were done to confirm the diagnosis. All 50 of the patients treated with the active powder were cured or improved, whereas only 47 percent (39/83) of those treated with talc were cured. Undecylenic acid was concluded to be superior to the control.

Sulzberger and Kanof (Ref. 11) evaluated the prophylactic activity of various topical preparations in athlete's foot. Length of treatment is unclear, but the study was run "throughout the summer." Admission to the study was based on a negative clinical examination. No KOH preparation or cultures were done. The effects of 20 percent zinc undecylenate-2 percent undecylenic acid powder, 15 percent calcium propionate-5 percent zinc propionate powder, and 20 percent sodium propionate powder were compared to no treatment in the prevention of athlete's foot. Table 5 shows the results.

TABLE 5.—PROPHYLACTIC EFFECT OF TOPICAL PREPARATIONS

Athlete's foot	Number of patients	Number and percentages new infections
No treatment	1,384	387(28%)
2% Undecylenic acid-20% zinc undecylenate	1,213	49(4%)
15% Calcium propionate-5% zinc propionate	814	64(8%)
20% Sodium propionate	135	20(15%)

Sulzberger and Kanof concluded that undecylenic acid used prophylactically reduced the incidence of infection by 85 percent. Undecylenic acid appears to be effective in the prevention of athlete's foot, but the Panel concludes that there are too many deficiencies in the study design (particularly the lack of cultures and KOH preparations) to permit a prophylactic assessment.

In a double-blind study, Roberts and Champion (Ref. 12) evaluated 54

patients with athlete's foot, jock itch, and ringworm of the body as confirmed by positive KOH preparations or positive cultures of *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*. Patients were treated twice daily with either 1 percent tolnaftate cream or 20 percent zinc undecylenate-5 percent undecylenic acid ointment. There was no control group. Seventy-three percent (19/26) of the tolnaftate group as compared to 68 percent (19/28) of the zinc undecylenate group were rated "good" at the end of the study. The criteria for a good rating included negative KOH, negative culture, and negative clinical examination. There was no post-treatment followup of patients. Although the authors presented no statistical evaluation of results, zinc undecylenate and tolnaftate appeared to be equally effective.

The Panel concludes that undecylenic acid and its copper, calcium, and zinc salts are effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(3) *Dosage*—(i) *Concentration*. Undecylenic acid, calcium undecylenate, copper undecylenate, and zinc undecylenate may be used individually or in any ratio which provides a total undecylenate concentration of 10.0 to 25.0 percent.

(ii) *Directions for use*. See part III, paragraph A.2. below—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. below—Category I Labeling.)

References

- (1) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1234, 1973.
- (2) Peck, S. M., et al., "Role of Sweat as a Fungicide with Special Reference to the Use of Constituents of Sweat in Therapy of Fungous Infections," *Archives of Dermatology*, 39:126-148, 1939.
- (3) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products, 4th Ed., The Williams and Wilkins Co., Baltimore, p. 135, 1976.
- (4) OTC Volume 070024.
- (5) Patty, F. A., "Industrial Hygiene and Toxicology," Volume II, 2d Ed., Interscience Publishers, New York, p. 1789, 1967.
- (6) Lubowe, I. L., and L. Wexler, "Comparative Study of Tolnaftate Solution and Compound Undecylenic Acid Ointment N.F. in the Treatment of Epidermophytosis," *Current Therapeutic Research*, 7:401-405, 1965.
- (7) OTC Volume 070025.
- (8) Combes, F. C., R. Zuckerman, and A. Bobroff, "Copper Undecylenate in the

Treatment of Dermatophytes," *Journal of Investigative Dermatology*, 10:447-453, 1948.

(9) Smith, E. B., et al., "Topical Undecylenic Acid in Tinea Pedis: A New Look,"

International Journal of Dermatology, 16:52-56, 1977.

(10) OTC Volume 070029.

(11) Sulzberger, M. B., and A. Kanof, "Undecylenic and Propionic Acids in the Prevention and Treatment of Dermatophytosis," *Archives of Dermatology and Syphilology*, 55:391-395, 1947.

(12) Roberts, S. O., and R. H. Champion, "Treatment of Ringworm Infections with Tolnaftate Ointment," *Practitioner*, 199:797-798, 1967.

2. *Category I labeling*—a. *For products used for the treatment of athlete's foot, jock itch, and ringworm.* The Panel makes the following recommendations for the indications statements of products used for the treatment of athlete's foot, jock itch, and ringworm. In table 6, which follows, column A contains acceptable descriptions of product action. Column B contains acceptable phrases for specific conditions to which the product action applies. To accurately describe the indications to the consumer, one or more of the terms in Column A should be combined as appropriate with one or more of the terms in Column B.

TABLE 6.—TERMINOLOGY FOR INDICATIONS STATEMENTS

A. Product action	B. Conditions to which the product action applies
"Treats * * *	"Athlete's foot."
For the treatment of * * *	"Athlete's foot (dermatophytosis)."
"Cures * * *	"Athlete's foot (tinea pedis)."
"For the cure of * * *	"Tinea pedis (athlete's foot)."
"Clears up * * *	"Jock itch."
"Proven clinically effective in the treatment of * * *	"Jock itch (tinea cruris)."
"For effective treatment of * * *	"Tinea cruris (jock itch)."
"Kills * * * fungi"	"Ringworm."
"Proven to kill * * * fungi."	"Ringworm (tinea corporis)."
	"Tinea corporis (ringworm)."

Based on the above lists, an example of acceptable labeling is: "Treats athlete's foot, jock itch, and ringworm."

b. *For products containing tolnaftate as a single antifungal active ingredient when used for the prevention of athlete's foot.* Table 7 contains two lists of acceptable phrases for athlete's foot prevention claims. Any one of the phrases in Column B may be inserted in any one of the phrases in Column A.

TABLE 7.—ATHLETE'S FOOT PREVENTION CLAIMS

Column A	Column B
"Clinically proven to prevent * * * with daily use"	"Athlete's foot."
"Prevents * * * with daily use"	"Athlete's foot (tinea pedis)."
"Proven effective in the prevention of * * * with daily use"	"Tinea pedis (athlete's foot)."
Helps prevent * * * with daily use"	"Athlete's foot (dermatophytosis)."
"For the prevention of * * * with daily use"	
"For the prophylaxis (prevention) of * * * with daily use"	
"Guards against * * * with daily use"	
"Prevents the recurrence of * * * with daily use"	

Based on the lists of terms in table 7, an example of acceptable labeling is: "Prevents the recurrence of athlete's foot with daily use."

The following labeling may also be used: "Clears up athlete's foot infection and with daily use helps keep it from coming back."

c. *For haloprogin, miconazole nitrate, or nystatin as single antifungal active ingredients in products used in the treatment of external feminine itching associated with vaginal yeast (candidal) infection.* Acceptable labeling is: "For the treatment of external feminine itching associated with vaginal yeast (candidal) infection."

d. *For haloprogin, miconazole nitrate, or nystatin as single antifungal active ingredients in products used in the treatment of superficial skin infections caused by yeast (Candida).* Acceptable labeling is: "For the treatment of superficial skin infections caused by yeast (Candida)."

e. *For products with activity against both dermatophytes and yeast.* For haloprogin or miconazole nitrate used alone or in combination, and nystatin used only in combination with up to two antifungal ingredients, the following phrases are optional:

"Kills dermatophytic fungi and yeast (causes of athlete's foot, jock itch, and ringworm)."

"Proven to kill dermatophytic fungi and yeast (causes of athlete's foot, jock itch, and ringworm)."

f. *Symptomatic relief.* Unlike other OTC products, OTC topical antifungal products treat disease rather than symptoms. Thus, symptomatic relief is the result rather than the aim of treatment.

"Relieves * * *," "for the relief of * * *," "for effective relief of * * *," and "soothes * * *" may be used with the following terms to describe the symptoms relieved by topical antifungal

drug products and are to be used when appropriate only with the Category I phrases for treatment: "itching," "scaling," "cracking," "burning," "redness," "soreness," "irritation," "discomfort," "chafing associated with jock itch," "itchy, scaly skin between the toes," " * * * itching, burning feet."

Examples of acceptable labeling for symptomatic relief are: "Cures athlete's foot and relieves itching, scaling, and soreness."

"For the treatment of athlete's foot and for the relief of itching."

"For the treatment of athlete's foot; soothes itching, burning feet."

g. *Product attributes.* The Panel accepts the use of terms describing certain physical and chemical qualities of OTC topical antifungal drug products, as long as these terms do not imply any therapeutic effect and are distinctly separated from labeling indications.

Product attributes pertain to the inherent characteristics or the pharmaceutical elegance of the formulation. These properties are usually due to specific inactive (and in some cases active) ingredients included in the final product formulation. Product characteristics appear in the labeling for consumer information or product appeal and involve terms relating to the product's color, odor, and feel.

The Panel considers the following list and similar terms acceptable: "colorless," "odorless," "pleasantly scented," "greaseless," "usually does not sting," "non-staining," "drying," "cooling," "cools hot, tender feet," "helps keep feet dry."

h. *Warnings.* Labeling for all products should include the following warnings:

"Do not use on children under 2 years of age except under the advice and supervision of a doctor."

"For external use only."

Labeling for products used for the treatment of athlete's foot and ringworm should include the following warning:

"If irritation occurs or if there is no improvement within 4 weeks, discontinue use and consult a doctor or pharmacist."

Labeling for products used for the treatment of jock itch should include the following warning:

"If irritation occurs or if there is no improvement within 2 weeks, discontinue use and consult a doctor or pharmacist."

Labeling for products used for the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*) should include the following warning:

"Do not use this product for more than 14 days without consulting a doctor or pharmacist if condition persists or recurs."

Labeling for products used for the prevention of athlete's foot should include the following warning:

"If irritation occurs, discontinue use and consult a doctor or pharmacist."

i. *Directions.* Depending on dosage form, manufacturers may vary directions for treatment or prevention, e.g., "Spray affected area * * *

(1) *For products used for the treatment of athlete's foot, jock itch, and ringworm.* "Cleanse skin with soap and water and dry thoroughly. Apply a thin layer over affected area morning and night or as directed by a doctor. For athlete's foot, pay special attention to the spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily. Best results in athlete's foot and ringworm are usually obtained with 4 weeks' use of this product and in jock itch with 2 weeks' use. If satisfactory results have not occurred within these times, consult a doctor or pharmacist. Children under 12 years of age should be supervised in the use of this product. This product is not effective on the scalp or nails."

(2) *For products used for the prevention of athlete's foot.* "To prevent fungal infection of the feet (athlete's foot), cleanse skin with soap and water and dry thoroughly. Apply a thin layer to feet once or twice daily, paying special attention to the toenails and the spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily."

(3) *For products used for the treatment of external feminine itching associated with vaginal yeast (candidal) infection, and superficial skin infections caused by yeast (Candida).* "Cleanse skin with soap and water and dry thoroughly. Apply a thin layer over affected area morning and night or as directed by a doctor. If satisfactory results have not occurred within 2 weeks, consult a doctor or pharmacist."

j. *Professional labeling.* Professional labeling for any topical antifungal drug product may contain suitable information which has been approved by FDA through a new drug application for such antifungal drug. This information may be disseminated to health professionals but not to the general public.

B. *Category II Conditions Under Which Topical Antifungal Products Are Not Generally Recognized As Safe and Effective or Are Misbranded.* The safety

and effectiveness of the following ingredients were classified on the basis of activity and use as antifungal agents. Ingredients that have been reviewed by the Panel and placed in Category II for antifungal effectiveness may still be included for nonantifungal purposes in formulations, providing that these ingredients are safe at the concentrations used and are in compliance with the Panel's combination policy.

The Panel recommends that the Category II conditions be eliminated from OTC topical antifungal products effective 6 months after the date of publication of the final monograph in the *Federal Register*.

1. Category II Active Ingredients

Camphor
Cantharidin
Coal tar
Menthol
Phenolates
Phenol
Phenolate sodium
Resorcinol
Tannic acid
Thymol
Tolindate

a. *Camphor.* The Panel concludes that camphor is safe but is not effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm at concentrations greater than 0.2 percent. The Panel also concludes that at concentrations less than or equal to 0.2 percent, camphor is an inactive ingredient that can be used in formulations for product identification.

Camphor ($C_{15}H_{11}O$) has the chemical formula of a ketone. Camphor is a solid, translucent, crystalline substance with a characteristic odor and an aromatic, pungent taste. Natural crude camphor is prepared by steam distilling the bark and wood of the camphor tree, *Cinnamomum camphora*, an evergreen of Southeast Asia. Synthetic camphor is produced from pinene, a hydrocarbon obtained from oil of turpentine. Camphor is relatively insoluble in water, but readily soluble in alcohol, chloroform, ether, and volatile oils.

Camphor is physically incompatible with several chemicals including menthol, phenol, thymol, resorcinol, and salicylic acid, forming a liquid or soft mass (eutectic mixture) when mixed with them (Ref. 1).

(1) *Safety.* Most of the recorded cases of acute toxicity from camphor resulted from accidental poisoning, by taking a preparation called "camphorated oil" instead of the intended castor oil. Absorption through mucous membranes occurs rapidly, and toxic symptoms may begin shortly after ingestion. Camphor is rapidly removed from the blood by the

liver, where it is conjugated with glucuronic acid. Early symptoms of poisoning include headache, excitement, nausea, vomiting, and delirium. Death occurs in severe cases as a result of convulsions and respiratory collapse (Ref. 2).

In mice the LD_{50} intraperitoneally is 3,000 mg/kg. The intraperitoneal minimum lethal dose in rats is 900 mg/kg. The toxic dose varies greatly in humans. The oral minimum lethal dose in humans is reported as 50 mg/kg (Ref. 3). Death has occurred in children from as little as 0.75 g (Refs. 4 and 5), but an adult has taken 20 g without harm (Ref. 4). In fact, camphor has been given by injection intramuscularly as a respiratory stimulant in doses of 60 to 200 mg (Ref. 6).

From the above discussion of the toxicology of camphor, the Panel concludes that camphor poses no serious problem in concentrations for 2 percent or less.

If a person used 2 g of a 2-percent camphor preparation, then the skin would be exposed to a total of 40 mg of camphor. Assuming total rapid absorption of the entire amount (certainly not likely), this would still be less than that given by injection on some occasions. The Panel therefore concludes that camphor would be safe for OTC topical use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* When camphor is rubbed on the skin, it is a rubefacient (a substance that produces redness of the skin). When gently applied to the skin, camphor may produce a feeling of coolness caused by selective stimulation of cold-sensitive nerve endings. Camphor also has a mild local anesthetic action that may help to relieve itching. Camphor 0.5 percent is still commonly added to topical preparations as an antipruritic (an ingredient that relieves itching) (Ref. 7). Camphor has also been used as a counterirritant in concentrations of 10 to 22 percent.

Camphor is one of the essential oils which are obtained from natural sources, usually plants. Frequently these oils are combinations of chemical ingredients including hydrocarbons, alcohols, phenols, aldehydes, ketones, acids, and esters in varying mixtures.

The antimicrobial activity of these oils does not necessarily depend on the type or concentration of the major ingredient. Their activities vary widely, making it difficult to predict either antibacterial or antifungal activity. Generally, essential oils high in phenolic compounds are the most active while the ones containing terpene are the least active. Because

most essential oils are effectively insoluble in water, other solvents must be found in order to perform in vitro tests.

Camphor has been classified as a highly active essential oil (Ref. 8). Camphor is known to have preservative and "germicidal" activity; it may be hypothesized that camphor may well have antibacterial or antifungal activity. Mixtures of essential oils have often been used. Combining resins with these oils resulted in increased and longer lasting preservative activity. Antimicrobial activity has been indicated to be greater when camphor or other oils are not in the colloidal form.

Camphor is weakly antiseptic, but it is a poor fungicide. One in vitro study showed that a 1:1,000 aqueous dilution of camphor killed only 7 percent of various dermatophytes after 24 hours (Ref. 9).

Further specific in vitro testing with more modern testing procedures is required before any final conclusion can be made on the antibacterial and antifungal activity of camphor.

When camphor is mixed with phenol, "an unexplained chemical reaction takes place" and phenol is converted to a "relatively innocuous material" (Ref. 10). In 1941 a eutectic mixture containing either equal parts of camphor and phenol or 3 parts phenol and 1 part camphor was introduced for the treatment of athlete's foot (Ref. 11). This mixture was painted between the toes for the immediate relief of itching and was said to be nonirritating. But users were warned not to apply it to wet skin because the preparation became caustic in contact with water. Although this treatment was widely publicized to cure athlete's foot after 1 week of daily applications (Ref. 12), there was concern about the unsupervised use of the product because of its potential causticity and resulting localized necrosis. There was also concern about the potential absorption of phenol if the preparation was applied liberally and then bandaged (Ref. 13).

Experimental studies with rabbits were done to determine the irritation potential of camphor-phenol mixtures. The mixtures were applied twice daily to clipped rabbit skin, which was then covered with gauze to simulate shoes and socks. A 1A:1 camphor-phenol mixture produced slight irritation and redness on dry skin, but severe burns and scabs were produced after the fourth application on moist skin. Application of a 3:1 phenol-camphor mixture produced a severe burn after two treatments on dry skin. This burning was even worse on wet skin. If one part of liquid petroleum was added to the 3:1

mixture, almost no irritation occurred. Warnings were again issued about the potential causticity of the camphor-phenol mixture (Ref. 14).

In vitro studies using the camphor-phenol mixture on agar plates showed that it effectively inhibited mycelial growth and suppressed sporulation of the pathogenic fungus, *Trichophyton rosaceum* (*T. rosaceum*) (Ref. 15). However, clinical trials in the early 1940's came to conflicting conclusions about the effectiveness of the 1:1 camphor-phenol mixture. In 1942, 40 soldiers in Florida with mild to moderately severe athlete's foot were treated with either Whitfield's ointment (benzoic acid-salicylic acid ointment) or the camphor-phenol mixture (Ref. 16). No KOH preparations or cultures were taken. The results were essentially identical in each of the 20-member groups. "Cures" occurred in about 3 to 5 days with Whitfield's ointment and about 3 to 6 days with camphor-phenol. Patients preferred the camphor-phenol treatment, as it stopped the pain almost immediately, was easy to apply, did not irritate, and did not soil clothing.

In 1943, a study of 85 naval aviation students with clinical athlete's foot compared the use of camphor-phenol on the right foot with an alcoholic solution of iodine 2 percent, benzoic acid 5 percent, and salicylic acid 3 percent on the left foot (Ref. 10). The treatments were observed to be equally effective in patients who had only scaling and peeling of the toes, with exfoliation and clinical improvement evident after 3 days of treatment. But 1 week after stopping treatment, both groups had positive cultures. The camphor-phenol mixture caused immediate tingling and anesthetizing of the skin for about 4 hours, followed by the reappearance of discomfort. Patients who initially had blistering showed no healing of tissue after 3 days of camphor-phenol treatment, and many blisters had enlarged and spread. The researchers concluded that the camphor-phenol mixture did not cure athlete's foot. Also, patients objected to the unpleasant odor of this mixture.

A controlled study of athlete's foot in 137 British soldiers was also reported (Ref. 17). Although no cultures were performed, all subjects had positive KOH preparations before treatment. The left foot was painted four times daily with a 1:1 camphor-phenol mixture, then exposed to the air for 1 hour. The right foot was treated twice daily with the control, Whitfield's ointment containing 0.5 percent dithranol (an ingredient used to treat psoriasis). The feet were kept dry. The camphor-phenol mixture was nonirritating except for slight smarting

in fissured areas, but irritation developed in many of the controls. The average time to "cure" was 4.5 days with camphor-phenol and 5.5 days with Whitfield's containing dithranol. A case was considered a failure if it did not clear within 9 days. Three failures occurred in the camphor-phenol group, compared to 11 failures in the Whitfield's group.

The relapse rate, determined by examining the soldiers weekly for 3 months, was significantly less in soldiers with athlete's foot, jock itch, and ringworm of the underarm treated with camphor-phenol (1.73 percent) than with the control (6.08 percent). It was concluded that camphor-phenol was a specific remedy for dermatophytosis. Again, camphor-phenol was found to be clean and not greasy. It was also nonirritating and was easily applied. The Panel concludes that this study is not adequate proof of effectiveness of the camphor-phenol combination.

The Panel has seen no data on the effectiveness of camphor as a single antifungal ingredient. The only clinical studies are of camphor combined with phenol. The Panel concludes that camphor is not effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(3) *Evaluation.* The Panel concludes that because it has seen no data on the effectiveness of camphor as a single antifungal ingredient, camphor should be placed in Category II for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. The Panel also concludes that camphor in concentrations less than or equal to 0.2 percent is safe and may be used in formulations for product identification purposes.

References

- (1) Osol, A., and J. E. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 720, 1975.
- (2) Arena, J., "Poisoning, Toxicology, Symptoms, Treatments," 3d Ed., Charles C. Thomas Co., Springfield, IL, pp. 368-9, 1974.
- (3) Fairchild, E., "Registry of Toxic Effects of Chemical Substances," United States Department of Health, Education, and Welfare, Cincinnati, p. 258, 1977.
- (4) Thienes, C., and T. Haley, "Clinical Toxicology," 5th Ed., Lea and Febiger, Philadelphia, pp. 16-17, 1972.
- (5) Deichmann, W., and H. Gerarde, "Symptomatology and Therapy of Toxicological Emergencies," Academic Press, New York, p. 103, 1964.
- (6) Blacow, N. W., "Martindale. The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, pp. 372-373, 1972.
- (7) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 4th Ed., The Macmillan Co., London, p. 993, 1970.

(8) Gatti, G., and R. Cayola, "Therapeutic Action of Essential Oils," *Rivista Italiana delle Essenze, dei Profumi e delle Pianta Officinali*, 4:16-23, 1922.

(9) Kingery, L., and A. Adkisson, "Certain Volatile Oils and Steroids as Fungicides," *Archives of Dermatology and Syphilology*, 17:499-511, 1928.

(10) Glenn, W., and H. Hailey, "Fungal Infections of the Feet Treated with a Camphor-Phenol Mixture," *Archives of Dermatology & Syphilology*, 47:239-241, 1943.

(11) Francis, E., "Phenol-Camphor for 'Athlete's Foot,'" *Journal of the American Medical Association*, 117:1973, 1941.

(12) Dekruif, P., "A Working Cure for Athlete's Foot," *Readers Digest*, 40:46, 1942.

(13) "Phenol-Camphor for 'Athlete's Foot,'" *Journal of the American Medical Association*, 119:182-183, 1942.

(14) Calvery, H., "Warning on Use of Phenol-Camphor in Cases of 'Athlete's Foot,'" *Journal of the American Medical Association*, 119:366, 1942.

(15) Georgi, C., "Inhibitory Effect of Monochloromercuricavacrol on Growth of Pathogenic Fungi," *Archives of Dermatology and Syphilology*, 48:497-510, 1943.

(16) Strauss, S., "Trichophyton Foot Infections. Empirical Study of Camphor-Phenol Treatment," *The Military Surgeon*, 91:348-349, 1942.

(17) Phillips, B., "The Phenol-Camphor Treatment of Dermatophytes," *British Journal of Dermatology and Syphilology*, 56:219-227, 1944.

b. *Candididin*. The Panel concludes the candididin is not generally recognized as safe and effective for the treatment of athlete's foot, jock itch, ringworm, external feminine itching associated with vaginal yeast infection, or superficial skin infections caused by yeast (*Candida*).

The Panel received only one submission on candididin (Ref. 1). This submission contained in vitro data but no information on safety or clinical effectiveness for the conditions listed above. Candididin has been marketed as intravaginal tablets, capsules, and ointment for prescription use only. This ingredient has never been marketed for the treatment of extra-vaginal conditions such as external feminine itching associated with vaginal yeast infection.

The Panel concludes that because candididin has never been marketed for the conditions discussed in this report and is not generally recognized to be effective in these conditions, it should be classified in Category II.

Reference

(1) OTC Volume 070253.

c. *Coal tar*. The Panel concludes that coal tar is not safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm and that there are insufficient data available on its effectiveness for this use.

Coal tar, a blackish-brown liquid obtained from the destructive distillation of bituminous coal, was first described in 1681 (Ref. 1). Most coal tars produced in the United States are byproducts from coke ovens and are further refined by fractional distillation in closed retorts. Coal tar varies widely in composition depending on its source, the temperature of distillation, and type of equipment used in its production. It is a hetero-geneous mixture of tar acids and hydrocarbons which polymerize at high temperatures (Ref. 1), forming about 10,000 different compounds of which only about 400 had been identified as of 1963 (Ref. 2). Therapeutic coal tar is generally available as either crude coal tar or as liquid carbonis detergens, a 20-percent coal tar solution in alcohol. Coal tar has a characteristic odor similar to naphthalene. It is slightly soluble in water and partly soluble in alcohol, chloroform, and ether (Ref. 3).

During the 20th century, coal tar has gradually replaced other types of tar for dermatologic use, including shale tar (ichthyol) and wood tars, such as juniper tar (oil of cade) and pine tar (pix liquida). Coal tar was first used therapeutically by German, French, and English dermatologists around the turn of the century. Other tars known as pitch and asphalt had been used to treat skin diseases since ancient times (Ref. 1).

(1) *Safety*. Although various coal tar preparations have been used to treat skin conditions for many years, documented safety data are few; for example, one submission (Ref. 4) gave only an estimated LD₅₀ for mice and rats (14.5 ml/kg). Blacow (Ref. 5) stated that coal tar may cause irritation and acne-like eruptions of the skin. Arena (Ref. 6) reported that coal and wood tars are photosensitizing compounds.

The composition of coal tar varies, but it generally consists of 2 to 8 percent light oils (benzene, toluene, xylene); 8 to 10 percent middle oils (phenols, cresols, naphthalene); 8 to 10 percent heavy oils (naphthalene and derivatives); 16 to 20 percent anthracene oils; and about 50 percent pitch. In such a mixture, phenol confers the highest acute toxicity potential (Ref. 7).

Sax (Ref. 8) classified coal tar as a slight local irritant and allergen and further stated that coal tar may contain carcinogens.

Determining the safety of coal tar is complicated by the myriad of names appearing in the older literature used to describe coal tar and its preparations, e.g., coal tar, coal tar oil, tar extract, tar, coal tar distillate, crude coal tar, Brazilian tar, pityrol, and coal tar pitch. Safety assessment was further

complicated by loose terminology, such as "coal tar solutions," and by the failure to specify the solvent systems.

One of the major concerns about the use of coal tar is its cancer-inducing potential. Fisher (Ref. 9) reviewed some of the aspects of tar and its effect on the skin. He reported that tar erythema was a common effect of exposure and is provoked by sunlight acting on skin which has been photosensitized by tar or pitch. Fisher also indicated that except for the scrotum (Chinmey Sweep's cancer), the effect of tar on the skin was limited to exposed parts. He described tar keratoses as patches of rough, dirty, gray keratin with irregular outline. After building up for a few weeks, they drop off and leave white, rough patches where new patches then form.

De Moragas (Ref. 10) said that the eruption of multiple keratoacanthomas on the exposed areas of a patient with pemphigus foliaceus (a chronic, generalized, vesicular and scaling skin eruption) treated with the Brazilian tar preparation (Jamarsan) attested to the strong carcinogenic properties of the compound. Keratoacanthomas are rapidly growing papular lesions which consist of craters filled with a horny plug. De Moragas indicated that two types of tumors occurred on the light-exposed areas of the skin. Most of the lesions had the clinical appearance of keratoacanthomas, and a few looked like verrucae filiformis (warts with soft, thin, threadlike projections on their surfaces). This report suggests that light may enhance the carcinogenic potential of coal tar.

Greither, Gisbertz, and Ippen (Ref. 11) found 13 confirmed cases of carcinoma in patients who reported using tar over many years. The most frequent use reported was for scrotal eczema. The investigators theorized that the lengthy, uncontrolled self-medication contributed to the cancer. They suggested careful medical supervision, a low tar concentration, and only periodic application of tar as the most appropriate safeguards against the risk of skin carcinoma.

Shabad et al. (Ref. 12) suggested that the benz(a)pyrene content of a tar can serve as an indicator of the carcinogenicity of tars and ointments. These workers found that the benz(a)pyrene concentration in wood tars varied from 0 to 338.2 µg/g, whereas the benz(a)pyrene content in coal tars was about 15 times higher (5,000 µg/g). A corticosteroid-tar ointment (benz(a)pyrene content 225 µg/g) was tested by skin application in C57x CBA mice. By the end of the 1-year treatment

period, all surviving animals had malignant skin tumors (carcinomas and sarcomas) which metastasized and were transplantable.

Linnik (Ref. 13) studied the benz(a)pyrene content of pit coal tar used in a corticosteroid-tar ointment and found that the pit coal tar contained 5 µg/g benz(a)pyrene. The ointment containing this tar was studied in 18 mice hybrids (F, C57x CBA) by rubbing in the ointment five times weekly for 1.5 months, then three times weekly for 10.5 months. The total benz(a)pyrene dose administered in the ointment was 4.3 µg for each animal. Within 4 months, cutaneous papillomas (nonmalignant tumors) developed in two mice. One and one-half years later, 16 of 17 surviving mice had developed cutaneous neoplasms, which are new and abnormal growths of tissue. Linnik concluded that the carcinogenic activity was due to the benz(a)pyrene content of the pit coal tar.

Wallcave et al. (Ref. 14) evaluated the carcinogenic potential of eight asphalts and two coal tar pitches of known polynuclear aromatic hydrocarbon content applied topically to Swiss mice. Thirty-one epidermal carcinomas and 22 papillomas (benign tumors) were observed in over 90 percent of the 58 animals treated with coal tar pitch. One carcinoma and five papillomatous growths were observed in 218 mice treated with asphalts. The coal tars contained much larger amounts of polynuclear aromatic hydrocarbons than the asphalts. The investigators also suggested that some aromatic hydrocarbons played a prominent role in carcinogenesis.

Hirohata et al. (Ref. 15) evaluated the carcinogenicity of a variety of tar-containing skin preparations. Chemical analysis of aromatic hydrocarbons was performed on each product. It was found that carcinogenic activity correlated with the benz(a)pyrene content of the preparation.

These reports dealing with the carcinogenicity of coal tar preparations suggest to the Panel that there is a very real potential for certain coal tars to induce skin cancer. The reviewed literature also appears to strongly substantiate this concern. These specific questions remain to be answered: (1) What specific ingredients are carcinogenic; (2) What period of time is involved; (3) Are other factors involved in the carcinogenic process?

In addition to carcinogenesis, a variety of other skin reactions to coal tar have been reported in the literature from 1965 to the present. Most of these are not life threatening, but can be quite irritating topically. One of the more commonly

noted effects of coal tar on the skin is a phototoxic effect. Kaidbey and Kligman (Ref. 16) and Burckhardt and Schmid (Ref. 17) are among several who have noted the role of coal tar in photosensitization. The reported reactions range from mild to severe; the reactions, to an extent, are strongly influenced by the vehicle (Ref. 16).

It has been reported that coal tar preparations may actually cause skin problems, some of them similar to conditions being treated. Hitch (Ref. 18) has reported an acneform (resembling acne) eruption at the site of contact to oils and tars. Characteristics that distinguish this drug-induced reaction from acne include age of patient, sites of eruption, and history of exposure to oils and tars. Kaidbey and Kligman (Ref. 19) also reported a dose-related acneform effect of crude coal tar or distilled coal tar. These investigators noted lesions of the inflammatory papulopustular type appearing in whites, while in blacks, small open comedones (blackheads) appeared. Stankler (Ref. 20) noted that tar preparations are messy and can cause irritation, folliculitis, and dermatitis. In a patient with psoriasis tar preparations may also precipitate generalized pustular psoriasis.

Several other investigators have attested to the varying degrees of severity of dermal irritation produced by coal tar use.

Stone (Ref. 21) noted that 5 percent crude coal tar produced a 45.9-percent delay in wound healing in animals. He suggested that this delay may have resulted from the direct effect of the tar on the wound or because tar increases the severity of infections.

The Panel has carefully reviewed the recorded toxicity of industrial and medicinal coal tar. In view of the reported scrotal cancers (Ref. 9), the animal carcinogenicity of coal tar, and the potential for long-term use in athlete's foot, jock itch, and ringworm, the Panel concludes that coal tar is not a safe OTC topical antifungal drug for these indications.

(2) *Effectiveness.* The antibacterial activity of a large class of coal tar disinfectants depends on phenol homologues, with a variety of substituted groups added onto the phenol. Certain kinds of soap solubilize the components in these coal tar disinfectants, thus increasing their activity. No in vitro data were submitted for coal tar, but it could be expected that a large portion of the coal tar component may be neutral oils. As the proportion of neutral oils increases, the antibacterial activity decreases. Lacking other data, one would have to assume minimal, if

any, antibacterial or antifungal activity for these compounds.

Coal tar is generally used in concentrations of 0.5 to 5.0 percent in ointments, creams, and shampoos. In the dilute concentration of 0.1 percent, it is astringent (Ref. 22). At 2 to 4 percent concentrations it is antipruritic, and in concentrations of 6 to 20 percent, it is keratoplastic, causing thickening of the upper layers of the skin (Ref. 23). Coal tar is rarely used in concentrations above 10 percent because of frequent irritation of hair follicles resulting in folliculitis.

At present, coal tar is commonly used to treat skin conditions such as psoriasis, seborrhea, and atopic dermatitis, while it is rarely prescribed for treatment of fungal skin infections. In 1956, however, crude coal tar (2 to 50 percent) in a base of lanolin and petrolatum was still listed in a major dermatology textbook (Ref. 24) as one of several possible treatments for unresponsive tinea, being described as "messy but effectively antiparasitic, rarely irritating."

The earliest use of coal tar for fungus infections is uncertain, but in the late 1800's unspecified types of tar were mentioned as being useful in the treatment of ringworm (Ref. 25) and jock itch (Ref. 26). In 1917, a coal tar paint composed of equal parts of tar, acetone, and flexible collodion was reported to be successful in treating a case of jock itch, diagnosed with positive skin scrapings. The authors reported that itching was relieved within 1 hour and skin lesions cleared in 2 days, although they recurred after 10 days (Ref. 27). However, no culture was reported. A similar coal tar paint (or varnish), which was applied thickly to the skin with a cotton swab then dusted with talcum powder, was still used in 1942 for the treatment of chronic dermatophytosis of the hands and feet (Ref. 28).

The first major experience with crude coal tar in the United States was reported by White (Ref. 29) in 1921. White treated several skin diseases with a 5-percent concentration of coal tar in an ointment base of petrolatum, cornstarch, and zinc oxide. This coal tar ointment was reported to be of "distinctive benefit" in treating two phases of epidermophytosis: (1) moist eczematoid conditions with uncomfortable, raw, red areas (not specified as to feet or groin), and (2) chronically itchy and thickened scaly patches on the upper thighs (jock itch). The author recognized that the coal tar was mainly soothing and palliative and recommended it be followed by

treatment that would more effectively destroy the fungus.

The same coal tar formula used by White (Ref. 29) was cited in textbooks appearing in 1925 (Ref. 23) and 1942 (Ref. 28) as being useful. Additional ingredients used in combination with coal tar included phenol (purported to make the product more soothing) (Ref. 23) and an alkali, such as potassium subcarbonate (included to soften and remove the outer horny layer of skin) (Ref. 30).

In contrast to White's advice (Ref. 29), several authors have cautioned against using coal tar on the irritated, weeping skin lesions that sometimes occur in dermatophyte infections of the feet and groin (Refs. 1 and 28). These investigators felt that coal tar may unduly irritate skin which is already inflamed, although no evidence was presented to substantiate this concern.

Evidence that tar will irritate skin infected with bacteria was supplied by Stone and Willis (Ref. 31). A 5-percent crude coal tar ointment in a base containing 94 percent petrolatum and 6 percent cholesterol esters applied to the skin of rabbits which had previously been injected with bacteria (*Micrococcus*) caused induration (redness and thickening) of the skin. After 24 hours, skin induration measured 12.7 mm at the tar-treated sites, compared with 4.3 mm at sites treated with the base alone.

The Panel concludes that the inclusion of coal tar in antifungal medications is mainly of historic interest. To the Panel's knowledge, there are no controlled studies demonstrating the clinical effectiveness of coal tar for treating either athlete's foot, jock itch, or ringworm.

(3) *Evaluation.* The Panel concludes that coal tar should be placed in Category II for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

In view of the abundant data demonstrating a carcinogenic potential of crude coal tar or preparations from crude coal tar containing aromatic hydrocarbons, and a lack of data supporting antifungal effectiveness, the Panel concludes that the small benefit and serious risk incurred from coal tar does not justify its use in the treatment of athlete's foot, jock itch, and ringworm.

Also, there are no double-blind, controlled clinical studies supporting the effectiveness of coal tar for the treatment of athlete's foot, jock itch, or ringworm. It appears that the inclusion of coal tar in antifungal medications is mainly of historic interest.

References

- (1) Downing, J. G., and C. W. Bauer, "Low and High Temperature Coal Tars in the Treatment of Eczema and Psoriasis. A Clinical Investigation and Evaluation," *Archives of Dermatology and Syphilology*, 57:985-990, 1948.
- (2) Farber, E. M., and A. J. Cox, "Psoriasis. Proceedings of the International Symposium," Stanford, University Press, Stanford, CA, p. 348, 1971.
- (3) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott, Philadelphia, p. 1140, 1973.
- (4) OTC Volume 070108.
- (5) Blacow, N. W., "Martindale. The Extra Pharmacopoeia," The Pharmaceutical Press, London, p. 579, 1972.
- (6) Arena, J. M., "Poisoning. Toxicology, Symptoms, Treatments," 3d Ed., Charles C. Thomas Publishing Co., Springfield, IL, p. 417, 1974.
- (7) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, p. 128, 1976.
- (8) Sax, N. I., "Dangerous Properties of Industrial Materials," 3d Ed., Reinhold Book Corp., New York, p. 576, 1968.
- (9) Fisher, R. E. W., "Cancer of the Skin Caused by Tar," *Transactions of the Association of Industrial Medical Officers*, 15:122-131, 1965.
- (10) De Moragas, J. M., "Multiple Keratoacanthomas. Relation to Jamsaran Therapy of Pemphigus Foliaceus," *Archives of Dermatology*, 93:679-683, 1966.
- (11) Greither, A., C. Gisbertz, and H. Ippen, "Treatment with Tar and Cancer," *Zeitschrift für Haut-Geschlechtskrankheiten*, 42:631-635, 1967.
- (12) Shabad, L. M., et al., "Possible Carcinogenic Hazards of Several Tars and of Locacorten-Tar Ointment (Spectrofluorescent Investigations and Experiments in Animals)," *International Journal of Cancer*, 6:314-318, 1970.
- (13) Linnik, A. B., "Carcinogenic Effect of 'Locacorten Tar' Ointment on Experimental Animals," *Vestnik Dermatologii i Venerologii*, 44:32-36, 1970.
- (14) Wallcave, L., et al., "Skin Tumorigenesis in Mice by Petroleum Asphalts and Coal Tar Pitches of Known Polynuclear Aromatic Hydrocarbon Content," *Toxicology and Applied Pharmacology*, 18:41-52, 1971.
- (15) Hirohata, T., et al., "Carcinogenicity of Tar-Containing Skin Drugs: Animal Experiment and Chemical Analysis," *GANN; Japanese Journal of Cancer Research* 64:323-330, 1973.
- (16) Kaidbey, K. H., and A. M. Kligman, "Topical Photosensitizers—Influence of Vehicles on Penetration," *Archives of Dermatology*, 110:868-870, 1974.
- (17) Burckhardt, W., and P. Schmid, "Das Licht als Pathogene Noxe," *Schweizerische Medizinische Wochenschrift*, 99:439-444, 1969.
- (18) Hitch, J. M., "Acneiform Eruptions Induced by Drugs and Chemicals," *Journal of the American Medical Association*, 200:879-880, 1967.
- (19) Kaidbey, K. H., and A. M. Kligman, "A Human Model of Coal Tar Acne," *Archives of Dermatology*, 109:212-215, 1974.
- (20) Stankler, L., "Diseases of the Skin. Psoriasis," *British Medical Journal*, 1:27-29, 1974.
- (21) Stone, O. J., and J. A. Anthony, "The Effect of Tar on Wound Healing," *Archives of Environmental Health*, 20:602-603, 1970.
- (22) Combes, F. C., "The Use of Coal Tar in the Treatment of Skin Diseases," *New England Journal of Medicine*, 228:384-386, 1943.
- (23) Pusey, W. A., "The Principles and Practice of Dermatology," 4th Ed., D. Appleton and Co., New York, pp. 132-135, 1924.
- (24) Sutton, R. L., Jr., "Diseases of the Skin," 11th Ed., the C. V. Mosby Co., St. Louis, p. 521, 1956.
- (25) Morris, M., "Diagnosis and Treatment of Ringworm," *The Lancet*, 1:241-242, 1881.
- (26) Stedman, T. L., "Twentieth Century Practice," Volume V, "Diseases of the Skin," William Wood and Co., New York, p. 72, 1896.
- (27) Semon, H. C., "Some Recent Experiences with Pure Coal Tar (Pix Carbonis Preparata, B. P.) at a Base Hospital in France," *British Journal of Dermatology*, 29:83-92, 1917.
- (28) Stokes, J. H., "Fundamentals of Medical Dermatology," 7th Revision, Department of Dermatology Book Fund, University of Pennsylvania, Philadelphia, pp. 257-258 and 344, 1942.
- (29) White, C. J., "Crude Coal Tar in Dermatology," *Archives of Dermatology and Syphilology*, 4:796-806, 1921.
- (30) Ormsby, O. S., "A Practical Treatise on Diseases of the Skin," 4th Ed. Lea and Febiger, Philadelphia, p. 103, 1934.
- (31) Stone, O. J., and C. J. Willis, "The Effect of Tar on Infection," *Toxicology and Applied Pharmacology*, 15:677-678, 1969.

d. *Menthol.* The Panel concludes that menthol is not effective and that there are insufficient data available to determine its safety at concentrations greater than 0.2 percent for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. The Panel also concludes that at concentrations less than or equal to 0.2 percent, menthol is an inactive ingredient that can be safely used in formulations for product identification.

Menthol (peppermint camphor) is an alcohol which is either extracted from peppermint or other mint oils or prepared synthetically. It consists of colorless, hexagonal needlelike crystals with a pleasant, minty odor and cool taste. Menthol is only slightly soluble in water, but is very soluble in alcohol, ether, and chloroform. Chemically incompatible with camphor, phenol, thymol, resorcinol, and other substances, menthol forms a liquid or soft mass when mixed with them (Ref. 1). In currently marketed products, menthol is present in a concentration of 0.1 to about 125 percent.

(1) *Safety.* In rats the oral LD₅₀ is 3,180 mg/kg, and the lowest lethal dose

subcutaneously is 2,000 mg/kg. In humans, the lowest lethal oral dose is reported to be 50 mg/kg (Ref. 2).

Toxic effects in humans from excessive ingestion of mentholated products can include nausea, vomiting, abdominal pain, flushed face, and symptoms of central nervous system depression, such as dizziness, staggering gait, sleepiness, slow respiration, and coma (Ref. 3). The fatal dose of menthol in humans is approximately 2 g (Ref. 4).

Menthol may cause hypersensitivity reactions including contact dermatitis in certain individuals. Symptoms include hives, erythema, and other cutaneous lesions. However, the sensitization index is low. Nasal drops containing menthol may cause spasm of the glottis in young children. Cases of dangerous asphyxia from menthol have been reported in infants following such local application (Ref. 4).

The Panel considers the following data necessary to establish the safety of menthol: (1) absorption from small areas of application to broken and intact skin; (2) local effects on wound healing; and (3) potential for hypersensitivity or idiosyncratic reactions.

The Panel concludes that more data are needed to determine the safety of menthol in concentrations greater than 0.2 percent for OTC topical application in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* Menthol in concentrations of 0.1 to 2 percent is usually added to topical medications to produce a counterirritant effect on the skin, with resulting antipruritic and mild analgesic actions (Ref. 1). Menthol stimulates nerve endings, thus inducing a feeling of refreshing coolness on the skin. This feeling may temporarily bring great comfort, but is often later replaced by sensations of heat, tingling, and slight pain, resembling the reestablishment of circulation after a limb has been "asleep". Menthol 2 percent was added to dusting powders recommended in the past for the treatment of fungal infections (Ref. 5).

Menthol is a poor fungicide. At a 1:1,000 dilution, menthol killed no dermatophytes after a 60-minute exposure and only 21 percent of dermatophyte cultures after a 24-hour exposure (Ref. 6). Dermatophytes were also not inhibited in vitro by a powder containing 2 percent menthol in talc (Ref. 7). However, a 1:250 dilution of menthol (in a base containing alcohol, glycerin, ethylene glycol, soap, and water) was bactericidal to *Staphylococcus albus* (*S. albus*) and *Bacterium typhosus* (*B. typhosus*) in 2.5 minutes. A similar 1:750 dilution of menthol was bactericidal to the same

organisms in 15 minutes (Ref. 8). From these results the phenol coefficient for menthol was calculated to be 5.1.

Although menthol may be useful in providing symptomatic relief of fungal infections through its antipruritic action, the Panel concludes that it is not an effective antifungal ingredient.

(3) *Evaluation.* The Panel has placed menthol in concentrations greater than 0.2 percent in Category II because no controlled, clinical trials have been performed on this ingredient to determine its effectiveness in the treatment of athlete's foot, jock itch, and ringworm. Also, the limited in vitro data available show menthol to be a poor fungicide. The Panel concludes that menthol in concentrations less than or equal to 0.2 percent is safe and may be used in formulations for product identification purposes.

References

- (1) Osol, A., and J. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, pp. 721-722, 1975.
- (2) Fairchild, E., "Registry of Toxic Effects of Chemical Substances," Vol. II, United States Department of Health, Education, and Welfare, Cincinnati, p. 526, 1977.
- (3) Arena, J., "Poisoning. Chemistry. Symptoms, Treatments," Charles C. Thomas Co., Springfield, IL, p. 245, 1963.
- (4) Blacow, N., "Martindale. The Extra Pharmacopeia," 28th Ed., The Pharmaceutical Press, London, p. 374, 1972.
- (5) Becker, S. W., and M. E. Obermayer, "Modern Dermatology and Syphilology," J. B. Lippincott Co., Philadelphia, p. 434, 1940.
- (6) Kingery, L., and A. Adkisson, "Certain Volatile Oils and Stereoptens as Fungicides. An Experimental Study," *Archives of Dermatology and Syphilology*, 17:499-511, 1928.
- (7) Fredell, W., V. Burlingame, and G. Reddish, "Antiseptic Powders," *Drug Standards*, 22:107-112, 1954.
- (8) Miller, R., "Bactericidal Efficiency of Essential Oils," *American Journal of Pharmacy*, 103:324-328, 1931.

e. *Phenolates (phenol and phenolate sodium).* The Panel concludes that the phenolates (phenol and phenolate sodium) are not effective and that there are insufficient data available on their safety in concentrations less than or equal to 1.5 percent for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Phenol is hydroxybenzene and was discovered in coal tar in 1834 by Ringe who named it "carbolic acid." It was also once called phenic acid. Originally produced through the dry distillation of hardwoods and coal, it is now produced synthetically from benzene (Ref. 1). In 1865 Lister began to use carbolic acid for the prevention and treatment of sepsis. He sprayed it in operating rooms, cleansed the skin with it before surgery,

and applied it in wound dressings (Ref. 2). Phenol soon gained wide acceptance as a disinfectant for sanitary, medical, and surgical purposes, and was adopted as a standard for comparison of disinfectant power. The phenol coefficient expresses the ratio of killing effectiveness of a disinfectant as compared to phenol under standard test conditions against the same bacteria (Ref. 1). Today phenol has been largely replaced by more effective and less toxic compounds (Ref. 3).

Phenol consists of colorless to light pink, needle-shaped crystals which gradually darken on exposure to light and air. It has a distinctive aromatic odor. Phenol contains not less than 98 percent C_6H_5OH , while liquefied phenol USP contains 10 percent water (1 g of phenol dissolves in 15 g of water). Phenol is very soluble in alcohol, ether, glycerin, and volatile and fixed oils (Refs. 1 and 3). When combined with camphor, menthol, resorcinol, or thymol, it forms a liquid or soft mass (Ref. 1). Since the pKa of phenol is 10.0 at 25° C (Ref. 4), the phenolate ion will predominate only at extremely alkaline pH. Therefore, for the purpose of the present discussion, only un-ionized phenol need be considered.

Phenolate sodium (C_6H_5ONa), also known as sodium phenoxide, sodium carbolate, and sodium phenate, is the sodium salt of phenol. It is a white to reddish deliquescent substance composed of rods or granules. It is soluble in water and alcohol. Aqueous solutions are strongly alkaline and caustic (Ref. 4).

The Panel considers phenol and phenolate sodium to be a single ingredient when both are contained in a product formulation. The total level of phenol and phenolate sodium is expressed as percent phenol.

(1) *Safety.* The toxicology of phenol has been extensively reviewed in the literature (Ref. 5). The potential toxicity of phenol in concentrations greater than 1.5 percent was described by the Advisor Review Panel on OTC Antimicrobial I Drug Products in the Federal Register published September 13, 1974 (39 FR 33121). The Advisory Review Panel on OTC Antimicrobial II Drug Products agrees that phenol is toxic in aqueous or alcoholic solutions in concentrations greater than 1.5 percent.

In rats the oral LD_{50} of phenol is 414 mg/kg; the topical LD_{50} (by skin absorption) is 669 mg/kg. In humans the minimum lethal oral dose is 140 mg/kg (Ref. 6).

According to Goodman and Gilman (Ref. 7), "Phenol is absorbed by all

routes of administration and can reach the circulation even when applied to the intact skin." Ingestion of even small amounts may cause nausea, vomiting, circulatory collapse, tachypnea, (excessively rapid respiration), paralysis, convulsions, coma, greenish or smoky-colored urine, necrosis of the oral tissue and gastrointestinal tract, jaundice, and death (Ref. 4). In fatal cases, death usually occurs in less than 2 hours as a result of respiratory failure, although occasionally cardiac arrest is the cause (Ref. 3).

Concentrated solutions are toxic and cause death if ingested. Phenol has been used for suicide and is a common cause of accidental poisoning. The symptoms of toxicity usually develop rapidly and death has occurred within 2 or 3 minutes after ingestion. The average fatal dose of phenol is 15 g, but death has been reported following the ingestion of as little as 1.5 g. Conversely, recovery has followed the ingestion of as much as 30 g (Ref. 3).

Systemic absorption causes central nervous system effects seen as a momentary stimulation followed by a depression of the central nervous system. The blood pressure falls, partly because of central vasomotor depression out mainly because the myocardium and the smaller blood vessels are affected by a direct toxic action of phenol (Ref. 7).

Mild to severe signs of systemic poisoning have been reported following application of 2 or 3 percent aqueous solutions of phenol to open wounds. In mice, aqueous solutions of phenol too dilute to cause local irritation were absorbed through the skin in a quantity sufficient to cause systemic poisoning (Ref. 5). Absorption through the skin depends on the area exposed rather than on the concentration applied (Ref. 3).

When phenol is applied directly to the skin, it forms a white film of precipitated protein. This turns red and eventually sloughs. Phenol that remains in contact with the skin penetrates deeply and may cause extensive necrosis. Phenol exerts a local anesthetic action. A 5-percent solution produces almost complete local anesthesia, but is irritating to exposed tissue and may also cause necrosis (Ref. 7 and 8).

Even though dilute solutions of phenol (up to 3 or 4 percent) are only mildly irritating (Ref. 3), even lower concentrations have not been shown to be totally safe. A 1-day-old baby died 11 hours after application of a 2-percent solution on an umbilical bandage. Another baby, aged 6 days, was treated for a skin ulcer with phenol-camphor

complex (strength not given) and developed circulatory failure, cerebral intoxication, and methemoglobinemia which required exchange blood transfusion (Ref. 9). This author suggested that even greatly diluted phenol was a dangerous material to apply to the skin.

Gosselin et al. (Ref. 2) reported that "much evidence exists to suggest that in man phenol may be considerably less toxic by mouth than by absorption from wounds, body cavities, or even intact unbroken skin. The safest viewpoint is to regard any amount of phenol as dangerous." The major hazard of phenol poisoning is its systemic effects. Gosselin et al. also stated that severe or fatal phenol poisonings have occurred after topical exposure, suggesting a hypersensitivity or idiosyncratic reaction. They cite two cases of collapse from 5 percent carbolic acid compresses. Although phenol poisoning begins very abruptly, the intoxication's dangerous phase is usually complete in 24 hours.

Deichmann (Ref. 5) reviewed the literature on phenol toxicity before 1948 and gave an excellent summary of the toxicity potential of dilute aqueous preparations of phenol. Dilute solutions of from 1 to 5 percent phenol when used as wet compresses over a period of time have caused gangrene of the extremities, as well as systemic toxicity when applied to open wounds or large body areas.

The Panel is not aware of any more recent research on the use of dilute solutions of phenol. Therefore, there is still an open question on the safety of dilute aqueous or alcoholic solutions when applied to small body surfaces once or twice daily. But there is no doubt that such dilute solutions are absorbed and have a local effect. Deichmann says of Freystadt's findings, "five minutes of contact of 2 percent aqueous phenol with the human skin affected the sensations of cold, touch, pain, and heat." From this one can conclude that sufficient phenol was absorbed to affect local nerve endings.

The Panel received no data on the effect of dilute solutions of phenol on broken skin, such as might be the case with athlete's foot, jock itch, or ringworm. In most reports of toxicity from dilute solutions of phenol, bandaging the application was necessary to produce severe local changes (Ref. 5). Using phenol in athlete's foot, jock itch, and ringworm would be similar to using it under a bandage because the affected areas would be covered by clothing.

Based on the above review, the Panel concludes that there are insufficient data on the safety of aqueous or

alcoholic solutions of phenol in concentrations less than or equal to 1.5 percent. Specifically lacking are controlled studies evaluating (1) the absorption from small areas of application to either broken or intact skin, (2) the local effects on wound healing, and (3) the potential for hypersensitivity or idiosyncratic reaction.

(2) *Effectiveness.* Phenol, in concentrations of 1 to 2 percent, has frequently been added to aqueous solutions, ointments, and creams for its antipruritic effects (Ref. 1), although 0.5 to 1.0 percent phenol is now more commonly used (Ref. 10). In 3 to 4 percent solutions, phenol is mildly irritating but actively anesthetic to skin (Ref. 3). A 15-percent phenol solution in alcohol has marked irritant and anesthetic action on skin, inducing local redness and edema after 10 minutes of contact (Ref. 5). Liquified phenol (80 percent phenol in water) is widely used as a superficial skin caustic (Ref. 10).

In products submitted to the Panel, phenol was incorporated in aqueous, ointment, and powder vehicles. The vehicle is crucial to phenol's activity. For instance, an *in vitro* study in 1933 showed that 2 percent phenol ointment, also called carbolic acid ointment and "antiseptic ointment," was not bactericidal against *Staphylococcus aureus* (*S. aureus*) using agar plate tests (Ref. 11). The ointment base consisted of petrolatum or a combination of petrolatum and anhydrous wool fat (lanolin). In contrast, 2 percent phenol in water-miscible bases, such as vanishing cream, did show zones of inhibition against *S. aureus* in agar plate tests (Ref. 12). In aqueous and alcoholic solutions, phenol is bacteriostatic in concentrations of 1:800 (Ref. 3). In another source, phenol was reported to be bacteriostatic in a 1-percent strength (Ref. 10). It is absorbed by bacterial cells and combines and denatures the cell proteins (Ref. 13).

Reports of *in vitro* studies vary widely in describing fungicidal concentrations of phenol. Rook, Wilkinson, and Ebling (Ref. 10) reported phenol to be fungicidal in a concentration of 1.3 percent. Golden and Oster (Ref. 14) determined the minimal fungicidal concentration of phenol dissolved in 95 percent alcohol against cultures of *T. mentagrophytes* to be 9 percent against 5-day cultures, 15 percent against 10-day cultures, and greater than 15 percent against 15-day and 20-day cultures. In another study, concentrations of 0.7 to 1.0 percent phenol were fungicidal for several dermatophyte fungi (Ref. 15).

Other, much older studies found fungicidal dilutions of phenol to be 1:25 for *T. rosaceum* and 1:100 for *M. audouinii* (Ref. 16). Another source listed 1:70 for *T. rosaceum* (Ref. 17). O'Brien and Bonisteel (Ref. 18) reported that phenol 2 percent in a petrolatum ointment base had little or no activity against *T. interdigitale*. Riley and Flower (Ref. 19) reported that phenol 5 percent also has antifungal activity after 48 hours against *C. albicans* in a 1:25 dilution, but not a 1:50 dilution. O'Brien and Bonisteel further reported that phenol 2 percent in petrolatum ointment did not inhibit *M. albicans*, whereas in cold cream or vanishing cream it was slightly fungistatic against *M. albicans* (Ref. 18).

Phenol has not been widely used as an antifungal agent to treat dermatophytic fungal infections. Carbolic acid mixed with equal parts of glycerin was mentioned in 1881 as a treatment for ringworm of the scalp, but was thought to be to irritate and toxic (Ref. 20). In the 1940's, equal parts of phenol and camphor were popularized as an athlete's foot remedy. (See part III, paragraph B.1.a. above—Camphor.) Despite warnings about potential toxicity from this mixture, at least one death resulted from its application. An 18-year-old man died of acute pulmonary congestion within a few minutes of applying a mixture of 1:4 camphor-phenol to a 60-square inch area of raw, inflamed ringworm on the trunk (Ref. 21). The inflamed skin was believed to have helped induce the rapid absorption of phenol, which led to acute phenol poisoning.

In 1948, Hopkins et al. (Ref. 22) tested various fungicides including DN phenol (2,4, dinitro-ortho-cyclohexyl-phenol) and trichlorophenol in soldiers at Fort Benning who had athlete's foot verified by positive KOH preparations. The fungicides were used in various concentrations and vehicles. In these studies no control subjects using the vehicle alone were included. No cultures were performed after treatment, and no lag period following treatment was included. Table 8 shows the results for DN phenol and trichlorophenol:

TABLE 8.—DN PHENOL AND TRICHLOROPHENOL AS FUNGICIDES

	Time period		
	1 to 2 weeks	3 to 4 weeks	4-plus weeks
<i>Trichlorophenol</i>			
Clinically cleared.....	27 (18%)	34 (47%)	22 (51%)
KOH negative.....	90 (59%)	53 (73%)	34 (79%)
Total number of cases.....	152	72	43

TABLE 8.—DN PHENOL AND TRICHLOROPHENOL AS FUNGICIDES—Continued

	Time period		
	1 to 2 weeks	3 to 4 weeks	4-plus weeks
<i>DN phenol</i>			
Clinically cleared.....	73 (18%)	116 (49%)	92 (72%)
KOH negative.....	235 (58%)	192 (81%)	114 (89%)
Total number of cases.....	405	237	128

The best results were seen with a 10-percent DN phenol solution in alcohol and propylene glycol, although 5 to 20 percent concentrations were also tested. Irritation was noted in 13 percent of the soldiers treated with DN phenol. Fifteen percent of those treated with trichlorophenol showed irritation; 1 percent had severe irritation. Trichlorophenol was concluded to be rapidly fungistatic, but often too irritating, particularly in concentrations greater than 1.0 percent.

(3) *Evaluation.* The Panel concludes that phenol and phenolate sodium should be placed in Category II for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. It agrees with the "United States Dispensary" (Ref. 3) which says: "Phenol has had some use as a fungistatic agent, but other agents are considered more effective and less toxic." The Panel also agrees with Reddish's (Ref. 23) assessment which states that "other derivatives of phenol have been suggested for the treatment of dermatophytosis. Most of them, however, have been abandoned or were very short-lived, because of either insufficient activity or excessive skin irritation." The Panel concludes that the use of phenol for athlete's foot, jock itch, and ringworm is outdated, irrational, and potentially dangerous. The in vitro concentrations required for effective antifungal action often exceed a 1.5-percent concentration of phenol. In fact, one study (Ref. 14) demonstrated that a phenol concentration of 15 percent or greater was necessary to kill cultures of *T. mentagrophytes*, a fungus frequently seen on the feet and in the groin. The Panel further concludes that the symptomatic antipruritic relief which would be offered by the inclusion of phenol does not justify the potential risks of skin irritation or systemic toxicity that may result from the topical application of phenol.

References

- (1) Cook, E., and E. Martin, "Remington's Practice of Pharmacy," 10th Ed., Mack Publishing Co., Easton, PA, pp. 716, 719-720, 1951.
- (2) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed.,

The Williams and Wilkins Co., Baltimore, Section III, pp. 271-273, 1976.

(3) Osol, A., and R. Pratt, "The United States Dispensary," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 900-901, 1973.

(4) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 940-941 and 1,118, 1976.

(5) Deichmann, W., "Local and Systemic Effects Following Skin Contact with Phenol. A Review of the Literature," *Journal of Industrial Hygiene and Toxicology*, 31:146-154, 1949.

(6) Fairchild, E., "Registry of Toxic Effects of Chemical Substances," 1977 Ed., Volume II, U.S. Department of Health, Education, and Welfare, Cincinnati, p. 638, 1977.

(7) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of therapeutics," 5th Ed., Macmillan Publishing Co., Inc. New York, pp. 990-991, 1975.

(8) Thienes, C., and T. Haley, "Clinical Toxicology," 5th Ed., Lea and Febiger, Philadelphia, p. 138, 1972.

(9) Cooper, P., "Poisoning by Drugs and Chemicals, Plants and Animals," 3d Ed., Year Book Medical Publishers, Inc., Chicago, p. 171, 1974.

(10) Rook, A., D. S. Wilkinson, and F. J. G. Ebling, "Textbook of Dermatology," 2d Ed., Volume II, Blackwell Scientific Publications, Oxford, pp. 2072, 2075, and 2097, 1972.

(11) Gershenfeld, L., and R. Miller, "Bactericidal Efficiency of Two Percent Phenol Ointments," *American Journal of Pharmacy*, April 1933, pp. 186-193.

(12) Gershenfeld, L., and R. Miller, "Ointment Bases for Bactericidal Agents," *American Journal of Pharmacy*, April 1933, pp. 194-198.

(13) Sykes, G., "Disinfection and Sterilization," 2d Ed., J. B. Lippincott Co., Philadelphia, p. 312, 1965.

(14) Golden, M., and K. Oster, "Studies on Alcohol-Soluble Fungistatic and Fungicidal Compounds. II. Evaluation of a Fungicidal Laboratory Test Method," *Journal of the American Pharmaceutical Association (Scientific Edition)*, 36:359-362, 1947.

(15) Reiss, F., and B. Lustig, "Evaluation of Fungicides. Phenols, Quaternary Ammonium Compounds, Undecylenic Acid, their Mixtures and Salts," *Dermatologica*, 97:312-319, 1948.

(16) Schamberg, J., and J. Kolmer, "Studies in the Chemotherapy of Fungus Infections. I. the Fungistatic and Fungicidal Activity of Various Dyes and Medicaments," *Archives of Dermatology and Syphilology*, 6:746-756, 1922.

(17) Georgi, C., "Inhibitory Effect of Monochloromercuricarsvacrol on Growth of Pathogenic Fungi," *Archives of Dermatology and Syphilology*, 48:497-510, 1943.

(18) O'Brien, F., and W. Bonisteel, "The Fungistatic Value of Certain Ointments," *Journal of the American Pharmaceutical Association (Scientific Edition)*, 30:191-196, 1941.

(19) Riley, K., and A. Flower, "A Comparison of the Inhibitory Effect of Castellani's Paint and of Gentian Violet Solution on the In Vitro Growth of *Candida*

albicans," *Journal of Investigative Dermatology*, 15:355-361, 1950.

(20) Morris, M., "Diagnosis and Treatment of Ringworm," *The Lancet*, Feb. 12, 1881, p. 241.

(21) Miller, F., "Poisoning by Phenol," *Canadian Medical Association Journal*, 46:615-616, 1942.

(22) Hopkins, J. G., et al., "Fungistatic Agents for Treatment of Dermatophytosis," *Journal of Investigative Dermatology*, 7:239-253, 1946.

(23) Reddish, G. F., "Antiseptics, Disinfectants, Fungicides, and Chemical and Physical Sterilization," 2d Ed., Lea and Febiger, Philadelphia, pp. 659-660, 1957.

f. *Resorcinol*. The Panel concludes that resorcinol is not safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm and that there are insufficient data available on its effectiveness for this use.

The chemical name of resorcinol is 1,3-benzenediol. Resorcinol is a white powder and belongs to the phenolic group of chemicals. It was discovered in 1863, synthesized in 1868, and used dermatologically in 1884. Soluble in water, alcohol, ether, and fats, resorcinol is a strong reducing agent in alkaline solution (Ref. 1). Resorcinol forms a liquid or softens when mixed with camphor, menthol, or phenol. Upon exposure to the air, resorcinol turns pink and may discolor skin or light-colored hair (Ref. 2).

(1) *Safety*. Resorcinol, like phenol, is a protein precipitant. The compound resembles phenol in its systemic actions except that resorcinol causes more prominent central stimulation (Ref. 3). The Panel received only one product submission containing resorcinol in the rather high concentration of 10 percent. Overall, the data available on the toxicity of resorcinol are scarce and of poor quality. One source reports the acute oral LD₅₀ of resorcinol in the rat to be 980 mg/kg (Ref. 4). Another source listed 301 mg/kg as the acute oral LD₅₀ in the rat (Ref. 5). This source also listed the following lowest published lethal doses of resorcinol given subcutaneously: 340 mg/kg in the mouse; 400 mg/kg in the rat and guinea pig; but only 110 mg/kg in the cat.

Gosselin et al. (Ref. 6) reported that resorcinol has a toxicity rating similar to phenol but that convulsions are more prominent with resorcinol. Deichmann and Gerarde (Ref. 7) suggested that if percutaneous absorption of resorcinol should occur, the resulting effects may include edema, necrosis, methemoglobinemia, respiratory difficulty, convulsions, and even death. These investigators reported the probable lethal adult oral dose of resorcinol to be about 2g.

Blacow (Ref. 8) reported that resorcinol may be absorbed through the skin or from ulcerated surfaces and that prolonged use may lead to myxedema (severe hypothyroidism) due to the antithyroid action of the drug. He suggested that resorcinol could be a dangerous drug when applied over large surfaces of skin, especially when used in high concentrations.

Stenback and Shubik (Ref. 9) reported on a study dealing with the toxicity and carcinogenicity of a number of topically applied chemicals, including resorcinol. Fifty 7-week-old female mice were used for each tested concentration of the chemicals. The chemicals were dissolved in acetone, and 0.02 mL was dropped on shaved skin between the animals' flanks twice weekly for the life of the animals. The mice were examined weekly for lesions and tumors. Complete autopsies were performed and grossly observed tumors studied histologically. Animals treated with 50 percent, 25 percent, and 5 percent concentrations of resorcinol developed skin lesions with ulceration, inflammation, and hyperplasia. Two skin tumors and one subcutaneous fibrosarcoma were noted. These results were not statistically significant when compared to the control group.

Even though Blacow (Ref. 8) reported that resorcinol may be absorbed through the skin or ulcerated surfaces, no data were presented. The Panel therefore cannot determine the degree of absorption. Certainly it would be expected that some resorcinol would be consumed in its role as a protein precipitant and that this precipitated protein may even then prevent further absorption. Without data, however, this is pure speculation.

In view of the lack of data on the absorption characteristics of resorcinol, the Panel is concerned about the relatively high concentration currently marketed (10 percent) and the total amount that might reach systemic circulation, where it may have even more prominent effects than phenol. The Panel believes that the minimal antifungal benefits of resorcinol do not warrant the potentially high risk of using it in a 10-percent concentration to treat athlete's foot. A lower concentration may prove to be entirely safe, but no data were presented to allow the Panel to estimate a safe level.

(2) *Effectiveness*. Resorcinol is used topically for its antibacterial, antifungal, and local irritant effects on skin (Ref. 2). In vitro studies (Refs. 10 and 11) have shown resorcinol to be a rather weak fungistatic and fungicidal agent. When a 1:25 dilution of 5 percent resorcinol was tested against *C. albicans*, slight growth

was observed, but a 1:50 dilution allowed abundant growth after 48 hours (Ref. 10). Resorcinol was found to be fungistatic but not fungicidal against dermatophytic fungi at dilutions of 1:200, 1:300, and 1:1,600 tested against *T. rosaceum*, *M. audouinii*, and *Achoriia schoenleinii* (*A. schoenleinii*), respectively (Ref. 11).

The pharmacologic action of resorcinol varies markedly with its concentration. Resorcinol is antipruritic in 0.5 to 3 percent solutions and in ointments containing up to a 5-percent concentration (Ref. 12). Resorcinol is also keratoplastic in 1 to 3 percent concentrations (Ref. 1) and keratolytic in 10 to 50 percent concentrations (Ref. 12). The keratolytic action of resorcinol in 10 percent and 15 percent concentrations in various ointment bases is identical, implying that resorcinol is mildly caustic (Ref. 1). Resorcinol is usually used in concentrations of 5 percent in ointments, pastes, gels, and lotions, although concentrations from 1 to 20 percent are also used (Ref. 2) Compound Resorcinol Ointment NF XIII contains 6 percent resorcinol (Ref. 13).

Several old dermatology textbooks mention the use of resorcinol for dermatophytic fungal infections. In 1907, Whitfield recommended 10 percent resorcinol in alcohol or water for the treatment of ringworm of the groin (Ref. 14). He described this concoction as very irritating, but "prompt, cleanly, and effective." A later book listed a similar but less concentrated solution of 3 to 6 percent resorcinol in water for the treatment of jock itch (Ref. 15). A 1932 textbook mentioned resorcinol ointment or lotion in concentrations of 2 to 5 percent for the treatment of ringworm of the palms and soles (Ref. 16).

In the early 1940's resorcinol 0.25 to 2 percent was used as a wet dressing for treating the acute blistering an oozing states of dermatomycoses. In the concentration of 1:1,000 it was used as a daily footbath for "obstinate" cases of athlete's foot (Ref. 17). Another book listed resorcinol ointment 2 to 10 percent as a keratolytic for use about the face, but it was not specifically recommended for use in fungus infections (Ref. 18). Resorcinol 10 percent was still being listed in 1975 for treating athlete's foot, probably because of its mildly keratolytic action (Ref. 2).

The Panel knows of no clinical studies demonstrating the effectiveness of resorcinol as an antifungal ingredient. It therefore concludes that resorcinol is of questionable effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(3) *Evaluation.* The Panel has seen no data on the percutaneous absorption of resorcinol. The literature has proven vague on whether systemic toxicity has ever been observed from the topical application of resorcinol on intact or broken skin. The Panel is concerned that the 10-percent concentration of resorcinol in the currently marketed product may far exceed the concentration actually needed to produce the desired therapeutic effect. At a lower concentration resorcinol could possibly be safe and effective in the treatment of athlete's foot, jock itch, and ringworm. However, without data this is pure speculation.

References

- (1) Strakosch, E. A., "Studies on Ointments. V. Ointments Containing Resorcinol." *Archives of Dermatology and Syphilology*, 48:393-399, 1943.
- (2) Osol, A., and J. E. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Easton, PA, p. 1099, 1975.
- (3) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., MacMillan Publishing Co., Inc., New York, p. 991, 1975.
- (4) Christensen, H. E., "The Toxic Substances List," United States Department of Health, Education, and Welfare, Rockville, MD, p. 843, 1973.
- (5) OTC Volume 070228.
- (6) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, Section II, p. 128, 1976.
- (7) Deichmann, W. B., and H. W. Gerarde, "Symptomatology and Therapy of Toxicological Emergencies," Academic Press, New York, p. 352, 1964.
- (8) Blacow, N. W., "Martindale. The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, p. 571, 1972.
- (9) Stenback, F., and P. Shubik, "Lack of Toxicity and Carcinogenicity of Some Commonly Used Cutaneous Agents," *Toxicology and Applied Pharmacology*, 30:7-13, 1974.
- (10) Riley, K., and A. H. Flower, Jr., "A Comparison of the Inhibitory Effect of Castellani's Paint and of Gentian Violet Solution on the In Vitro Growth of *Candida albicans*," *Journal of Investigative Dermatology*, 15:355-361, 1950.
- (11) Schamberg, J. F., and J. A. Kolmer, "Studies in the Chemotherapy of Fungus Infections. 1. The Fungistatic and Fungicidal activity of Various Dyes and Medicaments," *Archives of Dermatology and Syphilology*, 6:746-756, 1922.
- (12) Ormsby, O. S., "Diseases of the skin," 4th Ed., Lea and Febiger, Philadelphia, p. 102, 1934.
- (13) "The National Formulary," 13th Ed., The American Pharmaceutical Association, Washington, DC, p. 624, 1970.
- (14) Whitfield, A., "A Handbook of Skin Diseases and Their Treatment," Edward Arnold, London, p. 64, 1907.
- (15) Pusey, W. A., "The Principles and Practice of Dermatology," 3d Ed., D. Appleton and Co., New York, p. 787, 1917.
- (16) Walker, N., "An Introduction to Dermatology," 9th Ed., W. Green and Son, Edinburgh, p. 244, 1932.
- (17) Becker, S. W., and M. E. Obermayer, "Modern Dermatology and Syphilology," J. B. Lippincott Co., Philadelphia, pp. 433-434, 1940.
- (18) Stokes, J. H., et al., "Fundamentals of Medical Dermatology," 7th revision, Department of Dermatology Book Fund, University of Pennsylvania, Philadelphia, p. 264, 1942.

g. Tannic acid. The Panel concludes that tannic acid is safe but is not effective for OTC antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Tannic acid, also known as tannin, occurs in the bark and fruit of many plants, especially in the bark of oak trees. It is also a naturally extractable material from tea and coffee. It is prepared commercially by extraction from nutgalls.

Tannic acid appears as yellowish-white to light brown, amorphous, bulky powder or flakes with a faint characteristic odor and astringent taste. It is very soluble in water, alcohol, and acetone and practically insoluble in organic solvents such as chloroform, ether, and benzene (Ref. 1).

(1) *Safety.* Tannic acid has been widely formulated as a component of topical ointments, gargles, irrigation solutions, lotions, lozenges, and mouthwashes. Tannic acid precipitates proteins and forms insoluble complexes with some alkaloids and glycosides. It is because of the latter property that tannic acid gained use orally as an antidote for ingested alkaloids and glycosides (Ref. 2).

Tannic acid has little action on intact skin. When applied to abraded tissue, however, it precipitates protein to form a protective film on the surface of the wound. This is why tannic acid was formerly used extensively in burn treatment (Ref. 3).

The oral LD₅₀ of tannic acid in rabbits is 5,000 mg/kg (Ref. 4). In veterinary medicine, the drug is used topically as a hemostatic astringent (Ref. 5).

Systemically, tannic acid causes liver toxicity; tannic acid in barium enemas reportedly has the potential to induce liver damage and even death (Ref. 2). The lowest published oral lethal dose of tannic acid in humans is 500 mg/kg (Ref. 4).

The Panel is mindful of the potentially hepatotoxic effect of tannic acid. Nevertheless, it concludes that topically used tannic acid is more likely to interact with surface proteins so extensively that even when used on the fissured areas of athlete's foot, percutaneous absorption of tannic acid

is unlikely. The Panel therefore concludes that tannic acid is safe when used topically in the treatment of athlete's foot, jock itch, or ringworm.

(2) *Effectiveness.* As a vegetable astringent, tannic acid has little action on intact skin, but, as stated above, precipitates proteins locally on the surface of abraded skin to form a mechanically protective tannate film (Ref. 3). Tannic acid has been used as a styptic and astringent in concentrations of 1 to 20 percent (Ref. 6).

The Panel found no in vitro data on tannic acid.

The only references known to the Panel on the use of tannic acid in fungal infections are dermatology textbooks from the early 1940's. During this period, tannic acid was used to treat hyperhidrosis, sometimes associated with athlete's foot (Refs. 7 and 8). Five percent tannic acid was used along with zinc peroxide, boric acid, bentonite, and talc in a foot powder. Tannic acid was also combined with menthol, phenol, glycerin, and alcohol and used as a tincture to relieve itching (Ref. 7).

A 2-percent tannic acid aqueous soak was used to help "hasten epithelialization" in the subacute phase of dermatophytosis of the hands and feet (Ref. 8). A 5-percent aqueous solution was used to treat athlete's foot associated with a "great deal of weeping and oozing" until the acute manifestations subsided (Ref. 9). After the acute skin lesions were largely healed, markedly hyperhidrotic cases of athlete's foot were sometimes treated once daily with a dusting powder containing equal parts of tannic acid, zinc oxide, and boric acid. The powder was to act as an antiperspirant and astringent (Ref. 8).

Based on the above review, the Panel concludes that the inclusion of tannic acid in antifungal medications is largely of historical interest. The Panel knows of no studies demonstrating either antifungal activity in vitro or clinical effectiveness of tannic acid as an antifungal agent in the treatment of athlete's foot, jock itch, or ringworm. The Panel therefore concludes that tannic acid is not effective for the treatment of these conditions.

(3) *Evaluation.* The Panel concludes that because it has found no in vitro or clinical data on the effectiveness of tannic acid, this ingredient should be placed in Category II for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

References

- (1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, pp. 1172-1173, 1976.
 - (2) Blacow, N. W., "Martindale. The Extra Pharmacopoeia," The Pharmaceutical Press, London, pp. 268-269, 1972.
 - (3) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 4th Ed., The Macmillan Co., London, p. 992, 1970.
 - (4) Fairchild, E. J., "Registry of Toxic Effects of Chemical Substances," United States Department of Health, Education, and Welfare, Cincinnati, P. 887, 1977.
 - (5) Rossoff, I. S., "Handbook of Veterinary Drugs," Springer Publishing Co., New York, p. 583, 1974.
 - (6) "Stedman's Medical Dictionary," 20th Ed., The Williams and Wilkins Co., Baltimore, p. 34, 1961.
 - (7) Pillsbury, D. M., M. B. Sulzberger, and C. S. Livingood, "Manual of Dermatology," W. B. Saunders Co., Philadelphia, pp. 363-364, 370, 377, 1942.
 - (8) Stokes, J. H., "Fundamentals of Medical Dermatology," 7th Ed., University of Pennsylvania, Philadelphia, p. 343, 1942.
 - (9) Peck, S. M., and S. Schwartz, "A Practical Plan for the treatment of Superficial Fungus Infections," *Public Health Reports*, 58:337-345, 1943.
- h. *Thymol*. The Panel concludes that thymol at concentrations greater than 0.2 percent is not effective and that there are insufficient data available to determine its safety for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. The Panel also concludes that at concentrations less than or equal to 0.2 percent, thymol is an inactive ingredient and can be safely used in formulations for product identification.
- The chemical formula of thymol is $C_{10}H_{14}O$; its chemical name is 5-methyl-2-(1-methylethyl) phenol. Thymol is also known as thyme camphor. It is obtained by fractional distillation from the volatile oil of *Thymus vulgaris*, *Monarda punctata* (horsemint), and other related plants. It may also be prepared synthetically from *p*-cymene or *m*-cresol. It occurs as large colorless crystals or white crystalline powder with an aromatic odor similar to thyme and pungent taste. Thymol is practically insoluble in water (1 g in 1,000 mL), but is soluble in alcohol and ether. Because it is affected by exposure to light, it must be stored in light-resistant containers. When thymol is triturated with an equal weight of either camphor, menthol, chloral hydrate, or some other substances, a liquefied mixture results (Ref. 1).
- Thymol was originally introduced as a disinfectant with uses similar to those of phenol. Thymol has a more agreeable odor than phenol and is also a more powerful bactericide, although its activity is greatly reduced in the

presence of organic matter and protein. Thymol is used in concentrations of 1 percent in alcohol and 2 percent in dusting powder as an antiseptic and antifungal agent (Ref. 2). Thymol occurs in concentrations of 0.125 to 1.25 percent in the antifungal products submitted for review.

Safety. Thymol is physically and structurally related to phenol; hence, its toxicology is similar to that of phenol. (See part III. Paragraph B.1.e. above—Phenolates (phenol and phenolate sodium).) However, toxic signs and symptoms for thymol are much less severe than for phenol in equal concentrations.

The oral LD_{50} of thymol in mice is 1.8 g/kg (Ref. 3). The intravenous LD_{50} in mice was reported as 74 mg/kg (Ref. 4). Jenner (Ref. 5) studied the acute oral toxicity of thymol by intubation in the rat and guinea pig. The LD_{50} for the rat was found to be 980 mg/kg, and for the guinea pig, 880 mg/kg.

In humans, ingested thymol can cause nausea, vomiting, albuminuria (albumin in the urine), headache, tinnitus (ringing in the ears), dizziness, muscular weakness, thready pulse, slow respiration, and lowered body temperature. "Therapeutic" doses depress the heart (Ref. 2). Ingestion of 1 g thymol does not usually cause adverse symptoms other than a feeling of warmth in the stomach. Doses larger than 1 g have resulted in toxic symptoms. Fats and alcohols increase the absorption of thymol and aggravate the toxic symptoms (Ref. 6).

Worm infestations were treated in the past with thymol, especially in the Far East. In 1922, Barnes (Ref. 7) estimated that over the years nearly 1½ million doses of thymol had been administered for hookworm and tapeworm. The usual oral dose was 1.3 g. Barnes noted that fewer than 20 fatalities resulting from the use of thymol are reported in the literature.

Samitz and Shmunes (Ref. 8) noted that dentists and dental technicians found thymol one of the less frequent sensitizers in occupational dermatoses. However, rashes are not uncommon. A recent textbook noted that thymol 0.5 percent in lotions was irritating (Ref. 9). Also, because of its strong irritancy potential thymol has had little value as a bactericide for wounds or mucous membranes. It is better tolerated on intact skin (Ref. 2). Safety data are not available on the absorption of thymol from small areas of application to broken skin and intact skin. Data on the local effects of thymol on wound healing and thymol's irritation potential are also needed. The Panel concludes that more information is needed to determine the

safety of thymol at concentrations greater than 0.2 percent in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness*. In the past, thymol was called a "strong fungicide" based on in vitro tests with dermatophytes. A 1:1,000 aqueous solution of thymol was fungicidal to 100 percent of the dermatophytic organisms tested for a 30-minute exposure time, whereas a 1:7,500 aqueous solution of thymol was fungistatic to dermatophytic cultures after 4 to 6 weeks of exposure (Ref. 10). Thymol was found to have a phenol coefficient of 26 against *T. gypseum* (Ref. 11). In another in vitro study with *T. mentagrophytes*, the minimal fungicidal concentration of thymol in 95 percent ethyl alcohol was found to be 1.5 percent at 5 days, 2.0 percent at 10 and 15 day, 3.0 percent at 20 days (Ref. 12).

Thymol was felt to have potential value as an antifungal therapeutic agent when all the fungi in human scales infected with dermatophytes were killed after 30-minute exposures to 3 percent thymol in 50 percent alcohol or 5 percent thymol in 95 percent alcohol (Ref. 13). *T. interdigitale* was completely inhibited by 5 percent thymol in an ointment base of petrolatum, wool fat, and yellow wax (Ref. 14). A 1-percent concentration of thymol in talc completely prevented culture growth of *T. inguinale* and caused a 2.8-cm zone of inhibition in the growth of *T. interdigitale* (Ref. 15). Thymol 10 percent in chloroform has been used to preserve fungus cultures. Application of a few drops of the mixture to the culture tube's cotton stopper promptly stops fungal growth (Ref. 16). If the culture is then sealed in wax, it will last up to 6 years.

Thymol is also fungicidal against *M. albicans*, and a phenol coefficient of 17 has been reported (Ref. 11). A saturated aqueous solution of thymol killed 10 species of yeasts obtained from human isolates after 1-minute exposure times. The minimal effective fungicidal concentrations for three different yeasts were 7, 8, and 10 percent thymol in water (Ref. 17).

A 5-percent thymol ointment (petrolatum, wool fat, and yellow wax) was fungistatic to *Candida* in vitro. The most effective base tested for releasing 5 percent thymol in cultures of *M. albicans* was vanishing cream, which resulted in a 20-mm zone of inhibition. Bases containing either cold cream or petrolatum with yellow wax and wool fat were less effective in releasing 5 percent thymol, with zones of inhibition of 16 mm and 12 mm, respectively (Ref. 14).

Against *Candida tropicalis*, a 1:1,500 dilution of thymol was fungicidal after a 1-minute exposure, and a 1:2,000 dilution was fungicidal after 30-minute and 60-minute exposures (Ref. 18). Thymol has in vitro antibacterial activity similar to that of phenol. (See part III. paragraph B.1.e. above—Phenolates (phenol and phenolate sodium).)

Thymol 0.044 percent was bactericidal to *S. albus* and *B. typhosus* after 2.5 minutes of exposure; thymol 0.033 percent was bactericidal to the same bacteria after 15 minutes of exposure. The solvent in this study contained alcohol, glycerin, ethylene glycol, soap, and water, and was not, itself, bactericidal in the dilutions used in testing (Ref. 19).

In a study performed in 1925, a mixture containing 5 percent thymol and 2 percent cinnamon in alcohol was painted on areas of candidiasis in fruit handlers working in a canning plant (Ref. 19). The mixture brought "speedy relief." "Prompt relief" resulted when the same mixture was painted between the toes and on the soles of persons with *Epidermophyton* infections (Ref. 20). In another study, 10 to 20 percent thymol in olive oil was applied to skin lesions of actinomycosis, along with the oral administration of thymol 1 to 2 g daily, with good results (Ref. 21).

Clinical trials using thymol 2.5 percent and oil of cinnamon 1 percent in cold cream or vanishing cream base were recommended in 1941 on the basis of in vitro fungistatic activity against both dermatophytes and *M. albicans* (Ref. 14).

Thymol 10 percent in chloroform was applied twice daily to the scalp to treat favus caused by the dermatophyte fungus *A. schoenleinii* (Ref. 22). Thymol treatment resulted in less scale and less irritation within 2 weeks. After 3 months it was alternated with 4 percent chrysarobin in chloroform, acting as an irritant to the scalp. Treatment was stopped after 1 year except for thymol applications twice weekly. Hair regrowth was then normal and all fungal cultures were negative.

A clinical trial was performed at Fort Benning, Georgia (Ref. 23). Sixty-nine cases of KOH-positive athlete's foot were treated initially with thymol (concentration not given), and 34 percent experienced mild-to-moderate irritation. After 1 to 2 weeks, itching had been relieved in 37 percent of 52 cases, but only 17 percent were clinically clear. After 2 to 4 weeks of treatment, examination of 30 patients revealed that only 40 percent were clinically clear. It was concluded that thymol was not very effective and was often irritating.

Some years later, 2 to 4 percent thymol in chloroform was reported to control chronic *Candida* infections in and around the nails, with chloroform acting as a useful drying agent (Ref. 24).

Although thymol has been regarded as an active antiseptic and fungicidal agent in the past, there have been no controlled studies demonstrating its effectiveness when applied to skin for the treatment of athlete's foot, jock itch, or ringworm. Indeed, the only clinical trial performed with thymol on athlete's foot (Ref. 23) suggested that thymol was very irritating in many cases and not very effective in clearing athlete's foot.

The Panel concludes that thymol is not an effective antifungal ingredient for the treatment of athlete's foot, jock itch, and ringworm.

(3) *Evaluation.* The Panel has placed thymol at concentrations greater than 0.2 percent in Category II because the only clinical trial that evaluated this ingredient showed it to be ineffective in clearing athlete's foot. The Panel concludes that thymol at concentrations less than or equal to 0.2 percent is safe and may be used in formulations for product identification.

References

- (1) Osol, A., and J. E. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1101, 1975.
- (2) Osol, A., and R. Pratt, "The United States Dispensary," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1189, 1973.
- (3) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1214, 1976.
- (4) Edwards, E., and B. Hall, "Thymol as Bacteriostatic Agent," *The Pharmaceutical Journal*, 166:54, 1951.
- (5) Jenner, P., et al., "Food Flavours and Compounds of Related Structure. I. Acute Oral Toxicity," *Food and Cosmetics Toxicology*, 2:327-343, 1964.
- (6) Sollman, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 227-228, 1957.
- (7) Barnes, M. E., "Death Following the Administration of Thymol," *Journal of the American Medical Association*, 79:964-965, 1922.
- (8) Samitz, M., and E. Shmunes, "Occupational Dermatoses in Dentists and Allied Personnel," *CUTIS; Cutaneous Medicine for the Practitioner*, 5:180-184, 1964.
- (9) Domonkos, A. N., "Andrews' Diseases of the Skin," 6th Ed., W. B. Saunders Co., Philadelphia, pp. 63-64, 1971.
- (10) Kingery, L., and A. Adkisson, "Certain Volatile Oils and Stearoptens as Fungicides. An Experimental Study," *Archives of Dermatology and Syphilology*, 17:499-511, 1923.
- (11) Emmons, C. W., "Fungicidal Action of Some Common Disinfectants on Two Dermatophytes," *Archives of Dermatology and Syphilology*, 28:15-21, 1933.

(12) Golden, M. J., and K. Oster, "Studies on Alcohol-Soluble Fungistatic and Fungicidal Compounds. II. Evaluation of a Fungicidal Laboratory Test Method," *Journal of the American Pharmaceutical Association*, 26:359-362, 1947.

(13) Legge, R., L. Bonar, and H. Templeton, "Epidermomycosis at the University of California. Study III," *Archives of Dermatology and Syphilology*, 27:12-24, 1933.

(14) O'Brien, F., and W. Bonisteel, "The Fungistatic Value of Certain Ointments," *Journal of the American Pharmaceutical Association*, 30:191-201, 1941.

(15) Fredell, W., V. Burlingame, and G. Reddish, "Antiseptic Powders," *Drug Standards*, 22:107-112, 1954.

(16) Morris, G., "Use of Thymol as a Preservative for Fungi," *Archives of Dermatology and Syphilology*, 67:514, 1953.

(17) Myers, H., "An Unappreciated Fungicidal Action of Certain Volatile Oils," *Journal of the American Medical Association*, 89:1834-1836, 1927.

(18) Kingery, L., R. Williams, and G. Woodward, "Further Studies in Fungicides. Comparative Evaluation of Phenol Derivatives by Modified Laboratory Procedures," *Archives of Dermatology and Syphilology*, 31:452-460, 1935.

(19) Miller, R., "Bactericidal Efficiency of Essential Oils," *American Journal of Pharmacy*, 103:324-328, 1931.

(20) Myers, H., and C. Thienes, "The Fungicidal Activity of Certain Volatile Oils and Stearoptens. Their Comparative Toxicity on a Pathogenic Yeastlike Organism: Report of Clinical Utilization in Related Infections," *Journal of the American Medical Association*, 84:1985-1986, 1925.

(21) Myers, H., "Thymol Therapy in Actinomycosis," *Journal of the American Medical Association*, 108:1875, 1937.

(22) Morris, G., "Favus in Massachusetts. A Report Two Cases," *New England Journal of Medicine*, 230:667-669, 1944.

(23) Hopkins, J., et al., "Fungistatic Agents for Treatment of Dermatophytosis," *Journal of Investigative Dermatology*, 7:239-253, 1946.

(24) Wilson, J., "Paronychia and Onycholysis, Etiology and Therapy," *Archives of Dermatology*, 92:726-729, 1965.

1. *Tolindate.* The Panel concludes that tolindate is not generally recognized as safe and effective for the treatment of athlete's foot, jock itch, and ringworm. There are no reports in the medical or pharmaceutical literature that address its use, safety, or effectiveness in these diseases. It is not contained in any marketed OTC antifungal product, but data on this ingredient were submitted to the Panel (Refs. 1 and 2).

The Panel is aware that an active investigational new drug exemption (IND) exists for tolindate; however, because tolindate now has no clinical use it cannot be generally recognized as appropriate for OTC use.

The Panel questioned whether tolindate was chemically similar enough to tolnaftate (a Category I ingredient) to warrant including it in the review of the

safety and effectiveness of OTC drugs. The Panel concluded that although tolindate's antifungal action could possibly be predicted on the basis of structural similarity to the tolnaftate molecule, there was no way to scientifically assess its activity without complete antifungal testing. Also, the solubility and stability of these two drugs could be totally unrelated (Ref. 3).

The Panel therefore determined that because of (1) the lack of any scientific publications dealing with tolindate, (2) the lack of safety data in the public domain, and (3) the lack of effectiveness data in the public domain, tolindate should be classified in Category II.

References

- (1) OTC Volume 070170.
- (2) OTC Volume 070171.
- (3) Summary Minutes of the 26th Meeting of the OTC Antimicrobial II Panel, May 20, 1977, as incorporated in OTC Volume 07A PA2.

2. *Category II labeling.* The Panel concludes that certain labeling claims related to safety or effectiveness of an ingredient are unsupported by scientific data or, in some instances, by sound theoretical reasoning. The Panel therefore concludes that such labeling should be removed from the market.

Many claims from current labels have been placed in Category II either because they are vague, too broad, incomplete, or modified incorrectly, or because they do not specifically indicate that the product effectively treats or prevents athlete's foot, jock itch, or ringworm. Such labels mislead the lay person.

Many claims would appear to be acceptable; however, certain modifying words can make these claims unclear or even imprecise. For this reason, modifiers such as "most" or "fast" are not allowed. Other examples of vague modifiers are "scientific" as in "scientific treatment"; "persistent" as in "Persistent cases."

The Panel considers the following labeling claims to be unacceptable:

"Athlete's foot," "ringworm," "jock itch" (when these words are used alone).

"Antifungal" (when used alone).

"Adjunctive treatment."

"Promotes healing."

"Helps heal."

"Kills most athlete's foot fungi."

"Kills athlete's foot on contact."

"Kills athlete's foot fungi on contact."

"Kills jock itch fungi on contact."

"Kills athlete's foot fungi fast."

"Kills jock itch fungi fast."

"For the treatment of athlete's foot and ringworm of the skin, exclusive of bodyfold areas."

"Scientific treatment" for athlete's foot."

"Kills fungus spores."

"Temporary relief of ringworm."

"Temporary relief of itching and discomfort due to athlete's foot."

"Helps restore normal skin even in severe or persistent cases."

"Proven fungicide for athlete's foot, jock itch, and body ringworm fungi."

"Fungicidal against athlete's foot, jock itch, and ringworm fungi."

"The broadest proven dermatophyte spectrum."

"Speeds healing of athlete's foot."

"Speeds healing of jock itch."

"Broad spectrum antifungal (for treatment of athlete's foot and jock itch)."

"For fast relief of itching and burning of athlete's foot and jock itch."

"Penetrating action goes under crust and skin surface to kill athlete's foot fungi."

"Kills all known athlete's foot and jock itch fungi."

"Kills all major types of athlete's foot fungi."

"Kills all major types of jock itch fungi."

"Prevention and control of minor skin infections including athlete's foot."

"Minor fungus skin infections."

"Minor skin irritations associated with fungus."

"Other skin fungus infections."

"For the treatment of inflamed conditions of the skin, such as eczema, athlete's foot, and other fungal infections."

"Combats and controls infection-causing fungi."

"For irritations caused by fungus infections."

"Controls bacteria and fungi."

"For fungus infections of hands, groin, or body."

"For superficial fungal infections of the skin."

"Helps prevent fungal infections."

"Guards against fungus growth."

"Inhibits the growth of fungi and bacteria."

"Helps prevent germ and fungus infection."

Because the following labeling claims do not specifically indicate that the product effectively treats or prevents athlete's foot, jock itch, or ringworm, the Panel considers them misleading to the lay person:

"First-aid."

"Aids in drying up excessive secretions."

"As an antiseptic."

"An inhibitory antiseptic."

"Protects broken skin from infection."

"Invisible shield."

"Fungicidal."

"Fungistatic."

"Bactericide."

"Germicide."

Any claims that contain a "percent cured" rate have been placed in Category II because the percentages could change, depending on when and how the test is run.

Examples of this kind of labeling are as follows:

"Clinical studies show that it cured 78 percent of athlete's foot cases."

"Clinical improvement was obtained in 88 percent of the athlete's foot cases."

C. Category III Conditions for Which the Available Data Are Insufficient To Permit Final Classification at This Time.

The safety and efficacy of the following ingredients were classified on the basis of activity and use as antifungal agents. Ingredients for which no antifungal claim is made, including ingredients that have been reviewed by the Panel and placed in Category III for antifungal effectiveness, may still be included in formulations for nonantifungal purposes providing they are safe at the concentrations used and are in compliance with the Panel's combination policy.

Furthermore, the Panel believes that antifungal ingredients placed in Category I for the treatment of athlete's foot, jock itch, and ringworm may also be effective in the prevention of athlete's foot. At present, however, prophylaxis data on most of these ingredients are insufficient to support such a labeling claim. Before the prevention of athlete's foot may be included on labeling, a clinical trial should be conducted as detailed elsewhere in this document (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

1. Category III Active Ingredients

Aluminum salts
Alcloxa
Aluminum sulfate
Potassium alum
Basic fuchsin
Benzethonium chloride
Benzoic acid
Borates
Boric acid
Sodium borate
Caprylates
Sodium caprylate
Zinc caprylate
Chlorothymol
Chloroxylenol
Cresols
m-Cresol
Secondary amyltrichresols
Dichlorophen
Oxyquinolines
Benzoxiquine
Oxyquinoline

Oxyquinoline sulfate
Parabens
Methylparaben
Propylparaben
Phenyl salicylate
Povidone-iodine
Propionic acid and its salts
Sodium propionate
Zinc propionate
Salicylic acid
Sulfur
Triacetin

a. *Aluminum salts (alcloxa, aluminum sulfate, and potassium alum).* The Panel concludes that aluminum salts (alcloxa, aluminum sulfate, and potassium alum) are safe but that there are insufficient data available to permit final classification of their effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Alcloxa, also known as aluminum chlorohydroxy allantoinate, is a white powder. Its chemical formula is $Al_2(OH)_4ClC_4H_8N_4O_6$. It is soluble in 55 parts water and 200 parts alcohol. A saturated solution of alcloxa has a pH of about 4.7 (Ref. 1).

Aluminum sulfate, $Al_2(SO_4)_3 \cdot H_2O$, is a white, crystalline, odorless powder. It is also known as cake alum and patent alum. It is very soluble in water, 1 g dissolving in about 1 mL water, but is insoluble in alcohol. The aqueous solution of aluminum sulfate is acidic (Ref. 2).

Potassium alum, also known as aluminum potassium sulfate, has a chemical formula of $AlK(SO_4)_2 \cdot 12H_2O$. It has been known since ancient times when it was used as a styptic and as a mordant (a substance used to fix coloring matter in textiles or other materials) in dyes. Potassium alum is a white or colorless crystalline powder prepared from the mineral bauxite and sulfuric acid, with potassium sulfate added. One g potassium alum is soluble in about 7.5 mL water, but is insoluble in alcohol. When potassium alum is dispensed in powders containing phenol, salicylates, or tannic acid, a green or gray color may develop because of traces of iron found in the potassium alum (Ref. 2).

The aluminum salts have been submitted to the Panel in powder formulations in the following concentrations: alcloxa, 0.25 percent; aluminum sulfate, 1.5 percent; and potassium alum, 15 to 21 percent.

(1) *Safety.* Dreisbach (Ref. 3) reported that salts of metals are used as "astringents, deodorants, and antiseptics." When applied to the skin, aluminum salts are not usually absorbed, but may act by precipitating protein which forms a superficial

protective layer on mucous membranes or damaged skin (Ref. 4).

Sax (Ref. 5) reported that aluminum compounds have little or no toxicity. It has also been suggested that chronic poisoning does not occur and that fatalities from aluminum salts have not been cited in recent years (Ref. 3). Nevertheless, it is known that certain aluminum salts, namely chloride and sulfate, do tend to hydrolyze and produce the corresponding acid, which in turn is irritating.

Various aluminum salts have long been used as astringents and antiperspirants. Standard references (Refs. 3 and 5) report an absence of toxicity, and the Panel recognizes the safety of these salts when topically applied. For these reasons the Panel concludes that aluminum salts are safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* Leyden and Kligman (Ref. 6) tested various aluminum salts (chloride, chlorohydrate, acetate, and diacetate) for antibacterial, antifungal, and astringent properties. They found that a mere 1-percent concentration of aluminum chlorohydrate was needed to completely inhibit all organisms but *T. mentagrophytes* when tested in vitro. Test organisms included *S. aureus*, *Pseudomonas*, and *C. albicans*. Concentrations of 10 percent aluminum acetate and 30 percent aluminum chloride, however, were necessary to completely inhibit the microorganisms (*S. aureus*, *Pseudomonas*, *C. albicans*, and *T. mentagrophytes*) in vitro.

In vitro results did not correlate with in vivo results in patients with athlete's foot. Although least effective on agar plate tests, aluminum chloride in a concentration of 30 percent was clinically far superior to the other compounds. Leyden and Kligman believed that astringency was mainly responsible for these results and noted that aluminum chloride was the most effective astringent in the group of compounds tested. It is important to note that these investigators did not specifically define athlete's foot. They used any patient with a symptomatic, macerated intertrigo of the toe webs.

In view of the lack of well-designed, controlled, clinical studies, the Panel concludes that aluminum salts are of questionable effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. The Panel proposes that an upper limit of 10 percent is a sufficient concentration for antifungal activity to be demonstrated. Higher concentrations would be present for their drying effect.

(3) *Proposed dosage—(i) Concentration.* Aluminum salts (a) alcloxa 0.25 to 10.0 percent (b) aluminum sulfate 1.5 to 10.0 percent; (c) potassium alum 1.5 to 10.0 percent.

(ii) *Directions for use.* See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling.* The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation.* The Panel recommends in vitro testing and one double-blinded, placebo-controlled clinical trial to determine the effectiveness of each aluminum salt in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) OTC Volume 070100.
- (2) Osol, A., and J. E. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, pp. 717-718, 1975.
- (3) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 8th Ed., Lange Medical Publications, Los Altos, CA, p. 371, 1974.
- (4) Blacow, N. W., "Martindale. The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, p. 260, 1972.
- (5) Sax, N. I., "Dangerous Properties of Industrial Materials," 3d Ed., Reinhold Book Corp., New York, p. 391, 1968.
- (6) Leyden, J. J., and A. M. Kligman, "Aluminum Chloride in the Treatment of Symptomatic Athlete's Foot," *Archives of Dermatology*, 111:1004-1010, 1975.

b. *Basic fuchsin.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of basic fuchsin for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Basic fuchsin, a red dye used as a stain in histology and bacteriology, is composed of a mixture of rosaniline and pararosaniline hydrochlorides. It is a dark green, crystalline powder that is soluble in water and alcohol but insoluble in ether (Ref. 1). Basic fuchsin was submitted to the Panel in a concentration of 0.3 percent.

(1) *Safety.* Basic fuchsin is one of several triphenylmethane (rosaniline) derivatives that are active against certain fungi and gram-positive microorganisms. Some of the methylrosaniline dyes have been used orally as anthelmintics (agents that

destroy worms). For direct application to tissues, these dyes are generally used in concentrations of 1:5,000 to 1:1,000. For instillation into closed cavities the concentration is reduced to 1:10,000 (Ref. 2).

Little is known about the acute or chronic toxicity of basic fuchsin. The only report dealing with the specific toxicity of basic fuchsin gave the following information: The lowest published lethal dose was 150 mg/kg when given orally to rabbits. The lowest published toxic dose was 2,500 mg/kg when given orally to mice (Ref. 3). Obviously, this is not precise toxicity data and supports Sax's observation that the details of the safety of basic fuchsin are unknown (Ref. 4).

Plunkett (Ref. 5) reported that no threshold limit for gentian violet, another triphenylmethane dye, had been established. Occupational exposure to this compound came from its use in typewriter ribbons, carbon paper, and other such items where it might cause eczema, acne-like eruptions, papillary growth, or, occasionally, epitheliomata (a tumor derived from epithelium). On ingestion, gentian violet may produce inflammation of the lips, headache, nausea and vomiting, diarrhea, and weakness. (No specific dose was associated with these symptoms.)

Blacow (Ref. 6) reported that basic fuchsin is a controlled substance in Great Britain under the Carcinogenic Substance Regulations of 1967, which require all those engaged in manufacturing this compound to undergo 6-month medical examinations. Blacow observed that "this was good reason for considering its (basic fuchsin) disuse in the treatment of fungous skin lesions."

Although the Panel found no further information on the carcinogenic potential of basic fuchsin, it considers this to be its most serious toxicity potential.

(2) *Effectiveness.* The triphenylmethane dyes were used shortly before World War I as antiseptics for wounds, burns, and skin infections. They were usually used at concentrations of 0.1 to 0.5 percent in aqueous solutions. They are most active against gram-positive bacteria, inhibiting gram-positive cocci at concentrations between 1:750,000 and 1:100,000, but up to 10 times those concentrations were required to inhibit gram-negative bacteria (Ref. 7). The presence of serum greatly decreased their antibacterial activity (Ref. 8).

The dyes are most active in the basic than the acidic form, forming a liposoluble pseudo-base that can penetrate the cell membranes of

microorganisms (Ref. 9). The basic dyes apparently bind to the acid groups within bacterial cells, including nucleic acids (Ref. 10). Because the antimicrobial activity of the dyes generally increases with the degree of alkyl substitution in the molecule, basic fuchsin with only one methyl group is much less active than some of the other triphenylmethane dyes with more methyl groups, particularly crystal violet and malachite green (Ref. 11).

The in vitro antifungal activity of basic fuchsin has not been widely investigated; the Panel is aware of only a few reports which include such in vitro activity. In one report, the highest dilutions of basic fuchsin (in distilled water) that were fungistatic were 1:200 for *T. rosaceum*, 1:100 for *M. audouinii*, and 1:20 for *A. schoenleinii* (Ref. 12). A later report stated that basic fuchsin did not show any significant fungicidal or fungistatic activity against *T. interdigitale* or *Epidermophyton rubrum* (*E. rubrum*) (Ref. 13).

Basic fuchsin was first used as an antifungal agent by Castellani (Ref. 14), who reported its use in the 1920's in the form of carbol-fuchsin. This was a mixture of a saturated alcoholic solution of basic fuchsin and 5 percent aqueous carbolic acid. He wrote that "the simple carbol-fuchsin gives good results," but he did not provide supportive data or advocate the use of basic fuchsin as a single ingredient. Instead, he combined it with boric acid, acetone, and resorcinol to increase its action and make it more penetrating. The resulting carbol-fuchsin paint became commonly known as Castellani's Paint or Magenta Paint B.P.C. (British Pharmaceutical Codex).

Basic fuchsin was one of several antibacterial chemicals and formulations tested in 1974 to examine the inhibition of growth of microorganisms on human skin (Ref. 15). In an occlusion test, a 1-percent aqueous solution of basic fuchsin was painted on the skin, allowed to dry, and then covered with plastic film for 48 hours. Under the increased heat and moisture, basic fuchsin had an impressive antibacterial effect against gram-positive bacteria. In an expanded flora test, basic fuchsin also showed "high activity" against gram-positive organisms but did not prevent the growth of gram-negative bacteria when the flora expanded. (This test evaluates the antibacterial effect of substances on greatly increased bacterial flora with both gram-positive and gram-negative organisms after they have multiplied under occlusion with plastic wrap for 48 hours.) In both the occlusion tests and the expanded flora tests, basic fuchsin

was less effective than Castellani's Paint.

The Panel is not aware of any clinical studies using basic fuchsin alone as an antifungal agent. All reports involve the use of carbol-fuchsin paint which combines several ingredients which are potentially antifungal (phenol, boric acid, resorcinol, alcohol, and acetone) with basic fuchsin. (See part III, paragraph D. below—Combination Products Used in the Treatment of Athlete's Foot, Jock Itch, and Ringworm.)

Because of the lack of clinical effectiveness data using basic fuchsin as a single active antifungal ingredient, the Panel concludes that this ingredient is of questionable effectiveness in the treatment of athlete's foot, jock itch, and ringworm.

(3) *Proposed dosage*—(i) *Concentration.* Basic fuchsin 0.3 percent.

(ii) *Directions for use.* See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling.* The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation.* The Panel recommends complete safety testing of basic fuchsin. The Panel also recommends in vitro testing and one double-blind, placebo-controlled clinical trial to determine the effectiveness of basic fuchsin in the treatment of athlete's foot, jock itch, and ringworm. Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Osol, A., and J. E., Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1169, 1975.
- (2) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 4th Ed., The MacMillan Co., New York, p. 1056, 1970.
- (3) Christensen, H. D., and T. T. Luginbyhl, "The Toxic Substances List, 1974 Edition," United States Department of Health, Education, and Welfare, Rockville, MD, p. 813, 1974.
- (4) Sax, N. I., "Dangerous Properties of Industrial Materials," 4th Ed., Van Nostrand Reinhold Co., New York, p. 1213, 1975.
- (5) Plunkett, E. R., "Handbook of Industrial Toxicology," Chemical Publishing Co., Inc., New York, p. 275, 1976.
- (6) Blacow, N. W., "Martindale, The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, p. 198, 1972.

(7) Foster, J. H. S., and A. D. Russell, "Antibacterial Dyes and Nitrofurans," in "Inhibition and Destruction of the Microbial Cell," Edited by W. B. Hugo, Academic Press, New York, pp. 185-188, 1971.

(8) Goldacre, R. J., and J. N. Phillips, "The Ionization of Basic Triphenylmethane Dyes," *Journal of the Chemical Society*, pp. 1724-1732, 1949.

(9) Albert, A., "Selective Toxicity," 4th Ed., Methuen, London, pp. 260-276, 1968.

(10) Neville, D., and D. Davies, "The Interaction of Acridine Dyes with DNA: An X-ray Diffraction and Optical Investigation," *Journal of Molecular Biology*, 17:57-74, 1966.

(11) Gale, E. F., and P. D. Mitchell, "The Assimilation of Amino-acids by Bacteria: The Action of Triphenylmethane Dyes of Glutamic Acid Assimilation," *Journal of General Microbiology*, 1:299-312, 1947.

(12) Schamberg, J. F., and J. A. Kolmer, "Studies in the Chemotherapy of Fungus Infections. I. The Fungistatic and Fungicidal Activity of Various Dyes and Medicaments," *Archives of Dermatology and Syphilology*, 6:746-756, 1922.

(13) McCrea, A., "Fungicidal Value of Some Common Dyes Against Dermatophytic Fungi," *Mycologia*, 26:449-453, 1934.

(14) Castellani, A., "Carbol-fuchsin Paints in the Treatment of Certain Cases of Epidermophytosis," *American Medicine*, 34:351-352, 1928.

(15) Marples, R. R., and A. M. Kligman, "Methods for Evaluating Topical Antibacterial Agents on Human Skin," *Antimicrobial Agents and Chemotherapy*, 5: 323-329, 1974.

c. *Benzethonium chloride*. The Panel concludes that there are insufficient data available to permit final classification of the safety or effectiveness of benzethonium chloride for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Benzethonium chloride is a cationic, surface-active agent with a quaternary amine structure. It is very soluble in water and soluble in alcohol and acetone. Benzethonium chloride is incompatible with many commonly encountered substances. For example, it loses its activity in the presence of soap, tissue constituents, and pus. Acid and salt solutions may also precipitate it (Ref. 1).

(1) *Safety*. The Advisory Review Panel on OTC Antimicrobial I Drug Products reviewed benzethonium chloride for indications other than antifungal and placed it in Category III for safety. (See Federal Register of September 13, 1974 (39 FR 33131).) In reviewing benzethonium chloride for antifungal use, the Advisory Review Panel on OTC Antimicrobial II Drug Products concurs in the Category III safety classification.

Studies dealing with fertility, reproduction, and teratology have been done in rats and rabbits (Ref. 2). Oral

doses of benzethonium chloride ranging from 1.125 to 35.576 mg/kg were administered to the test animals. Except for the highest dose level, little or no toxic effects were observed. However, a reduction in average body weight gain was noted in test rats receiving 35.576 mg/kg in both subchronic and chronic exposures.

To determine the blood levels of C^{14} benzethonium chloride, the drug was given once daily at dose levels of 1.125 and 3.558 mg/kg to pregnant rats. Maximum blood levels of 1.5 nanograms per gram (ng/g) of C^{14} -benzethonium chloride were obtained after cumulative dosing to day 15. No adverse effects on the rats were observed at these blood levels.

If one assumes that as much as 5 g of a foot powder containing 0.13 percent benzethonium chloride were applied to broken skin, a total of 6.5 mg benzethonium would be available for absorption. Further assuming complete, rapid absorption into the blood, the 6.5 mg would be distributed into 7 L of blood, resulting in a blood concentration of about 1.0 μ g/mL. Of course, it is highly unlikely that complete absorption would occur. However, a potential for toxicity does exist. At the oral dose level of 35.576 mg/kg, there was a reduction in weight gain in rats. Assuming that at an oral dose 10 times the level mentioned in the C^{14} study (35.58 mg/kg), and assuming a blood concentration 10 times higher (15 ng/g), then one can see that if absorption from broken skin is significant (and this is unknown), a potential toxicity problem may exist. The Panel therefore recommends that studies be done to determine the degree of absorption from broken skin (as evidenced by blood levels) and the relationship between these blood levels and the blood concentration that produced no adverse effect in animals.

(2) *Effectiveness*. In vitro activity of benzethonium chloride, a quaternary ammonium compound, was described by the Advisory Review Panel on OTC Antimicrobial I Drug Products. (See Federal Register of September 13, 1974 (39 FR 33131).) Quaternary ammonium compounds are generally more active against gram-positive organisms than gram-negative organisms. Their activity is decreased in the presence of organic materials, anionic compounds, soaps, certain metallic ions, and hard water.

The data on the in vitro antifungal activity of benzethonium chloride are limited. Studies reviewed by the Panel included use-dilution tests and phenol coefficients (Ref. 3). Details of the testing procedures were not given. The Panel concludes that further in vitro

work needs to be done on this ingredient.

Benzethonium chloride is contained in only one product submission under review by the Panel (Ref. 3). In this product it appears in a 0.13-percent concentration in combination with at least one other active ingredient. The studies in this submission also evaluate a multi-ingredient product. Although the product appears to demonstrate in vivo effectiveness, the Panel has placed benzethonium chloride in Category III because of insufficient data on its antifungal effectiveness as a single active ingredient.

(3) *Proposed dosage*—(i) *Concentration*. Benzethonium chloride 0.13 percent.

(ii) *Directions for use*. See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation*. The Panel recommends that safety studies be done to determine the degree of absorption of benzethonium chloride from broken skin, as evidenced by blood levels, and the relationship between these blood levels and the blood levels that produced no adverse effects in pregnant rats (1.5 ng/g). The Panel also recommends in vitro testing and one double-blind, placebo-controlled clinical trial to determine the effectiveness of benzethonium chloride in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Windholz, M., et al., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 139, 1976.
- (2) OTC Volume 130115 (submitted to the Advisory Review Panel on OTC Oral Cavity Drug Products).
- (3) OTC Volume 070190.

d. *Benzoic acid*. The Panel concludes that benzoic acid is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Benzoic acid (C_6H_5COOH) is also known as phenylformic acid, flowers of benzoic, and flowers of Benjamin. It is a colorless, tasteless, crystalline

substance readily soluble in organic solvents and soluble up to 0.37 percent in water. Benzoic acid occurs in both the free and esterified state in various plants, the balsams and resins obtained from the plants, and in coal tar. It also occurs as a hippuric acid (benzoylglycine) in the urine of most vertebrates. Benzoic acid may be synthesized from a variety of compounds, such as toluene, benzaldehyde, and benzotrithloride (Refs. 1 and 2).

(1) *Safety.* Although none of the data submitted to the Panel for review gave direct toxicological data on benzoic acid, the Panel recognizes that general consensus exists on the safety of benzoic acid confirmed by its long history as a food preservative.

Goodman and Gilman (Ref. 2) report that a daily intake of 4 to 6 g benzoic acid does not cause toxic symptoms other than slight gastric irritation; large doses of benzoic acid produce systemic effects similar to those produced by the salicylates. Blacow (Ref. 3) has estimated that an acceptable daily benzoic acid intake for humans could be up to 5 mg/kg. According to Sax (Ref. 4), benzoic acid causes only slight local or systemic toxicity.

The Panel concludes that benzoic acid is safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* Benzoic acid has been widely used in a concentration of 0.1 percent as a food preservative, preventing bacterial growth when added to a slightly acidic medium. It is much less effective at an alkaline pH because benzoate salts are formed (Ref. 2).

The submissions reviewed by the Panel include cream, liquid, powder, and ointment formulations of benzoic acid in concentrations ranging from 0.75 to 12 percent.

Benzoic acid applied to the skin in high concentrations has been used as a keratolytic (Ref. 2). In an in vitro test to determine the antimicrobial activity of more than 100 antiseptic powders, benzoic acid, at concentrations of 1 percent and 2.5 percent, showed mild antifungal activity against *T. interdigitale* (Ref. 5).

A study by Oster and Golden (Ref. 6), based on in vitro results, concluded that a 0.91-percent solution of benzoic acid compared favorably in activity to a 1-percent solution of undecylenic acid.

Agar-cup testing showed benzoic acid to have very small zones of inhibition against *C. albicans*, *T. mentagrophytes*, and *T. purpureum*. The minimal fungicidal levels were not accurately determined but appeared high (Ref. 7). The Panel concludes that further in vitro

testing should be done on benzoic acid using current techniques.

In a 3-year study involving over 7,500 voluntary patients, Hopkins et al. (Ref. 8) studied many antifungal agents, including benzoic acid, in the treatment of dermatophytosis. Cultures were done before treatment, and KOH preparations were done at each following visit. Results were given for patients with positive KOH preparations. At the end of more than 4 weeks of treatment (exact time not given), 60 percent (55/92) of the patients treated with benzoic acid were clinically clear; 68 percent (63/92) were "fungus negative." Of the patients treated with undecylenic acid, 70 percent (204/292) were clinically clear; 79 percent (231/292) were "fungus negative." The researchers reported that benzoic acid compared favorably with undecylenic acid. Shortcomings in the study design include failure to obtain cultures at that end of the investigation, to list the causative organism, and to present data and study results clearly and concisely.

Because there is no well-designed, clinical study showing the effectiveness of benzoic acid in the treatment of athlete's foot, jock itch, and ringworm, the Panel recommends this ingredient be placed in Category III.

(3) *Proposed dosage*—(i) *Concentration.* Benzoic acid 0.075 to 12 percent.

(ii) *Directions for use.* See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling.* The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation.* The Panel recommends in vitro testing and one double-blind, placebo-controlled clinical trial to demonstrate the effectiveness of benzoic acid in the treatment of athlete's foot, jock itch, and ringworm. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Osol, A., and J. E. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, pp. 1164-1165, 1975.
- (2) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 4th Ed., The MacMillan Co., New York, pp. 994 and 1040-1041, 1970.
- (3) Blacow, N. W., "Martindale. The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, p. 1526, 1972.

(4) Sax, N. I., "Dangerous Properties of Industrial Materials," 3d Ed., Van Nostrand Reinhold Co., New York, p. 458, 1968.

(5) Fredell, W. G., V. L. Burlingame, and G. F. Reddish, "Antiseptic Powders," *Drug Standards*, 22:107-112, 1954.

(6) Oster, K. A., and M. J. Golden, Jr., "Studies on Alcohol-Soluble Fungistatic and Fungicidal Compounds. I. Evaluation of Fungistatic Laboratory Test Methods," *Journal of the American Pharmaceutical Association (Scientific Edition)*, 36:283-288, 1947.

(7) Florestano, H. J., and M. E. Bahler, "Antifungal Properties of the Polymyxins," *Proceedings of the Society for Experimental Biology and Medicine*, 79:141-143, 1952.

(8) Hopkins, J. G., et al., "Fungistatic Agents for Treatment of Dermatophytosis," *Journal of Investigative Dermatology*, 7:239-253, 1946.

e. *Borates (boric acid and sodium borate).* The Panel concludes that borates (boric acid and sodium borate) are safe in concentrations of 5 percent or less but are not safe in concentrations exceeding 5 percent. The Panel also concludes that there are insufficient data available to permit final classification of their effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Boric acid, H_2BO_3 , occurs as colorless or white crystals or powder. It is obtained from sodium borate and other borates by displacement with a stronger acid. One g boric acid dissolves in 18 mL water, 18 mL alcohol, and 4 mL glycerin.

Sodium borate, $Na_2B_4O_7$, also known as borax, is an odorless, colorless or white crystalline powder. It is found in several lake waters and brines and also in minerals. One g dissolves in about 16 mL water and about 1 mL glycerin. Sodium borate is insoluble in alcohol (Ref. 1).

(1) *Safety.* Borate compounds (boric acid and sodium borate) are used in concentrations ranging from about 0.5 percent to 12 percent.

Sodium borate has been used as a cleansing agent since ancient times. Its use as an internal cleanser was first recorded in the Middle East in 875 (Ref. 2). Since that time, many extensive reviews and articles have been written on the use of borated compounds. One of these reviews lists the LD_{50} of subcutaneously administered boric acid in animals as follows: 2.0 g/kg in mice; 1.2 g/kg in guinea pigs; 1.0 g/kg in dogs (Ref. 3). The oral LD_{50} for dogs was reported to be about twice that of the subcutaneous dose.

Toxicity data in humans appear to be unpredictable (Ref. 3). For example, a 70-year-old woman died after ingesting 7.5 g boric acid powder, but a 42-year-

old woman reportedly survived an intravenous dose of 15 g boric acid. Locksley and Farr (Ref. 4) reported administering 20 g borax (sodium borate) intravenously to human subjects over a period of 75 seconds. No deaths resulted. However, six infants died after receiving 3 to 6 g of this drug orally (Ref. 5).

Fisher et al. (Ref. 6) investigated the absorption of boron from borated talc. They reported that when a 10-percent ointment is applied to extensively denuded areas, up to 2 g boric acid may be excreted by a patient within 24 hours following the application. These investigators then used a preparation of 5 percent boric acid in talc to study its absorption in infants. The powder was applied freely to diapered areas, with each infant receiving about 168 g of powder (8.4 g boric acid) per month over a 12-month period. Blood samples taken every 2 months failed to show any significant increase in blood concentration of boron even when the infants had minor skin irritations. The investigators concluded that "the circumstances recounted in the literature under which true boric acid poisoning has been encountered appear to be largely, if not entirely, limited to the striking misuse of boric acid, in that it was applied repeatedly in copious quantities as pure or essentially full strength powder to extensive areas of denuded or macerated skin of a small infant."

In reviewing some cases of known intoxication, these same researchers (Ref. 6) found that the blood concentration of boric acid ranged from 52 to 296 mg/100 mL in those cases that were "unmistakably intoxication by boric acid." They concluded from their investigations that "there are few reliable data in the literature regarding the concentration of boric acid in the blood that is accompanied by evidence of toxic condition in the patient."

Kingma (Ref. 3) surveyed the literature from 1882 to 1957 and found 37 cases of alleged boric acid poisoning from topical application. In 26 of these cases it appeared that pure boric acid was applied to raw surfaces. In three cases a 5-percent boric acid solution was used in large quantities or applied to large surfaces. In two of the cases, boric acid ointment was used. Based on his review, Kingma recommended that pure boric acid should never be used on raw surfaces and that a 3-percent concentration limitation for solutions and ointments would greatly increase the safety margin of the drug. He further pointed out that experiments with 5-percent borated talcum had documented

the safety of this preparation. Kingma's conclusions were substantiated by two other review articles (Refs. 6 and 7).

Pfeiffer and Jenney (Ref. 2), in discussing the passage of boric acid through skin, mucous membranes, and serous surfaces, reported that when the torsos of two subjects were anointed with a 10-percent boric acid ointment, no detectable boric acid was found in the urine. These investigators concluded that boric acid is only negligibly absorbed through intact skin. Granulating wounds or surfaces, however, are rich in blood supply and permit the rapid absorption of boric acid applied in solution, as a powder, or as an ointment. Pfeiffer and Jenney suggested that the very young rank first and the very old rank second in susceptibility to boric acid or sodium borate poisoning.

Goldbloom and Goldbloom (Ref. 8) gave clinical histories of four infants poisoned from the topical application of various boric acid preparations. One of the four died, but the cause of death could not be pinpointed as the boric acid poisoning. They also surveyed the various routes of intoxication with mortalities for each group. There were 28 recorded cases of boric acid poisoning following the topical application of boric acid to wounds, burns, and skin eruptions. Nineteen of these cases were fatal. Based on this review, it appears that boric acid (or sodium borate) can be absorbed through broken skin to such a degree that toxic effects and even death may result. Most deaths from the topical application of boric acid occurred with pure boric acid powder or saturated solutions over large areas of skin. The risk factors for potential toxic absorption appear to be concentration of boric acid or sodium borate in a product, age of the patient, skin condition, and duration of exposure.

A review of the literature (Ref. 9) containing 81 references summarized the current status of boric acid poisoning. This review fairly well substantiated that preparations containing 5 percent or less of boric acid presented no great toxicity problem when applied to intact skin. When skin is inflamed or broken, concentrated forms of boric acid should never be used. Concentrations up to 5 percent when used on relatively small areas, such as jock itch or ringworm, should be safe. If one assumes that 1 g of a 5-percent preparation was applied to the skin and all of the boric acid was rapidly absorbed, a total of 50 mg would be absorbed and distributed into 7,000 mL of blood. This, of course, is far below the blood levels achieved by Locksley

and Farr (Ref. 4), who reported no deaths occurring from a 20-g intravenous dose of sodium tetraborate.

Based on the submitted data and a review of the pertinent literature, the Panel concludes that no great hazard exists from the topical application of borate preparations containing a concentration of 5 percent or less.

(2) *Effectiveness.* Boric acid has historically been used as a treatment for superficial fungal infections. It has also been used to treat oral candidal infections. In vitro data were not submitted for this ingredient nor are they available in the recent medical literature.

Boric acid is one of the more common components of OTC topical antifungal drugs. However, none of the literature submitted and reviewed met the Panel's definition of a well-designed clinical study. All studies lacked KOH microscopic examinations and cultures. The therapeutic trials were not blinded or controlled.

Only in a study by Weidman and Glass (Ref. 10) was boric acid tested as a single active ingredient. This study used a 5-percent boric acid in talc preparation and compared the treatment and prophylactic effects of this drug to various other topical agents. The authors stated that they made no attempt to discriminate between mycotic and bacterial toe web infections. There were no control subjects. Of the 20 patients originally treated, six were "cured," three "nearly cured," one "improved," seven remained "stationary," and three "worsened."

The Panel is not aware of any other studies evaluating the effectiveness of boric acid as a single ingredient in the treatment of fungal diseases. Therefore, because of the lack of data evaluating the topical use of boric acid as an antifungal agent, the Panel recommends Category III for effectiveness.

(3) *Proposed dosage—(i) Concentration.* Boric acid and sodium borate may be used alone or in combination to equal a total borate recommended concentration of 0.5 to 5 percent.

(ii) *Directions for use.* See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling.* The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation.* The Panel recommends in vitro testing and one double-blind, placebo-controlled clinical trial to determine the effectiveness of borates in

the treatment of athlete's foot, jock itch, and ringworm. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E, below—Guidelines for safety and Effectiveness Studies.)

References

- (1) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 199 and 1047, 1973.
- (2) Pleiffer, C. C., and E. H. Jenney, "The Pharmacology of Boric Acid and Boron Compounds," *Bulletin of the National Formulary Committee*, 18:57-66, 1950.
- (3) Kingma, H., "The Pharmacology and Toxicology of Boron Compounds," *Canadian Medical Association Journal*, 78:620-622, 1958.
- (4) Locksley, H. B., and L. E. Farr, "The Tolerance of Large Doses of Sodium Borate Intravenously by Patients Receiving Neutron Capture Therapy," *Journal of Pharmacology and Experimental Therapeutics*, 114:484-489, 1955.
- (5) McNally, W. D., and C. A. Rust, "The Distribution of Boric Acid in Human Organs in Six Deaths due to Boric Acid Poisoning," *Journal of the American Medical Association*, 90:382-383, 1928.
- (6) Fisher, R., et al., "Boron Absorption from Borated Talc," *Journal of the American Medical Association*, 157:503-505, 1955.
- (7) Anon., "Boric Acid and Baby Powders," *Food and Cosmetics Toxicology*, 1:249-250, 1963.
- (8) Goldbloom, R. B., and A. Goldbloom, "Boric Acid Poisoning. Report of Four Cases and a Review of 109 Cases from the World Literature," *The Journal of Pediatrics*, 43:631-643, 1953.
- (9) OTC Volume 070221.
- (10) Weidman, F. D., and F. A. Glass, "Dermatophytosis and Other Forms of Intertriginous Dermatitis of the Feet. A Comparison of Therapeutic Methods," *Archives of Dermatology and Syphilology*, 53:213-225, 1946.

f. *Caprylates (sodium caprylate and zinc caprylate)*. The Panel concludes that the caprylates (sodium caprylate and zinc caprylate) are safe but that there are insufficient data available to permit final classification of their effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Caprylic acid (normal octylic acid) is a long-chain saturated fatty acid with eight carbon atoms. It is one of several fatty acids occurring naturally in human sweat and sebum and has antifungal properties. As the pH shifts from acid to alkaline on the surface of the skin, caprylic acid is converted to its less active salt form, known as caprylate (Ref. 1). In the products reviewed by the Panel, sodium caprylate occurs in concentrations of 1 to 26 percent; zinc

caprylate is present in a 5-percent concentration.

At the Pasteur Institute in 1913, Kiesel investigated the ability of fatty acids to retard the germination of molds (Ref. 2). He demonstrated that the length of the carbon chain in the fatty acid determined the antifungal activity of the fatty acid. This antifungal activity increased up to 11 carbon atoms, provided that the carbon chain was unbranched and not substituted with hydroxyl groups (Ref. 3).

In 1938, Peck and Rosenfeld (Ref. 4) showed by in vitro testing that fatty acids could inhibit growth and be fungicidal to dermatophytes and various other pathogenic fungi. They further demonstrated in vitro that human sweat was fungicidal and fungistatic because of its fatty acid content. In clinical studies Peck et al. (Ref. 5) showed that sodium propionate, one of the fatty acid components of sweat, could be successfully used to treat jock itch and athlete's foot.

The clinical use of fatty acids in the form of caprylates, propionates, and nundercylenates as antifungal agents became common during the 1940's and has continued up to the present. Interestingly, it was during this same period that the fatty acids were commonly incorporated into bread as antimicrobial agents, following confirmation in 1939 by Hoffman et al. (Ref. 6) that the fatty acids had remarkable fungistatic activity against common bread molds.

(1) *Safety*. The oral LD₅₀ of caprylates in rats is reported to be 1,410 mg/kg. An intravenous LD₅₀ in mice is reported to be 600 mg/kg (Ref. 7). One report indicated a topical LD₅₀ in rabbits to be 710 mg/kg, which appears to be unexpectedly low compared to the previously mentioned LD₅₀'s (Ref. 7). The Panel concludes that either the rabbit is especially sensitive to the topically administered caprylates, or the reported figure may be incorrect.

Dreisbach (Ref. 8) indicated that the caprylates are nonirritating and that a toxic oral dose would be more than 2 g/kg. Sax (Ref. 9) suggested that many of the details of the toxicology of the caprylates are unknown. In humans, however, sodium caprylate has been used to treat various dermatophytoses without significant toxicity or irritation. A 10-percent sodium caprylate ointment was used in 46 patients without irritation or sensitization even where the epithelium had been denuded (Ref. 10). However, when a 10-percent jelly and powder were used to treat vaginitis, both preparations produced some irritation (Ref. 11). Cohen (Ref. 12) gave intravenous doses up to 8 g in humans

with no ill effects. Daily intravenous doses of 3 g for 3 months were also tolerated.

Considering Cohen's work (Ref. 12) and the lack of toxicity known to occur from the caprylates, the Panel concludes that the caprylates are safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness*. The caprylates have in vitro antimicrobial activity against dermatophytes, *C. albicans*, and bacteria. The antimicrobial activity varies significantly with the pH of the in vitro test system. Antimicrobial activity is greater at acid pH than at alkaline pH (Ref. 3).

The caprylates can be either fungistatic or fungicidal against dermatophytes, depending on the concentration of the caprylates, the pH of the environment, and the exposure time to the drug. In vitro, caprylic acid was found to be fungistatic at concentrations of 0.009 percent and 0.015 percent against *Trichophyton purpureum* (*T. purpureum*) and *T. interdigitale*, respectively. As the pH of the environment increased from 4.5 to 7.5, the concentration of caprylic acid required for fungistatic action against *T. interdigitale* increased tenfold from 0.003 to 0.03 percent. In the same study, at pH 6.5 the in vitro fungicidal concentration of caprylic acid against *T. interdigitale* was 0.45 percent (Ref. 3).

In another in vitro study carried out at a test system pH of 7.5, the concentrations of sodium caprylate necessary to completely inhibit fungal growth for 3 weeks were 0.1 percent for *T. rubrum*, *E. floccosum*, and *M. audouinii*, and 1.0 percent for *T. mentagrophytes* (Ref. 13). The same concentrations were also fungicidal to these same test organisms, and no growth occurred within 3 weeks after the fungal mats were removed from the culture tubes and replanted on dextrose agar slants.

The investigators also used the Burlingame-Reddish technique to determine the shortest time at pH 7.4 needed to kill fungi exposed to 0.1, 1, and 10 percent concentrations of sodium caprylate. A concentration of 0.1 percent was not fungicidal to any of the dermatophytes, whereas a 1-percent concentration of sodium caprylate was fungicidal after 5 minutes for *T. rubrum* and *T. mentagrophytes*. For *M. audouinii*, however, a 1-percent concentration was fungicidal only after 15 minutes, but a 10-percent concentration sodium caprylate killed *M. audouinii* after a 5-minute exposure time. Spores of *T. mentagrophytes* were not killed by 1:5 dilutions of sodium

caprylate after exposures of 5, 10, and 15 minutes (Ref. 13).

Lyons and Livingood (Ref. 14) performed a test procedure similar to the one described above but with 20 percent caprylic acid in an aerosol containing isopropyl alcohol and propylene glycol. These investigators showed that a 5-minute exposure was required to kill *T. purpureum*. In contrast to earlier studies by Golden and Oster (Ref. 15), these investigators found that a 1-minute contact with 5, 10, or 20 percent caprylic acid did not kill *T. purpureum* (Ref. 14).

Sing and Verhagen (Ref. 16) used 10 percent caprylic acid in an ointment base at pH 6.7 and found a 2.7-cm zone of inhibition after 96 hours in a culture of *T. mentagrophytes*. They observed that the fungus developed resistance to the caprylic acid over exposure periods of 1 to 3 months, and the zones of inhibition of the cultures gradually became smaller over a 4-week period. This observation raised the possibility that fungi living on the skin might develop a certain degree of resistance against caprylic acid and other fatty acids found naturally in sweat.

Vicher et al. (Ref. 17) found that in a subfungistatic concentration of 0.01 percent, sodium caprylate inhibited the metabolism and growth of *T. rubrum* as shown by decreased mycelial dry weight, decreased pigment formation, and altered fatty acid composition of the *T. rubrum*.

The effects of sodium caprylate on *C. albicans* have been extensively studied. In 1962, Watt et al. (Ref. 18) found that the inclusion of 2.5×10^{-3} molar (M) sodium caprylate in Sabouraud's dextrose agar was the maximum concentration of caprylate tolerated for slight growth of *C. albicans*. At this concentration the caprylate inhibited the separation of buds from the parent cells of *C. albicans*, changed the affinity of the yeast cells for staining, and caused enlargement of the nuclei of the cells and buds (Ref. 18). Sodium caprylate was bound to the cells within 5 minutes and began to inhibit them within that time. As the concentration of sodium caprylate was increased from 0.0025 to 0.1 M, the cellular integrity of *C. albicans* was progressively lost, with disorganization and collapse of the cells, leakage of important cellular constituents, and ultrastructural changes in cytoplasmic organelles (Ref. 19).

Tsukahara (Ref. 20) suggested that the adsorption of caprylic acid to the yeast cells must be extremely strong and specific because once the cells of *C. albicans* are exposed to caprylic acid, even rapid washing with distilled water does not affect its fungicidal activity. He

also found the minimal fungistatic and fungicidal concentrations of caprylic acid at pH 5.6 to be 1/1,600 M and 1/400 M, respectively. Tsukahara also showed that *C. albicans* cells were completely killed by treatment with 10^{-3} M caprylic acid for 10 minutes in a phosphate buffer solution at pH 5.91. However, he noted a sharp drop in fungicidal activity between pH 6.24 and 6.64 after 10 to 60 minutes of treatment with caprylic acid. Caprylic acid did not show fungicidal activity above pH 6.98 during a 1-hour exposure. After 24 hours of exposure, however, complete suppression was noted. Tsukahara concluded that caprylic acid should be used in an acid buffered solution at a pH below 6.24. It is interesting to note that Keeney, Ajello, and Lankford (Ref. 13) reported that at pH 7.4 the fungistatic and fungicidal concentrations of sodium caprylate against *C. albicans* were 0.1 and 1 percent, respectively.

In 1941, Cowles (Ref. 21) discovered that the fatty acids including sodium caprylate, were bactericidal at low pH values. This activity increased with increasing chain length of the fatty acids. In a later study, the concentration of caprylic acid necessary to inhibit the growth of *S. aureus* at pH 6.5 was reported to be 0.06 percent (compared with concentrations of 0.015 and 0.009 percent required to inhibit the growth of *T. interdigitale* and *T. purpureum*, respectively) (Ref. 3).

The Panel is aware of only two clinical studies in which caprylates were used as a single active ingredient to treat dermatophytic fungal infections (Refs. 10 and 22). In 1945, Keeney et al. (Ref. 10) used a 10-percent sodium caprylate ointment (carbawax base) in a controlled study to treat 91 midshipmen with athlete's foot at the U.S. Naval Academy. Forty-six men used the caprylate ointment; the other 45 used the ointment base alone. Athlete's foot was diagnosed by a positive KOH preparation and clinical signs and symptoms before beginning the study. Two cultures were also taken from each participant before beginning treatment. Of the 91 men, 57.3 percent (52/91) eventually had positive cultures, 5.8 percent (5/91) of which were positive for *C. albicans*.

The men were told to apply the ointment to the feet every evening and remove it in the morning. Followup examinations with KOH preparations were performed once weekly for 6 weeks. After the first 2 weeks, 43 percent (17/40) of the caprylate-treated group were clinically clear; only 27.5 percent (11/40) of this group still had positive KOH preparations. In contrast, only 2 percent of the control group had

cleared, and 74.3 percent (29/39) still had positive KOH preparations.

The best results in this study were seen after 4 weeks of treatment in the caprylate-treated group: 64 percent (25/39) of the men were symptomatically clear, and only 9.3 percent (4/43) had positive KOH evidence of fungi. These results contrasted with the 4-week results of the control group where only 8 percent (3/37) of the men were clinically clear and 56.7 percent (19/33) had positive KOH preparation. Interestingly, after the 4-week period the participants apparently became indifferent to following instructions and treatment became erratic. This resulted in a relapse of clinical symptoms in 76 percent (25/33) of the treated group in the fifth week of treatment, although only 14.2 percent (6/42) had positive KOH preparations at this time.

After the sixth week of treatment, 50 percent (19/38) of the treated group were again clear. This success contrasts sharply with the control group in which only 13 percent (5/39) of the men were clear after 6 weeks. No irritation or sensitization was reported even when the caprylate ointment was applied to denuded skin. Itching was also relieved soon after application of the sodium caprylate ointment. Although the results obtained with the caprylate ointment appear to be significantly better than those obtained with the ointment base, they must be viewed in light of the following inadequacies in study design: (1) No double-blinding, (2) no lag period after treatment stopped, and (3) no followup cultures.

In 1946, Hopkins et al. (Ref. 22) reported the use of a 5-percent sodium caprylate ointment in infantry soldiers at Fort Benning, Georgia, in hot, humid weather. This report was part of a large, uncontrolled study using 7,500 volunteers to test over 70 fungicides. The criteria for cure were strictly clinical and included the disappearance of itching, scales, and vesicles. A KOH preparation was performed at each visit to determine whether the patient was "fungus negative." A fungal culture was obtained before beginning treatment, but the results were not reported.

Among 44 men treated with 5 percent sodium caprylate ointment for 1 to 2 weeks, 27 percent (12/44) became clinically clear, 45 percent (20/44) were fungus negative, and itching was relieved in 58 percent (26/44). Half of these subjects remained in the study 3 to 4 weeks later. Of these 22 soldiers, 36 percent (8/22) were clinically clear and 83 percent (18/22) were fungus negative. Skin irritation developed in 2 percent (1/

44) of all participants, but was not severe.

As another part of the Fort Benning study, 26 men were treated for jock itch for 1 week only. Of these, 39 percent (10/26) were clinically clear and 48 percent (12/26) were fungus negative. Another subgroup of 15 patients was treated for 2 weeks only. Of these patients, 27 percent (4/15) were clear while 40 percent (6/15) were fungus negative. Hopkins et al. (Ref. 22) concluded that the results obtained from sodium caprylate ointment were similar to those from undecylenic acid.

Keeney (Ref. 23) reported that a 20-percent solution of sodium caprylate adjusted to pH 7.4 was effective in treating *C. albicans* lesions in the mouth when applied three to four times daily. He also reported that a 10-percent caprylate jelly appeared promising in the treatment of vaginal *C. albicans* infections.

In 1946, Keeney (Ref. 11) presented two detailed case reports in which caprylates were used successfully to treat candidiasis: A 20-percent aqueous solution of sodium caprylate completely cleared oral candidiasis of 6 months' duration in a 2-year-old child after 20 days of treatment. Similar results were noted in five other children with similar oral lesions. In addition, a 47-year-old woman with extensive candidiasis of the mouth, vagina, neck, arms, hands, thighs, and buttocks was treated with various dosage forms of 10 percent sodium caprylate. She was completely cleared in about 2 months.

Reich et al. (Ref. 24) reported the results of the treatment of 93 women with vaginitis caused by *C. albicans*. Each patient was seen twice weekly and treated intravaginally with 20 percent aqueous sodium caprylate and a cream and powder containing 10 percent sodium caprylate and 5 percent zinc caprylate. In addition, each patient douched nightly with dilute caprylate solution and inserted caprylate cream intravaginally. Fungal cultures were repeated weekly, and the patients were instructed not to douche within 24 hours before culture. A "cure" required three consecutive negative cultures. Culture results were negative in 62.3 percent (58/93) after 1 week, 70 percent (65/93) after 2 weeks, 76.4 percent (71/93) after 3 weeks, and 86.2 percent (80/93) after 5 weeks. Cultures of over half of the patients became negative after 7 days and remained negative throughout the following weeks. The treatment failed in 14 percent (13/93) of the patients. Reich et al. concluded that caprylic acid was a very effective agent for the treatment of vaginal candidiasis and noted the following advantages of caprylic acid:

"marked fungistatic and fungicidal action, ready penetration of epithelial layers, and considerable bacteriostatic effect on *Staphylococcus aureus* and beta-hemolytic streptococcus."

In 1954, Neuhauser (Ref. 25) administered a caprylic acid-resin complex in capsule form to treat intestinal candidiasis in two patients with severe diarrhea. One patient received a dose of 115 mg caprylic acid four times a day, and the other patient received a dose of 121 mg caprylic acid four times a day. Both patients improved dramatically within 1 week. Treatment was continued for about 1 month, at which time stool cultures were negative for *C. albicans*. No undesirable drug-related side effects were observed.

The Panel concludes that sodium and zinc caprylate should be placed in Category III for clinical effectiveness in the OTC treatment of athlete's foot, jock itch, and ringworm. The Panel notes that the controlled study by Keeney et al. (Ref. 10) in 1945, although it does not meet all of the criteria suggested elsewhere in this document for clinical testing of antifungal products, represented a well-designed study for its time. Nonetheless, further evidence of effectiveness is needed to fully assess the caprylates.

(3) *Proposed dosage*—(i) *Concentration*. Sodium caprylate and zinc caprylate may be used alone or in combination to equal a total caprylate concentration of 10 to 20 percent.

(ii) *Directions for use*. See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation*. The Panel recommends one double-blind, placebo-controlled clinical trial to determine the effectiveness of the caprylates in the treatment of athlete's foot, jock itch, and ringworm. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

In addition, the Panel concludes that the caprylates have the added desirable attribute of significant *in vitro* activity against *C. albicans*, which is often present in jock itch but less commonly found in athlete's foot. The Panel knows of no double-blind, controlled studies in which caprylates are compared to an inactive control, such as the ointment base, in the treatment of *C. albicans*

infections. Consequently, the Panel would require such a study before a product containing caprylates could be labeled as effective against *C. albicans* infections of the skin.

References

- (1) Peck, S. M., and W. R. Russ, "Propionate-Caprylate Mixtures in the Treatment of Dermatophytes, with a Review of Fatty Acid Therapy in General," *Archives of Dermatology and Syphilology*, 61:601-613, 1947.
- (2) Kiesel, A., "Recherches sur l'action de Divers Acides et Sels Acides sur le Developpement de *L'Aspergillus Niger*," *Annales de L'Institut Pasteur*, 27:391-420, 1913.
- (3) Wyss, O., B. J. Ludwig, and R. R. Joiner, "The Fungistatic and Fungicidal Action of Fatty Acids and Related Compounds," *Archives of Biochemistry*, 7:415-425, 1945.
- (4) Peck, S. M., and H. Rosenfeld, "The Effects of Hydrogen Ion Concentration, Fatty Acids and Vitamin C on the Growth of Fungi," *Journal of Investigative Dermatology*, 1:237-265, 1938.
- (5) Peck, S. M., et al., "Role of Sweat as a Fungicide, with Special Reference to the Use of Constituents of Sweat in Therapy of Fungus Infections," *Archives of Dermatology and Syphilology*, 39:126-146, 1939.
- (6) Hoffman, C., T. R. Schweitzer, and G. Dalby, "Fungistatic Properties of the Fatty Acids and Possible Biochemical Significance," *Food Research*, 4:539-545, 1939.
- (7) Christensen, H. E., "The Toxic Substances List, 1973 Edition," United States Department of Health, Education, and Welfare, Rockville, MD, p. 673, 1973.
- (8) Dreisbach, R., "Handbook of Poisoning: Diagnosis and Treatment," 7th Ed., Lange Medical Publications, Los Altos, CA, p. 236, 1971.
- (9) Sax, N., "Dangerous Properties of Industrial Materials," 3d Ed., Van Nostrand Reinhold Co., New York, p. 530, 1968.
- (10) Keeney, E. L., et al., "Sodium Caprylate. A New and Effective Treatment for Dermatophytosis of the Feet," *Bulletin of the Johns Hopkins Hospital*, 77:422-436, 1945.
- (11) Keeney, E. L., "Sodium Caprylate. A New and Effective Treatment for Moniliasis of the Skin and Mucous Membranes," *Bulletin of the Johns Hopkins Hospital*, 78:333-339, 1946.
- (12) Cohen, R., "Four New Fungicides for *Coccidioides Immitis*," *Archives of Pediatrics*, 68:259-64, 1951.
- (13) Keeney, E. L., L. Ajello, and E. Lankford, "Studies on Common Pathogenic Fungi and on *Actinomyces Bovis*," *Bulletin of the Johns Hopkins Hospital*, 75:377-392, 1944.
- (14) Lyons, R. E., and C. S. Livingood, "Laboratory Test for Evaluation of Fungicidal Solutions," *Archives of Dermatology and Syphilology*, 68:566-571, 1953.
- (15) Golden, M. J., and K. A. Oster, "Studies on Alcohol-Soluble Fungistatic and Fungicidal Compounds. II. Evaluation of a Fungicidal Laboratory Test Method," *Journal of the American Pharmaceutical Association (Scientific Edition)*, 36:359-362, 1947.
- (16) Sing, T. B., and B. A. Verhagen, "Comparative Investigation into the

Fungistatic Action of Fatty Acids and Other Anti-Mycotica In Vitro," *Dermatologica*, 99:139-151, 1949.

(17) Vicher, E. E., et al., "The Effect of Sodium Propionate and Sodium Caprylate on the Fatty acid Content of Trichophyton Rubrum," *Mycopathologia*, 35:208-214, 1968.

(18) Watt, L. S., J. N. Adams, and W. J. Payne, "Cytological and Physiological Effects of Sodium Caprylate on *Candida albicans*," *Antibiotics and Chemotherapy*, 12:173-181, 1962.

(19) Adams, J. N., B. G. Painter, and W. J. Payne, "Effects of Sodium Caprylate on *Candida albicans*. I. Influence of Concentration on Ultrastructure," *Journal of Bacteriology*, 86:548-557, 1963.

(20) Tsukahara, T., "Fungicidal Action of Caprylic Acid for *Candida albicans*: Quantitative Observation of the Action," *Japanese Journal of Microbiology*, 5:383-394, 1961.

(21) Cowles, P. B., "The Germicidal Action of the Hydrogen Ion and of the lower Fatty Acids," *Yale Journal of Biology and Medicine*, 13:571-578, 1941.

(22) Hopkins, J. G., et al., "Fungistatic Agents for Treatment of Dermatophytosis," *Journal of Investigative Dermatology*, 7:239-253, 1946.

(23) Keeney, E. L., "Medical Mycology," *Medical Clinics of North America*, p. 328, March 1945.

(24) Reich, W. J., et al., "The Treatment of Monilial Vaginitis with Caprylic Acid," *American Journal of Obstetrics and Gynecology*, 65:180-185, 1953.

(25) Neuhauser, L., "Successful Treatment of Intestinal Moniliasis with Fatty Acid-Resin Complex," *Archives of Internal Medicine*, 93:53-60, 1954.

g. *Chlorothymol*. The panel concludes that there are insufficient data available to permit final classification of the safety an effectiveness of chlorothymol for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Chlorothymol ($C_{10}H_{13}ClO$) is a white, crystalline, granular powder with an aromatic pungent taste and characteristic odor. It becomes yellowish-brown with age and exposure to light. *Chlorothymol* is almost insoluble in water, but soluble in alcohol, ether, benzene, and chloroform (Ref. 7). In marketed products, chlorothymol is present in concentrations of 0.2 to 1.0 percent.

(1) *Safety*. *Chlorothymol* is structurally and physically related to phenol; hence its toxicology is similar to that of phenol. (See part III, paragraph B.1.e. above—Phenolates (phenol and phenolate sodium).) In equal concentrations, however, toxic signs and symptoms for chlorothymol are much less severe than for phenol.

Chlorothymol is apparently strongly irritating to the skin (Ref. 2). Aqueous solutions are so intensely irritating to mucous membranes (Ref. 3) that by

themselves they are almost impossible to use in the mouth in a high enough concentration to be practical (Ref. 4).

The systemic effects of chlorothymol are presumably like those of thymol and phenol. However, it is probably less toxic than either of these two agents (Ref. 3).

(2) *Effectiveness*. *Chlorothymol* is a much stronger antifungal agent than thymol, a characteristic which is indicative of the general principle that substitution of halogen atoms on a phenol ring increases the fungicidal power of the chemical (Ref. 5). In vitro tests with *T. mentagrophytes* indicated that the minimal fungicidal concentration of chlorothymol dissolved in 95 percent ethyl alcohol is 0.1 percent for 5-day cultures and 0.5 percent for 10-day, 15-day, and 20-day cultures. In vitro testing of 10 antifungal agents (including thymol, phenol, salicylic acid, and undecylenic acid) found chlorothymol to be the most powerful (Ref. 2). Using *monilia tropicalis* (*M. tropicalis*) as a test organism, chlorothymol was found to inhibit growth at an aqueous solution concentration of 1:9,000. It did not, however, inhibit growth at a concentration of 1:5,000 if protein from vesicle fluid or blood serum was present. Fungicidal dilutions of chlorothymol were found to be 1:7,000 at 1 minute and 1:8,000 at 30 minutes and 60 minutes (Ref. 5). In another in vitro test of chlorothymol, guinea pig scales infected with *T. mentagrophytes* were immersed in various antifungal agents. After exposures of 5 to 60 minutes, 5 percent *p*-chlorothymol in propylene glycol did not inhibit fungal growth (Ref. 6).

Chlorothymol has phenol coefficients of 63.3 against the typhoid bacillus and 158 against staphylococci. In the presence of organic matter, these phenol coefficient values were reduced to 21.7 and 57.3, respectively (Ref. 7). *Chlorothymol* 0.005 percent (0.5 g in 1,000 mL solution), in combination with thymol, thyme oil, boric acid, eucalyptol, menthol, and methyl salicylate, was once an important antibacterial ingredient of NF antiseptic solution (Ref. 7). The solution was used chiefly as a mouthwash for halitosis.

The Panel is not aware of any clinical studies using chlorothymol as the sole antifungal ingredient.

(3) *Proposed dosage*—(i) *Concentration*. *Chlorothymol* 0.02 to 1 percent.

(ii) *Directions for use*. See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of

athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation*. The Panel recommends complete safety testing of chlorothymol. The Panel also recommends one double-blind, placebo-controlled clinical trial to determine the effectiveness of chlorothymol in the treatment of athlete's foot, jock itch, and ringworm. Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Osol, A., and J. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1102, 1975.
- (2) Golden, M., and K. Oster, "Studies on Alcohol-Soluble Fungistatic and Fungicidal Compounds. II. Evaluation of a Fungicidal Laboratory Test Method," *Journal of the American Pharmacy Association*, 36:359-362, 1947.
- (3) Gosselin, R., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins Co., Baltimore, p. 131, 1976.
- (4) Osol, A., and R. Pratt, "The United States Dispensary," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 300, 1973.
- (5) Kingery, L., R. Williams, and G. Woodward, "Further Studies in Fungicides. Comparative Evaluation of Phenol Derivatives by Modified Laboratory Procedure," *Archives of Dermatology and Syphilology*, 31:452-460, 1935.
- (6) Dolan, M., et al., "A Semi-In Vivo Procedure for Testing Antifungal Agents for Topical Use," *Journal of Investigative Dermatology*, 28:359-362, 1957.
- (7) Cook, E., and E. Martin, "Remington's Practice of Pharmacy," 10th Ed., Mack Publishing Co., Easton, PA, p. 724, 1951.

h. *Chloroxylenol*. The Panel concludes that chloroxylenol is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Chloroxylenol is a halogen-substituted phenolic compound developed in Germany in 1927. *Chloroxylenol* (4-chloro-3,5-dimethyl-phenol) is also known as parachlorometaxylenol or PCMX. It is a white, crystalline powder with a melting point around 115.5° C. One g chloroxylenol dissolves in 3 L of water at 20° C; in hot water it is more soluble. *Chloroxylenol* is also soluble in 95 percent alcohol, ether, benzene, terpenes, fixed oils, and in solutions of alkali hydroxides (Ref. 1).

In submission reviewed by the Panel, chloroxylenol occurs in concentration of 0.5 to 3.75 percent.

(1) *Safety.* The oral LD₅₀ of chloroxylenol in rats is 5 g/kg and in mice, 3.6 g/kg. The oral minimal lethal dose is 2.8 g/kg in the rat and 1.5 g/kg in the mouse. Rats can tolerate 10 consecutive daily oral doses of 20 to 30 mg/kg. The topical minimal lethal dose in the rabbit is 4 g/kg (5 to 7 daily doses). Rabbits can tolerate topical application of 2 g/kg daily for 10 days without adverse effects (Ref. 2).

In high concentrations (30 percent chloroxylenol in propylene glycol) this drug may be damaging to the rabbit eye (Ref. 3). But in concentrations normally used in topical antifungal preparations, chloroxylenol may be only a moderate irritant to the eye (Ref. 4).

Several studies have been conducted to assess the safety of chloroxylenol when applied to the skin. Unfortunately, most of these studies have been on the final formulation, which makes assessment of chloroxylenol a little more difficult.

A 30-day topical study was conducted at three dose levels of chloroxylenol (112.5, 360, and 1,200 mg/kg) in rabbits. The low dose was achieved by application of 1.5 mL of 3.75 percent chloroxylenol. Females in the low-dose group lost 0.65 percent body weight, while males gained 10.54 percent. (Control males also gained weight.) The females in the two higher-dose groups did not show this weight loss; rather, they gained 6 percent. No other adverse effects were noted in the group receiving 3.75 percent chloroxylenol (Ref. 2).

Dogs have also been treated topically with solutions of 3.75 percent chloroxylenol (0.5 mL/kg) for 1 year. Interim data after 8 months reveal no evidence of toxicity at this level (Ref. 2).

Rabbits were dosed topically with 1.8 percent and 18 percent solutions of chloroxylenol in propylene glycol at a rate of 1.0 mL/kg/day. Fifteen applications were made of abraded skin, 65 applications on intact skin. No gross signs of systemic toxicity were noted in any test animals. The 18-percent chloroxylenol solution caused moderate to extreme skin irritation, the 1.0-percent chloroxylenol caused only minimal skin irritation characterized by mild erythema and desquamation. These same signs were also noted in control animals receiving only propylene glycol vehicle. Representative tissue samples at autopsy showed no pathologic changes attributable to chloroxylenol treatment. (Ref. 5).

A patch test using 163 randomly assigned subjects (71 females, 92 males) showed that pure chloroxylenol did not irritate or sensitize under the test conditions (Ref. 3). In a repeated insult patch test involving 64 subjects, a 2-

percent solution of chloroxylenol in propylene glycol proved too irritating for continued application. One to three applications produced irritation resembling a chemical burn. In this same test, a 0.2-percent solution of chloroxylenol in propylene glycol irritated the skin no more than the vehicle (Ref. 3).

From these studies, it appears that high concentrations of chloroxylenol in a vehicle in which it is soluble can severely irritate the skin. In 2 percent concentrations, chloroxylenol apparently also retains some irritation potential, though considerably lessened, but a 1.8-percent solution in propylene glycol is no more irritating than the vehicle. It may therefore be concluded that in the concentrations used in athlete's foot preparations, chloroxylenol would not be irritating to the point of precluding its use.

In an inhalation study (Ref. 3) of aerosol chloroxylenol, rats were exposed to either 205 mg/L or 988 mg/L of aerosol formulation for 1 hour. (This would be 0.1 mg/L and 5 mg/L of chloroxylenol. Stated differently, if a rat inhales at the rate of 100 times per minute with a tidal volume of approximately 1.5 mL, then the lung exposure to chloroxylenol would be 3.6 mg/kg/h and 180 mg/kg/h, respectively.) The low dose resulted in no deaths. The high dose resulted in 6 deaths out of 10 animals during the exposure period and one death among the survivors during a 14-day observation period. The vehicle for the aerosol was ethanol, and the aerosolizer was a mixture of fluorinated hydrocarbons. The Panel recognizes that the vehicle may affect the final results of this study. Because deaths did not occur in the low-dose group at the same rate as the high-dose group, this was considered not to be the case.

It has recently been reported that chloroxylenol in doses in the general use range is rapidly and completely absorbed into systemic circulation from the oral, topical, or subcutaneous routes of administration (Ref. 6). A study was conducted comparing the oral and topical absorption, distribution, excretion, and biotransformation of C¹⁴-chloroxylenol in rats (Ref. 6). A 48-mg/kg dose of C¹⁴-chloroxylenol was applied to the shaved and abraded backs of the rats. The chloroxylenol was in a commercial product solution which was diluted to 25 percent. The solution was applied to a 25-cm² pad backed by aluminum foil and was allowed to stay in place for 6 hours. The orally dosed rats were given the same 25-percent solution (48 mg/kg chloroxylenol).

At the appropriate times after administration, the rats were killed.

Blood samples were taken, and urine and feces were collected for excretion analysis. Orally administered chloroxylenol was absorbed faster and more completely than the topically administered dose. About one-half of the topically applied chloroxylenol was absorbed in 6 hours with peak blood levels attained 2 hours after application. Peak plasma levels from oral doses occurred after 30 minutes and were about five times higher than those obtained from dermal application. Plasma half-life from the oral chloroxylenol was 60 minutes. Of the total urinary metabolites, 75 percent was chloroxylenol glucuronide, 13 percent was chloroxylenol sulfate, 10 percent was hydroxy-chloroxylenol glucuronide, and 2 percent was hydroxy-chloroxylenol sulfate (Ref. 6). The Panel considers this a well-conducted experiment that demonstrates the rather rapid detoxification of absorbed chloroxylenol when administered in relatively low doses on a single, acute dosing basis.

In a 90-day oral study in rats (Ref. 2), chloroxylenol was tested at dose levels of 8-mg/kg, 24 mg/kg, and 75 mg/kg. Propylene glycol was administered to the vehicle control group. Animals in the 8-mg/kg and control groups showed no effect from treatment. Groups receiving 24 or 75 mg/kg chloroxylenol showed treatment effects which included slight hemoconcentration, leucocytosis, monocytosis, and a few cases of nasal or ocular discharge.

Chloroxylenol was given orally in chronic studies in rats. Rabbits and dogs were treated topically. In these studies the most obvious signs of toxicity were decreased weight gain, gastrointestinal distress, sedation, liver degeneration and thickened, exudative skin (Ref. 2).

A diluted commercial solution of chloroxylenol was used in subchronic and chronic studies in dogs (Ref. 7). Doses of 120 mg/kg, 60 mg/kg, and 1.2 mg/kg chloroxylenol were administered orally to beagles for 13 weeks. The only dose-related effect observed was an increase in liver weight. Occasional vomiting was observed in the two higher-dose groups, but this could have been vehicle induced. Although this study is inconclusive because of the possible influence of the vehicle, it appears to the Panel that relatively low doses of chloroxylenol can be systemically tolerated, at least over a 13-week period. The Panel is concerned about the effect of chronic administration on the liver, but does not consider that topical application of chloroxylenol to small areas of the skin

over short periods of time would result in liver damage.

Zondek (Ref. 8) studied the use of chloroxylenol in humans, using the oral, percutaneous, and intramuscular routes of administration. He administered up to 94 g chloroxylenol over a 7-day period in an attempt to treat urogenital infections. Zondek noted that no toxic effects were seen in any of the cases he treated with chloroxylenol.

Zondek and Finkelstein (Ref. 9) studied the absorption, metabolism, and excretion of chloroxylenol administered percutaneously to 11 humans. The chloroxylenol was dissolved in an alcohol-oil mixture and was applied as a 40-percent solution of chloroxylenol. The area or size of application was not specified. Five g chloroxylenol was necessary to produce detectable blood levels, while 8 g applied topically resulted in blood levels of 10 µg/mL after 3 hours and 40 µg/mL after 24 hours. A 20-g dose resulted in 40 µg/mL in 30 minutes and 10 µg/mL remained 72 hours after dosing. The researchers stated that percutaneous administration of up to 30 g daily could be given without toxic effects.

Ten g chloroxylenol dissolved in olive oil was administered orally to one patient. Blood levels were found to be 20 µg/mL after 1 hour, 14 µg/mL after 24 hours, and 0 µg/mL after 48 hours (Ref. 9).

Twelve patients were injected intramuscularly with a 10-percent solution of chloroxylenol in olive oil containing 2 percent anesthesin (benzocaine). The blood was analyzed two to six times over a 48-hour period. Blood concentrations varied according to dose (either 1 or 2 g chloroxylenol), but blood levels never exceeded 40 µg/mL, which occurred in a patient with hepatitis. When 2 g chloroxylenol was given intramuscularly, blood concentrations of 12 to 30 µg/mL were observed 1 to 2 hours after injection. Forty-eight hours after injection, no chloroxylenol was present in the blood (Ref. 9). Zondek (Ref. 8) reported that following intramuscular injection, 10 percent was excreted in the urine as free chloroxylenol, 14 percent as chloroxylenol glucuronide, and 17 percent as chloroxylenol sulfate.

These studies in humans are rather old (early 1940's), and the mode of treating urinary infections described in these reports is no longer used. Nevertheless, these studies demonstrate that blood levels of chloroxylenol possibly attained from topical application to athlete's foot, jock itch, or ringworm would not be toxic. Human patients have been given doses of chloroxylenol by the oral, parenteral, or

percutaneous routes that are larger than would be used in antifungal products. Some of these large doses were administered over periods of at least 1 week, and no toxic effects were observed. Even though some cases of minor irritation have been reported, the Panel concludes that chloroxylenol in concentrations of 3.75 percent or less is safe for OTC antifungal use in treatment of athlete's foot, jock itch, or ringworm.

(2) *Effectiveness.* Chloroxylenol has been shown to be active in vitro against fungi and gram-positive and gram-negative bacteria. It was tested in a propylene glycol vehicle in tenfold serial dilutions from 8 mg/mL to 8×10^{-8} mg/mL. Chloroxylenol killed *C. Albicans* at 8×10^{-1} mg/mL, but growth was seen at 8×10^{-2} mg/mL. Against *T. Mentagrophytes*, chloroxylenol inhibited growth only at the highest concentration (8 mg/mL). The minimal inhibitory concentration of chloroxylenol in propylene glycol is reported as 0.125 mg/mL against *C. Albicans* and 1.0 mg/mL against *T. mentagrophytes* (Ref. 10).

The Panel reviewed in vitro data on 4.8 percent chloroxylenol in a pine oil-soap vehicle (Refs. 6 and 7). The submissions noted that studies on chloroxylenol alone are difficult to do because of the very low solubility of this ingredient in water. In vitro data included studies that had used the modified A.O.A.C. (Association of Official Agricultural Chemists) phenol coefficient test and determination of killing dilutions for a variety of species of fungi and bacteria. The comparative phenol coefficient test is appropriate because chloroxylenol is a substituted phenol. Spore suspensions of dermatophytic fungi were used in these tests.

Chloroxylenol is usually included in products for its antibacterial activity. The results of the studies mentioned above show that chloroxylenol has much greater activity against gram-positive organisms than gram-negative organisms. The most resistant strain was *P. aeruginosa*.

The killing dilution (defined as the extent to which the product may be diluted and still kill the test organism within 10, but not 5, minutes) was determined after velvet transfer of the organism from the skin. The results showed killing dilutions of 1:300 for *T. rubrum*, 1:160 for *T. mentagrophytes*, 1:200 for *E. floccosum*, and 1:125 for *C. albicans*. Using the modified A.O.A.C. testing procedure, the following killing dilutions were obtained: 1:130 for *C. albicans*, 1:150 for *M. canis*, *T. mentagrophytes*, and *T. interdigitale*, and 1:300 for *T. rubrum*. *C. albicans* was the most resistant organism, but

Candida species as a whole were more susceptible to chloroxylenol than dermatophyte spores. The minimal inhibitory concentrations are as follows: *C. albicans* 16,000 µg/mL, *T. rubrum* 48,000 µg/mL, *M. canis* 48,000 µg/mL, and *T. interdigitale*, 48,000 µg/mL (Ref. 7).

The effect of organic material (serum) on the antifungal activity of chloroxylenol was determined. Dilutions of chloroxylenol in distilled water, 5 percent serum in distilled water, and in some cases 20 percent serum in distilled water were tested. The results expressed in µg/mL in distilled water, 5 percent serum, and 20 percent serum, respectively, are as follows: *T. interdigitale*—3,125, 3,125, and 2,400; *C. albicans*—2,700, 4,000, and 1,040; *M. canis*—3,125 and 2,500; *T. mentagrophytes*—3,125 and <800; *T. rubrum*—6,250 and 4,800. As expected, the activity of chloroxylenol decreased in the presence of organic material (Ref. 7).

The Panel concludes that the susceptibility of the dermatophytes to chloroxylenol is not great. Because of the very high minimal inhibitory concentration values obtained, very high concentrations of chloroxylenol would have to be used in formulations to obtain any antifungal effect.

The Panel was able to locate only one published study (Ref. 11) examining the effectiveness of chloroxylenol in the treatment of athlete's foot. In this study by Walker, 128 patients with clinically diagnosed athlete's foot were treated with a 0.5-percent chloroxylenol solution containing various other ingredients (thymol, menthol, acetone, and wormwood). Diagnosis was confirmed by positive KOH preparation or positive culture in 112 patients. Shortcomings of the study design include the lack of controls and double-blinding and the failure to collect adequate followup data after therapy was discontinued. Patients were treated for varying lengths of time, ranging from 1 to 9 weeks. The author reported that "92 percent had symptoms cleared and improvement shown; 8 percent had poor results." But he gave no specific data on clinical appearance, KOH, and culture growths.

The Panel concludes that the effectiveness of chloroxylenol is questionable because of the lack of a controlled clinical trial.

(3) *Proposed dosage*—(i) *Concentration.* Chloroxylenol 0.5 to 3.75 percent.

(ii) *Directions for use.* See part III, paragraph A.2. above—Category I Labeling.

(4) **Labeling.** The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) **Evaluation.** The Panel recommends one double-blind, placebo-controlled clinical trial to determine the effectiveness of chloroxylenol in the treatment of athlete's foot, jock itch, and ringworm. This study should be conducted in accordance with the guidelines set forth for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 279, 1976.
- (2) OTC Volume 070206.
- (3) OTC Volume 070194.
- (4) OTC Volume 070042.
- (5) OTC Volume 070195.
- (6) OTC Volume 070201.
- (7) OTC Volume 070202.
- (8) Zondek, B., "The Excretion of Halogenized Phenols and Their Use in the Treatment of Urogenital Infections. Percutaneous Chemotherapy," *Journal of Urology*, 8:747-758, 1942.
- (9) Zondek, B., and M. Finkelstein, "Blood Concentration of p-Chloro-xylene in Man Following Parenteral, Percutaneous and Rectal Application," *Proceedings of the Society of Experimental Biology and Medicine*, 61:200-202, 1946.
- (10) OTC Volume 070227.
- (11) Walker, M. H., "A Chronicle of Tinea Pedis and Chloroxylenol for Control of Tinea Pedis," *Journal of the American Podiatry Association*, 52:737-745, 1962.

1. **Cresols (*m*-cresol and secondary amyltricrosols).** The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of cresols (*m*-cresol and secondary amyltricrosols) for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Cresols are methyl derivatives of phenol. Derived from coal tar, cresols are separated from phenol by fractional distillation (Ref. 1). They are soluble in organic solvents and fixed alkali hydroxides, but are relatively insoluble in water (Ref. 2).

Cresol is also known as cresylic acid and tricresol, as it contains a mixture of three chemical isomers of cresol. Cresol NF contains not more than 5.0 percent phenol. It is a colorless or yellowish-brown liquid which turns brown with aging and exposure to light and must be preserved in light-resistant containers (Ref. 3).

(1) **Safety.** Cresol is structurally and pharmacologically related to phenol and is just as toxic. (See part III, paragraph

B.1.e. above—Phenolates (phenol and phenolate sodium).) The symptoms and treatment of cresol poisoning are also similar to those of phenol (Refs. 2 and 4).

For *m*-cresol the oral LD₅₀ in rats is 242 mg/kg and the LD₅₀ via skin absorption is 620 mg/kg (Ref. 5).

Cresol is a general protoplasmic poison and associates with protein (Ref. 6). Many cases of cresol poisoning have been reported. In humans the oral ingestion of 8 g or more produces rapid circulatory failure and death. After ingestion, there is a severe burning sensation in the mouth and upper abdomen, difficulty in swallowing, vomiting, and diarrhea. White spots are seen on the mucous membranes. Unconsciousness and circulatory collapse then follow. If the patient survives, jaundice, reduced excretion of urine, and uremia may develop (Ref. 2). Chronic poisoning from oral or percutaneous absorption may produce digestive disturbances, neurological disorders, vertigo, and skin eruptions (Ref. 6).

Cresol is also a skin irritant and may cause erythema, a burning sensation, or numbness (Ref. 2).

One of the submissions to the Panel (Ref. 7) was for a product composed of camphorated *m*-cresol. It was stated that an inter-molecular complex was formed between camphor (66 percent) and *m*-cresol (22 percent). According to Francis (Ref. 8) such a complex is possible. Francis devised techniques to determine the amount of free cresol in such a complex and stated that "a mixture containing 20% total *m*-cresol by weight (26 mole percent) seems to contain about 1½% free *m*-cresol." He further stated that the low content of free cresol probably accounted for the high tolerance which wounds and tissues showed to these mixtures. The Panel believes that conclusive evidence that a complex forms between *m*-cresol and camphor is lacking.

It appears to the Panel that the real significance concerning the safety of camphor-cresol combinations is summed up in the following conclusion to Francis' paper: "The fact that these are equilibrium mixtures means that they will liberate free phenol or cresol as fast as that originally present is consumed and this may explain their known antiseptic and surface anesthetic effects."

Therefore the Panel concludes that in the combination of 66 percent camphor and 22 percent *m*-cresol all of the cresol would be available for absorption and thus has a significant toxicity potential. (For the Panel's discussion of camphor, see part III, paragraph B.1.a. above—Camphor.)

The Panel concludes that more data are needed to determine the safety of cresols for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. In marketed products, secondary amyltricrosols are present in a concentration of 0.1 percent and *m*-cresol, 22 percent. However, the Panel concludes that not enough safety data are available to justify a 22-percent concentration and proposes an upper limit for cresols of 2.2 percent.

(2) **Effectiveness.** Cresol is more active against bacteria than phenol and has a phenol coefficient of 2 to 3. The three chemical isomers of cresol (*m*-cresol, *o*-cresol, *p*-cresol) vary little in bactericidal properties (Ref. 1). Although cresol is a fairly effective antibacterial against common pathogenic bacilli, it is less active agent against cocci (Ref. 4). Bacterial spores are killed only after long exposure to high concentrations of cresol (Ref. 1).

Because cresol is relatively insoluble in water, it is usually marketed as saponated cresol solution (compound cresol solution). This consists of 50 percent cresol in saponified linseed oil or other vegetable oils (Ref. 4). This solution mixes readily with water to produce a milky mixture, containing 3 to 5 percent concentrations of cresol and is used for disinfecting inanimate objects, such as hospital floors, dishes, and instruments (Refs. 3 and 4). Saponated cresol solution has also been used as a handwash at 2 percent concentration (1 percent cresol), as a vaginal douche at 0.2 percent concentration (0.1 percent cresol), and on wounds at 1.0 percent concentration (0.5 percent cresol). Cresol has also been used in concentrations of 0.25 to 0.5 percent as a bacteriostatic agent in parenteral solutions (Ref. 2).

The local irritant action of *m*-cresol has been much reduced by esterification with acetic acid to produce *m*-cresylacetate, a colorless, oily liquid with characteristic odor. In the 1940's and 1950's, *m*-cresylacetate served as a local antiseptic and mild analgesic when applied to mucous membranes of the upper respiratory tract (Ref. 1). It was specifically used to treat infections of the nose and ear, including fungal infections of the external auditory canal (Refs. 9 and 10). It was also used to treat infected root canals and tooth sockets. Athlete's foot was also treated with *m*-cresylacetate (Ref. 9). It was relatively nontoxic and caused little irritation to skin or mucous membranes, even in full strength (Ref. 1).

The cresols have been regarded as good disinfectant agents against vegetative fungi as well as against

bacteria, although they are ineffective against spores (Ref. 3). In 1933, phenol coefficients for cresol were determined to be 1 for *T. gypseum* and 3 for *Monilia albicans* (*M. albicans*) (Ref. 11). Later, the fungicidal dilutions of cresol against *M. tropicalis* were determined to be 1:180, 1:200, and 1:300 after exposures of 1, 30, and 60 minutes, respectively (Ref. 12). In 1955, cresol disinfectant 0.25 to 5 percent was found highly effective in inhibiting the growth of *T. interdigitale* on matchstick fragments contaminated through direct contact with cultures. The exposure times ranged from 5 minutes to 24 hours, and cultures were performed both with and without a 1-minute washing in water (Ref. 13). In a later study, the skin of guinea pigs was artificially infected with *T. mentagrophytes*. The resulting scales which formed on the skin were used in the in vitro testing of a 1-percent cresol solution. This solution prevented the growth of *T. mentagrophytes* on infected guinea pig scales after immersion periods of 30 and 60 minutes, but not after 5- and 15-minute immersions (Ref. 14).

Cresol has not been widely used as an antifungal agent on skin. It has been used in prophylactic footbaths for athlete's foot (Ref. 15). The Panel is aware of only two clinical studies, neither one controlled, in which cresols were used to treat athlete's foot.

At Fort Benning, Georgia, tetrabromcresol in unstated concentrations was used to treat 41 soldiers with athlete's foot (Ref. 16). After 1 to 2 weeks, itching had been relieved in 45 percent of 36 cases; 8 percent were clinically clear and 36 percent had negative KOH examinations. After 3 to 4 weeks of treatment, only 5 percent of 21 cases examined were clinically clear although 57 percent were KOH negative. Severe irritation occurred in 2 percent of the cases. Tetrabromcresol seemed to give a low percentage of satisfactory results, but too few cases were studied to be conclusive.

The other study was done in a penitentiary (Ref. 17) where 69 cases of athlete's foot were treated with an unstated concentration of *m*-cresylacetate. Of these cases, 16 were cured, 7 were nearly cured, 28 improved, 16 remained stationary, and 2 were worse. Overall, *m*-cresylacetate was concluded to make an "excellent showing" with improvement or cure in 73.7 percent of the cases. Skin irritation occurred in only one case, and patients did not complain of the odor of *m*-cresylacetate. Although fungal cultures were done before treatment began,

culture results were not correlated with treatment results. No KOH examinations were performed, and no double-blind controls were included. However, *m*-cresylacetate was considered superior to both boric acid powder and Whitfield's ointment.

The Panel concludes that the effectiveness of the cresols is questionable because of the lack of a controlled clinical trial.

(3) *Proposed dosage*—(i) *Concentration*. *m*-Cresol and secondary amyltricresols may be used alone or in combination to equal a total cresol concentration of 0.1 to 2.2 percent.

(ii) *Directions for use*. See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation*. The Panel recommends the following toxicity studies for cresols: (1) Absorption from small areas of application to broken and intact skin; (2) local effects on wound healing; (3) irritation potential; and (4) potential for hypersensitivity. The Panel also recommends one double-blinded, placebo-controlled clinical trial to determine the effectiveness of cresols in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Cook, E., and E. Martin, "Remington's Practice of Pharmacy," 10th Ed., Mack Publishing Co., Easton, PA, p. 730, 1951.
- (2) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 355, 1973.
- (3) Osol, A., and J. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1102, 1975.
- (4) Goodman, L., and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., Macmillan Publishing Co., Inc., New York, p. 991, 1975.
- (5) Fairchild, E., "Registry of Toxic Effects of Chemical Substances," 1977 Ed., Volume II, United States Department of Health, Education, and Welfare, Cincinnati, p. 311, 1977.
- (6) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 335, 1976.
- (7) OTC Volume 070186.
- (8) Francis, A. W., "Physical Evidence of Association of Camphor with Phenol and the Cresols," *Journal of the American Pharmaceutical Association* (Scientific Edition), 30:229-240, 1941.
- (9) Lewis, A. J., "Modern Drug Encyclopedia and Therapeutic Index," 11th

Ed., Reuben H. Donnelley Corp., New York, p. 301, 1970.

(10) Pillsbury, D., M. Sulzberger, and C. Livingood, "Manual of Dermatology," W. B. Saunders Co., Philadelphia, p. 179, 1942.

(11) Emmons, C., "Fungicidal Action of Some Common Disinfectants on Two Dermatophytes," *Archives of Dermatology and Syphilology*, 28:15-21, 1933.

(12) Kingery, L., R. Williams, and G. Woodward, "Further Studies in Fungicides. Comparative Evaluation of Phenol Derivatives by Modified Laboratory Procedure," *Archives of Dermatology and Syphilology*, 31:454-460, 1935.

(13) Wustenberg, J., "Disinfectant Value of Various Crude Disinfectants on Epidermophyton Kaufman-Wolff," *Zeitschrift für Hygiene und Infektionskrankheiten*, 141:460-468, 1955.

(14) Dolan, M., et al., "A Semi-In Vivo Procedure for Testing Antifungal Agents for Topical Use," *Journal of Investigative Dermatology*, 28:359-362, 1957.

(15) Perkin, H., "Fungicides in Medicine and Pharmacy," *The Pharmaceutical Journal*, 162:471-472, 1949.

(16) Hopkins, J., et al., "Fungistatic Agents for Treatment of Dermatophytosis," *Journal of Investigative Dermatology*, 7:239-253, 1946.

(17) Weidman, F., and F. Glass, "Dermatophytosis and Other Forms of Intertriginous Dermatitis of the Feet. A Comparison of Therapeutic Methods," *Archives of Dermatology and Syphilology*, 53:213-225, 1946.

J. Dichlorophen. The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of dichlorophen for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Dichlorophen, commonly known as G-4, is a halogenated bis-phenol consisting of two phenolic rings attached by a methylene (CH₂) linkage.

Dichlorophen was first prepared in 1929 (Ref. 1). A light tan, free-flowing powder with a weak phenolic odor, dichlorophen darkens on exposure to bright light. Like other halogenated 2,2'-bis-phenols, including hexachlorophene, dichlorophen is practically insoluble in petrolatum solvents and has very low solubility in water (0.003 g in 100 mL at 25° C). However, dichlorophen is readily soluble in alcohols, glycols, ketones, esters, and ethers (Ref. 2).

(1) *Safety*. Dichlorophen has been formulated for topical veterinary use as a shampoo, a component in flea powders, and for use in ear, eye, and wound medicaments in concentrations of 0.1 to 2.0 percent. It is used orally in veterinary medicine for tapeworms.

Dichlorophen overdosage may cause tremors, depression, and loss of appetite (Ref. 3). The oral LD₅₀ of dichlorophen has been reported to be 1.24 g/kg for

guinea pigs, 2.0 g/kg for dogs, and 1.58 g/kg for mice (Ref. 4).

Dichlorophen was used in over 50 cases of tapeworm in dogs at an oral dose level of 0.18 g/kg body weight. Even though data on absorption from the gastrointestinal tract were not presented, the report stated that dichlorophen appeared to be well tolerated (Ref. 5). In another study (Ref. 6), 133 dogs were given 0.22 g dichlorophen and 0.22 mL toluene per kg body weight as an anthelmintic. No toxicity was observed from repeated doses (frequency or total number of doses were not reported). In a third study, the regimen just described was given to cats. Toxicity was minimal or absent in most animals (Ref. 7).

More recently, Kimbrough (Ref. 8) found an oral LD₅₀ of dichlorophen in peanut oil to be 1,660 mg/kg in female adult rats and 1,500 mg/kg in male adult rats. Signs of toxicity included diarrhea and central nervous system depression. The intravenous LD₅₀ of dichlorophen suspended in saline lecithin administered to adult male rats was reported to be 16.8 mg/kg.

In a two-generation rat reproduction study (Ref. 8), a dietary level as high as 1,000 parts per million (ppm) (50 mg/kg/day) dichlorophen produced no effect. Gross and microscopic examination of the various organs, including the brains of the parents as well as the offspring, showed no morphologic alterations attributable to dichlorophen. The marked disparity between the oral and intravenous LD₅₀ suggested either poor absorption from the gut or rapid breakdown.

The above data tend to suggest no high degree of toxicity from dichlorophen. Nevertheless, the Panel is still concerned that oral studies may not adequately reflect the true toxicity potential of this chemical when administered by other routes.

Dichlorophen has been used as a taeniocide (an agent that destroys tapeworms) in veterinary medicine for years, but is not marketed for oral use in humans in the United States. It is, however, listed in the British Pharmacopoeia. In Europe, adult oral doses of 2 to 3 g every 8 hours for three doses have been used for tapeworm; 1 to 2 g have been used in children. Because dichlorophen exerts a laxative effect, purgatives are not needed afterward. An appreciable number of patients treated with dichlorophen have colic, diarrhea, and nausea lasting 4 to 6 hours. Lassitude is another common symptom (Ref. 9). Dichlorophen sometimes causes hives (route of administration not given). Jaundice and even death have followed very large doses of dichlorophen (Ref.

10). The use of dichlorophen in dentifrices has "in exceptional cases" been followed by inflammation of the mucous tissue of the mouth and inflammation of the tongue and lips. Dermatitis around the mouth may also occur (Ref. 11).

Patch tests of 4 and 12 percent dichlorophen in petrolatum showed no irritation on human skin (Ref. 4). Gosselin et al. report no irritation at concentrations of 1 percent and little irritation at 4 percent (Ref. 12).

There are two reports of allergic contact sensitization caused by dichlorophen-containing ointments and powders used to treat athlete's foot in the United States (Ref. 13) and Germany (Ref. 14). Contact allergy to dichlorophen has also been reported from its use as a preservative in cosmetics (Ref. 15), dentifrices (Ref. 16 and 17), and medicated bandages applied to the lower legs for the treatment of dermatitis associated with varicose veins (Ref. 18). In one study, 48-hour patch testing with 4 percent dichlorophen in petrolatum in 194 humans gave three positive reactions (Ref. 2).

The Panel could not find any studies on the use of dichlorophen on broken skin, such as on athlete's foot or jock itch. Dichlorophen is structurally related to hexachlorophene and certain aspects of toxicity observed in dichlorophen suggest the possibility that dichlorophen, like hexachlorophene, may possibly affect the central nervous system. For example, dichlorophen in large oral doses has caused tremors, depression, loss of appetite, and lassitude in animals. All of these reactions possibly indicate central nervous system activity.

Hanig, Yoder, and Krop (Ref. 19) studied dichlorophen in rats to determine any effect this chemical might have on cerebrospinal fluid pressure as an indicator of possible central nervous system effects. These workers found no correlation between actions resulting in cerebrospinal fluid pressure changes and the degree of chemical similarity to hexachlorophene. They did not specify the dose of dichlorophen and the route of administration, though it may be assumed that hexachlorophene and dichlorophen were treated similarly. This evidence also suggests differences between hexachlorophene and dichlorophen, though it does not answer the question of effect of route of administration on toxicity potential.

The Panel is concerned that potentially toxic amounts of dichlorophen may be absorbed into the bloodstream from topical application for the following reasons: (1) Preparations

for athlete's foot, jock itch, and ringworm may be used for an extended period of time; (2) these areas of application (diseased skin) may afford a significant route for absorption; and (3) occlusion of these areas of application by clothing or shoes may enhance absorption. Therefore, the Panel recommends Category III for safety pending a full assessment of the absorption characteristics of dichlorophen and its toxicity potential from extended use.

(2) *Effectiveness.* The linkage of two phenolic rings greatly increases bactericidal and bacteriostatic potency and generally decreases toxicity and irritancy compared to the corresponding monophenols (Ref. 1). Maximum antibacterial and antifungal activity of a bis-phenol occurs when hydroxyl groups are linked in the ortho positions of each phenolic group, and chlorine is attached in the para position to the hydroxyl groups in each phenolic group (Ref. 20). The presence of chlorine generally increases activity against gram-positive bacteria, but the chlorine must be in the 4-position of each phenolic ring for maximum activity against gram-negative bacteria and fungi (Ref. 2).

Years ago, dichlorophen was found to have special merit as a mildew-proofing agent for fabrics (Ref. 1). Other antifungal uses of dichlorophen have included slime control in paper mills, mold control in meats, and mildew prevention in paper, boards, felt, and rope (Ref. 2).

Dichlorophen is fungicidal and fungistatic against several types of fungi. Fabric has been impregnated with dichlorophen in concentrations of 0.2 to 0.5 percent of fabric weight. This treatment was highly effective against cellulose-decomposing fungi. Dichlorophen is less active against protein decomposers, requiring 1 to 3 percent levels on the basis of material weight to give full mildew protection (Ref. 1).

Less information is available about the antidermatophytic properties of dichlorophen. Shoe dubbing and shoe leather impregnated with dichlorophen 5 percent failed to inhibit growth of either *T. interdigitale* or *E. floccosum* (Ref. 21). In vitro studies indicated that 1 percent dichlorophen in talc was fungistatic against three dermatophytes, with zones of inhibition of 1.1 cm for *T. rubrum*, 0.9 cm for *T. gypsum*, and 1.2 cm for *Trichophyton inguinale* (*T. inguinale*) (Ref. 22). A dilution of 1:2,000 of dichlorophen killed *T. interdigitale* in 10 minutes but not in 5 minutes (Ref. 2). The minimal inhibitory concentration of

dichlorophen against *T. mentagrophytes* was reported to be 6.25 µg/mL (Ref. 23).

The halogenated bis-phenols are generally much more active against gram-positive than gram-negative bacteria. They are markedly bacteriostatic but slow acting, requiring a contact time of several hours to provide reasonable germicidal action. Because phenol coefficients are based on end points of 100 percent kill after a maximum of 15 minutes' contact time, single numerical values cannot be determined for dichlorophen. However, phenol coefficients ranging from 20 to 40 at 20° C and 45 to 62 at 37° C have been determined for dichlorophen. The bacteriostatic dilution of dichlorophen was 1:750,000 against *S. aureus* and 1:25,000 against *Escherichia coli* (Ref. 1). Although a concentration of 1:2,500 of dichlorophen did not kill *S. aureus* in 5 minutes, it did kill *S. aureus* in 10 minutes (Ref. 2). The minimal inhibitory concentration of dichlorophen against *S. aureus* has been reported to be 3.12 µg/mL (Ref. 23). There is no evidence of development of bacterial resistance to dichlorophen. Formulated in soap solutions, dichlorophen has antimicrobial powers equivalent to other phenolic compounds, such as cresol.

The antimicrobial activity of bis-phenols is decreased by the presence of organic matter, although much of the loss is probably overcome through prolonged contact time. The antibacterial and antifungal activity of dichlorophen is also decreased by the presence of nonionic emulsifying agents (Ref. 1). For instance, the growth of *S. aureus* is inhibited by one part of dichlorophen in 2 to 5 million parts of plain broth, but only by 1:1,000 dilutions of dichlorophen if a nonionic detergent is present in the broth (Ref. 2). The antimicrobial activity of dichlorophen in cosmetic and drug formulations containing nonionic detergents must therefore be carefully considered.

Dichlorophen ointment has been used to treat ringworm infections in animals. In 1947, 2 percent dichlorophen in a petrolatum base was used to successfully treat 50 cases of ringworm in cattle (Ref. 24) and was judged superior to topical medications containing iodine, mercury, or sulfur in arresting the spread of *Trichophyton album* infections in cattle (Ref. 25). Later, 2 percent dichlorophen in vanishing cream base or petrolatum was used successfully to treat fungus infections in dogs and cats (Ref. 26). Two percent dichlorophen was reported not to be effective against *Trichophyton verrucosum* infections in cattle (Ref. 27). But in 1964, 10 percent dichlorophen in

diacetone alcohol was used in Australia to successfully treat contagious foot rot in sheep, a disease with mixed bacterial causes (Ref. 28).

In 1955, 2 percent dichlorophen in polyethylene glycol ointment USP was one of several antifungal ointments screened for effectiveness against *T. mentagrophytes* in a guinea pig animal model system (Ref. 29). In this study, dichlorophen ointment was no better than the ointment base alone, since neither could prevent the establishment of *T. mentagrophytes* infection within 12 to 14 days following spore inoculation. In contrast, tests using the same ointments and spore concentrations with agar cup plate method and wet filter paper test demonstrated dichlorophen to be highly active in vitro (Ref. 29).

Dichlorophen is included in many topical proprietary preparations as a preservative. A concentration of 0.5 percent dichlorophen in aqueous solution (prepared by combining it with the salts of aliphatic amines which contain an alkyl group with 12 to 18 carbon atoms) showed bacteriostatic and fungistatic activity (Ref. 2). Cosmetics and topical medications frequently contain lower concentrations of dichlorophen, with 0.05 percent and 0.25 percent listed as preservative levels in one report (Ref. 18). In the antifungal products submitted to the Panel, dichlorophen was always combined with other agents used against fungi, including undecylenates, chlorothymol, salicylic acid, or boric acid.

Dichlorophen has not been widely used as an antifungal agent to treat dermatophyte fungal infections in humans. No clinical trials, controlled or uncontrolled, using dichlorophen as a single antifungal ingredient have been submitted to the Panel. In fact, the Panel is aware of only a few anecdotal and poorly documented cases in the literature in which dichlorophen was used to treat fungal infections in humans (Refs. 25 and 26).

Based on the above review of available data on dichlorophen's effectiveness, the Panel concludes that dichlorophen, in concentrations less than or equal to 0.5 percent, should be classified as a preservative rather than an active antifungal agent. The Panel further concludes that dichlorophen in concentrations above 0.5 percent should be Category III for clinical effectiveness, as the Panel knows of no data on the use of dichlorophen as a single active ingredient in the treatment of athlete's foot, jock itch, or ringworm.

(3) *Proposed dosage*—(i) *Concentration*. Dichlorophen 0.5 to 5.0 percent.

(ii) *Directions for use*. See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation*. The Panel requires a full toxicological assessment of dichlorophen, including blood concentrations that cause toxic effects, definition of target organs, metabolic rate, and possible blood levels obtainable from applications to broken skin. The Panel also recommends one double-blind, placebo-controlled clinical trial to determine the effectiveness of dichlorophen in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Cade, A. R., and W. S. Gump, "The Bis-Phenols," in "Antiseptics, Disinfectants, Fungicides, and Chemical and Physical Sterilization," 2d Ed., Edited by G. F. Reddish, Lea and Febiger, Philadelphia, pp. 319-354, 1957.
- (2) OTC Volume 070008.
- (3) Rossoff, I. S., "Handbook of Veterinary Drugs. A Compendium for Research and Clinical Use," Springer Publishing Co., New York, p. 165, 1974.
- (4) OTC Volume 070019.
- (5) Biddis, J. K., "A New Taeniocide for Dogs," *The Veterinary Record*, 62:841, 1950.
- (6) Blair, H. E., "A New Anthelmintic for Dogs," *North American Veterinarian*, 30:306, 1949.
- (7) Burch, G. R., and H. E. Blair, "Vermiplex, an Anthelmintic for Cats," *North American Veterinarian*, 31:329, 1950.
- (8) Kimbrough, R. D., "The Toxicity of Polychlorinated Polycyclic Compounds and Related Chemicals," *CRC Critical Reviews in Toxicology*, p. 456, Jan., 1974.
- (9) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., The Macmillan Co., New York, p. 1020, 1975.
- (10) Blacow, N. W., "Martindale. The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, p. 144, 1972.
- (11) Arena, J. M., "Poisoning. Toxicology, Symptoms, Treatments," 3d Ed., Charles C. Thomas Publishing Co., Springfield, IL, p. 450, 1974.
- (12) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins Co., Baltimore, p. 131, 1976.

- (13) Gaul, L. E., and G. B. Underwood, "The Cutaneous Toxicity of Dihydroxydichlorophenylmethane. A New Fungicide for Athlete's Foot," *Journal of the Indiana Medical Association*, 42:22-24, 1949.
- (14) Bier, A. G., "Allergy to a Derivative of Diphenylmethane [2,2'-dihydroxy-5,5'-dichlorodiphenylmethane]," *Berufsdermatosen*, 8:40-43, 1958.
- (15) Epstein, E., "Dichlorophene Allergy," *Annals of Allergy*, 24:437-439, 1966.
- (16) Loewenthal, K., "Eczematous Contact Dermatitis of the Palm Due to Toothpaste," *New York State Journal of Medicine*, 52:1437-1438, 1952.
- (17) Fisher, A. A., and L. Tobin, "Sensitivity to Compound G-4 ("Dichlorophene") in Dentifrices," *Journal of the American Medical Association*, 151:998-999, 1953.
- (18) Schorr, W. F., "Dichlorophene (G-4) Allergy," *Archives of Dermatology*, 102:515-520, 1970.
- (19) Hanig, J. P., P. Yoder, and S. Krop, "Toxicity and Effects Upon Rat Cerebrospinal Fluid Pressure of Hexachlorophene Analogs," *Abstracts, Toxicology and Applied Pharmacology*, 37:186, 1976.
- (20) Corey, R. R., and H. G. Shirk, "The Influence of Chemical Structure on Fungal Activity. IV. The Effect of Bisphenolic-Type Compounds," *Archives of Biochemistry and Biophysics*, 56:196-203, 1955.
- (21) Klemme, D. E., and A. C. Baldwin, "Effectiveness of Fungicidal Chemicals in Preventing Growth of *Trichophyton interdigitale* and *Epidermophyton floccosum* in Shoe Leather," U.S. Department of Agriculture, Circular 758, February 1947.
- (22) Fredell, W. G., V. L. Burlingame, and G. F. Reddish, "Antiseptic Powders," *Drug Standards*, 22:107-112, 1954.
- (23) Gump, W. S., and G. R. Walter, "Chemical Structure and Antimicrobial Activity of Bis-Phenols," *Journal of the Society of Cosmetic Chemists*, 11:307-314, 1960.
- (24) Sweatman, J. G., "Clinical Manifestations and Treatment of Bovine Ringworm," *Cornell Veterinarian*, 37:3-7, 1947.
- (25) Horsey, R. E., and R. F. Bacon, "Use of G-4 for Bovine Ringworm," *Drug and Cosmetic Industry*, 61:462-463, 1947.
- (26) Brook, E. I., "Treatment of Canine and Feline Fungus Infections," *Veterinary Medicine*, 44:179-180, 1949.
- (27) O'Brien, J. D. P., and K. C. Sellers, "A Clinical Trial of the Treatment of Cattle Ringworm," *The Veterinary Record*, 70:319-321, 1958.
- (28) Hart, C. B., J. C. Malone, and W. B. Sparrow, "The Assessment of the Value of Topical Applications for the Treatment of Contagious Foot-Rot in Sheep, with Particular Reference to Dichlorophen," *The Veterinary Record*, 74:416-420, 1962.
- (29) Molines, S., "In Vivo Screening of Antifungal Ointments," *Journal of Investigative Dermatology*, 25:33-42, 1955.
- k. Oxyquinolines (benzoxiquine, oxyquinoline, and oxyquinoline sulfate). The Panel concludes that there are insufficient data available to permit

final classification of the safety and effectiveness of oxyquinolines (benzoxiquine, oxyquinoline, and oxyquinoline sulfate) for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Oxyquinoline, also as 8-hydroxyquinoline and 8-quinolinol, is a white or faintly yellow crystalline powder with a pleasant characteristic odor. Its chemical formula is C_8H_7NO . One g oxyquinoline dissolves in 1,500 mL water. It is freely soluble in alcohol, acetone, chloroform, benzene, and mineral acids. Oxyquinoline is obtained by heating *o*-aminophenol with *o*-nitrophenol, glycerol, and sulfuric acid. It has bacteriostatic, fungistatic, deodorant, and keratolytic properties (Refs. 1 and 2).

Benzoxiquine is the benzoate ester of oxyquinoline and is also known as 8-hydroxyquinoline benzoate and 8-quinolinol benzoate. It is practically insoluble in water, but soluble in alcohol and ether.

Oxyquinoline sulfate, the sulfuric acid salt of oxyquinoline, is also referred to as 8-hydroxyquinoline sulfate and 8-quinolinol sulfate. It is a pale yellow, crystalline powder with a slight saffron odor and burning taste. It is freely soluble in water, slightly soluble in alcohol, and insoluble in ether (Ref. 7). Pharmacologically, the sulfate and benzoate salts are similar in action to oxyquinoline.

The oxyquinolines are contained in currently marketed products in concentrations of 0.06 to 2.5 percent.

(1) *Safety*. Acute toxicity studies in mice showed oxyquinoline to be more toxic to female than to male mice at every concentration tested. The salt forms of oxyquinoline, however, were found to be less toxic than the parent compound. The intraperitoneal LD_{50} in mice was reported as 48 mg/kg (Ref. 3). The oral LD_{50} in guinea pigs was 1,200 mg/kg (Ref. 4) and the oral LD_{50} in rats was 1,200 mg/kg (Ref. 5). An intramuscular injection of 30 mg/kg oxyquinoline was lethal to mice. Rabbits have tolerated single oral doses of 3.7 g/kg (Ref. 6).

Humans have been given oral doses of 3 g in solution four times daily without apparent ill effect. When infected in animals, oxyquinoline is "distinctly toxic and causes marked stimulation of the central nervous system" (Ref. 6).

The Panel is concerned about Hueper's report (Ref. 7) that oxyquinoline may be a carcinogen. In this study, 20 percent oxyquinoline in a gelatin solution vehicle was administered to rats twice weekly intravaginally or intrarectally for a maximum of 2 years. Of the 30 rats that

received the drug intravaginally, the author reported:

In seven rats, which received intravaginal instillations of oxyquinoline, there was a marked glandular and sometimes papillary hyperplasia of the endometrium. This condition was in most cases associated with a purulent endometritis. The vaginal epithelial lining was markedly hyperplastic in three rats. In two instances, there existed in the mucosa of the cervical canal beneath a single layer of mucous-producing cylindrical cells, a stratified squamous-cell epithelial lining. The uterine cancers occurring in this series were adenocarcinomas of squamous-cell carcinomas.

These observations additionally supported the thesis that oxyquinoline is a carcinogen. Hueper advised that this chemical should be used with definite caution in humans until such time that epidemiologic studies on population groups show it to be innocuous to humans.

A recent report (Ref. 8) summarized the studies which attempted to evaluate the carcinogenic potential of oxyquinoline. The summary included tests on mice and rats by the oral, subcutaneous, and intravaginal routes of administration. Most of the studies were reported as being either inadequately controlled or involving too few animals. The authors concluded that the carcinogenicity of oxyquinoline could not be evaluated on the basis of available data in animals. However, a mutagenicity study at a dose of 20 to 40 μ g per plate noted point mutations in *Salmonella typhimurium* (S. typhimurium) TA100 in the presence of rat liver homogenate (Ref. 9).

To assess oxyquinoline's potential for toxicity the following "worst case" is presented: If it is assumed that an average application of a 2.5-percent preparation of oxyquinoline is 1 g and that rapid complete absorption of the drug occurs, it is conceivable that the total absorbed dose could be 25 mg. This would be equivalent to an absorbed dose of 0.35 mg/kg in an adult. The Panel is concerned about this potential absorbed dose because it is known that the lethal intramuscular dose in mice is 30 mg/kg. Also, the metabolic rates of oxyquinoline are unknown. If three or four applications of the drug are made and if amounts larger than 1 g are applied (not an unusual occurrence), then oxyquinoline levels in the blood may be reached that could manifest toxic symptoms.

(2) *Effectiveness*. Oxyquinoline is reported as active only in the presence of divalent metal ions, such as iron and copper. The activity of the divalent metal-chelate complex is antagonized by

cobalt ions (Ref. 10). Oxyquinoline is active under these circumstances against gram-positive and acid-fast organisms and fungi (Ref. 11). Dolan et al. (Ref. 12) conducted an in vitro study using epidermal scales taken from guinea pigs infected with *T. mentagrophytes*. The scales were suspended in test tubes of normal saline and a different antifungal agent was added to each tube. The *T. mentagrophytes* organisms were removed from the antifungal agent and tested for viability. Table 9 presents the results expressed as the time it took to kill the organisms in the presence of the antifungal agent:

TABLE 9.—FUNGICIDAL EFFECTS OF THREE ANTIFUNGAL AGENTS

Antifungal agent	Immersion time (minutes)			
	5	15	30	60
5% Undecylenic acid.....	+	0	0	0
10% Oxyquinoline.....	+	+	0	0
6% Salicylic acid, 12% benzoic acid..	+	0	0	0

+ = Still viable.

The Panel notes that the 10-percent concentration of oxyquinoline is about four times the concentration present in the products on the market. Even at this high concentration, oxyquinoline was less effective than undecylenic acid or Whitfield's ointment.

In vitro data (antifungal and antibacterial) on oxyquinolines have been submitted to the Panel (Refs. 13, 14, and 15), but the details of the testing procedures were not given. The Panel recommends in vitro studies using current methods.

A number of poorly designed in vivo studies have evaluated the effectiveness of oxyquinoline (Refs. 15, 16, and 17). Two unpublished studies (Ref. 15) were uncontrolled and lacked double-blinding. Because they were done with 2.5 percent oxyquinoline combined with several other ingredients (benzoic acid, salicylic acid, thymol, menthol, propylparaben, methylparaben), it is difficult to assess the effect of oxyquinoline.

Oster and Golden (Ref. 16) evaluated the effectiveness of a 2.5-percent solution of oxyquinoline in 50 percent ethanol on 40 cases of athlete's foot. Diagnosis was based on clinical appearance. KOH preparations were not used, and the study was not blinded or controlled. Of the 40 cases, only 11 had positive cultures for dermatophytes (*T. gypsum* and *E. floccosum*). Patients with mild cases of athlete's foot were clinically cleared in 1 to 2 weeks. After 3 months of treatment all patients were reported as cleared.

Seldowitz (Ref. 17) studied the therapeutic effectiveness of a rubber insole impregnated with unknown concentrations of oxyquinoline, chloroxylenol, and chlorothymol. The investigator treated only those patients with athlete's foot whose diagnosis had been documented by a KOH preparation and a culture. A total of 44 patients were included in the study; 27 patients were given the medicated insole therapy, and 17 patients were not treated. Of the 27 treated patients, 19 (70.4 percent) cleared clinically and had negative cultures after a varying period of treatment (1 to 9 months with an average of 4 months). The disease course of the untreated patients was either unchanged or had deteriorated. Thirteen of the untreated patients were then given the medicated insole therapy. The results of all 40 treated patients showed that 29 were clinically and mycologically cleared after an average treatment time of 4 months.

The Panel concludes that the effectiveness of 2.5 percent oxyquinoline in various vehicles has not been demonstrated in a well-designed clinical trial.

(3) *Proposed dosage*—(i) *Concentration*. Benzoxiquine, oxyquinoline, and oxyquinoline sulfate may be used alone or in combination to equal a total oxyquinoline concentration of 0.06 to 2.5 percent.

(ii) *Directions for use*. See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation*. The Panel recommends that adequate studies be undertaken to show (1) the minimal blood levels of oxyquinoline that cause toxic symptoms in animals; (2) the highest "no-effect" blood levels in animals; and (3) metabolic rates of oxyquinoline in humans, including time for total elimination of the drug from the body. A complete assessment of the carcinogenic potential from topically applied oxyquinoline to broken skin is also needed.

In addition, the Panel recommends in vitro testing and one double-blinded, placebo-controlled clinical trial to determine the effectiveness of oxyquinolines in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E.

below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 146 and 644, 1976.
- (2) Blacow, N., "Martindale. The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, p. 564, 1972.
- (3) Bernstein, E., P. Pienta, and H. Gershon, "Acute Toxicity Studies on 8-Quinolol and Some Derivatives," *Toxicology and Applied Pharmacology*, 5:599-604, 1963.
- (4) Stecher, P., "The Merck Index," 8th Ed., Merck and Co., Rahway, NJ, p. 555, 1968.
- (5) Fairchild, E., "Registry of Toxic Effects of Chemical Substances," United States Department of Health, Education, and Welfare, Cincinnati, p. 839, 1977.
- (6) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., William and Wilkins Co., Baltimore, p. 234, 1976.
- (7) Hueper, W. C., "Experimental Studies on 8-Hydroxyquinoline in Rats and Mice," *Archives of Pathology*, 79:245-250, 1965.
- (8) "World Health Organization, International Agency for Research on Cancer Monographs on Evaluation of Carcinogenic Risk of Chemicals to Man," Volume 13, World Health Organization, Lyons, France, pp. 101-112, 1976.
- (9) Talcott, R., M. Hollstein, and E. Wei, "Mutagenicity of 8-Hydroxyquinoline and Related Compounds in the *Salmonella typhimurium* Bioassay," *Biochemical Pharmacology*, 25:1323-1328, 1976.
- (10) Albert, A., M. I. Gibson, and S. D. Rubbo, "The Influence of Chemical Constitution on Antibacterial Activity. VI. The Bactericidal Action of 8-Hydroxyquinoline (oxine)," *British Journal of Experimental Pathology*, 34:119-130, 1953.
- (11) Rubbo, S. D., and J. F. Gardner, "A Review of Sterilization and Disinfection, as Applied to Medical, Industrial, and Laboratory Practice," Lloyd-Luke, Ltd., London, pp. 142-143, 1965.
- (12) Dolan, M. M., et al., "A Semi-In Vivo Procedure for Testing Antifungal Agents for Topical Use," *Journal of Investigative Dermatology*, 28:359-362, 1957.
- (13) OTC Volume 070135.
- (14) OTC Volume 070161.
- (15) OTC Volume 070017.
- (16) Oster, K. A., and M. J. Golden, "Studies on Alcohol Soluble Fungistatic and Fungicidal Compounds. IV. Treatment of Dermatophytosis Pedis with 8-Hydroxyquinoline," *Experimental Medicine and Surgery*, 7:37-45, 1949.
- (17) Seldowitz, M., "Treatment of Dermatophytosis Pedis with Medicated Insoles," *Archives of Dermatology and Syphilology*, 42:576-586, 1940.

1. *Parabens (methylparaben and propylparaben)*. The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of parabens (methylparaben and propylparaben) for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and

ringworm. The Panel also concludes that at a total concentration of less than 0.4 percent, parabens may be safely used in antifungal formulations as preservatives.

Paraben is an abbreviation used in the United States by the pharmaceutical profession to denote esters of parahydroxybenzoic acid. The methylparabens and propylparabens are the esters most commonly used.

Methylparaben occurs as white crystals with a melting point of 131° C and is slightly soluble in water, soluble in oil, and freely soluble in alcohol.

Propylparaben is less soluble in water and more soluble in oil because of its longer chain of carbon atoms. Propylparaben occurs as a white crystalline powder with a melting point of 96 to 97° C (Ref. 1).

(1) *Safety.* Methylparaben and propylparaben are widely used as preservatives in a variety of pharmaceutical preparations in concentrations up to 0.3 percent (Ref. 2). The parabens in concentrations exceeding 0.3 percent have shown in vitro activity against fungi.

At these concentrations, parabens are reported to be devoid of systemic toxicity (Ref. 2). Gosselin et al. (Ref. 3) assigned propylparaben a toxicity rating of 3, indicating moderate toxicity, i.e., where the probable oral lethal dose in humans may be from 0.5 to 5 g/kg. These investigators also stated that propylparaben is less toxic than benzoic or salicylic acid. Dogs injected with propylparaben showed no pathological changes in liver or kidneys (no dose specified).

Goodman and Gilman (Ref. 2) report that as a component of dermatological and proprietary preparations the parabens are recognized "causes of severe and intractable contact dermatitis." Sax, however, described the parabens as being "slight" allergens (Ref. 4).

Fisher's original paper on contact dermatitis noted that 3 percent of the patients sensitive to vehicles were sensitive to parabens (Ref. 5). There has been controversy, however, over this sensitization rate because it is well known that only small quantities of parabens are used as preservatives in skin medications.

Schorr and Mohajerin (Ref. 6) and Hjorth (Ref. 7) have indicated that repeated topical applications of low concentrations of these agents can sensitize an individual. This is particularly true when the medications are applied to areas of easy absorption. Although allergic hypersensitization to parabens has been reported in this country, the number of sensitized

persons is quite small, considering the wide use of these ingredients.

There are no sensitization data on parabens at antifungal concentrations (greater than 0.4 percent). The Panel concludes that these data are needed to determine the safety of methylparaben and propylparaben for OTC topical application in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* Parabens have gained widespread use as preservatives in cosmetics, foods, and pharmaceuticals. Their antibacterial and antifungal properties were first reported in 1924 in Europe; their commercial production began in the early 1930's in the United States (Ref. 8).

Parabens in low concentrations are effective against a variety of microorganisms in acid, neutral, and alkaline solutions (Refs. 8 and 9). The methyl, ethyl, propyl, and butyl esters of paraben are most commonly used as preservatives. Methylparaben 0.1 to 0.2 percent and propylparaben 0.05 percent (approaching the concentration of aqueous saturation) are commonly used preservative concentrations (Ref. 9). The antifungal products now under review contain either propylparaben 1.75 percent or the combination of methylparaben 1.35 percent and propylparaben 0.45 percent (total parabens 1.80 percent). In these products, parabens are found in combination with other antifungal agents, particularly benzoic and salicylic acid. Parabens have also been combined with oxyquinoline, thymol, chlorothymol, and boric acid.

These *p*-hydroxy benzoate compounds are desirable preservatives because they are essentially colorless, odorless, and stable. Activity among the esters increases with increasing chain length, while water solubility decreases. Mixtures of the esters have been used in preference to a single ester, with claims for their use varying from being simply additive to synergistic. The hexyl and heptyl esters have the greatest antifungal activity (Refs. 8 and 10).

The parabens have limited solubility in water, but by dissolving them in alcohols, oils, propylene glycol, or sodium hydroxide, the parabens may be incorporated into aqueous products (Ref. 8). As the chain length of the paraben increases, its lipid solubility also increases. By combining methylparaben and propylparaben in pharmaceutical preparations, manufacturers take advantage of the different solubilities of these two ingredients, permitting an additive preservative effect by having parabens present in both the aqueous and lipid phases of the product. Preservatives must suppress the

multiplication of microorganisms in the aqueous phase of the product and also have a high affinity for their microbial hydrophobic lipid cell membranes (Ref. 11).

In emulsion base creams, nonionic surfactants may bind the parabens, removing them from the aqueous phase and thereby reducing their effective concentration as free preservatives. This reaction can be compensated for during formulating by adding higher concentrations of parabens. Parabens do not interact significantly with other additives likely to be found in emulsion base creams, including methyl cellulose, carboxymethylcellulose, tragacanth, polyethylene glycol, gelatin, or polyvinylpyrrolidone (Ref. 11).

The parabens are bacteriostatic against gram-positive bacteria and fungistatic as well. Their activity is only slightly decreased in the presence of human serum (Ref. 12). Studies (Ref. 8) show that the percentages of methylparaben and propylparaben required to inhibit *S. aureus* were 0.4 percent and 0.05 percent, respectively. In the same study, gram-negative bacteria (*E. coli*, *Proteus vulgaris*, and *Aerobacter aerogenes*) were also inhibited by methylparaben and propylparaben at concentrations of 0.2 percent and 0.05 to 0.1 percent, respectively. Summaries of the inhibitory concentrations of the parabens from tests made in nutrient media with results read in 24 hours at 37° C, showed the following: 0.1 to 0.4 percent methylparaben and 0.0125 to 0.05 percent propylparaben inhibited gram-positive types of bacteria; 0.2 percent methylparaben and 0.05 to 0.1 percent propylparaben inhibited gram-negative types of bacteria (Ref. 13).

The parabens are also fungistatic, being mainly active against dermatophytes, *C. albicans*, and common fungi frequently found in the environment. In one study, inhibition concentrations for *T. mentagrophytes* and *T. rubrum* were found to be 0.016 percent for methylparaben and 0.004 percent for propylparaben (Refs. 8). Another study showed that a concentration of 0.004 percent propylparaben and concentrations greater than 0.008 percent methylparaben were required to inhibit *T. interdigitale* (Ref. 14). Against *T. mentagrophytes*, the lowest effective concentrations of methylparaben, propylparaben, and butylparaben for growth inhibition varied from 0.01 to 0.1 percent. When 0.2 percent concentrations of propylparaben and butylparaben were combined in a petrolatum and silicone oil base, they

effectively inhibited growth of *T. mentagrophytes* suspended in melted agar (Ref. 15). In another study in which parabens were suspended in Sabouraud's agar, 200 µg/mL of methylparaben and 50 µg/mL of propylparaben, were the lowest concentrations to completely inhibit *T. rubrum* and *T. mentagrophytes* (Ref. 16).

The effective inhibitory concentrations of parabens against *C. albicans* were reported to be 0.1 percent for methylparaben and 0.0125 percent for propylparaben (Refs. 8 and 13). Another report showed similar inhibition of *C. albicans* at 350 µg/mL for methylparaben and 100 µg/mL for propylparaben (Ref. 16). Methylparaben and propylparaben at concentrations of 1,000 to 2,500 µg/mL in Sabouraud's medium delayed the yeast growth of four strains of *Candida* to 96 hours, in contrast to the normal growth present at 24 hours (Ref. 17). Another study used cup plate tests with methylparaben and propylparaben dissolved in 25 to 33 percent ethyl alcohol. This study found that most yeasts (*Candida*, *Saccharomyces*, and *Geotrichum*) were sensitive to as little as 1.0 mg of the esters, but were inhibited more markedly by 5 mg and 10 mg of the esters, with methylparaben the most active ester (Ref. 18).

The activity of parabens against *C. albicans* in vitro led to several clinical studies on the effects of parabens against candidiasis developing secondary to antibiotic treatment (Refs. 17 through 22). In one study, 186 patients were treated with either parabens alone, aureomycin alone, or aureomycin with parabens administered by the oral, vaginal, or rectal routes (Ref. 17). Among patients treated with oral aureomycin alone, 50 percent developed *C. albicans* in the stool. In contrast, 13 percent of the patients treated orally with aureomycin with parabens developed yeast in the stool. It was concluded that parabens "are of value" in preventing overgrowth of *Candida* during aureomycin treatment.

In 1953, 0.2 g parabens was given orally four times daily to a man with widespread candidal infection following antibiotic use (Ref. 19). After 3 days of parabens treatment, fungal elements were gone from the sputum and feces. In vivo studies were conducted with 17 hospitalized patients who were given daily oral doses of 3 g chlortetracycline and 1.35 g methylparaben and propylparaben (Ref. 18). Daily stool counts for total yeast content showed that parabens caused anti-yeast activity in some but not all patients. In vitro studies suggested that certain antibiotics

(aureomycin, neomycin, and bacitracin) stimulated the growth of *Candida* in broth cultures greater than the growth in control cultures (Ref. 20). This growth stimulation could be eliminated by the addition of methylparaben and propylparaben, but the total growth of the cultures remained similar to the growth of control cultures.

Two European reports described the oral use of parabens in cases of systemic candidiasis caused by antibiotic treatment. In one report, two of four patients with positive blood smears for *C. albicans* survived (Ref. 21). In the other study, seven children survived after treatment with 600 mg parabens daily (Ref. 22).

The clinical use of parabens against dermatophyte fungal infections has not been extensive. According to one report, parabens were successfully used to treat fungus infections and were found to be colorless, odorless, agreeable, and easy to use (Ref. 23). Another report discussed the use of 5 percent methylparaben to treat athlete's foot caused mainly by *Epidermophyton interdigitale* (Ref. 24). Preparations containing parabens and salicylic acid were used, including a tincture, ointment, and powder, all applied twice daily. Rapid healing occurred in many cases, but the exact number of cases treated was not reported. No KOH preparations, fungal cultures, or controls were included.

Another investigator reported the use of 5 percent ethylparaben ointment to treat athlete's foot (Ref. 25). In this partially controlled study, all patients with athlete's foot seen in a dermatology clinic for about 6 months were treated with an ointment containing 5 percent ethyl paraoxybenzoate (paraben). The ointment given to alternate patients contained 3 percent salicylic acid in addition to the 5 percent ethylparaben. Every patient in the study had clinical findings of fungal infection and positive KOH preparations or cultures or both before beginning treatment. Reexamination with KOH preparations and cultures was performed weekly. After the fungi had disappeared, at least two additional examinations for fungus were done at intervals of 1 to 2 weeks.

Among 23 patients treated with the ointment containing ethylparaben alone, 18 (78 percent) were cured; with the disappearance of fungi documented after 6 to 34 days of treatment (average 22 days). The treatment length averaged 37 days. Of 23 patients treated with the ethylparaben-salicylic acid ointment, 17 (74 percent) were cured, with fungi disappearing after 8 to 63 days (average 26 days). The average duration of

treatment was 49 days. Eleven (24 percent) of 46 patients who did not respond used one of the two ointments for periods ranging from 28 to 137 days. It was concluded that both ointments had the same therapeutic effect, regardless of the presence or absence of salicylic acid, and that clinical effectiveness was due to the presence of ethylparaben.

Although this study met many of the study design criteria proposed by the Panel, neither it nor any of the other reviewed studies included a treatment group using the ointment base alone, or a lag period between treatment and final examination for fungi. The study design also lacked double blinding.

The Panel is aware of only three other brief reports of clinical trials using parabens to treat dermatophyte fungal infections. In 1935, epidermophytosis of the feet and hands was treated successfully with a salve containing 5 percent propylparaben (Ref. 26). Later, a 5-percent methylparaben solution in 70 percent alcohol and 5 percent methylparaben ointment were used to successfully treat fungus infection of the scalp (Ref. 27). After 5 months the infection did not recur. In the late 1940's, numerous cases of tinea of the hands and feet were treated with paraben ointments and solutions (Ref. 28). Favorable results occurred with a 6-percent solution of butyl ester in peanut oil, a 10-percent mixture of paraben esters in ointment, and a 20-percent mixture of paraben esters in alcohol solution. The solution form, in either alcohol or propylene glycol, was the most effective.

The Panel is not aware of any controlled studies using either methylparaben or propylparaben for the treatment of athlete's foot, jock itch, or ringworm. Despite promising results obtained with 5 percent methylparaben in the treatment of athlete's foot reported in 1944 (Ref. 25), no recent studies have confirmed the earlier results. Also, no clinical studies have been submitted to the Panel showing that concentrations of parabens less than 5.0 percent are effective antifungal agents in vivo. While all clinical studies reviewed by the Panel used parabens in concentration of at least 5.0 percent, the total paraben concentration in currently marketed antifungal products is only 1.75 to 1.80 percent. This concentration greatly exceeds the 0.1 to 0.4 percent concentrations usually required for the preservative effects of parabens.

The Panel concludes that parabens in total concentrations of less than 0.4 percent should be classified as preservatives rather than as active

antifungal ingredients. Parabens in concentrations equal to or greater than 0.4 percent may have antifungal activity, but this has yet to be verified in a well-designed, controlled clinical trial.

(3) Proposed dosage—(i)

Concentration. Methylparaben and propylparaben may be used alone or in combination to equal a total parabens concentration of 0.4 to 5.0 percent.

(ii) Directions for use. See part III, paragraph A.2. above—Category I Labeling.

(4) Labeling. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) Evaluation. The Panel recommends that the sensitization potential of parabens in concentrations greater than 0.4 percent be determined. The Panel also recommends one double-blind, placebo-controlled clinical trial to determine the effectiveness of parabens in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 796 and 1018, 1976.
- (2) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., MacMillan Publishing Co., Inc., New York, p. 992, 1975.
- (3) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, p. 137, 1976.
- (4) Sax, N. I., "Dangerous Properties of Industrial Materials," 3d Ed., Van Nostrand Reinhold Co., New York, p. 828, 1968.
- (5) Fisher, A. A., F. Pascher, and N. B. Kanof, "Allergic Contact Dermatitis Due to Ingredients of Vehicles. A 'Vehicle Tray' for Patch Testing," *Archives of Dermatology*, 104:286-290, 1971.
- (6) Schorr, W. P., and A. H. Mohajerin, "Paraben Sensitivity," *Archives of Dermatology*, 93:721-723, 1966.
- (7) Hjorth, N., and C. Trolle-Lassen, "Skin Reactions to Ointment Bases," *Transactions of St. John Hospital Dermatological Society*, 49:127-140, 1963.
- (8) Aalto, T. R., M. C. Firman, and N. E. Rigler, "p-Hydroxybenzoic Acid Esters as Preservatives. I. Uses, Antibacterial and Antifungal Studies, Properties and Determination," *Journal of the American Pharmaceutical Association*, (Scientific Edition), 42:449-457, 1953.
- (9) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, pp. 746-747, 975-976, 1973.
- (10) Huppert, M., "The Antifungal Activity of a Homologous Series of Parabens," *Antibiotics and Chemotherapy*, 7:29-36, 1957.
- (11) Osol, A., and J. E. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, pp. 1366 and 1540, 1975.
- (12) D'Arcy, P. F., "Inhibition and Destruction of Moulds and Yeasts," in "Inhibition and Destruction of the Microbial Cell," Edited by W. B. Hugo, Academic Press, New York, pp. 653-656, 1971.
- (13) Sokol, H., "Recent Developments in the Preservation of Pharmaceuticals," *Drug Standards*, 20:89-106, 1952.
- (14) Lawrence, C. A., and S. S. Block, "Disinfection, Sterilization and Preservation," Lea and Febiger, Philadelphia, p. 421, 1968.
- (15) Bocobo, F. C., et al., "In Vitro Activity of p-Hydroxybenzoic Acid Esters on Pathogenic Fungi," *Journal of Investigative Dermatology*, 26:239-242, 1956.
- (16) Siegel, M., "Fungistatic Activity of Methylparaben and Propylparaben," *Antibiotics and Chemotherapy*, 3:478-480, 1953.
- (17) McVay, L. V., Jr., and D. H. Sprunt, "A Study of Moniliasis in Aureomycin Therapy," *Proceedings of the Society for Experimental Biology and Medicine*, 78:759-761, 1951.
- (18) Metzger, W. I., L. T. Wright, and J. C. DiLorenzo, "Effect of Esters of Parahydroxybenzoic Acid on Candida and Yeast-like Fungi," *Journal of the American Medical Association*, 155:352-358, 1954.
- (19) Rossier, P. H., and T. Wegmann, "Fungal Diseases as a Complication of Antibiotic Therapy; with Special Reference to Pulmonary Mycoses," *Wiener Medizinische Wochenschrift*, 103:358-360, 1953.
- (20) Huppert, M., and J. Cazin, Jr., "Pathogenesis of *Candida albicans* Infection Following Antibiotic Therapy. II. Further Studies of the Effect of Antibiotics on the In Vitro Growth of *Candida albicans*," *Journal of Bacteriology*, 70:435-439, 1955.
- (21) Maier, C., T. Wegmann, and A. Lichtensteiger, "The Demonstration of *Candida albicans* in Blood Smears in Fungal Pyaemia," *Schweizerische Medizinische Wochenschrift*, 86:331-333, 1956.
- (22) Hottinger, A., "Clinical Contribution to the Incidence of Moniliasis in Childhood," *Annales Paediatrici International Review of Pediatrics*, 187:218-237, 1956.
- (23) Bonnevie, P., "Experimental Investigations on the Antimycotic Effect of Ethylparaoxybenzoate and of Allied Substances," *Acta Dermato Venereologica*, 17:576-588, 1936.
- (24) Lomholt, S., "Dermatophytoses of the Feet in Copenhagen and their Treatment with Mykoken," *Medizinische Klinik*, 34:118-119, 1938.
- (25) Holm, K., "Treatment of Dermatophytosis Pedis with Ethyl Paraoxybenzoate, Ascertained by Systematic Examination for Fungi," *Acta Dermato Venereologica*, 25:60-64, 1944.
- (26) Loos, H. O., "The Treatment of Dermatophytosis of the Feet and Hands with Benzoic Acid Preparations," *Archiv fuer Dermatologie und Syphilis*, 173:109-116, 1935.
- (27) Bang, H., "A New Treatment of Tinea Capitis with Mykoken," *Dermatologische Wochenschrift*, 105:1096-1098, 1937.
- (28) Delpiana, J., and D. Ugazio, "Trials with Esters of p-Hydroxybenzoic Acid in Dermatology," *El Dia Medica*, 21:354-358, 1949.

m. *Phenyl salicylate*. The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of phenyl salicylate for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Phenyl salicylate, also known as salol, is the salicylic acid ester of phenol. Phenyl salicylate was introduced into medical practice in 1886, but is no longer official in the "United States Pharmacopeia." It is a white, crystalline powder with a melting point between 41° and 43° C. One g phenyl salicylate dissolves in 6,700 mL water and 6 mL alcohol. It is very soluble in chloroform and ether (Ref. 1).

(1) Safety. The mechanism of action of phenyl salicylate as an intestinal antiseptic was based on its hydrolysis to phenol and salicylic acid. The usual dose was 300 mg, although doses as large as 1 g were sometimes given. Phenyl salicylate was formerly used as an enteric coating for capsules and tablets (Ref. 1).

No data on the safety of phenyl salicylate have been submitted to the Panel, and there are only extremely limited data in the literature on the topical use of this ingredient. Presumably, and antifungal activity it may possess would occur only after hydrolysis, if indeed this does occur when phenyl salicylate is applied topically. However, in view of its oral use in the past as an intestinal antiseptic, the Panel can visualize no systemic toxicity potential by absorption through the skin in the concentrations now used. On the other hand, if hydrolysis on the skin does occur and if hydrolysis is complete, then the products of hydrolysis would be 44 percent phenol and 56 percent salicylic acid. In the concentration currently used (2 percent), the total amount of phenol and salicylic acid would not cause systemic toxicity from localized application such as to athlete's foot, jock itch, or ringworm. Local effects of the intact molecule of phenyl salicylate, such as irritation, sensitization potential, or effect on healing of cracks and fissures are unknown. Therefore, in view of the absence of data establishing the effects of phenyl salicylate mentioned above, the Panel recommends additional safety testing.

(2) Effectiveness. As mentioned above, phenyl salicylate hydrolyzes to yield phenol and salicylic acid. If

hydrolysis occurs after topical application, the effectiveness of phenyl salicylate should be similar to that of phenol (see part III. paragraph B.1.e. above—Phenolates (phenol and phenolate sodium)) and salicylic acid (see part III. paragraph C.1.p. below—Salicylic acid). The effectiveness of phenyl salicylate is questionable because the Panel has received no effectiveness data.

(3) *Proposed dosage*—(i) *Concentration*. Phenyl salicylate 2.0 percent.

(ii) *Directions for use*. See part III. paragraph A.2. above—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III. paragraph A.2. above—Category I Labeling.)

(5) *Evaluation*. The Panel recommends testing of the local toxicity of phenyl salicylate (irritation, sensitization, and effect on broken skin). If it is established that hydrolysis on the skin occurs, the toxicity of phenol which is produced should be evaluated. (See part III. paragraph B.1.e. (1) above—Phenolates (phenol and phenolate sodium) safety.) The Panel also recommends in vitro testing and one double-blind, placebo-controlled clinical trial to determine the effectiveness of phenyl salicylate in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

Reference

(1) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 911, 1973.

n. *Povidone-iodine*. The Panel concludes that povidone-iodine is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Povidone, formerly known as polyvinylpyrrolidone or PVP, was developed during World War II as a plasma expander. It is formed by reacting acetylene, ammonia, and formaldehyde under pressure, yielding a water-soluble polymer. Preparations commonly used in the United States have an average molecular weight of either 33,000 or 56,000. Povidone binds many drugs, including iodine, producing a colloidal solution in water (Ref. 1).

Povidone-iodine is a yellowish-brown amorphous powder with a slight,

characteristic odor. In aqueous solutions it is acidic. Povidone-iodine is soluble in alcohol, but is practically insoluble in chloroform, ether, and acetone. Povidone-iodine contains about 10 percent available iodine (Ref. 2).

(1) *Safety*. The safety of povidone-iodine was reviewed by the Advisory Review Panel on OTC Antimicrobial I Drug Products in the Federal Register published September 13, 1974 (39 CFR 33129). Since then, certain new safety data have been made available to the Advisory Review Panel on OTC Antimicrobial II Drug Products.

The intravenous LD₅₀ of 10 percent povidone-iodine (1 percent available iodine) in rabbits is 1.1 mL/kg. The oral LD₅₀ in rats is 80 mL/kg. Safe intraperitoneal doses of povidone-iodine ranged from 2.5 mL/kg for rats to 4 mL/kg for dogs (Ref. 3 and 4).

To determine the subacute oral toxicity of 10 percent povidone-iodine, researchers fed this drug to growing rats for 3 months. No significant effects on the rats were noted other than a temporary elevation in protein-bound iodine levels and nonspecific changes in thyroid tissue. These tissue changes returned to normal within 90 days of the last dose (Ref. 3).

Skin irritation studies on animals and humans on both normal and damaged skin showed no significant degree of irritation from povidone-iodine (Ref. 5). Instillation into rabbit eyes showed only slight or mild reactions which generally subsided in 24 to 48 hours (Refs. 3, 5, and 6).

One report of the mutagenicity potential of povidone-iodine (Ref. 7) indicated that it was positive in a modification of the Ames S. typhimurium model, but these results could not be reproduced by another researcher (Ref. 3). Another test using mouse lymphoma and Balb/3T3 cells showed that povidone-iodine has no significant mutagenic or transformation capabilities. Other data indicated that it does not produce mutagenic effects in mice or hamsters according to the dominant lethal test, micronucleus test, and chromosome analysis (Ref. 3).

Numerous reports in the literature indicate the lack of toxicity or irritation to skin from povidone-iodine. These reports include application of povidone-iodine to eyebrows, eyelids, and mucous membranes. It was also applied to athlete's foot and used in catheter cut-downs and in preoperative preparation (Refs. 3, 5, and 6).

A tissue culture study (Ref. 8) was run in which skin specimens were degermed in vivo with povidone-iodine. Growth of epithelial cells in culture was then determined. The authors reported 83

percent positive skin cultures after povidone-iodine treatment, but the Panel observes that it was applied to the intact skin (primarily stratum corneum) where available iodine would have been bound to tissue before reaching the epithelial (viable) layer.

In another study (Ref. 9), minute cutaneous wounds were studied microscopically after application of 1:100 dilutions of povidone-iodine. Tissue injury was very slight, less than with hydrogen peroxide, quaternary ammonium compounds, or soaps. Nevertheless, the investigators that disinfectants in general (including iodine solutions) "damaged tissue and interfered with tissue function, thereby increasing the injury already existing in a damaged tissue and delaying wound healing." The Panel observes that the very high dilution of povidone-iodine used in this study does not provide adequate data on its effect on wound healing.

Another submission (Ref. 10) resolved most of the Panel's concern about the effect of povidone-iodine on wound healing. A 10-percent povidone-iodine solution was applied to "split-skin" and "full-thickness" wounds in rats and to human skin graft wounds to determine any effects on wound healing (Ref. 11). Control sites were treated with saline or dry Owens gauze. Treatments were given four times daily until epithelialization was complete. The results showed that povidone-iodine had no gross or microscopic effect on wound healing. In both the animal and human experiments, no statistically significant difference was seen between treated and control sites in mean healing time of wounds. Other supporting data (Ref. 10) showed that there was no reaction when 10 percent povidone-iodine was used on varicose ulcers or wound infections. These data removed the Panel's previous concern over the effect of povidone-iodine on wound healing. However, the Panel still believes that in some instances iodine may be an irritant or sensitizer (particularly with long-term use and under occlusion). For this reason the Panel recommends that a caution be included in povidone-iodine labeling.

The Panel concludes that povidone-iodine is safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness*. Studies by a number of investigators (Ref. 3) reveal that 10 percent povidone-iodine has considerable in vitro effectiveness against a wide variety of bacteria, yeast, and fungi which are commonly found in the toewebs. Povidone-iodine killed *T.*

mentagrophytes in 20 to 30 minutes, *M. audouinii* in 30 to 60 minutes, and *E. floccosum* in 3 to 4 hours. A 1:160 dilution killed *T. mentagrophytes* in 20 to 30 minutes. Ten percent povidone-iodine killed *C. albicans* (identified strains and clinical isolates) in 15 seconds. Various dilutions were also tested against clinical isolates of *C. albicans*. A 1:1 dilution required 15 seconds for fungicidal effect, and a 1:10 dilution required 60 seconds.

Meyer-Rohn and Liehr (Ref. 12) studied 10 percent povidone-iodine solution and ointment in a plate diffusion test. They used "Kimmig" agar for dermatophytes and maltose indicator agar for *Candida*. A 14-mm punch hole was filled with 0.2 mL of the povidone-iodine solution or ointment and the plates were inoculated after 1-hour diffusion. Plates were incubated at 37° C for *Candida* and 27° C for dermatophytes. Results were read as mm of inhibition at 24 hours for *Candida* and 4 weeks for dermatophytes. *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, and *M. canis* were inhibited by 10 percent povidone-iodine solution (20 mm zone). The zone of inhibition for a 1:10 dilution was 18 mm for *M. canis* and 16 mm for the other three dermatophytes. The 1:100 dilution showed no inhibition of these microorganisms. Although dilutions of povidone-iodine up to 1:5 inhibited *C. albicans*, growth was seen at 1:10.

The in vitro antibacterial activity of iodine was discussed in the report of the Advisory Review Panel on OTC Antimicrobial I Drug Products published in the Federal Register of September 13, 1974 (39 FR 33129). Data indicate that povidone-iodine is more active against bacteria than against fungi. This report also describes some effectiveness concerns, such as the stability of the preparation and the availability of elemental iodine from the povidone-iodine complex. This Panel has seen no data which completely resolve those concerns.

Kuttin, Beemer, and Amani (Ref. 13) have described their experiences treating *T. mentagrophytes* infections in a laboratory rabbit colony. The animals had inflamed skin lesions and hair loss. Sometimes the nails were affected. The infection was documented by KOH preparation and culture. Seventeen of 133 rabbits in the colony (12.7 percent) developed this infection which did not appear to be self-limited. Several months after the lesions first appeared each infected rabbit was treated with a single application of 10 percent povidone-iodine solution, with no concomitant therapy. Response was

swift; new hair growth was seen in 3 to 4 days, and no further lesions developed. All animals responded completely and remained free of disease for 1 year.

Rinaldi and Sabia (Ref. 14) used 40 patients in a double-blind, controlled, and randomly assigned study of 10 percent povidone-iodine solution in the treatment of athlete's foot. A positive culture (on Sabouraud's), clinical symptoms of athlete's foot, and a history of no prior topical antifungal therapy were necessary to enter the study group. Patients were then graded clinically for symptoms and signs of pain itching, fissuring, vesiculation, erythema, scaling, etc. The treatment groups did not differ significantly in age and sex, in duration and severity of disease, or in type of organisms.

One group was treated twice daily with 10 percent povidone-iodine solution and the other group with the vehicle which had "a small amount of preservative and color" added. Feet were washed twice daily and the appropriate solution applied after drying. Patients were evaluated at 7, 14, and 25 days of therapy and 7 days after treatment stopped. Patients were considered cleared if they had no signs or symptoms of the disease and if followup cultures were negative.

After 4 weeks of treatment, 75 percent (15/20) of the povidone-iodine group and 25 percent (5/20) of the control group were clear. This difference is statistically significant ($p < 0.01$, by chi-square analysis). A followup (by telephone) 1 year later on 17 patients from each group suggested that "approximately 25 percent in each group reported later reoccurrences," but no specific data were given about how such figures were compiled. The authors concluded that povidone-iodine is effective in the treatment of athlete's foot.

The major shortcoming of the Rinaldi and Sabia study (Ref. 14) is an inadequate followup of patients. Otherwise it generally meets the Panel's criteria. The Panel notes that none of the standard dermatology textbooks refer to athlete's foot as an indication for the use of povidone-iodine. To the Panel's knowledge, this ingredient was marketed for only 1 year (1960) for the treatment of athlete's foot. Because povidone-iodine is not generally recognized as effective in the treatment of athlete's foot, jock itch, and ringworm, the Panel requires a well-designed, controlled study to substantiate the ingredient's effectiveness in these conditions.

(3) *Proposed dosage*—(i) *Concentration*. Povidone-iodine 10 percent.

(ii) *Directions for use*. See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

Cautions should include the following statement: "If redness or itching occurs or persists, discontinue use and consult a doctor or pharmacist."

(5) *Evaluation*. The Panel recommends that studies be conducted to determine the stability of povidone-iodine and availability of elemental iodine from the complex. The Panel also recommends one double-blind, placebo-controlled clinical trial to determine the effectiveness of povidone-iodine in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Cornbleet, T., "The Use of Polyvinylpyrrolidone Iodine in Eczematoid Ringworm," *Archives of Dermatology*, 77:335-336, 1958.
- (2) Osol, A., and J. E. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1098, 1975.
- (3) OTC Volume 070229.
- (4) Lavigne, J. E., et al., "The Treatment of Experimental Peritonitis with Intraperitoneal Betadine Solution," *Journal of Surgical Research*, 16:307-311, 1974.
- (5) Shelanski, H. A., and M. V. Shelanski, "PVP-Iodine: History, Toxicity, and Therapeutic Uses," *Journal of the International College of Surgeons*, 25:727-734, 1956.
- (6) Chase, R. C., and P. P. Ellis, "Iodophors as Skin Antiseptics before Ophthalmic Surgery," *Annals of Ophthalmology*, 2:312-317, 1970.
- (7) Wloakowski, T. J., W. T. Speck, and H. S. Rosenkranz, "Genetic Effects of Povidone-Iodine," *Journal of Pharmaceutical Sciences*, 64:1235-1236, 1975.
- (8) Georgiade, N., et al., "The Effects of Various Skin Sterilization Techniques on the Viability of Skin," *Plastic and Reconstructive Surgery*, 21:479-482, 1958.
- (9) Branemark, P. I., et al., "Tissue Injury Caused by Wound Disinfectants," *Journal of Bone and Joint Surgery*, 49A:48-62, 1967.
- (10) OTC Volume 070239.
- (11) Gruber, R. P., L. Vistnes, and R. Pardoe, "The Effect of Commonly Used Antiseptics on Wound Healing," *Plastic and Reconstructive Surgery*, 55:472-476, 1975.
- (12) Meyer-Rohn, J., and W. Liehr, "Experimental Study of the Action of an

Iodine-Containing Broad Spectrum Antiseptic on Bacteria and Dermatophytes," *Infection*, 4:215-218, 1976.

(13) Kuttin, E. S., A. M. Beemer, and H. Amani, "Trichophyton Mentagrophytes Infections in Rabbits Successfully Treated with a Polyvinyl Iodine Solution," *Laboratory Animal Science*, 26:960, 1976.

(14) Rinaldi, R. R., and M. L. Sabia, "A Double-Blind Controlled Study: Betadine Solution Treatment of Athlete's Foot," *Archives of Podiatric Medicine and Foot Surgery*, 3:1-9, 1976.

o. Propionic acid and its salts (sodium propionate and zinc propionate). The Panel concludes that propionic acid and its salts (sodium propionate and zinc propionate) are safe but that there are insufficient data available to permit final classification of their effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Propionic acid, $C_2H_5CO_2H$, is also known as propanoic acid. It is a colorless liquid with a characteristic odor. The sodium and zinc salts of propionic acid are colorless or white crystalline or granular powders. Propionic acid is miscible with water, alcohol, chloroform, and ether (Ref. 1).

(1) *Safety.* Heseltine (Ref. 2) concluded that the acute toxicity of sodium propionate in animals was so low that he considered it "neither practicable nor necessary" to determine the LD_{50} of the drug. The oral LD_{50} of propionic acid in rats is reported to be 4,290 mg/kg; the intravenous LD_{50} of sodium propionate in mice is 2,100 mg/kg (Ref. 3). The installation of a 10-percent solution of sodium propionate into rabbits' eyes was reported to aid the healing of experimental lesions; doubling the concentration produced no harmful effects (Ref. 2).

In humans the estimated "acceptable" daily intake of sodium, potassium, and calcium propionate is as high as 10 mg/kg (Ref. 1). Heseltine reported that daily oral doses of 6 g sodium propionate given to an adult male patient turned the urine faintly alkaline but had no appreciable diuretic, cathartic, or other side effects (Ref. 2). Propionic acid and its sodium and calcium salts are widely used as food preservatives (Refs. 4 and 5).

Several studies report little local irritation from the topical use of propionates (Ref. 6). Some of these studies consisted of treatment regimens extending over several months with continuous use of propionates.

The concentration of total propionates (propionic acid, sodium propionate, and zinc propionate) in antifungal preparations ranges from 4 to about 12 percent. Based on the total amount of propionic acid available for absorption

and the absence of acute toxicity, the Panel concludes that no toxicity hazard exists from the topical application of the propionates.

(2) *Effectiveness.* Propionates were first used in the treatment of fungal diseases in 1939 after Peck et al. (Ref. 7) reported that many short-chain fatty acid molecules were effective antifungal agents.

Propionic acid and its sodium and calcium salts have been widely used as food preservatives by the baking industry to inhibit mold growth (Ref. 1). In vitro antifungal data suggest that propionates are bacteriostatic and fungistatic (Ref. 8). However, the in vitro data is quite old and uses zone of inhibition and contact-time testing so that only general conclusions can be drawn. The Panel recommends further in vitro testing to characterize the activity of propionates against dermatophytes.

Keeney et al. (Ref. 9) compared the effectiveness of 16.4 percent sodium propionate and 3.6 percent propionic acid in carbowax ointment (39 patients) to a 10-percent undecylenic acid in carbowax ointment (40 patients) and the carbowax base alone (41 patients). Athlete's foot was diagnosed by KOH preparations and by culture. During the study the patients used no medication other than the ointment, which they were instructed to apply once in the evening and wash off with soap and water in the morning. After the first examination, the patients were seen at intervals of 1, 3, 5, and 6 weeks.

At the beginning of treatment, only 31 percent of the propionate group had positive cultures. The researchers considered this number too small to "draw decisive conclusions" based on causative organisms. When treatment began, KOH preparations were negative in 15 percent of the propionate group, 12 percent of the undecylenic acid group, and 7 percent of the placebo group.

After the first week of therapy, 54 percent of the patients treated with the propionate ointment and 51 percent treated with the undecylenic acid ointment were KOH negative. In the third week, KOH preparations were negative in 80 percent of those treated with propionate ointment compared to 67 percent in the undecylenic acid group. In the fifth week, KOH preparations were negative in 73 percent of the propionate group and 70 percent of the undecylenic acid group. The authors reported that after 5 weeks the patients had become careless in following instructions and that this carelessness was reflected in the study results. At the 6-week examination, 82 percent of the propionate ointment group and 59 percent of the controls were KOH

negative. The undecylenic acid group could not be observed at 6 weeks. Keeney et al. concluded that the two ointments were equally effective in the treatment of athlete's foot.

The Panel notes that the above study was not double-blinded. Also, no lag period followed treatment, and culture results of the placebo group were not reported.

Keeney and Broyles (Ref. 10) conducted an uncontrolled study on 55 naval cadets to evaluate the effectiveness of 10 percent sodium propionate ointment and powder on athlete's foot. The powder was applied in the morning and the ointment at night. Before treatment, positive KOH preparations were obtained in only 11 (20 percent) of the cases; only 9 of these produced positive cultures. It appears that athlete's foot was diagnosed mainly on clinical impression. The authors reported that after 8 weeks of treatment, 90 percent (10/11) of the cadets with "advanced" cases were "cleared" of the disease. Criteria for judging a case "cleared" were not specified.

Sulzberger, Shaw, and Kanof (Refs. 11 and 12) evaluated the effectiveness of various preparations in the treatment of athlete's foot and jock itch. Diagnosis was made on clinical impression. No KOH preparations or cultures were done. The length of treatment time is unclear. The authors state that treatment lasted "throughout the summer." Seventy-five percent (123/164) of the patients receiving 20 percent sodium propionate powder were cured or improved at the end of treatment. This compared with 81 percent (396/489) cured or improved in the 2-percent undecylenic acid-20 percent zinc undecylenate group. Of patients receiving boric acid-salicylic acid powder, only 48 percent (106/221) were cured or improved. The researchers concluded that "undecylenic acid-undecylenate powder was slightly more effective than sodium propionate powder, which in turn was definitely more effective than the boric acid-salicylic acid powder."

Sulzberger, Shaw, and Kanof (Ref. 11) also compared 20 percent sodium propionate in talc (17 patients) to 20 percent zinc undecylenate and 2 percent undecylenic acid in talc (44 patients) in the treatment of jock itch. They obtained the following results: 59 percent (10/17) of the patients treated with the propionate powder and 80 percent (35/44) of those treated with the undecylenate powder were reported as "cured." Unfortunately, only 17 patients received the propionate ointment, a number too small to justify valid

statistical inferences. Also, the methods of assigning patients to a treatment group are unknown.

The prophylactic effect of various preparations of propionic acid was studied by Sulzberger and Kanof (Ref. 12). For details, see part III, paragraph A.1.f. above—Undecylenic acid and its salts (calcium undecylenate, copper undecylenate, and zinc undecylenate).

None of the above studies meet the effectiveness criteria set by the Panel. The Panel therefore concludes that at least one well-designed, controlled clinical trial is necessary to establish propionic acid and its salts (sodium propionate and zinc propionate) as effective in the treatment of athlete's foot, jock itch, and ringworm.

(3) Proposed dosage—(i)

Concentration. Sodium propionate, zinc propionate, and propionic acid may be used alone or in any combination to equal a total propionate concentration of 20.0 percent.

(ii) Directions for use. See part III, paragraph A.2. above—Category I Labeling.

(4) Labeling. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) Evaluation. The Panel recommends in vitro testing and one double-blinded, placebo-controlled clinical trial to determine the effectiveness of propionates in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Blacow, N., "Martindale. The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, pp. 781-783, 1972.
- (2) Heseltine, W. W., "A Note on Sodium Propionate," *Journal of Pharmacy and Pharmacology*, 4:120-122, 1952.
- (3) Christensen, H. E., et al., "The Toxic Substances List," United States Department of Health, Education, and Welfare, Rockville, MD, pp. 785 and 793, 1973.
- (4) Arena, J. M., "Poisoning," 3d Ed., Charles C. Thomas Publishing Co., Springfield, IL, p. 670, 1974.
- (5) Goodman, L.S., and A Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., MacMillan Publishing Co., Inc., New York, p. 1010, 1975.
- (6) OTC Volume 070032.
- (7) Peck, S.M., et al., "Role of Sweat as a fungicide with Special Reference to the Use of Constituents of Sweat in the Therapy of Fungous Infections," *Archives of Dermatology and Syphilology*, 39:126-148, 1939.

(8) Peck, S.M., E.F. Traub, and H.J. Spoor, "Aqueous Solutions of Sodium Propionate with Chlorophyll as a Therapeutic Agent," *Archives of Dermatology and Syphilology*, 67:263-277, 1953.

(9) Keeney, E.L., et al., "Propionate and Undecylenate Ointments in the Treatment of Tinea Pedis and an In Vitro Comparison of Their Fungistatic and Antibacterial Effects with Other Ointments," *Bulletin of the Johns Hopkins Hospital*, 75:417-439, 1944.

(10) Keeney, E.L., and E.N. Broyles, "Sodium Propionate in the Treatment of Superficial Fungus Infections," *Bulletin of the Johns Hopkins Hospital*, 73:479-487, 1943.

(11) Sulzberger, M.B., H.C. Shaw, and A. Kanof, "Evaluation of Measures for Use Against Common Fungous Infections of the Skin. Screening Tests by Means of Paired Comparisons on Human Subjects," *United States Naval Medical Bulletin*, 45:237-248, 1945.

(12) Sulzberger, M.B., and A. Kanof, "Undecylenic and Propionic Acids in the Prevention and Treatment of Dermatophytosis," *Archives of Dermatology and Syphilology*, 55:391-395, 1947.

p. Salicylic acid. The Panel concludes that salicylic acid is safe when used in a concentration less than or equal to 3 percent. But the Panel believes that there are insufficient data available to permit final classification of this ingredient for effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Salicylic acid is ortho-hydroxybenzoic acid and occurs as white crystals in fine needles or as a fluffy crystalline powder. It is slightly soluble in water, sparingly soluble in oils, fats, and waxes, and freely soluble in alcohols (Ref. 1).

Salicylic acid was discovered in 1839 and was soon found to be the chief constituent of oil of wintergreen. Kolbe, a German organic chemist, developed a process for synthetically preparing salicylic acid from phenol. A modification of his method has been used since 1885 for commercial preparation (Ref. 2).

The pharmacologic action of salicylic acid is diminished in the presence of alkaline substances because of the ionization of the acid (Ref. 2).

(1) Safety. Preparations containing salicylic acid have been used topically for many years; however, salicylate toxicity and some deaths have been reported. A review of the literature revealed 13 deaths caused by the percutaneous absorption of salicylic acid. Ten of these deaths occurred in children. The diseases being treated included such varied conditions as psoriasis, scabies, dermatitis, and lupus vulgaris (Ref. 3).

Salicylic acid applied to relatively small areas of skin or in concentrations less than 10 percent has been used

without apparent ill effects as a kerytolytic agent in the treatment of various skin disorders. In humans a blood level of from 30 to 50 mg of salicylic per 100 mL is generally considered to be toxic (Ref. 4). The minimum intraperitoneal lethal dose in guinea pigs is 900 mg/kg. The minimum lethal dose orally in dogs is 450 to 550 mg/kg (Ref. 5).

Kimura (Ref. 6) reported that a 10-percent salicylic acid preparation in lanolin was applied for 3 hours to the legs of healthy male infants aged 3 to 16 months. Salicylate could be detected in the infants' urine 1 to 2½ hours after the drug was applied. The total amount of salicylic acid excreted in the urine varied between 0.55 and 3.0 mg, or between 0.06 and 0.3 percent of the total amount of drug applied. The surface area of application was 10 x 10 cm and was covered by a gauze pad.

Sautter, Buckwalter, and Ziffren (Ref. 4) applied 40 percent salicylic acid in hydrophilic ointment to a surface burn covering 10 percent of a dog's body. The peak blood level of salicylic acid was 6.5 mg/100 mL with no toxic symptoms noted.

Forty percent salicylic acid ointment was applied to two human patients with burn surfaces no greater than 5 to 6 percent of the body. Serum salicylate levels were determined every 8 hours for 48 hours; the highest salicylate level reached was 15 mg/100 mL. No clinical symptoms of toxicity were observed (Ref. 4).

Signs of toxicity were noted by von Weiss and Lever (Ref. 3) after 3 to 6 percent salicylic acid ointment was applied to psoriatic lesions over a large part of the body six times a day. Serum levels of salicylic acid ranged from 46 to 64 mg/100 mL. Toxic effects were nausea, difficulty in breathing, impaired hearing, confusion, and hallucination. Most symptoms disappeared within 1 day after treatment stopped.

A more recent report described four patients with psoriasis on more than 25 percent of their bodies (Ref. 7). A preparation containing 6 percent salicylic acid in a gel base was applied to the entire body surface below the neck immediately after showering. The treated areas were covered with a plastic wrap for 10 hours, after which the patients were allowed to shower again. This treatment was repeated daily for 5 days. Serum salicylate levels never exceeded 5 mg/100 mL in any of the patients, although more than 60 percent of the total applied salicylic acid was absorbed. No toxicity or accumulation of salicylic acid was observed.

Salicylic acid is a keratolytic agent. At concentrations higher than 3 percent it will destroy keratinized skin. Because of its keratolytic action, salicylic acid is known to be irritating to both the skin and the eyes. However, the concentration necessary to establish clinical signs of skin irritation depends on many factors, such as the vehicle, exposure time, and surface area occlusion. In higher concentrations, salicylic acid may delay wound healing, but this has not been fully assessed in the treatment of athlete's foot.

The systemic toxicity of topical salicylic acid, like its keratolytic effects, appears to result from a combination of factors. Some of these factors are (1) a high concentration of salicylic acid in a vehicle which allows rapid absorption, (2) the frequency of application, (3) whether the surface area is occluded, and (4) the condition and area of skin to which the preparation is applied (Ref. 7).

It is recognized that absorbed salicylic acid is rapidly metabolized and excreted (Ref. 3, 4, and 7). Therefore, if the area of application is small, such as in athlete's foot or jock itch, systematic toxic concentrations of salicylic acid probably would not be reached. For example, if one assumes complete instantaneous absorption of the total dose of 1 g of a 3-percent salicylic acid preparation, the maximum amount in the blood at any one time would be 30 mg. This 30 mg of salicylic acid would be distributed into 7 L of blood, resulting in a maximum blood concentration of approximately 0.4 mg/100 mL. This is well below the 30- to 50-mg/100 mL level considered to be toxic.

Therefore, considering the worst case of absorption as described above, and the known rapid elimination of salicylic acid, the Panel considers the use of salicylic acid in topical preparations to be safe if the concentration is 3 percent or less, and if the use of this drug is restricted to relatively small body areas.

(2) *Effectiveness.* Salicylic acid is generally applied in ointment form and is used in dermatology for the following reasons: (1) to produce a keratolytic or macerating action; (2) as an antiseptic and antiparasitic; and (3) on the assumption that the addition of salicylic acid to an ointment will promote the absorption of the other ingredients. Davies and Marks (Ref. 8), using scanning electron microscopy of skin surface biopsies, suggested that the peeling effect of salicylic acid is due to the dissolution of intercellular cement material.

In vitro studies (Refs. 9 through 13) have indicated that salicylic acid has some fungicidal activity. Dolan et al. (Ref. 14) conducted a "semi-in vivo"

study using epidermal scales of guinea pigs infected with *T. mentagrophytes*. Scales were placed in a stainless steel tissue capsule which was immersed in the test solution for 5, 15, 30, or 60 minutes. Then the scales were cultured on a Sabouraud's agar plate to see if the *T. mentagrophytes* were still living. The results were expressed as the time it took to kill the organism while in the presence of the antifungal ingredient. Salicylic acid was reported to have fungicidal activity with *T. mentagrophytes* cultured at 15 minutes, but not at 30 minutes.

The most extensive in vivo testing of salicylic acid was done by Hopkins et al. (Ref. 15). Over 7,500 patients at Fort Benning, Georgia, were treated for athlete's foot during a 3-year period. Cultures were obtained before treatment, but the cultured organisms were not identified. KOH preparations were examined at each visit. Although the total number of patients in the study was large, only 258 apparently received salicylic acid. Twenty-eight patients completed 4 weeks of treatment with salicylic acid; 47 percent were clinically clear at this time. The data were presented in an ambiguous fashion so that the actual success of salicylic acid is undeterminable.

Because of the lack of data on the effectiveness of topical salicylic acid for the treatment of athlete's foot, jock itch, and ringworm, the Panel recommends additional effectiveness testing.

(3) *Proposed dosage—(i) Concentration.* Salicylic acid 0.05 to 3.0 percent.

(ii) *Directions for use.* See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling.* The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part II, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation.* The Panel recommends one double-blind, placebo-controlled clinical trial to determine the effectiveness of salicylic acid in the treatment of athlete's foot, jock itch, and ringworm. This study should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) "The United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 445-446, 1975.
- (2) Osol, A., and G. E. Farrar, "The Dispensary of the United States of

America," 25th Ed., J. B. Lippincott Co., Philadelphia, pp. 1207-1209, 1955.

(3) von Weiss, J. F., and W. F. Lever, "percutaneous Salicylic Acid Intoxication in Psoriasis," *Archives of Dermatology*, 90:614-619, 1964.

(4) Sautter, R., J. A. Buckwalter, and S. E. Ziffren, "Chemicals and Enzymes in Debridement of Thermal Burns," *American Medical Association Archives of Surgery*, 76:744-748, 1958.

(5) OTC Volume 070045.

(6) Kimura, G., "Studies on Absorptive Function of the Skin and the Mucous Membrane of the Intestinal Canal of Infants in Respect to Salicylic Acid," *Oriental Journal of Diseases of Infants*, 28:13-14, 1940.

(7) Taylor, J. R., and K. Halprin, "Percutaneous Absorption of Salicylic Acid," *Archives of Dermatology*, 111:740-743, 1975.

(8) Davies, M., and R. Marks, "Studies on the Effect of Salicylic Acid on Normal Skin," *British Journal of Dermatology*, 95:187-192, 1976.

(9) Lyons, R. E., and C. S. Livingood, "Laboratory Test for the Evaluation of Fungicidal Solutions," *Archives of Dermatology and Syphilology*, 68:566-571, 1953.

(10) Scigliano, J. A., T. C. Grubb, and D. E. Shay, "Fungicidal Testing of Some Organo-Copper Compounds," *Journal of the American Pharmaceutical Association*, 39:673-676, 1950.

(11) Oster, K. A., and M. J. Golden, "Studies on Alcohol-Soluble Fungistatic and Fungicidal Compounds. I. Evaluation of Fungistatic Laboratory Methods," *Journal of the American Pharmaceutical Association*, 36:283-288, 1947.

(12) Legge, L. T., L. Bonar, and H. J. Templeton, "Epidermomycosis at the University of California," *Archives of Dermatology and Syphilology*, 27:12-24, 1933.

(13) Emmons, C. W., "Fungicidal Action of Some Common Disinfectants on Two Dermatophytes," *Archives of Dermatology and Syphilology*, 28:15-21, 1933.

(14) Dolan, M. M., et al., "A Semi-In Vivo Procedure for Testing Antifungal Agents for Topical Use," *Journal of Investigative Dermatology*, 28:359-362, 1957.

(15) Hopkins, J. G., et al., "Fungistatic Agents for Treatment of Dermatophytosis," *Journal of Investigative Dermatology*, 7:239-253, 1946.

q. *Sulfur.* The Panel concludes that sulfur is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. Goodman and Gilman (Ref. 1) summarize the history of sulfur as follows:

Sulfur has a long history in medicine. The practice of burning sulfur for the purification of the air is mentioned in the *Odyssey*. Hippocrates considered sulfur an effective antidote against plague. For the layman, sulfur has an undeserved reputation as an intestinal antiseptic, and the practice of an annual "spring cleansing" of the intestinal

tract with sulfur and molasses was once prevalent. The legitimate medical uses of sulfur preparations are as fungicides and parasitocides and for the treatment of various cutaneous disorders (Ref. 7).

Elemental sulfur is a dry powder made from a yellow, brittle solid of crystalline texture. It can exist in several different crystalline forms as well as an amorphous or polymeric form. The solubility may vary depending on the form of sulfur but, in general, sulfur is insoluble in water, sparingly soluble in alcohol, and soluble in organic solvents (Ref. 2).

The four forms of elemental sulfur used in dermatology are: (1) Sublimed sulfur (flowers of sulfur), a fine, yellow, crystalline powder; (2) washed sulfur (sulfur lotum), made by washing sulfur with ammonia; (3) precipitated sulfur (milk of sulfur), a fine yellowish-white, amorphous, odorless powder with smooth texture, and (4) colloidal sulfur, in which minute particles of elemental sulfur are stabilized (prevented from aggregation) in an aqueous medium containing a colloid such as egg albumin or gelatin (Ref. 3). Precipitated sulfur and colloidal sulfur are the forms used most commonly in dermatology.

Sulfur is contained in currently marketed antifungal products in concentrations of 0.2 to 8 percent. The Panel also received a submission on a soap containing 10 percent sulfur.

(1) *Safety.* Toxicological data on sulfur are practically nonexistent. The safety record of sulfur is based on its long and varied use. Sax (Ref. 4) rated the toxicity of sulfur as very low. Sulfur is reported to be nontoxic for man and mammals. If taken orally in sufficient doses, however, sulfur may have a laxative or cathartic effect possibly due to formation of hydrogen sulfide in the intestinal tract (Ref. 5). In concentrations above 15 percent, sulfur is very irritating to the skin. Also, concentrations below 15 percent applied for prolonged periods may cause severe topical irritation to some people. Sulfur may cause progressive reddening, thickening, and scaling of the skin, with eventual total body redness and scaling (erythroderma), as injury to the skin exceeds the ability of the skin to repair itself (Ref. 6).

After a careful review of the literature, Lorenc and Winkelmann (Ref. 6) noted that, despite the long history and almost universal acceptance of sulfur by dermatologists, there were only three references in the literature which attempted to describe the histologic effects of sulfur on the skin. One of these reported that sulfur did not injure the deeper layers of skin; the other two papers described a

parakeratosis (an abnormality of the horny layer of the skin resulting in the process of keratinization) of the stratum corneum.

Lorenc and Winkelmann studied the histological effects of concentrations of 5 to 40 percent sulfur in petrolatum during a 4-week period of exposure on hairless mouse skin. These investigators concluded that the reaction caused by sulfur was a single manifestation of unknown mechanism, namely one or injury to the skin. The reported keratolytic and keratoplastic actions of sulfur are a single manifestation, but the end result depends on the concentration used. Lorenc and Winkelmann concluded that sulfur injures the epidermis; the injury is then followed by a reparative process. However, when higher concentrations of sulfur are used, the injury exceeds the reparative process and thus exfoliation (peeling) results. Hence, the terms "keratoplastic" and "keratolytic" describe certain phases of the same basic reaction. Lorenc and Winkelmann also reported that the sequence of events in the skin of hairless mice after the application of various strengths of sulfur was essentially the same as the sequence reported in the human thigh, abdomen, and scrotum.

Rossoff (Ref. 7) reported that 5 to 10 percent sulfur preparations are keratolytic. Rossoff did not suggest that lower concentrations were primarily keratoplastic, though he did indicate that a sulfur concentration of 2 percent in combination with salicylic acid is popular in antiseborrheic preparations.

Sulfur, in various forms, has had a long history of oral and topical use. It has been reported that dermatologists almost universally accept sulfur for topical use (Ref. 6). For these reasons the Panel concludes that topically applied sulfur does not have a serious toxicity potential and is safe at the dosage cited below.

(2) *Effectiveness.* Colloidal sulfur is the most active form of sulfur because of its minute particle size, enabling intimate contact between the sulfur and the epidermis (Ref. 6). Although colloidal sulfur was first isolated from a sulfur spring in 1830 (Ref. 9), it was not further studied until 1888 and 1911 or used therapeutically until the early 1930's (Refs. 8 and 10). Before this, precipitated sulfur was considered to be the most active form of sulfur (Ref. 11).

Hydrogen sulfide is produced when sulfur is applied to human skin and can be recognized by its characteristic "rotten egg" odor. The formation of hydrogen sulfide within the epidermis results from a biochemical reaction between sulfur and cysteine. Cysteine is

the principal molecular carrier of sulfur in the epidermal protein keratin (Refs. 12 and 13). Sulfur is absorbed by the skin (Ref. 11) and is detectable in the epidermis about 2 hours after application. Sulfur is detectable throughout the skin after 8 hours but is gone after 24 hours (Ref. 14). Reactions to sulfur presumably begin within the first 2 hours after application and continue until sulfur is completely absorbed by the bloodstream.

Topically, sulfur causes an injury to the epidermis, followed by a reparative reaction (Ref. 6). The extent of injury probably depends on the amount of hydrogen sulfide produced within the epidermis, which in turn depends upon the following circumstances: (1) the concentration of sulfur applied (Refs. 6 and 10), (2) the length of time of application (Ref. 12), and (3) the degree of intactness of the skin surface (Ref. 10). Low concentrations of sulfur (1 to 2 percent) cause only minor epidermal damage. This damage is soon followed by a thickening of the epidermis (acanthosis) as the process of keratin formation is stimulated. This thickening may sometimes occur atypically and incompletely (Refs. 11, 12, and 15). The keratoplastic action of sulfur is most marked when sulfur is applied in a water-washable emulsion base (Ref. 12).

Sulfur concentrations in the range of 5 to 15 percent cause more injury to the skin and are keratolytic, especially when applied in a petrolatum base (Ref. 12). The release of hydrogen sulfide in the epidermis dissolves young prickle cells in the epidermis and causes swelling and softening of the top horny layer of the skin. These events are followed by the peeling off of the upper epidermis and stratum corneum (Refs. 6 and 10). Hence the antifungal action of sulfur on the skin is probably largely due to its keratolytic effect. In other words, when the stratum corneum is shed, the fungal spores and hyphae embedded within it are also shed (Refs. 10 and 11). Hydrogen sulfide may also be directly toxic to the fungus in the stratum corneum, although this remains speculative (Ref. 16). The keratolytic action of sulfur in an alkaline medium is enhanced by heat and light (Ref. 11).

In vitro studies with dermatophyte fungal cultures reveal that sulfur is not a potent fungicidal or fungistatic agent. In one study, precipitated sulfur in a 1:10 dilution caused no inhibition of dermatophytes (Ref. 17). In another study a 1:50 dilution did not inhibit dermatophyte growth, and a 1:1,000 dilution of sulfur killed only 29 percent of dermatophytes tested after a 24-hour exposure (Ref. 18). Sulfur ointment (15

percent sulfur in petrolatum) was found to have little or no fungistatic activity when tested against *M. albicans* or *T. interdigitale* (Ref. 19).

Another study found sulfur in a 5-percent dilution to be neither fungicidal nor fungistatic to *M. tropicalis* after a 2-minute exposure. However, other 2-minute exposure tests were more favorable in that a 1-percent dilution was found to be fungicidal to *T. interdigitale* (Ref. 10). Solutions of 1:10,000 sulfur in carbowax were found by investigators to completely inhibit a 3-hour broth culture of *C. albicans*. Higher dilutions of up to 1:200,000 sulfur in carbowax suppressed growth of *Candida* for up to 24 hours, but then lost their activity through sedimentation and allowed subsequent visible growth of the organism (Ref. 20).

Elemental sulfur has been reported to have antibacterial activity, with the activity largely depending on the size of the sulfur particles (especially with colloidal sulfur). A calcium phosphate-sulfur precipitate, in which fine particles of elemental sulfur were embedded in a calcium phosphate gel, was found to have a strongly inhibitory action against several strains of hemolytic streptococci (Ref. 21). This same gel had only moderate activity against *S. aureus* and no antibacterial activity against gram-negative organisms. It was postulated that sulfur might act on bacterial cells by inactivating the sulfur-hydrogen (SH) groups contained in enzyme systems of the bacteria. Indeed, the antibacterial action of sulfur was neutralized by the addition of cysteine and other SH-containing compounds to the culture medium which presumably restored the activity of the bacterial enzymes requiring free SH groups.

The popularity of sulfur baths for treating skin diseases in the 19th century probably stemmed from their success in treating scabies, a very itchy skin disease caused by a mite. However, by 1880 sulfur was also recognized as being destructive to the fungi causing the skin diseases of favus, ringworm, and tinea versicolor (Ref. 22).

Renewed interest in sulfur as an antifungal agent occurred in the 1930's following its use against fungal diseases of plants (Ref. 10). In 1932, sulfur was mentioned as being "of definitive value" in the treatment of tinea, although no specific types of fungal infection were documented (Ref. 11). At the same time, sulfur was felt to be beneficial in treating bacterial infections by withdrawing oxygen and moisture from the tissue to make conditions less favorable for bacterial proliferation (Ref. 11). To this end, the use of sulfur for bacterial

infections, such as boils, dates to at least the 1880's (Ref. 22).

In 1935, colloidal sulfur in a 2- to 5-percent aqueous solution was sponged twice daily between the toes involved with athlete's foot. The results were favorable. The same solution proved satisfactory for vesicular (blistered) athlete's foot treated 7 to 10 days with wet compresses of aluminum acetate. The colloidal sulfur solution did not, however, work well on either the hyperkeratotic (thickened) or eczematized (inflamed) types of athlete's foot. Jock itch and ringworm of the body responded well to the 2- to 5-percent colloidal sulfur in an aqueous, glycerinated or cholesterolized, hydrous wool fat base. But treatment with the colloidal sulfur was not superior to other forms of treatment (Ref. 10).

Sulfur ointment was listed as one of several possible prescriptions for athlete's foot of the hyperkeratotic variety. This preparation contained 15 percent sulfur in a base of wool fat, yellow wax, and white petrolatum. Half-strength sulfur ointment diluted with petrolatum was also effective in treating interdigital *C. albicans* infection on the hands and around the nails (paronychia) (Ref. 23).

In 1942, athlete's foot and jock itch were treated successfully with Wilkinson's ointment diluted one-third with zinc oxide ointment (Ref. 24). Before dilution, the original ointment consisted of 15 percent sublimed sulfur and 10 percent precipitated calcium carbonate in a mixture of 15 percent juniper tar, 30 percent soft soap, and 30 percent lard. The ointment was applied "sparingly" to prevent the development of dry scaly skin. Application of the ointment, together with daily foot baths in freshly prepared formaldehyde solution, was shown to decrease the number of cases of athlete's foot seen at a military clinic.

In 1945, about 100 British soldiers at a military clinic were treated for athlete's foot with Vlemminckx's solution (liquor calcis sulphuratae, BPC) (Ref. 25). The solution was prepared by boiling a mixture of 25 g quicklime and 50 g sublimed sulfur in 1 L water until only two-thirds of the original volume remained. The supernatant fluid was decanted and swabbed twice daily onto the feet and between the toes of the affected soldiers. The solution stung when applied to raw areas. Cases of athlete's foot were clinically cured in 3 to 10 days and no relapses were observed during variable observation periods of a few weeks to a few months. No cultures or controls were included in the study.

In 1951, *C. albicans* infections in several intertriginous skin areas were treated with carbowax-sulfur, which was prepared by heating 500 g carbowax with 5 g sublimed flowers of sulfur (Ref. 20). Among the 35 patients treated twice daily with the carbowax-sulfur ointment, 13 were cured, 18 were markedly improved, 3 improved temporarily, and 1 developed skin irritation. The length of treatment time varied from 1 to 4 months, with one exception of intermittent treatment for 2 years. Treatment was discontinued only after cultures were negative for *C. albicans* and the skin appeared normal. Several patients had involvement of multiple areas (groin, interdigital areas, and nails) which cleared. Unfortunately, no controls were included in the study. In patients with multiple involved areas it was not possible to separate the treatment times and responses of different anatomical areas under treatment.

Based on the above available data, the Panel concludes that sulfur is of questionable effectiveness in the treatment of athlete's foot, jock itch, and ringworm. Although elemental sulfur, particularly in colloidal form, is a strong antifungal agent in plants, there are no controlled studies demonstrating that sulfur is effective in treating fungal diseases in humans. A few uncontrolled studies which did not use cultures suggest that various sulfur ointments and solutions may be beneficial in the treatment of dermatophyte fungal infections (Refs. 10, 23, 24, and 25). Other uncontrolled studies (Refs. 20 and 23) suggest that sulfur may be effective in the treatment of *C. albicans* infections of the skin. In vitro studies suggest that sulfur has only mild antifungal and antibacterial activity (Refs. 17, 18, and 19).

(3) *Proposed dosage*—(i) *Concentration*. Sulfur 0.2 to 8.0 percent. A concentration of 8 to 10 percent sulfur may be used providing it is in a soap formulation which will be rinsed off after application.

(ii) *Directions for use*. See part III, paragraph A.2. above—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm. (See part III, paragraph A.2. above—Category I Labeling.)

(5) *Evaluation*. The Panel recommends in vitro testing and one double-blind, placebo-controlled clinical trial to determine the effectiveness of sulfur in the treatment of athlete's foot, jock itch, and ringworm. This study should be

conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th Ed., MacMillan Publishing Co., Inc., New York, p. 1005, 1975.
- (2) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 1162, 1976.
- (3) Osol, A., "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, pp. 1169, 1180-1181, 1202, 1975.
- (4) Sax, N. I., "Dangerous Properties of Industrial Materials," 3d Ed., Van Nostrand Reinhold Co., New York, p. 1127, 1968.
- (5) OTC Volume 070135.
- (6) Lorenc, E., and R. K. Winkelmann, "Evaluation of Dermatologic Therapy," *Archives of Dermatology*, 83:761-767, 1961.
- (7) Rossoff, I. S., "Handbook of Veterinary Drugs," Springer Publishing Co., New York, p. 580, 1974.
- (8) Macias-Sarria, J., "Colloidal Sulfur Earns Its Place in Cosmetics," *The American Perfume and Essential Oil Review*, pp. 39-40, April, 1945.
- (9) Monaghan, W. J., and F. Garai, "Treatment of Acute and Chronic Polyarthritides, Arthritis Deformans, and Septicemias, with Activated Colloidal Sulphur," *Medical Journal and Record*, 120:24-26, 1924.
- (10) Miller, H. E., "Colloidal Sulphur in Dermatology," *Archives of Dermatology and Syphilology*, 31:516-525, 1935.
- (11) Combes, F. C., "The Role of Sulfur in Dermatology," *New York State Journal of Medicine*, 32:1019-1023, 1932.
- (12) Strakosch, E. A., "Studies on Ointments. III. Ointments Containing Sulfur," *Archives of Dermatology and Syphilology*, 47:216-225, 1943.
- (13) Strakosch, E. A., "Studies on Ointments. IV. Local Action of Salicylic Acid Plus Sulfur from Various Ointment Bases," *Archives of Dermatology and Syphilology*, 48:384-392, 1943.
- (14) Scott, A., "The Behaviour of Radioactive Sulphur After Its External Application to the Skin," *British Journal of Dermatology*, 69:39-49, 1957.
- (15) Combes, F. C., "Colloidal Sulfur. Some Pharmacodynamic Considerations and Their Therapeutic Application in 'Seborrheic Dermatoses'," *New York State Journal of Medicine*, 46:401-406, 1946.
- (16) Ormsby, O. S., "A Practical Treatise on Diseases of the Skin," 4th Ed., Lea & Febiger, Philadelphia, p. 102, 1934.
- (17) Schamberg, J. F., and J. A. Kolmer, "Studies in the Chemotherapy of Fungus Infections. I. The Fungistatic and Fungicidal Activity of Various Dyes and Medicaments," *Archives of Dermatology and Syphilology*, 6:746-756, 1922.
- (18) Kingery, L. B., and A. Adkisson, "Certain Volatile Oils and Stearoptens as Fungicides, An Experimental Study," *Archives of Dermatology and Syphilology*, 17:499-511, 1928.
- (19) O'Brien, F. J., and W. J. Bonisteel, "The Fungistatic Value of Certain Ointments," *Journal of the American Pharmaceutical Association*, 30:191-196, 1941.
- (20) Hopkins, J. C., J. T. Weld, and B. M. Keston, "The Treatment of Monilia (Candida Albicans) Infections with Carbowax-Sulfur Ointment (A Preliminary Report)," *Journal of Investigative Dermatology*, 18:419-422, 1952.
- (21) Libenson, L., et al., "Antibacterial Effect of Elemental Sulfur," *Journal of Infectious Diseases*, 93:28-35, 1953.
- (22) Bulkley, L. D., "On the Use of Sulphur and Its Compounds in Diseases of the Skin," *Archives of Dermatology*, 6:233-241, 1880.
- (23) Wise, F., and J. Wolf, "Use of the Dermal Parasitocides," *Journal of the American Medical Association*, 107:1126-1132, 1936.
- (24) Atsatt, R. F., "A Simple Procedure for the Control of Fungus Infection of the Feet," *United States Naval Medical Bulletin*, 41:1450-1451, 1943.
- (25) James, T., "Interdigital Ringworm Treated with Solution of Sulphurated Lime," *The Lancet*, 2:401-402, 1945.

r. *Triacetin*. The Panel concludes that triacetin is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Triacetin, or glyceryl triacetate, is a colorless, somewhat oily liquid with a slight, fatty odor. It is prepared by the acetylation of glycerol. Triacetin is soluble in 14 parts water and is miscible with alcohol, ether, and chloroform (Ref. 1).

Triacetin is contained in currently marketed products in concentrations of 15 to 33.3 percent.

(1) *Safety*. The subcutaneous LD₅₀ of triacetin in mice is reported to be 2.3 mL/kg (Ref. 2). Li et al. (Ref. 2) also reported that triacetin in a 50-percent aqueous solution caused marked congestion and moderate edema when placed in rabbits' eyes. Triacetin was shown to be irritating to tissues and slightly hemolytic. It produces an emulsion when mixed with serum.

In contrast to this data, information supplied to the Panel indicates that triacetin, when tested as the pure compound or as a cream formulation, is completely devoid of local toxicity when evaluated on rabbit skin (both intact and abraded) and in rabbit eyes (Ref. 3). According to a letter from the Department of the Army (private communication), ointments containing 40 to 50 percent triacetin were nonirritating to the skin when tested behind the ears of human subjects (Ref. 3). Another private communication in this same submission reported that following the 10th consecutive application of a 25-percent triacetin cream in a repeated insult patch test,

there was no evidence of primary irritation.

Because of the chemical structure of triacetin and because the hydrolytic products of this agent (glycerin and acetic acid) are known to be systemically nontoxic in the amounts used, the Panel is not concerned about systemic toxicity from triacetin. In addition, the "Dispensatory of the United States of America" (Ref. 4) specifies that chloroazodin dissolved in triacetin 1:500 "may be used undiluted in open traumatic wounds * * *".

Therefore, in view of the evidence presented about and the rather extended history of use without significant problems of toxicity, the Panel concludes that triacetin is safe in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness*. The mechanism of action of triacetin is the apparent production of free acetic acid from the hydrolysis of the compound by esterases. When triacetin is exposed to esterase (produced by dermatophytes), acetic acid is split from the glycerin molecule until the pH of the environment is changed to about 4.0. At this pH level the activity of the esterase is inhibited, and no further acetic acid is liberated until the pH rises to the level where the esterase again becomes active.

In vitro, triacetin has shown activity (reduction of colony size) against a series of clinical isolates of dermatophytic fungi cultured on Sabouraud's agar (Refs. 5 and 6). In general, inhibition was noted at 0.1 percent, although there was considerable variation between dermatophytes. For instance, the colony diameters at this concentration were as follows: *E. floccosum*, 19 mm; *T. mentagrophytes*, 66 mm; *T. rubrum*, 59 mm; and *M. canis*, 37 mm. Triacetin 0.5 percent completely inhibited all dermatophytes except *M. Gypseum* which had a 3-mm colony diameter. Activity against *C. albicans*, however, was minimal. Testing against bacteria was not included.

Contrary to most antimicrobial agents, triacetin's activity increases in the presence of serum. Knight (Ref. 5) states that this is not surprising because "the ubiquitous esterase would be expected in serum." Two studies (Refs. 7 and 8) have dealt with the effectiveness of triacetin in the treatment of athlete's foot.

A double-blind study by Cahn and Levy (Ref. 7) in 1959 evaluated the effectiveness of triacetin in patients diagnosed with symmetrical ringworm of the body, athlete's foot, or

dermatophytosis. Cultures were performed before treatment began. The product was evaluated in ointment, liquid, and powder form (concentration not specified). The patients were used as their own controls. The length of treatment varied depending on the dosage form; the ointment was used for 1 to 12 weeks, the liquid for 2 to 8 weeks, and the powder for 3 weeks. Applications were made twice daily for all treatments (active ingredient and placebo). Both the subjective symptomatic relief and the objective clearing of the lesions were evaluated. Table 10 shows the results:

TABLE 10.—RESULTS OF DOUBLE-BLIND COMPARISON OF TRIACETIN IN OINTMENT, LIQUID, AND POWDER

Dosage form	Number of patients	Percent cleared	Percent no improvement
Ointment.....	45	46.7 (21)	*53.3 (24)
Liquid.....	40	60.0 (24)	*40.0 (16)
Powder.....	40	22.5 (9)	77.5 (31)

*NOTE: Infections due to *T. rubrum* did not respond to either the ointment or the liquid.

The authors concluded that successful responses, including symptomatic relief, usually occurred within the first week of therapy.

The Panel notes the small patient population in this study. Placebo results were not reported, and apparently neither followup cultures nor KOH preparations were performed. Also, it is unclear whether the results for the liquid and ointment are statistically significant.

A second study by Johnson and Tuura (Ref. 8) evaluated triacetin ointment 25 percent and triacetin liquid 5 percent in the treatment of various types of fungal infections. This study was not blinded and did not use a placebo control. Some patients received a combination of 25 percent triacetin ointment with 5 percent salicylic acid. However, results of the study were not correlated with treatment groups. Twenty-two of the 80 patients studied had athlete's foot caused by *T. mentagrophytes*. In 3 weeks, 15 of the 22 patients had negative KOH preparations and negative cultures. In seven patients the KOH preparation was positive, but the culture was negative. Four patients with *E. floccosum* infections (athlete's foot and jock itch) were cleared at the end of 3 weeks. It seems that *E. floccosum* and *T. mentagrophytes* infections of the feet clear with the topical application of triacetin. However, again, the patient population was small.

Although triacetin may clear athlete's foot caused by *T. mentagrophytes* or *E.*

floccosum, the Panel concludes that a well-designed, clinical study is necessary to establish triacetin as an effective antifungal ingredient. According to the preceding studies, triacetin is not indicated in the treatment of *T. rubrum* infections.

The Panel concludes that triacetin may be effective in the treatment of inflammatory, soggy toeweb athlete's foot but should be labeled as contraindicated for the dry form of the disease (caused by *T. rubrum*).

(3) *Proposed dosage*—(i) *Concentration*. Triacetin 15.0 to 33.3 percent.

(ii) *Directions for use*. See part III, paragraph A.2 above—Category I Labeling.

(4) *Labeling*. The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot. (See part III, paragraph A.2. above—Category I Labeling.)

Warning: "Use only for soggy, wet forms of athlete's feet."

(5) *Evaluation*. The Panel has seen no evidence that triacetin may be effective in any fungal disease other than the soggy toeweb form of athlete's foot. Moisture may be necessary for the activity of triacetin. Because ringworm of the body is almost always dry and is generally caused by *T. rubrum*, triacetin may not be effective in this condition. The Panel therefore recommends one double-blind, placebo-controlled clinical trial of each type of fungal disease—athlete's foot, jock itch, or ringworm—to establish the effectiveness of triacetin in each particular condition. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

- (1) Windholz, M., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1232, 1976.
- (2) Li, R. C., P. P. T. Sah, and H. H. Anderson, "Acute Toxicity of Monacetin, Diacetin, and Triacetin," *Proceedings of the Society for Experimental Biology and Medicine*, 48:28–28, 1941.
- (3) OTC Volume 070087.
- (4) Osol, A., and G. Farrar, "The Dispensatory of the United States of America," 25th Ed., J. B. Lippincott Co., Philadelphia, p. 291, 1955.
- (5) Knight, S. G., "The In Vitro Antifungal Activity of Triacetin," *Antibiotics and Chemotherapy*, 7:172–174, 1957.
- (6) Knight, S. G., "The Mechanism of Tricycleride Therapy in Dermatophytosis," *Journal of Investigative Dermatology*, 28:363–366, 1957.
- (7) Cahn, M. M., and E. J. Levy, "The Use of Triacetin (Fungacitin) in the Treatment of

Superficial Dermatophytosis," *International Record of Medicine*, 172:303–309, 1959.

(8) Johnson, S. A. M., and J. L. Tuura, "Glyceryl Triacetate (Triacetin) as a Fungicide," *Archives of Dermatology*, 74:73–75, 1956.

2. *Category III labeling*. The Panel concludes that the following labeling claims for products used in the treatment of athlete's foot, jock itch, and ringworm are unsupported by sufficient scientific data to permit classification in Category I. As indicated elsewhere in this document, additional data are required in order to place them in Category I. (See part III, paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

a. *Product performance labeling*. Specific statements relating to product performance must be substantiated by adequate data. This includes "speed of action" claims. In general, any Category I labeling of effectiveness that includes a time, such as "cures athlete's foot in 2 weeks," automatically becomes Category III until the time claimed is substantiated.

b. *Antibacterial activity*. Some antifungal ingredients, such as miconazole nitrate and iodochlorhydroxyquin, have antibacterial activity as well as antifungal activity. Although antifungal agents may have antibacterial activity in vitro, the Panel concludes that these ingredients may not use the term "antibacterial" in the labeling without supportive clinical trials demonstrating an antibacterial effect when the ingredient is applied to the toeweb.

D. *Combination Products Used in the Treatment of Athlete's Foot, Jock Itch, and Ringworm*.

The Panel acknowledges and concurs with the rationale expressed in the OTC drug combination policy regulation (21 CFR 330.10(a)(4)(iv)) as follows:

An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel concludes that combination products for the treatment of athlete's foot, jock itch, and ringworm should contain the minimal number of ingredients necessary to achieve effectiveness. In general, the fewer the ingredients, the safer and more rational

the therapy. Consumer interests are best served by exposure to the fewest ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness.

1. *Category I combination drug products.* a. *Combinations of antifungal ingredients.* (1) Each antifungal ingredient in the combination must be a Category I ingredient.

(2) Each antifungal ingredient in the combination must be present within the dosage range for a Category I ingredient as set forth elsewhere in this document.

(3) The combination may contain up to three antifungal ingredients provided each ingredient broadens the antifungal spectrum.

For example, the combination may contain nystatin, an anticandidal ingredient, to broaden the spectrum.

An antidermatophytic drug combined with an anticandidal drug would be a rational approach to the treatment of diseases caused by both dermatophytes and *Candida*. Because most consumers cannot distinguish between these diseases, such a combination would offer them broader therapy.

If one ingredient is shown to be very effective against a certain dermatophyte, such as *T. rubrum*, it may be useful to combine this ingredient with a Category I ingredient which is not so active against *T. Rubrum*.

b. *Combinations of antifungal ingredients with other ingredients.*

Combinations may include nonantifungal ingredients which have been classified as Category I by any OTC advisory review panel and are designed to aid the antifungal agent in relieving symptoms or enhancing activity. Antiperspirants and keratolytics may each be added provided that they are safe and effective and that their inclusion in a combination product does not decrease the effectiveness of the antifungal ingredient(s) nor decrease consumer safety. In general, combination topical antifungal products should contain no more than one active nonantifungal ingredient from each of the categories mentioned below.

(1) Combinations of up to three antifungal ingredients with an antiperspirant.

One class of ingredients that may be added is antiperspirants. The Panel believes that drying the affected area will aid in the treatment of athlete's foot. Examples of acceptable antiperspirants would be aluminum salts and other similar agents that can be shown to follow the above guidelines.

(The Panel considers drying agents

such as talc and bentonite as inactive ingredients present in formulations for nonantifungal purposes.)

(2) Combinations of up to three antifungal ingredients with a keratolytic agent.

Keratolytic chemicals are another permissible added ingredient class, provided that they can be shown to be safe and effective in the concentrations used. Theoretically, an effective keratolytic agent could remove the outer layers of the stratum corneum, thus better exposing the infecting fungus to the action of the antifungal ingredient. Salicylic acid is an example of such an agent. It should be recognized, however, that in carrying out their keratolytic action, many of the keratolytic agents irritate the skin.

(3) Combinations of up to three antifungal ingredients with hydrocortisone or hydrocortisone acetate, 0.5 to 1 percent.

Combinations of an antifungal agent with hydrocortisone or hydrocortisone acetate 0.5 to 1.0 percent have been submitted for evaluation of potential OTC use against fungal infections of the skin. Antifungal agents included in the various submitted combinations with hydrocortisone include iodochlorhydroxyquin, miconazole nitrate, and calcium undecylenate (Refs. 1, 2, and 3). Double-blind, controlled studies have been performed on each of these combinations except calcium undecylenate (Ref. 1).

Topical hydrocortisone and hydrocortisone acetate when used alone in the management of athlete's foot significantly reduce the itch and pain as well as the signs of inflammation. Despite this reduction of signs and symptoms, the growth of the organism continues as the inflammation is reduced. A positive KOH preparation is easily obtained from a lesion of athlete's foot or ringworm of the body that has been treated with topical hydrocortisone for 48 to 72 hours. This local reduction of inflammation is occasionally followed in 48 to 72 hours by a generalized eruption of erythema multiforme (a skin disease characterized by pimply or blistering lesions and reddening or discoloring of the skin about the lesions) or an "id" reaction. Consequently, hydrocortisone should never be used alone in the treatment of athlete's foot.

The inflammation produced by the organisms causing athlete's foot may act as a barrier and prevent a weak antibacterial or antifungal agent from effectively eradicating the infection. Hydrocortisone in 0.5 to 1.0 percent concentration is an effective anti-inflammatory agent capable of reducing

or eliminating the itching and burning in the skin caused by athlete's foot. It is reasonable to assume that a Category I antifungal agent for athlete's foot plus hydrocortisone would be a rational combination drug for the management of this condition.

In 1976 a combination cream containing miconazole nitrate 2 percent and hydrocortisone 1 percent was tested in a double-blind, controlled trial in Belgium (Ref. 4). Inflamed skin lesions of bacterial and fungal origin were treated in 63 patients (ages 12 to 60 years) with either the miconazole-hydrocortisone combination, miconazole 2 percent, or hydrocortisone 1 percent cream. Each cream was applied twice daily for 4 weeks. Dermatophytic fungi were identified by microscopic evaluation or culture in 41 patients. Bacteria (staphylococci and streptococci) were isolated in 21 patients, and no growth occurred in one patient.

After 3 weeks of treatment, dermatophytes were found only in patients using hydrocortisone alone, including 11 of 13 patients. No dermatophytes were found after 3 weeks in patients using either the miconazole-hydrocortisone or miconazole creams, whereas 28 of these patients originally had dermatophyte infections. The miconazole-hydrocortisone combination was superior to miconazole or hydrocortisone alone in producing symptomatic relief of itching and redness within 1 week, and in suppressing inflammation. At the end of the trial (4 weeks), cure rates were 85.7 percent with the miconazole-hydrocortisone combination, 40.0 percent with miconazole, and 4.5 percent with hydrocortisone alone.

An unpublished, double-blind, controlled study of miconazole nitrate 2 percent-hydrocortisone 1 percent cream was performed by Taplin in Colombia, South America in 1976 (Ref. 3). The 99 patients were male Caucasian soldiers with severe jock itch and ringworm of the body. All patients except one were infected by the dermatophyte *E. floccosum*. KOH preparations and fungal cultures were performed on days 0, 7, and 14 of treatment. Clinical evaluation of signs and symptoms was performed on days 0, 1, 2, 3, 4, 7, and 14, with scores of mild to severe included for fissuring, maceration, erythema, scaling, pustules/vesicles, erosions, and excoriations. Subjective symptoms of burning, pain, and itching were also evaluated on the same days. The clinical results are summarized in Table 11.

TABLE 11.—RESULTS OF TREATMENT WITH MICONAZOLE-HYDROCORTISONE

	Day 7		Day 14	
	Cured	Not cured	Cured	Not cured
Miconazole-hydrocortisone.....	27	6	32	1
Miconazole.....	22	11	25	7
Hydrocortisone.....	3	30	2	31

After 14 days, 97 percent of the combination miconazole-hydrocortisone group were cured, in contrast to 78 percent of the miconazole group and 6 percent of the hydrocortisone group. There were not enough subjects in the study to attain a "p value" of .05 between the miconazole-hydrocortisone and the miconazole-treated groups. However, Taplin felt that the 97-percent success of the combination product indicated "significantly greater efficacy" than miconazole, especially when tested under the "worst conditions of heat, humidity, and poor hygiene."

During the first 4 days of treatment the miconazole-hydrocortisone combination tended to reduce the intensity of signs and symptoms more than either miconazole alone or hydrocortisone alone. After 4 days of treatment, 16 patients in the miconazole-hydrocortisone group were free of symptoms, compared to only 8 in the miconazole group and 7 in the hydrocortisone group, but these differences were much less marked after 7 and 14 days of treatment. The fungal culture results (using DTM agar) were almost identical after 7 and 14 days of treatment, with negative cultures after 14 days in 33 of the miconazole-hydrocortisone group, 32 of the miconazole group, and only 4 of the hydrocortisone group. No followup cultures were done after treatment stopped.

In 1978 Maibach (Ref. 5) reported a randomized, double-blind, multicenter study comparing iodochlorhydroxyquin-hydrocortisone cream with its individual components in 354 patients with fungal infections of the skin. (The Panel had previously received both published and unpublished data from this same study which had been conducted by Carpenter et al. in 1972 (Refs. 2 and 6 through 9).) All patients had positive KOH and fungal cultures before treatment, and cultures were repeated on the final visit after 7 days of treatment. The types of fungal infections treated included athlete's foot (121), jock itch (105), ringworm of the body (80), moniliasis (37), and "other" (11), exclusive of hair and nail infections.

Patients received identical-appearing tubes of cream with instructions to

apply the cream three times daily. They were randomly assigned to 4 treatment groups: 89 patients received the combination cream containing 3 percent iodochlorhydroxyquin and 1 percent hydrocortisone; 83 received 3 percent iodochlorhydroxyquin cream; 96 received 1 percent hydrocortisone cream; and 86 received the cream vehicle alone. Patients were seen on day 2 or 3 of treatment and after 7 days of treatment for evaluation of signs and symptoms. Physicians rated the overall clinical response and graded the severity of erythema, scaling, vesiculation, and exudation. Patients rated the severity of itch and their overall change in discomfort. The results of the study after 7 days of treatment are summarized in Table 12.

TABLE 12.—COMPARISON OF IODOCHLOR-HYDROXYQUIN-HYDROCORTISONE (I+HC) CREAM WITH ITS INDIVIDUAL COMPONENTS

Treatment	[Percent]		
	Rated "good to excellent," by M.D.	Discomfort "gone or much better"	KOH(+) to (-) conversion
3% I+HC.....	65	64	49
3% I.....	46	55	56
1% HC.....	32	42	19
Vehicle.....	25	30	28

The combination of iodochlorhydroxyquin-hydrocortisone was concluded to be consistently better than either of its active components or the vehicle alone in the treatment of athlete's foot, jock itch, and ringworm of the body. The iodochlorhydroxyquin-hydrocortisone combination was also the best treatment for cutaneous candidiasis, although the number of patients treated was small.

The Panel believes that the prophylactic use of antifungal-hydrocortisone combinations is irrational because long-term use may introduce risks to the consumer, such as possible skin atrophy and other long-term steroid effects. The Panel therefore recommends that there be no claim of prevention made for these products.

The Panel recommends that hydrocortisone and hydrocortisone acetate combination products contain the following warning: "Do not use longer than 30 days without consulting a doctor or pharmacist."

The Panel recommends that all Category I combinations be labeled according to Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm, as outlined elsewhere in this document. (See part III, paragraph A.2. above—Category I Labeling.)

References

- (1) OTC Volume 070141.
- (2) OTC Volume 070209.
- (3) OTC Volume 070217.
- (4) Mertens, R. L. J., J. Morias, and G. Verhamme, "A Double-Blind Study Comparing Daktacort, Miconazole, and Hydrocortisone in Inflammatory Skin Infections," *Dermatologica*, 153:228-235, 1976.
- (5) Maibach, H. I., "Iodochlorhydroxyquin-Hydrocortisone Treatment of Fungal Infections. Double-Blind Trial," *Archives of Dermatology*, 114:1773-1775, 1978.
- (6) OTC Volume 070152.
- (7) OTC Volume 070153.
- (8) OTC Volume 070154.
- (9) Carpenter, C. L., et al., "Combined Steroid-Antifungal Topical Therapy in Common Dermatoses: A Double-Blind, Multi-Center Study of Iodochlorhydroxyquin-Hydrocortisone in 277 Patients," *Current Therapeutic Research*, 15:650-659, 1973.

2. *Category II combination drug products.*—a. *Criteria for Category II classification.* A combination is classified by the Panel as a Category II product, i.e., one that is not generally recognized as safe or effective, if any of the following apply:

(1) The combination contains any ingredient that is listed elsewhere in this document as a Category II ingredient for safety reasons. If classified by another Panel as a Category II ingredient for safety, its inclusion in a topical antifungal combination must be adequately justified.

(Ingredients in Category II for antifungal effectiveness but which the Panel has determined to be safe are permitted in combinations if they are used for nonantifungal purposes, such as keratolytic activity. See part III, paragraph B above—Category II Conditions.)

(2) The combination contains more than three antifungal ingredients.

(3) The combination contains a local anesthetic.

The Panel concludes that a combination of an antifungal ingredient with a local anesthetic, such as benzocaine, is irrational. Although local anesthetics may be useful in relieving the symptoms of athlete's foot, jock itch, and ringworm, these ingredients actually mask the symptoms of the fungal infection without helping to eradicate the fungus. Because any Category I antifungal drug will kill the fungus, thereby relieving symptoms, the Panel believes that the inclusion of local anesthetics in combination products is unnecessary. Also, through potential sensitization they may increase risk to the consumer and offer little added benefit.

b. *Category II combination product: Carbol-fuchsin solution.* The

combination of basic fuchsin 0.3 percent, phenol 4.5 percent, boric acid 1 percent, resorcinol 10 percent, alcohol, and acetone into a carbol-fuchsin paint is commonly known as "Castellani's paint" or "Magenta paint B.P.C." A paint is a medicated liquid preparation with antiseptic, astringent, caustic, fungicidal, or analgesic properties which is applied to the skin with a brush, a sponge, or a cotton applicator (Ref. 1). Carbol-fuchsin solution is usually kept in a dark bottle with a glass stopper (Ref. 2).

In 1928 and 1929, Castellani originally advocated the use of carbol-fuchsin solution for treatment of chronic cases of fungal infection of the feet ("epidermophytosis"), especially cases associated with secondary bacterial infection. He also used it to successfully treat jock itch and itching of the anogenital area associated with both dermatophyte and yeast-type (monilial, saccharomycetic, and cryptococcal) fungal infections (Refs. 3 and 4).

The combination of saturated alcohol solution of basic fuchsin and 5 percent aqueous phenol gave "good results" when used in treating fungal infections, but Castellani believed that the addition of boric acid and acetone made it more penetrating and increased its action. Resorcinol was thought to further enhance the action of the paint, especially in chronic cases of athlete's foot resistant to other forms of therapy, but was not absolutely necessary for the effectiveness of the paint. The frequency of application varied from several times daily to twice weekly. For use on acutely inflamed areas, Castellani recommended diluting the paint with an equal part of water. He recognized the disadvantage of the paint, which colored the skin a deep red, but thought that most patients with chronic fungal infections would not object to it (Refs. 3 and 4).

Carbol-fuchsin solution became a popular antifungal remedy during the 1930's and was still commonly used through the 1960's. Seale and Clark (Ref. 2) reported on the use of carbol-fuchsin solution in 50 cases of intertriginous moniliasis (*C. albicans* infections of overlapping skinfolds under the arms, beneath the breasts, in the groin area, and between the toes). The diagnosis in each case was confirmed with KOH preparations or cultures. The paint was applied several times daily. Discomfort and intense itching were relieved within a few hours; in most cases, recovery was "complete" within a week. If lesions were widespread or acutely inflamed with raw surfaces, the paint was diluted 1:1 to 1:3 to avoid harmful

effects from absorption of the 5-percent phenol in the paint.

The authors concluded that results were "usually prompt and frequently dramatic." They also concluded that basic fuchsin was not always a necessary component of carbol-fuchsin solution, because the therapeutic value of the paint was only slightly lessened if basic fuchsin was omitted from the formula. However, they observed that toeweb infections with *Candida* often have deep, erosive lesions between and beneath the toes, which respond more readily to a fuchsin-containing paint. Seale and Clark felt that basic fuchsin had a drying, adhesive quality which enabled the paint to adhere well to the toeweb. The presence or absence of basic fuchsin in the paint did not seem to alter the in vitro growth of *Candida* suspensions on Sabouraud's media. Full-strength carbol-fuchsin solution completely inhibited the growth of *Candida*. Although the Panel was impressed by the seemingly favorable response of candidal skin infections to carbol-fuchsin solution in this study, it concluded that the study was markedly deficient because of the absence of controls and followup fungal cultures.

Leyden and Kligman (Ref. 5) searched for a substitute for carbol-fuchsin solution which would not stain the skin. They stated that "carbol-fuchsin solution (Castellani paint) deserves the esteem accorded it by generations of therapists. Not only is it drying, but basic fuchsin is a powerful antimicrobial agent." They felt that eliminating the dye would destroy the antimicrobial effect. In their experience, colorless carbol-fuchsin solution had only "feeble therapeutic value." They did find, however, that carbol-fuchsin solution was equivalent to 30 percent aluminum chloride for promoting drying of soggy toeweb and effectively treating symptomatic athlete's foot. The two solutions were tested in paired comparison studies in 10 volunteers with athlete's foot. After 1 week of treatment, improvement was equal in both feet as judged clinically. No KOH preparations or cultures were included in the study, and treatment for longer than 1 week was not reported.

Riley and Flower (Ref. 6) compared the in vitro effects of carbol-fuchsin solution and gentian violet solution against *C. albicans*. Their study was undertaken in response to the favorable clinical trial of carbol-fuchsin solution reported by Seale and Clark (Ref. 2). As Riley and Flower did not believe that the solution was clinically effective. In vitro studies were performed by mixing dilutions of carbol-fuchsin solution (1:50

to 1:5000) into the melted Sabouraud's agar and then plating the cultures with a saline suspension of 1:1,000 *C. albicans*. The various components of the paint were similarly tested, including a 7-percent alcoholic solution of basic fuchsin. Dilutions of 1 percent gentian violet ranging from 1:10 to 1:10,000 were similarly tested.

After 24 hours, complete inhibition of *C. albicans* was seen on all gentian violet plates and the plates containing 1:50 and 1:100 dilutions of carbol-fuchsin solution. After 48 hours, only the gentian violet plates and the 1:50 dilution of carbol-fuchsin still showed complete inhibition of growth. Among the individual components of carbol-fuchsin solution, only 7 percent basic fuchsin and 5 percent aqueous phenol in 1:25 dilutions gave complete inhibition of growth at 48 hours, while 1:25 dilutions of 8 percent aqueous resorcinol allowed only slight growth after 24 hours.

The authors concluded that gentian violet was much superior to carbol-fuchsin solution or any of its components in inhibiting *C. albicans*. They also concluded that against intertriginous candidiasis the most active component of the paint was basic fuchsin. They were unable to explain the effectiveness reported by Seale and Clark (Ref. 2). They postulated that the therapeutic effectiveness of carbol-fuchsin solution was probably due to its drying qualities and keratolytic ability (Ref. 6).

Carbol-fuchsin solution was evaluated for its antibacterial effectiveness by Marples and Kligman (Ref. 7), using occlusion tests on human forearms. The paint contained 0.4 percent basic fuchsin, 4.5 percent phenol, and 10 percent resorcinol in acetone-water and was extremely effective in preventing multiplication of bacteria in the occlusion test and in reducing the number of bacteria in the expanded flora test. The solution did not allow overgrowth of gram-negative bacteria, as did basic fuchsin when tested alone.

Carbol-fuchsin solution was evaluated in infants in the treatment of diaper rash and seborrheic dermatitis (often infected with *C. albicans*) of other intertriginous areas (Ref. 8). For many years the standard treatment at a hospital in Belfast had included twice daily applications of the paint for 48 hours, followed by nystatin cream or ointment. It had been observed that children who had fair complexions or had been bathed just before being painted became mildly shocky and drowsy.

A 6-month-old infant whose entire body had been painted with carbol-fuchsin became drowsy, had shallow

respiration, and passed blue urine 12 hours after painting. Central nervous system depression secondary to the paint was suspected. The painting was stopped, and the infant recovered. Because phenol toxicity was suspected, 16 infants, ages 2 to 5 months, with seborrheic dermatitis were monitored with 24-hour urine collections for phenol after 11 to 15 percent of their body surfaces were painted with carbolfuchsin solution. Phenol was detected in the urine of four children. This led to discontinuation of the treatment in infants. The authors pointed out that the paint is usually applied to intertriginous areas of skin for its drying ability and anti-yeast and antibacterial actions, and that these areas are ideal for absorbing chemicals found in the paint. They also stated that carbolfuchsin solution was withdrawn from production because of the presence of carcinogenic compounds involved in its synthesis (Ref. 8).

The Panel concludes that carbolfuchsin should be placed in Category II for safety. The concentration of phenol (4.5 percent) exceeds the minimal safe concentration of 1.5 percent previously set by the Panel. Also, the concentration of resorcinol (10 percent) is not safe for OTC antifungal use. A third safety problem involves basic fuchsin, considered to be a potential carcinogen. The Panel also concludes that the effectiveness of carbolfuchsin solution in the treatment of athlete's foot, jock itch, and ringworm is questionable because of the lack of any placebo-controlled, double-blind clinical trials. The Panel recognizes, however, that carbolfuchsin has been widely used for over 50 years without apparent documented toxic effects in adults. The Panel concludes that the use of carbolfuchsin solution, prescribed and supervised by a physician, might be an appropriate treatment for some cases of athlete's foot and jock itch.

References

- (1) Welsh, A. L., "The Dermatologist's Handbook," Charles C. Thomas Publishing Co., Springfield, IL, p. 36, 1957.
- (2) Seale, E. R., and W. A. Clark, "Treatment of Intertriginous Moniliasis," *Southern Medical Journal*, 41:926-930, 1948.
- (3) Castellani, A., "Carbolfuchsin Paints in the Treatment of Certain Cases of Epidermophytosis," *American Medicine*, 34:351-352, 1928.
- (4) Castellani, A., "Further Observations on the Treatment of Epidermophytosis of the Toes (Mango Toe) and Certain Other Forms of Epidermophytosis by a Fuchsin Paint," *Journal of Tropical Medicine and Hygiene*, 32:77-79, 1929.
- (5) Leyden, J. J., and A. M. Kligman, "Aluminum Chloride in the Treatment of Symptomatic Athlete's Foot," *Archives of Dermatology*, 111:1004-1010, 1975.

(6) Riley, K., and A. H. Flower, "A Comparison of the Inhibitory Effect of Castellani's Paint and of Gentian Violet Solution on the In Vitro Growth of *Candida albicans*," *Journal of Investigative Dermatology*, 15:355-361, 1950.

(7) Marples, R. R., and A. M. Kligman, "Methods for Evaluating Topical Antibacterial Agents on Human Skin," *Antimicrobial Agents and Chemotherapy*, 5:323-229, 1974.

(8) Rogers, S. C., F. G. Burrows, and D. Neill, "Percutaneous Absorption of Phenol and Methyl Alcohol in Magenta Paint B. P. C.," *British Journal of Dermatology*, 98:559-560, 1978.

3. *Category III combination drug products*—a. *Criteria for Category III classification.* A combination is classified as a Category III product if any of the following apply:

(1) The combination contains one or more Category III antifungal ingredients. (Category III ingredients are permitted in combinations if they are safe and are used for nonantifungal purposes, such as keratolytic activity. See parts III, paragraph C. above—Category III Conditions.)

(2) The concentration of any Category I antifungal ingredient is below the minimal effective dosage set by the Panel for such ingredient.

(3) The combination contains an antibacterial ingredient.

The Panel concludes that a broad-spectrum antibacterial ingredient which is active against gram-positive and gram-negative bacteria combined with an antifungal ingredient is a rational combination for the treatment of athlete's foot.

In 1973, Amonette and Rosenberg (Ref. 1) demonstrated that characteristic recalcitrant eruptions of the toeweb, with "soggy wetness" and denuded skin, were associated with infection by gram-negative bacteria. The infection occurred mainly in adult males and could be present concurrently with athlete's foot caused by dermatophytes. Either *P. aeruginosa* or *Proteus mirabilis* or both were cultured from all 12 patients with the soggy toeweb infections. Treatment was difficult and required a combination of bed rest, exposure to air, and various applications of silver nitrate solution, Castellani's paint, and gentamicin sulfate cream to be successful.

Leyden and Kligman (Ref. 2) demonstrated that the bacterial population of toeweb greatly increases with experimental occlusion of the feet or toes, similar to conditions produced by hot weather, sweating, exercise, and tight shoes. They further showed that if dermatophytes were present before occlusion, the toeweb became red, macerated, keratotic, and symptomatic

(uncomfortable), whereas normal toeweb without fungi did not develop such changes despite the expanding bacterial flora. They believe that the fungi probably damaged the stratum corneum, enabling the high level of bacterial growth to aggravate the "athlete's foot" between the toes.

The bacteria most commonly isolated from toeweb were diphtheroids, but as moisture and maceration increased in the toeweb, *S. aureus* and gram-negative bacteria (*Proteus* and *Pseudomonas* species) greatly increased. As the bacteria increased, the athlete's foot became more severe and the recovery of dermatophytes markedly decreased, with fungi being found in only 36 percent of the toeweb in severe cases in contrast to 84 percent in the mild cases. (Although the fungi are still present in the skin (as shown by biopsy), they are apparently forced deeper into the stratum corneum in the soggy toeweb and are often not evident on either KOH preparation or culture.)

In the same study, antibacterial agents (hexachlorophene 5 percent and neomycin 1 percent) were applied to occluded toeweb infected with dermatophytes and also to some toeweb that were not infected. The hexachlorophene suppressed gram-positive bacteria, but allowed proliferation of gram-negative bacteria in the toeweb. Although all toeweb infected with dermatophytes became red, macerated, and hyperkeratotic, the hexachlorophene-treated areas did not develop the foul odor and intense itching characteristic of untreated infected toeweb. Normal toeweb (without contaminating dermatophytes) treated with hexachlorophene developed only a white, moist appearance despite the heavy growth of *Pseudomonas*. The treatment of toeweb with neomycin was beneficial in the wet, macerated form of athlete's foot but not in the dry, scaling form. Leyden and Kligman concluded that topical antibacterial agents produced definite clinical benefit in the treatment of athlete's foot, although the disease was "not cured, merely curbed."

The combination of neomycin 1 percent and tolinaftate 1 percent in ointment was also evaluated in the same study. The combination was thought to be clinically more effective than either treatment alone in both the wet and dry forms of athlete's foot involving toeweb. The combination of the antibiotic and the antifungal agent resulted in "swifter and greater resolution of signs and symptoms" of macerated interdigital athlete's foot (Ref. 2).

A previous study by the same authors demonstrated that 30 percent aluminum chloride (hexahydrate form) produced resolution of macerated hyperkeratotic toeweb after 7 to 10 days of twice daily application (Ref. 3). This effect was attributed to the local drying and astringent effect, as well as the antimicrobial effect of aluminum chloride.

The Panel concludes that the combination of an antifungal ingredient with a broad-spectrum antibacterial agent is sometimes desirable for the treatment of athlete's foot characterized by soggy toeweb. Before such an ingredient could be included, however, the Panel would require a double-blind, controlled clinical study demonstrating effectiveness. There is no evidence that an antifungal-antibacterial combination is beneficial in the treatment of jock itch or ringworm of the body. The Panel therefore concludes that until such a combination is proven effective, it is not rational for the treatment of jock itch or ringworm.

The Panel does not approve the inclusion of either hexachlorophene or neomycin as an antibacterial agent in athlete's foot products, but has cited them merely as examples of antibacterial agents used in previous studies. The Panel concludes that any antibacterial agent considered for inclusion in a combination antifungal product should be safe and effective. The Panel is particularly concerned that chronic use of certain antibacterial ingredients could result in potential toxicity, including contact sensitization. This sensitization is likely to occur on the feet because of prolonged contact between sensitizers and the skin under conditions of heat, moisture, and occlusion produced by shoes. The Panel further concludes that antibiotics (with the exception of nystatin) should not be included in athlete's foot products because of the potential hazard of developing widespread antibiotic-resistant strains of bacteria.

b. *Category III combination product: Whitfield's ointment.* Whitfield's ointment has been a popular antifungal ointment since the 1930's. It was originally made of benzoic acid 12 percent, salicylic acid 6 percent wool fat 5 percent, and white petrolatum. The composition has been modified; Whitfield's ointment USP XVI contained benzoic acid 6 percent and salicylic acid 3 percent in polyethylene glycol.

Molinas (Ref. 4) evaluated the effectiveness of various antifungal ointments in an in vivo guinea pig study. Treatment was begun immediately after inoculation with the test organism, *T. mentagrophytes*. The in vivo study was

followed by in vitro testing on the same compounds using agar cup plate and wet filter paper methods. Whitfield's ointment (12 percent benzoic acid-6 percent salicylic acid) compared favorably with the control (5 percent undecylenic acid-20 percent zinc undecylenate) in all tests.

Dolan et al. (Ref. 5) evaluated the activity of several antifungal agents by measuring the immersion time necessary to kill *T. mentagrophytes* in infected epidermal scales obtained from guinea pigs. The fungicidal effect depends upon the penetration and fungicidal activity of the test material, which the authors believed correlated well with actual clinical conditions. Whitfield's ointment (12 percent benzoic acid-6 percent salicylic acid) allowed growth at 5 minutes, but inhibited *T. mentagrophytes* at immersion times of 15 minutes and longer. The same results occurred with 5 percent undecylenic acid, implying similar antifungal activity. Salicylic acid 5 percent was also tested and found to be fungicidal. It required 30 minutes' immersion time to inhibit growth.

In an uncontrolled study, Hopkins et al. (Ref. 6) evaluated the modified Whitfield's ointment (6 percent benzoic acid-3 percent salicylic acid) in the treatment of athlete's foot. Forty-eight percent of the 29 patients had negative KOH preparations after 1 to 2 weeks of treatment, although only 10 percent were reported as clinically cleared. Fifteen patients remained in the study for up to 4 weeks. Of these, 40 percent were KOH negative, and 27 percent were clinically cleared. Eight percent of the cases treated showed mild irritation from Whitfield's ointment. The authors noted that benzoic acid rarely caused irritation. Salicylic acid was thought to be more irritating because of its keratolytic action. Whitfield's ointment was also tested in patients with jock itch. It was more effective in treating jock itch than in treating athlete's foot, but was also more irritating in the groin. Twenty-two percent of 65 patients reported irritation, with severe irritation in 5 percent.

Holti (Ref. 7) conducted a double-blind trial comparing the effectiveness of the modified Whitfield's ointment (6 percent benzoic acid-3 percent salicylic acid) and pecilocin in the treatment of athlete's foot (12 patients) and ringworm (2 patients). The organisms cultured were either *T. rubrum* or *T. interdigitale*. Treatment was for 8 weeks. Patients were assessed clinically and by cultures 1 month after treatment stopped. If the disease was still present, the patient was then treated with the other

ointment. Followup continued at 3-month intervals for the next 2 years.

The two patients with ringworm were treated with pecilocin. They were free of infection on the first examination and did not relapse. Of the 12 with athlete's foot, 5 had been treated with pecilocin and 7 with Whitfield's ointment. Only two patients (one Whitfield's and one pecilocin) required a switch to the other treatment. After 6 months, the two still had positive cultures. Three other patients (two treated with Whitfield's and one with pecilocin) who had been clear at 3 months were found to have positive cultures at 6 months. The remaining seven patients maintained negative cultures at 6 months.

Holti concluded that Whitfield's ointment and pecilocin were equally effective fungicidal ointments. He believed that nail involvement was responsible for the recurring athlete's foot infections. Although the study design was adequate, patient numbers were small and a placebo control was not used.

The Panel concludes that Whitfield's ointment (6 percent benzoic acid-3 percent salicylic acid) is of questionable effectiveness in the treatment of athlete's foot, jock itch, and ringworm. It recommends one double-blind, placebo-controlled trial to determine the effectiveness of this ointment.

References

- (1) Amonette, R. A., and E. W. Rosenberg, "Infection of Toe Webs by Gram-Negative Bacteria," *Archives of Dermatology*, 107:71-73, 1973.
- (2) Leyden, J. J., and A. M. Kligman, "Interdigital Athlete's Foot. The interaction of *Dermatophytes* and Resident Bacteria," *Archives of Dermatology*, 114:1466-1472, 1978.
- (3) Leyden, J. J., and A. M. Kligman, "Aluminum Chloride in the Treatment of Symptomatic Athlete's Foot," *Archives of Dermatology*, 111:1004-1010, 1975.
- (4) Molinas, S., "In Vivo Screening of Antifungal Ointments," *Journal of Investigative Dermatology*, 25:33-42, 1955.
- (5) Dolan, M. M., et al., "A Semi-In Vivo Procedure for Testing Antifungal Agents for Topical Use," *Journal of Investigative Dermatology*, 28:359-362, 1957.
- (6) Hopkins, J. G., et al., "Fungistatic Agents for Treatment of *Dermatophytosis*," *Journal of Investigative Dermatology*, 7:239-253, 1946.
- (7) Holti, G., "A Double-Blind Controlled Trial of Whitfield's Ointment and Variotin in Ringworm Infections with a Two-Year Follow-Up," *Acta Dermatovenereologica*, 50:229-231, 1970.

E. Guidelines for Safety and Effectiveness Studies

The following guidelines are for studies which the Panel recommends be

conducted in order to move a Category III topical antifungal drug product into Category I. These guidelines are in accord with the present state of the art, but do not preclude the use of any advances or improved technology.

The Panel's approach has been to completely study the potential toxicity of active ingredients used in topical antifungal products. Even though these ingredients are to be used topically, their oral toxicity should be studied for the following reasons: (1) To identify the target organ or system and having identified it, to (2) determine the safety factor which permits safe use when absorption and systemic toxicity occur.

1. *Safety guidelines.* The Panel recommends that the following studies be performed to evaluate topical antifungal ingredients classified in Category III because of inadequate safety data.

a. *Acute studies in animals.* (1) Determine the acute oral toxicity of the total formulation in appropriate species to define the response curve and allow determination of the LD₅₀, LD₅₀, and LD₅₀.

(2) Conduct short-term topical toxicity tests on the total formulation on both intact and abraded skin.

(3) Conduct an appropriate rabbit skin irritation study on intact and abraded skin on the vehicle and total formulation.

(4) Conduct an appropriate rabbit eye irritation study on the vehicle and total formulation.

(5) Conduct a skin sensitization study in guinea pigs on the total formulation and its vehicle.

b. *In vitro screening for carcinogenic potential.* (1) A bacterial mutagenesis assay would be a logical first step in screening for carcinogenic potential. One of the assays using the *Salmonella* histidine auxotroph back mutation, such as that described by Ames (Ref. 1) or Frantz and Mallin (Ref. 2), would be suitable. Because the compounds in question are likely to be antibacterial, parallel dose-response curves for viability must be done. Where obvious antibacterial activity occurs, other cellular testing procedures should be used.

(2) Depending on the properties of the chemical tested and the results of the bacterial mutagenesis assay, other *in vitro* tests could be conducted for clarification. These tests should use a mammalian cell culture system designed to test either mutagenicity or transformation. Strategies for selecting tests in this rapidly developing field can be found in current literature.

c. *Subchronic studies in animals.* Conduct a 28-day dermal toxicity study

in the rabbit or other appropriate species on abraded skin at suitable dose levels to ensure adequate exaggeration of normal "use" levels. At the conclusion of this study, conduct a full pathological assessment on vital organs and skin. It would be desirable to evaluate the direct effects on the skin following application for a longer period of time, but the Panel is not aware of a suitable model for such a study.

(2) Conduct a subchronic (90 days or longer) feeding study with the total formulation. Determine blood levels and conduct full pathology at termination of the study. This study should attempt to determine the "no effect" blood level of the total formulation. Determine the target organ(s) for toxic effects.

d. *Chronic studies in animals.* (1) Conduct a 1-year chronic feeding study with at least two dose levels. Monitor blood levels at 3-month intervals. Conduct a full pathology evaluation at conclusion of study.

(2) a carcinogenicity evaluation following dermal application will be necessary only if the appropriate *in vitro* screening assays are positive or have yielded questionable results. For example, antifungal agents may have bacterial activity which can cause false negative or misleading results in the *Salmonella* mutagenicity test because the assay procedure involves bacterial enumeration.

e. *Studies in humans.* (1) Determine the irritation potential of the vehicle and the total formulation using the best current procedures.

(2) Conduct an appropriate sensitization potential study on the total formulation using the most reliable procedure for identifying both potent and weak sensitizing potential(s). It is especially important to test for sensitization in ingredients that are intended for prophylactic use.

(3) Because absorption studies in animals do not necessarily parallel those in humans, appropriate transepidermal studies should be conducted in humans. These studies should be conducted only where the safety of the ingredient has been adequately established in animals.

References

- (1) Ames, B. N., J. McCann, and E. Yamasaki, "Methods for Detecting Carcinogens and Mutagens with *Salmonella* Mammalian Microsome Mutagenicity Test," *Mutation Research*, 31:347-364, 1975.
- (2) Frantz, C. N., and H. V. Mallin, "The Quantitative Microsomal Mutagenicity Assay Method," *Mutation Research*, 31:365-380, 1975.

2. *Effectiveness guidelines.* An antifungal ingredient must have at least

one well-designed clinical study demonstrating effectiveness in the treatment of athlete's foot as the minimal indication of effectiveness. It is generally accepted that fungal infections of the feet may be more difficult to control than those of the groin. For this reason the Panel believes that any ingredient that is effective in the treatment of athlete's foot will also be effective in the treatment of jock itch or ringworm. It is important to note, however, that any ingredient with effectiveness demonstrated only in jock itch or ringworm and supported by a clinical trial may use "jock itch" or "ringworm" but not "athlete's foot" as a labeled indication.

The study population for any clinical study of athlete's foot, jock itch, or ringworm infections should be carefully selected. Certain populations may be desirable because environmental conditions and regimented routines and dress may predispose these groups to develop infections; military populations are an example. University dormitory or athletic populations may be acceptable if proper control can be instituted.

Other studies have used accessible patients, such as those referred to clinics or large dermatology centers in universities. This patient population frequently includes those with chronic fungal disease who are most difficult to treat satisfactorily.

a. *Helpful procedures in performance of trial.* Regardless of the study population selected, the patients must have significant disease. In all cases, a positive KOH and culture is an essential requirement for admission to a study. Symptoms alone are not a reliable basis for entering a study because different diseases may have similar symptoms.

An anatomical diagram (map) of the foot is helpful when it is used to indicate the sites from which skin scrapings were taken for KOH preparations and cultures. These sites should be sampled again for cure cultures. Any additional sites should also be marked on the map. This technique provides a permanent record for each patient.

The preferred site is the one the clinician determines to be most likely to produce a fungal isolate. Mushy toe sites should not be used because the rate of fungal isolation is low. Sampling of this preferred site and one other site on all patients, as opposed to sampling a standardized site on every patient, shows the highest number of recoveries.

Numerical grades for evaluating the severity of each symptom and definitions of these grade values should be recorded, thereby providing defined grading scores. Investigators should be

trained and experienced on the grading scale to be used.

Clinical photography with paired photographs may also be helpful in the preparation of a final record. These photographs are not essential, but when they are used, they should be standardized.

The Panel recommends that the following studies be performed to evaluate topical antifungal ingredients classified in Category III because of inadequate effectiveness data.

b. Criteria for determining antifungal activity. To determine the specific antibacterial and antifungal activity of ingredients, specific in vitro testing procedures will be required. These procedures will also apply when these ingredients are tested against clinical isolates during clinical testing.

In in vitro testing, the antifungal ingredient should be tested in the concentration used in the formulated product. The testing procedure should state whether the single ingredient or the formulated product was tested. It is often useful to establish an activity curve so that tests need not be limited to this single concentration. Test data should also include specific details of the organisms, the media, and the neutralizers that were used.

Some ingredients reviewed by the Panel may have antifungal activity, but were included at very low concentrations. These are recognized by microbiologists as preservative levels, i.e., they have been included to maintain the quality of the product and to prevent contamination on repeated use. It is necessary to establish whether an ingredient is included in an antifungal preparation as an antifungal agent or as a preservative. The results of in vitro testing and determination of the spectrum of the chemical should reveal this.

An ingredient included as a preservative should be present at a level necessary for adequate preservation of the product. The minimal effective preservation level can be determined by the standard preservative effectiveness test contained in the "United States Pharmacopeia" (Ref. 1) or the CTFA preservatives test (Ref. 2). Modifications of this procedure allow more accurate estimation of the effectiveness of a preservative ingredient and involve rechallenge and organic load testing.

c. Characterization of clinical isolates. When clinical studies are performed, the microorganisms infecting each patient should be identified. When a specimen is taken for culture, the researcher should specify the medium used, the type of inoculation, the

temperature and time of incubation, and the identification of isolates.

Several media and techniques for isolating clinical specimens are described in the literature. Because there is considerable disagreement on the best procedure for in vitro testing, alternative procedures are presented. References are included in which supporters of each technique discuss the specific attributes of that particular technique.

(1) *Dermatophytes*. The Panel stresses the importance of the isolation of a positive culture as part of any protocol for an acceptable clinical study. The testing procedures should indicate the degree of susceptibility of various clinical isolates to the antifungal ingredient being tested. This includes the ingredient and the final product formulation. Specific suggestions concerning susceptibility testing procedures are discussed below.

(i) For clinical isolation of dermatophytes, Dermatophyte Test Medium (DTM) is strongly recommended. It offers advantages since it contains specific inhibitors for other microorganisms and in comparative trials has shown a higher rate of positive cultures (Ref. 3). However, some clinics may prefer to use another suitable medium for isolation. If so, the rate of isolation and method of identification should be reported.

(ii) Identification of the isolate from DTM should be made according to Rebell and Taplin (Ref. 4).

(2) *Candida*. The following specific information and procedures should be used in order to identify isolates believed to be *Candida*.

(i) Perform KOH or wet mount to determine whether the isolate is yeastlike.

(ii) Identify the specific strain of *Candida* as follows: Pagano-Levine medium should be used because specific and positive identification of *C. albicans* can be made with this medium based on the presence of chlamydoconidia. If another similar suitable medium is used for isolation, the rate of isolation and method of identification should be reported. Other biochemical tests exist for the identification of other less frequently isolated candidal species, such as *Candida parapsilosis*, *Candida tropicalis*, or *Candida stellatoidea* (Ref. 5) which do not produce chlamydoconidia.

(iii) Determine whether the isolate is pathognomonic according to yeast morphology and site of isolation.

(3) *Bacterial isolates*. If the sampling of mushy toes is avoided, as mentioned above, and the specific media mentioned are used, bacteria will not ordinarily be isolated. If they are found,

they frequently gram negatives, especially *Pseudomonas*. (Ref. 6).

References

- (1) "The United States Pharmacopeia," 20th Ed., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 873-874, 1979.
- (2) "A Guideline for the Determination of Adequacy of Preservation of Cosmetics and Toiletry Formulations," *Toilet Goods Association Cosmetic Journal*, 2:20-23, 1970.
- (3) Taplin, D., et al., "Isolation and Recognition of Dermatophytes on a New Medium (DTM)," *Archives of Dermatology*, 99:203-209, 1969.
- (4) Rebell, G., and D. Taplin, "Dermatophytes: Their Recognition and Identification," 2d Ed., University of Miami Press, Coral Gables, FL, 1970.
- (5) Winner, H. L., and R. Hurley, "Candida Albicans," J. and A. Churchill, Ltd., London, 1964.
- (6) Amonette, R. A., and E. W. Rosenberg, "Infection of Toe Webs by Gram-Negative Bacteria," *Archives of Dermatology*, 107:71-73, 1973.

d. In vitro testing of antifungal ingredients. Many ingredients placed in Category III have never been adequately characterized for their antifungal activity. The Panel has indicated that some agents have specific activity where only minimal testing has been done. Knowledge of the type of inhibitory activity or killing activity is required to adequately test and formulate ingredients. The results of well-conducted in vitro testing may help one prudently decide whether to invest funds in clinical trials. Also, data derived from activity testing permit a significant increase in predictability when the ingredient is used.

Culturing and susceptibility testing procedures in hospital settings have not been well developed for antifungal agents because diseases caused by fungi, although often serious, are less common than infectious diseases of bacterial origin. The development of testing procedures has also been discouraged in dealing with potentially active ingredients because the correlation of the results of in vitro testing with clinical effectiveness has not been high for antifungal agents. Improved procedures now permit more rapid, reliable, and simplified culturing. The Panel has attempted to describe techniques which may help improve the correlation between in vitro and in vivo activity.

(1) *Testing for fungicidal or fungistatic activity.* Identification of the specific type of activity is important. Fungistatic agents probably are effective because they keep the fungus from reproducing while allowing body responses to act effectively in

eliminating the fungus. Frequently, fungistatic agents are not as immediately effective as are agents which eliminate the fungus rapidly. Although these two activities have been considered divergent, in reality there may only be a difference in the rate at which fungal cells are killed.

(2) *Preparation of inoculum.* The following comments on the preparation of inoculum apply to all testing of antifungal agents including antifungal activity and susceptibility testing.

The inoculum size and incubation time directly affect the *in vitro* activity of antimicrobial agents (Ref. 1). Consequently, it is essential to determine the number of colony-forming units in the inoculum. A colony-forming unit is either one single cell or a single clump of cells. Spores are often used in the preparation of inocula instead of mycelial growth because they are more often single and distinct and provide easier handling for dispersion and enumeration.

The Panel recognizes that there may often be specific problems in developing techniques for the preparation and standardization of inocula. The highly variable culturing results which have been obtained with dermatophytic fungi make it necessary to develop a method that works for each specific dermatophytic organism. One method may not necessarily work for all, but as methods are refined, more uniform procedures are possible.

The inoculum preparation and standardization can be controlled using the following suggestions. The Panel recommends that for each microorganism to be tested, the following considerations be included in a protocol:

- (i) Specify the incubation time of the inoculum.
- (ii) Inoculum size. Specify the number of colony-forming units by performing a viable cell count. Determining the inoculum size is necessary to obtaining the optimal results in the actual test procedure.
- (iii) Freshly prepared agar plates should be used.
- (iv) Known and confirmed strains of fungi should be tested.
- (v) A suggested control isolate is helpful.

(vi) Comparative culture testing. A known test culture run at the same time as the isolate is helpful to ensure that all aspects of the test are controlled.

(3) *Media selection.* (i) A standardized medium is absolutely essential. The more reproducible the medium, the better.

(ii) The media now in use for growing the clinical isolate are Sabouraud's with

dextrose plus yeast extract and brain-heart infusion plus 50 µg/mL ampicillin. Mueller-Hinton medium has also been used. (This is standard antibiotic susceptibility testing medium.)

The Panel generally recommends Sabouraud's with dextrose plus yeast extract, although other appropriate media may be used. Comparative effectiveness for growth and susceptibility testing should be done where new media are considered. Some agars will selectively pick up ingredients from the formulation that is being tested on them. (The active ingredient binds to agar.)

(iii) Comparative data have shown that DTM is superior for clinical isolation. In use, DTM suppresses the bacterial flora and allows growth of the dermatophytes. If clinical specimens are being prepared for culture and subsequent susceptibility testing, the following suggestions should be considered: (a) No transport medium should be used.

(b) A temperature of 30° C is the standard. Any variation in temperature should be noted.

(c) The time of incubation should be at least 2 weeks. Cultures should be read at 5, 10, and 14 days.

(d) Sabouraud's medium rather than DTM should be used for nail cultures.

(e) A suggested alternative is Sabouraud's with 100 µg/mL gentamicin and yeast extract.

(4) *Examples of susceptibility testing procedures.* (i) Drop test. This procedure has been described by Miles and Misra for bacteria (Ref. 2).

(ii) Agar dilution. If agar dilution is used, a problem may develop when the inoculated fungal mycelium grows to the surface of the plate and spreads.

(5) *Organisms to test to ensure reliability of the procedure—(i) E. floccosum.*

(ii) *T. mentagrophytes* (granular).

(iii) One suggested *T. mentagrophytes* strain is D-1-ATCC 18748 (Vietnam).

(iv) *T. rubrum*—sporulating (organism difficult to sporulate).

(v) *Trichophyton tonsurans* (clinical isolate).

(vi) *C. albicans*.

(vii) More than one type of organism should be tested. Examples are *M. canis* and *T. mentagrophytes* for ringworm; *T. rubrum* and *E. floccosum* for jock itch; and *T. mentagrophytes* and *T. rubrum* for athlete's foot.

(6) *Test details.* (i) The test should be repeated to ensure reproducibility.

(ii) A recognized active antifungal agent as control should be tested with a reference strain of organism of known susceptibility and with the clinical isolates.

(iii) Incubate at 30° C.

(iv) A specific endpoint should be selected; 5 days is suggested. Cultures should be held and read at 2 weeks for any changes that may occur.

(v) If the active ingredient is diluted for the test, the vehicle should be used as a diluent.

(vi) The vehicle should be tested alone.

(vii) The activity of the final product must be greater than the activity of the vehicle alone.

(7) *Zone of inhibition testing.* Historically, many types of direct contact testing are related to the zone of inhibition test. Often, materials have simply been placed on culture plates.

A zone of inhibition test is not likely to be decisive because many molecules are large, and the solubilities of ingredients vary greatly. Although this type of test is still used, it is not recommended. It alone is not sufficient to characterize antifungal activity.

(8) *Activity testing.* A distinct test to determine the type of action of the active ingredient should be done. Endpoints may be difficult to determine with antifungal agents (for instance, with imidazoles). The stability of the antifungal agent must be considered in any test procedure. The following procedures may be used when testing for fungicidal and fungistatic activity:

The fungistatic and fungicidal concentration against known organisms can be determined and recorded in standard units (µg/mL or U/mL). These concentrations are most often determined using a multiple tube method. Subculturing is usually carried out from "test" tubes to determine whether activity is fungicidal. Descriptions of testing procedure can be found in standard references such as the "United States Pharmacopeia." Other suggestions are made in the following pages.

When establishing antifungal activity, the antifungal action of the specific ingredient must be tested using all the following fungi: *T. mentagrophytes*, *T. rubrum*, *E. floccosum*, *M. canis*, and *Candida*. Testing a wide selection of organisms helps to establish the spectrum of a specific ingredient.

The following suggestions may be helpful in conducting these tests:

(i) After sufficient incubation of the agar dilution or other test cultures to allow growth in the absence of inhibitory chemicals, a subculture should be made. It should include an effective neutralizer. The neutralizer is required to stop the action of the inhibitory chemical.

(ii) Liquid test medium can be removed by filtration and the membrane filter placed on fresh medium to check for growth.

(iii) A plug of agar can be leached of active ingredients and this plug added to fresh medium and incubated for growth.

Unfortunately, with antifungal agents and even with the best testing procedures, some agents will show in vitro activity but will not show effectiveness in a clinical test.

(9) *Antifungal activity—testing the clinical isolate.* The testing of recent clinical isolates of fungal cultures is very important. The considerations for selecting media and inoculum preparations (discussed above) also apply to clinical isolates. DTM has been shown to be superior for clinical isolation, but difficulty in batch-to-batch reproducibility has prevented widespread acceptance. Consequently, Sabouraud's is still commonly used for primary clinical isolation, though it is not as reliable.

Reference

(2) Waitz, J. A., E. L. Moss, and M. J. Weinstein, "Chemotherapeutic Evaluation of Clotrimazole [Bay b 5097, 1-*o*-Chloro-alpha-alpha-Diphenylbenzyl] Imidazole," *Applied Microbiology*, 22:891-896, 1971.

(2) Miles, A. A., and S. S. Misra, "The Estimation of the Bactericidal Power of the Blood," *Journal of Hygiene*, 38:732-749, 1938.

e. Effectiveness standards for labeling indications of antifungal drug products. The Panel recommends that all OTC topical antifungal products be labeled in a manner which will clearly indicate their ability to effectively treat jock itch or ringworm and treat and prevent athlete's foot. This label claim should be based on a well-designed, controlled, clinical trial of the active ingredient in the treatment of prevention of established fungal infections.

(1) *Treatment.* To be moved into Category I, the effectiveness of a Category III OTC ingredient used for the treatment of athlete's foot, jock itch, and ringworm must be demonstrated in a study of infected human subjects which meets the following criteria:

(i) The disease must be diagnosed clinically and confirmed by positive KOH preparation and culture of skin scrapings. Clinical signs and symptoms, such as redness, cracking, fissuring, scaling, swelling, itching, burning, or pain, should be present.

(ii) Patients with active disease should be randomly assigned to total formulation or vehicle groups and treated and evaluated in a double-blind fashion.

(iii) Total formulation should be compared to the vehicle, preferably in

parallel groups of patients and not with a paired comparison test. Paired comparisons allow contamination of vehicle-treated sites with active ingredients. It is desirable to confirm the in vitro minimal inhibitory concentration of the test ingredient for the clinical isolate in refractory cases.

(iv) The final evaluation of clinical results should be corroborated with the finding of a negative KOH preparation and culture at least 2 weeks after therapy stops.

(2) *Analysis of results.* A sufficient number of subjects should be studied to yield a statistically significant result. Significance should be found at the $p=.05$ level. A realistic projection of the degree of effectiveness of the ingredient compared to the vehicle should be made before starting the clinical trial. A drug that is projected to have borderline effectiveness will require larger numbers of patients in the trial.

The demonstration of effectiveness in a clinical trial designed to include the following points provides the minimal acceptable data for consideration in order to move an ingredient from Category III to I. However, final judgment will depend on clinical judgment. Ingredients so tested should be significantly more effective than the vehicle which is used to disperse them. Patients will be considered clear of fungal infection when the following criteria are met:

(i) For the feet, a 4-week treatment period followed by 2 weeks without treatment, with KOH preparation and culture at 0, 4, and 6 weeks. The 4-week and 6-week readings are to be negative for both KOH preparation and culture. Signs and symptoms must be cleared.

(ii) For the groin, a 2-week treatment period followed by 2 weeks without treatment, with KOH preparation and culture at 0, 2, and 4 weeks. The 2-week and 4-week readings are to be negative for both KOH preparation and culture. Signs and symptoms must be cleared.

(iii) For ringworm of the body, a 4-week treatment period followed by 2 weeks without treatment. KOH preparation and culture should be done at 0, 4, and 6 weeks. The 4-week and 6-week readings are to be negative for both KOH preparation and culture. Signs and symptoms must be cleared.

The Panel recognizes the difficulty and expense of conducting this type of study; however, it cannot rely solely on in vitro or in vivo animal studies as proof of effectiveness.

The Panel agrees that experimentally induced fungal infections in humans may be used to study the effectiveness of OTC antifungals but that the results of such studies cannot be used as sole

support of claims of effectiveness. It believes that therapeutic studies of the naturally occurring fungal infections yield more meaningful results.

The Panel agrees that a drug shown to be effective in the treatment of fungal infections of the feet will also be effective in the treatment of fungal infections of the groin or other parts of the body, excluding the scalp and nails, when these infections are caused by susceptible organisms. The Panel does not insist that label claims of effectiveness in treating athlete's foot, jock itch, and ringworm be supported by controlled studies done at each site.

(3) *Prevention.* The principles for a well-designed prophylactic trial of a drug are not unique for antimicrobial agents. Such studies should be ethically justifiable and use adequate patient-protection procedures including informed consent and guarantees of confidentiality. It is not the intent of this Panel, however, to deny the value of data from early studies even though they do not meet current standards.

The basic question the investigator wishes to answer is: Do patients who are given the prophylactic agent have fewer recurrences than those who are not?

(i) *Selection of patients.* The fixed population at risk will generally include two types of patients. Type one is the group with recurrent interdigital athlete's foot with minimal involvement of the remaining skin of the foot. This group would not have chronic fungal infection in the toenails. Type two includes those patients who have had the eruption in a "moccasin" distribution over the skin of the foot. This group will usually have fungal disease in the toenails. Although the Panel recognizes two patient types, it believes that random patient selection suffices for a prophylactic trial.

There are frequent outbreaks of disease in most of the population after a change in environmental conditions or a change in physical activity. The Panel also recognizes that segments of the population have dramatically increased their participation in sports and in group physical activities, thus increasing the likelihood that an individual may develop dermatophytic fungal infection. The incidence of infection in populations such as those in university dormitories or military groups is high enough to use comparative groups in a prophylactic study in which all subjects begin the study free from disease.

Because an adequate prophylactic trial is one of the most difficult studies to perform and because of the lack of chronic toxicity data, the Panel

concludes that any ingredient to be labeled for prophylactic use must have studies that conform to the guidelines establishing both safety and effectiveness. The Panel recognizes that many Category I drugs effective in treatment might also be effective in the prevention of athlete's foot. For most of these drugs, however, the Panel has found no human studies to support this belief. The long-term effects of prophylactic drugs on the feet or on the fungi which cause athlete's foot are also unknown. The Panel recognizes the difficulty in organizing a human study to produce such data.

Another consideration is that there are so many variables that can influence the growth of fungi: type and amount of clothing; activity level of an individual; the skin temperature, skin moisture, or natural immunity of an individual; the virulence of the organism; and the possibility of the presence of other complicating organisms.

The Panel recognizes that in vivo studies in animals of the effectiveness of Category I antifungal ingredients cannot duplicate or substitute for the study of human fungal infections to support claims of effectiveness in prophylaxis. For this reason a clinical trial will be required to justify prophylaxis labeling claims, e.g., "prevents athlete's foot."

The Panel also believes that nonantifungal drugs (such as drying agents) and antifungal drugs which have not been proven effective (Category III) may play a role in the prevention of athlete's foot. However, no evidence has been found to either support or disprove this idea. The Panel does not believe that it is scientifically valid to accept data obtained from animal studies as proof of prophylaxis in humans.

For prophylactic trials, the Panel recommends that KOH and cultures be performed on specific anatomical sites. One recommended site is the space between the third and fourth toe. The goal of prophylaxis should be the prevention of signs and symptoms. Patients studied should have no symptoms on admission to the study, but should have a high likelihood of developing an infection.

(ii) *Prophylactic trial.* (a) The trial should involve a sufficient number of subjects established by using accepted statistical procedures.

(b) Patients should be randomly assigned to total formulation or vehicle groups.

(c) A vehicle control group is used.

(d) Comparability of the total formulation and vehicle groups is established by analysis of pertinent variables.

(e) Both investigators and subjects are unaware of who is receiving the total formulation or the vehicle (double-blinding).

(f) Efficacy is established by analysis of the incidence of infection in the two groups of the study.

(g) A precise definition and objective measure of the presence or absence of the disease is decided before the study.

(h) The length of the trial should be a minimum of 12 weeks.

(i) Regular followup of the groups is preferably carried out at 4 and 8 weeks. Local adverse effects and compliance should be observed. KOH and cultures should be done at baseline and at 12 weeks. Observations should be systematically recorded.

(j) The number of patients should be estimated from the expected difference between the formulation and vehicle groups.

(4) *Premarketing effectiveness testing.* The Panel recognizes that differences in pharmaceutical formulation can cause significant differences in the availability and activity of antifungal ingredients.

An objective effectiveness study (see below) comparing an old and new formulation or dosage form not previously marketed is required before such formulation changes may be made. Although some effects and incompatibilities are known, the effect produced by changes in concentration or by deletion and addition of ingredients is entirely unknown.

Limited clinical trials have historically replaced bioavailability studies for topically applied drugs. Ideally, the specific test to determine the effectiveness of altered or new formulations should be relatively simple. It should not require a very large number of subjects and should not be time consuming or expensive because such requirements discourage innovation.

The Panel recommends that in vitro studies be performed to establish that the antifungal ingredient is available when alterations in formulation are made.

Following these procedures, the innovator may choose one of the tests described and affirm that the new formulation is equal in effectiveness and safety to the formulation being replaced.

(i) *Criteria for changes in vehicles.* In its report on OTC topical antibiotics published in the *Federal Register* on April 1, 1977 (42 FR 17647), the Panel recognized that there may be a significant influence of vehicle on effectiveness. The Panel still maintains the viewpoint that an antifungal ingredient may demonstrate varying results as a consequence of altering the

vehicle carrying the antifungal ingredient. It is concerned that vehicles other than those used in clinical studies reviewed by the Panel may be used as carriers for a Category I ingredient without adequate studies demonstrating bioavailability. For example, if a powder formulation of an antifungal agent was shown to be safe and effective, there is no scientific reason to assume that any or all other dosage forms will be as safe or effective as the one that was evaluated by the Panel.

On the other hand, the Panel sees no legitimate reason to recommend full clinical studies or full safety studies on a Category I antifungal ingredient because of alterations in the dosage form of a proven antifungal. The Panel recommends that any change in a currently marketed dosage form of a Category I ingredient be subjected to an adequately controlled in vivo study to demonstrate equivalent bioavailability (± 20 percent is the standard for bioequivalence).

An in vitro study using the already evaluated formulation as the standard and the proposed formulation as the test system may be helpful in determining whether to proceed with a formulation change. The new vehicle should also be used as a vehicle control.

After routine in vitro tests have indicated that the agent is available, one of the described procedures can be used to demonstrate the equivalence of the new formulation.

(ii) *The use and validation of animal models.* Historically, animal models have been used in studies which cannot be done in humans. Frequently these procedures have involved inoculation with many organisms or the use of very large numbers of animals. They are often used as a means of screening prior to human studies. Animal models are also used because it is not practical to perform a clinical trial for minor alterations in formulation.

In order to be reliable, comparability between the model and the clinical entity must be determined. In some models the disease is self-limiting so that the exposure time to any drug is limited.

The following considerations should be applied if a model is used to determine any changes in effectiveness of a formulation:

(a) The model must be validated against a human clinical trial.

(b) The specific details of the model, for example, the number of animals, method of preparation, and inoculation, should be detailed because several variations of models have been used.

(c) The drug level required to obtain a difference in the test results should be determined.

(d) If the new formulation exceeds the criterion of ± 20 percent of the activity of the old formulation, additional testing may be required.

(e) The procedures and calculations involved in the statistical analysis of the model studies should be determined and specified before performing the test.

(iii) *In vivo guinea pig testing.* The *in vivo* study in guinea pigs infected with the fungi specified in the protocol and using the original formulation as the standard and the proposed formulation containing the Category I drug as the test system may be used. The proposed vehicle would also be used as a placebo control. If equivalent bioavailability can be demonstrated, the vehicle may be changed. If equivalent bioavailability cannot be demonstrated using an *in vivo* test, the Panel recommends that a full clinical study be conducted as outlined elsewhere in this document. (See part III, paragraph E.2. above—Guidelines for Safety and Effectiveness Studies.)

There are four situations in which *in vivo* guinea pig testing would be particularly useful:

(a) Continued marketing of all formulations of Category I ingredients which have not been specifically demonstrated effective in clinical trials.

(b) Introduction of new dosage forms of Category I ingredients.

(c) Significant formulation modifications of existing products, i.e., change in active ingredient concentrations within Category I range or significant inactive ingredient adjustments.

(d) Initial marketing of a formulation containing a Category I ingredient.

Each of the above must be shown to be as effective as a standard of the same Category I ingredient. Either of the following standards may be used: (a) *Primary standard.* This is a formulation, containing the same Category I active ingredients, which has been shown effective in a clinical study.

(b) *Secondary standard.* This is a formulation, containing the same Category I active ingredients, which has been shown statistically equivalent to a primary standard in the guinea pig test.

(3) *The use of an excised skin model.* Reference is made to the description of Stoughton's procedure (Refs. 1 through 4). Rather sophisticated measurements can be made using this system.

(4) *Limited clinical trials.* This kind of study may be desirable where the new formulation offers a significant advance over the existing one. This method of assuring bioavailability has been used

for products submitted under new drug applications.

Reference

- (1) Stoughton, R. B., "Bioassay of Antimicrobials. A Method for Measuring Penetration of Agents into Human Skin," *Archives of Dermatology*, 101:160-166, 1970.
- (2) Stoughton, R. B., and G. S. Stoughton, "Topical Control of Skin Bacterial Growth with Hexachlorophene in Dimethylacetamide," *Journal of Investigative Dermatology*, 50:332-335, 1968.
- (3) Munro, D. D., and R. B. Stoughton, "Dimethylacetamide (DMAC) and Dimethylformamide (DMFA) Effect on Percutaneous Absorption," *Archives of Dermatology*, 92:585-586, 1965.
- (4) Stoughton, R. B., "Hexachlorophene Deposition in Human Stratum Corneum," *Archives of Dermatology*, 94:646-648, 1966.

PART 333—TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), under the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 (see 46 FR 26052; May 11, 1981), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding in Part 333, new Subpart C, to read as follows:

Subpart C—Topical Antifungal Drug Products

Sec.

- 333.201 Scope.
 333.203 Definitions.
 333.210 Antifungal active ingredients.
 333.220 Permitted combinations of active ingredients.
 333.250 Labeling of antifungal drug products.
 Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

SUBPART C—TOPICAL ANTIFUNGAL DRUG PRODUCTS

§ 333.201 Scope.

(a) An over-the-counter antifungal drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart and each general condition established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 333.203 Definitions.

As used in this part:

(a) *Antifungal agent.* An agent which either kills or inhibits the growth and reproduction of fungal cells.

(b) *Athlete's foot.* The term "athlete's foot" refers to infections of the feet caused by dermatophytic fungi.

(c) *Candida.* A yeast type of fungus, which under certain circumstances may cause infection.

(d) *Dermatophyte.* A fungus that is parasitic upon the skin, hair, or nails of humans or animals.

(e) *Fungus.* Any of a large division of plants, including dermatophytes, yeasts, and molds, characterized by a simple cell structure and the absence of chlorophyll.

(f) *Jock itch.* The term "jock itch" refers to a chronic and recurrent dermatophyte infection which occurs in men and affects the upper, inner thighs and sometimes extends to the groin and the pubic area.

(g) *Ringworm.* The term "ringworm" applies to skin infections cause by dermatophytic fungi.

(h) *Unit of nystatin.* A measure of the potency of nystatin as defined in § 430.6(a)(3).

§ 333.210 Antifungal active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage and labeling limits established for each ingredient.

- (a) Haloprogin 1 percent.
- (b) Iodochlorhydroxyquin 3 percent.
- (c) Miconazole nitrate 2 percent.
- (d) Nystatin 100,000 unit/gram in accordance with § 333.220(a) or § 333.250(b) (3) and/or (4).
- (e) Tolnaftate 1 percent in accordance with § 333.220(a), (b)(1), (b)(2), and (b)(3), or § 333.250(b)(1) and/or (2).
- (f) Undecylenic acid, calcium undecylenate, copper undecylenate, and zinc undecylenate may be used individually or in any ratio which provides a total undecylenate concentration of 10 to 25 percent.

§ 333.220 Permitted combinations of active ingredients.

(a) *Combinations of antifungal active ingredients.* Two or three antifungal ingredients identified in § 333.210 may be combined provided each ingredient broadens the antifungal spectrum and provided the product is labeled according to § 333.250(b)(1).

(b) *Combinations of antifungal active ingredients with nonantifungal active ingredients.* (1) Any single antifungal active ingredient identified in § 333.210 (a), (b), (c), (e), or (f) or any combination identified in § 333.220(a) may be combined with any single antiprespirant active ingredient which is generally recognized as safe and effective in an OTC final monograph provided the combination is labeled according to § 333.250(b)(1).

(2) Any single antifungal active ingredient identified in § 333.210(a), (b), (c), (e), or (f) or any combination identified in § 333.220(a) may be combined with any single keratolytic active ingredient agent which is generally recognized as safe and effective in an OTC final monograph provided the combination is labeled according to § 333.250(b)(1).

(3) Any single antifungal active ingredient identified in § 333.210(a), (b), (c), (e), or (f) or any combination identified in § 333.210(a) may be combined with either hydrocortisone or hydrocortisone acetate 0.5 to 1 percent provided the product is labeled according to § 333.250(b)(1).

§ 333.250 Labeling of antifungal drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antifungal."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" and is limited to the following:

(1) *For products containing any ingredient identified in § 333.210(a), (b), (c), (e), or (f) or any combination of ingredients identified in § 333.220 for the treatment of athlete's foot, jock itch, and ringworm.* As appropriate, combine one or more of the terms describing antifungal product action in § 333.250(b)(1)(i) with one or more of the terms describing conditions for use in § 333.250(b)(1)(ii).

(i) *Product action.* (a) "Treats * * *"
(b) "For the treatment of * * *"
(c) "Cures * * *"
(d) "For the cure of * * *"
(e) "Clears up * * *"
(f) "Proven clinically effective in the treatment of * * *"

(g) "For effective treatment of * * *"
(h) "Kills * * * fungi."
(i) "Proven to kill * * * fungi."
(ii) *Conditions for use.* (a) "Athlete's foot"
(b) "Athlete's foot (dermatophytosis)"
(c) "Athlete's foot (tinea pedis)"
(d) "Tinea pedis (athlete's foot)"
(e) "Jock itch"

(f) "Jock itch (tinea cruris)"
(g) "Tinea cruris (jock itch)"
(h) "Ringworm"
(i) "Ringworm (tinea corporis)"
(j) "Tinea corporis (ringworm)"

(2) *For products containing tolnaftate identified in § 333.210(e) as a single ingredient labeled for the prevention of athlete's foot.* Use any one of the phrases describing product action in § 333.250(b)(2)(i) with any one of the phrases describing the condition for use in § 333.250 (b) (2) (ii).

(i) *Product action.* (a) "Clinically proven to prevent * * * With daily use."

(b) "Prevents * * * with daily use."

(c) "Proven effective in the prevention of * * * with daily use."

(d) "Helps prevent * * * with daily use."

(e) "For the prevention of * * * with daily use."

(f) "For the prophylaxis (prevention) of * * * with daily use."

(g) "Guards against * * * with daily use."

(h) "Prevents the recurrence of * * * with daily use."

(ii) *Condition for use.* (a) "Athlete's foot"

(b) "Athlete's foot (tinea pedis)"

(c) "Tinea pedis (athlete's foot)"

(d) "Athlete's foot (dermatophytosis)"

(3) *For products containing either haloprogin, miconazole nitrate, or nystatin identified in § 333.210(a), (c), or (d) as a single ingredient labeled for the treatment of external feminine itching associated with vaginal yeast (candidal) infection.* "For the treatment of external feminine itching associated with vaginal yeast (candida) infection."

(4) *For products containing either haloprogin, miconazole nitrate, or nystatin identified in § 333.210 (a), (c), or (d) as a single ingredient labeled for the treatment of superficial skin infections caused by yeast (Candida).* "For the treatment of superficial skin infections caused by yeast (Candida)."

(5) *Other allowable statements for any antifungal product.* Any of the phrases describing product action in § 333.250(b)(5)(i) may be combined, as appropriate, with any of the terms or phrases describing symptoms in § 333.250(b)(5)(ii) provided that the resulting phrases are used in conjunction with the indications identified in § 333.250(b)(1), (3), and (4).

(i) *Product action.* (a) "Relieves * * *"

(b) "For relief of * * *"

(c) "For effective relief of * * *"

(d) "Soothes * * *"

(ii) *Symptoms.* (a) "Itching"

(b) "Scaling"

(c) "Cracking"

(d) "Burning"

(e) "Redness"

(f) "Soreness"

(g) "Irritation"

(h) "Discomfort"

(i) "Chafing associated with jock itch"

(j) " * * * itchy, scaly skin between the toes."

(k) " * * * itching, burning feet."

(6) *Other allowable statements for products containing haloprogin identified in § 333.210(a), miconazole nitrate identified in § 333.210(c), or any combination identified in § 333.220 that contains nystatin identified in § 333.210(d).*

(i) "Kills dermatophytic fungi and yeast (causes of athlete's foot, jock itch, and ringworm)."

(ii) "Proven to kill dermatophytic fungi and yeast (causes of athlete's foot, jock itch, and ringworm)."

(7) *Other allowable statement for products labeled according to § 333.250(b)(2).* "Clears up athlete's foot infection and with daily use helps keep it from coming back."

(8) *Product attributes.* Terms to describe certain physical and chemical qualities may be used as long as these terms do not imply any therapeutic effect and are distinctly separated from the indications identified in § 333.250(b)(1), (2), (3), and (4). These terms are intended to provide consumer information and relate to a product's color, odor, or feel. The following or similar terms may be used:

(i) "Colorless"

(ii) "Odorless"

(iii) "Pleasantly scented"

(iv) "Greaseless"

(v) "Usually does not sting"

(vi) "Non-staining"

(vii) "Drying"

(viii) "Cooling"

(ix) "Cools hot, tender feet."

(x) "Helps keep feet dry."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredient identified in § 333.210.* (i) "Do not use in children under 2 years of age except under the advice and supervision of a doctor."

(ii) "For external use only."

(2) *For products labeled according to § 333.250(b)(1) for the treatment of athlete's foot and ringworm.* "If irritation occurs or if there is no improvement within 4 weeks, discontinue use and consult a doctor or pharmacist."

(3) *For products labeled according to § 333.250(b)(1) for the treatment of jock itch.* "If irritation occurs or if there is no improvement within 2 weeks, discontinue use and consult a doctor or pharmacist."

(4) For products labeled according to § 333.250(b)(2) for the prevention of athlete's foot. "If irritation occurs, discontinue use and consult a doctor or pharmacist."

(5) For products labeled according to § 333.250(b)(3) for the treatment of external feminine itching associated with vaginal yeast (candidal) infection or when labeled according to § 333.250(b)(4) for the treatment of superficial skin infections caused by yeast (*Candida*). "Do not use this product for more than 14 days without consulting a doctor or pharmacist if condition persists or recurs."

(6) For combinations containing hydrocortisone or hydrocortisone acetate identified in § 333.220(b)(3). "Do not use longer than 30 days without consulting a doctor or pharmacist."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions." Depending on dosage form, directions may vary, e.g., "Spray affected area * * *"

(1) For products labeled according to § 333.250(b)(1) for the treatment of athlete's foot, jock itch, and ringworm. "Cleanse skin with soap and water and dry thoroughly. Apply a thin layer over affected area morning and night or as directed by a doctor. For athlete's foot,

pay special attention to the spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily. Best results in athlete's foot and ringworm are usually obtained with 4 weeks' use of this product, and in jock itch, with 2 weeks' use. If satisfactory results have not occurred within these times, consult a doctor or pharmacist. Children under 12 years of age should be supervised in the use of this product. This product is not effective on the scalp or nails."

(2) For products labeled according to § 333.250(b)(2) for the prevention of athlete's foot. "To prevent fungal infection of the feet (athlete's foot), cleanse skin with soap and water and dry thoroughly. Apply a thin layer to feet once or twice daily, paying special attention to the toenails and the spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily."

(3) For products labeled according to § 333.250(b)(3) for the treatment of external feminine itching associated with vaginal yeast (candidal) infection, or when labeled according to § 333.250(b)(4) for the treatment of superficial skin infections caused by yeast (*Candida*). "Cleanse skin with

soap and water and dry thoroughly. Apply a thin layer over affected area morning and night or as directed by a doctor. If satisfactory results have not occurred within 2 weeks, consult a doctor or pharmacist."

Interested persons may, on or before June 21, 1982, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before July 21, 1982. Received comments may be seen in the Office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: January 19, 1982.

Arthur Hull Hayes, Jr.,
Commissioner of Food and Drugs.

Dated: March 16, 1982.

Richard S. Schweiker,
Secretary of Health and Human Services.

[FR Doc. 82-7684 Filed 3-22-82; 8:45 am]

BILLING CODE 4160-01-M

Registered Federal Land

Tuesday
March 23, 1982

Part IV

Department of the Interior

Bureau of Land Management

Amendment to Rights-of-Way Regulations
Under Federal Land Policy and
Management Act and Mineral Leasing
Act; Final Rules

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

43 CFR Part 2800

[Circular No. 2500]

Rights-of-Way, Principles and Procedures; Amendment

AGENCY: Bureau of Land Management, Interior.

ACTION: Final rulemaking.

SUMMARY: This final rulemaking will eliminate burdensome, outdated and unneeded provisions in the existing right-of-way regulations for right-of-way grant issued under the provisions of title V of the Federal Land Policy and Management Act of 1976. This amendment came about as a result of the efforts of the Administration and the Secretary of the Interior to streamline existing regulations.

EFFECTIVE DATE: April 22, 1982.

ADDRESS: Any inquiries or suggestions should be sent to: Director (330), Bureau of Land Management, 1800 C Street, N.W., Washington, D.C. 20240.

FOR FURTHER INFORMATION CONTACT: John Hafterson, (202) 653-8842 or Robert C. Bruce, (202) 343-8735.

SUPPLEMENTARY INFORMATION: The proposed rulemaking amending the regulations on Rights-of-Way, Principles and Procedures, was published in the Federal Register on August 5, 1981 (46 FR 39968), with a 45-day comment period ending on September 21, 1981. Forty-two comments were received on this proposed rulemaking and the proposed rulemaking on Rights-of-Way under the Mineral Leasing Act which was published the same day. Most of those making comments combined their comments and for the purposes of these two rulemakings, we have combined all of the comments and considered them as applying to both rulemakings. The comments came from the following sources: 22 from industry, 9 from Federal agencies, 8 from industry associations, 1 from an association of State governments and 1 from an individual.

The comments were unanimous in their praise of the effort of the Department of the Interior in reducing the impact of the right-of-way regulations on the using public. As one comment pointed out, the Department of the Interior deserves praise for its efforts to reduce the paperwork burden imposed on the public by its regulations. The comments noted that the rights-of-way regulations were developed in close consultation with the affected public,

but that these changes were an improvement to that effort. In addition to these general comments, comments were made on specific sections of the proposed rulemaking and will be discussed in connection with each of the sections.

Nearly all of the comments pointed out the numbering area contained in section 1 of the proposed rulemaking. The number "2801.3-1" has been corrected in the final rulemaking to "2802.3-1" as the title to that change clearly shows what was intended.

Nearly all of the comments praised the decision to remove the citizenship requirement that had been made a part of the regulations by the Secretary of the Interior in the exercise of his discretionary authority. One comment did object to its removal, stating that removal of the provisions will operate to encourage foreign competition for limited domestic resources. The citizenship requirement is deleted from the existing regulations by the final rulemaking.

The other deletions relating to applicant qualifications and disclosure were also favored by the majority of those commenting. One comment noted that the stockholder disclosure requirement was required by section 501 of the Federal Land Policy and Management Act and recommended that the requirement for stockholder disclosure not be removed from the regulations. The final rulemaking removes the stockholder and other disclosure requirements from the regulations, but these requirements are continued in the new application form. In administering these requirements, the Bureau of Land Management will, as a practical matter, require disclosure of the information only when it is needed to carry out its responsibility to manage the public lands and preserve them for the use of the public.

One comment objected strongly to the three percent stockholder requirement in the regulations and suggested that it be dropped entirely. Since this requirement is imposed by the Federal Land Policy and Management Act, the Bureau of Land Management has the authority to require a corporate entity to reveal the information if it is needed to make a determination as to whether a right-of-way should be granted, issued or renewed. Any change in this authority would have to be made by the Congress.

One comment favored the deletion of the requirement on technical and financial capability of a right-of-way applicant and recommended that it be deleted from the new application requirement section. The view was expressed that this requirement was not

needed because the bonds required of an applicant protected the United States from the failure of an applicant to fulfill the requirements of the right-of-way grant. The final rulemaking deletes the technical and financial capability requirement from § 2803.3-2 but places a similar requirement in the § 2803.2-3, the new application content section. Section 504(j) of the Federal Land Policy and Management Act requires a finding that the applicant is financially and technically qualified to construct the project as a prerequisite to granting the right-of-way. The Bureau of Land Management, in administering this requirement, will accept a statement by the applicant that it is financially and technically qualified to go forward with the project, except in those instances where previous experience has shown the applicant lacks adequate financial or technical capacity to carry out its obligations under a grant. Further, the bonds required of an applicant are for the purpose of protecting the public lands from damage that might occur as a result of the actions of an applicant, not for the purpose of assuring the applicant's financial and technical qualifications.

The comments favored the change made by the proposed rulemaking and carried out in the final rulemaking that removes the section on project description and replaces it with a short requirement in the § 2802.3. The new requirement is greatly streamlined and imposes a less burdensome requirement on the public.

A number of comments expressed their views on the deletion of the environmental protection plan requirements contained in § 3802.3-4 of the existing regulations and which is deleted by the proposed rulemaking. Most of the comments favored the change, but one of the comments expressed the view that a decision on a right-of-way should not be made without the benefit of an environmental assessment. We concur in the need for analyzing the impact of a right-of-way before the right-of-way grant is issued. However, we do not believe that the plan required by section 504(d) of the Federal Land Policy and Management Act should be submitted with the application for a right-of-way. To require an applicant to prepare a protection plan prior to completion of the environmental evaluation is both unfair and wasteful. After the environmental assessment has been completed and a decision has been made that the right-of-way can be granted, then the applicant can be requested to submit the protection plan.

If the decision is made that the right-of-way should not be granted, the applicant has not borne the cost of preparing a protection plan. The final rulemaking has not made any change in the amendment made by the proposed rulemaking on this subject, but does add a new paragraph (h) to § 2802.4 that authorizes the authorized officer to place a provision concerning a protection plan in the right-of-way grant to provide the public lands adequate protection and fulfill the requirements of the Federal Land Policy and Management Act.

All of the comments supported the deletion of § 2802.3-5, the authority for the authorized officer to obtain additional information for use in making a decision on the application. If additional information is needed by the authorized officer to allow a decision on the application, it can be obtained under § 2802.4. The final rulemaking makes no change in the provisions of the proposed rulemaking on this point.

The comments on maps made by the proposed rulemaking raised a number of issues. Most of the comments supported the deletion of the detailed map requirements in § 2802.3-6 of the existing regulations, with a few questioning the need for information required by the new map provision that the proposed rulemaking adds to § 2802.3. The final rulemaking contains in § 2802.3(a)(3) a new, simplified, minimum map requirement that will furnish sufficient information to allow the authorized officer to determine the general location of the project and make a general evaluation of it. If more detailed maps are needed, they can be requested under other provisions of the existing regulations. As a result of a couple of comments that objected to the deletion of the mapping requirement relating to roads established under the provisions of section 2477 of the Revised Statutes contained in § 2802.3-6(d), the final rulemaking has added a new paragraph (b) to § 2802.5 of the regulations that contains the requirement relating to R.S. 2477 roads. This was done because the section on R.S. 2477 roads provides a convenient, but optional means, to resolve road status questions. The furnishing of the maps on the public roads remains at the option of the road owner.

A number of the comments on the application content requirements contained in the proposed rulemaking were concerned about the use of the consolidated application form that was developed primarily for use in Alaska. We are aware of these concerns and are designing instructions to accompany the

consolidated form that will not require the completion of application items in excess of those needed to complete action on the application under consideration. Therefore, the Bureau of Land Management will be able to use the consolidated form that was published in the Federal Register on March 12, 1981 (46 FR 16342), for all rights-of-way.

All of the comments expressed agreement with the proposed reduction in the requirements for information to be included in applications. Most of the comments, however, recommended further changes in the requirements of the proposed rulemaking. After careful review of the comments and a thorough study of the requirements contained in the proposed rulemaking, the final rulemaking has been changed further. The requirements have been divided into two categories in the final rulemaking. The items that are required to be submitted with the application have been reduced to five, with the additional items that were part of the proposed rulemaking being listed as information that the applicant may submit to be of assistance to the authorized officer. There is no requirement that any of the information in paragraph (b) be submitted with the application.

There was considerable concern expressed in the comments about the provision requiring a statement of compliance with the standards of State governments. This requirement has been removed by the final rulemaking because it is not needed at the time the application is filed. However, in compliance with the provisions of section 505 of the Federal Land Policy and Management Act, § 2802.4 requires the authorized officer to require compliance with applicable State standards when granting the right-of-way. Section 2802.4 remains in the regulations and will be followed in the processing of a right-of-way grant.

Virtually all of the comments supported the change in the wheeling provisions made by the proposed rulemaking, but went on to suggest further changes or elimination of any reference to wheeling in the final rulemaking. After careful review of the wheeling provision and the comments, the final rulemaking deletes § 2802.6 in its entirety, along with Subpart 2805 which the proposed rulemaking deleted. The wheeling requirements are left to the Department of Energy, where the responsibility lies, as provided in Title II the Public Utility and Regulatory Policies Act of 1978 (16 U.S.C. 824j).

The principal author of this final rulemaking is John Hafterson, Division of Rights-of-Way and Project Review, assisted by the staff of the Office of Legislation and Regulatory Management, Bureau of Land Management.

The Department of Interior has determined that this document is not a major rule under Executive Order 12291 and will not have a significant economic effect on a substantial number of small entities under the Regulatory Flexibility Act (Pub. L. 96-354).

The information collection requirements contained in 43 CFR Part 2800 have been approved by the Office of Management and Budget under 44 U.S.C. 3507 and assigned clearance numbers 1004-0060 and 1004-0107.

Under the authority of title V of the Federal Land Policy and Management Act of 1975 (43 U.S.C. 1761-1771), Part 2800, Group 2800, Subchapter B, Chapter II of Title 43 of the Code of Federal Regulations is amended as set forth below.

Garrey E. Carruthers,
Assistant Secretary of the Interior
December 4, 1981.

PART 2800—RIGHTS-OF-WAYS, PRINCIPLES AND PROCEDURES

1. Group 2800 is amended by adding the following note to the beginning of the Table of Contents:

Group 2800—Use; Rights-of-Way

Note.—The information collection requirements contained in Parts 2800 and 2880 of Group 2800 have been approved by the Office of Management and Budget under 44 U.S.C. 3507 and assigned clearance numbers 1004-0060 and 1004-0107. The information is being collected to allow the authorized officer to determine if the applicant is qualified to hold a right-of-way grant, to determine if the issuance of a grant is in the public interest and to make other land management decisions. This information will be used in making those determinations. The obligation to respond is required to obtain a benefit.

§§ 2802.3-1—2802.2-6 [Removed]

2. Sections 2802.3-1, 2802.3-2, 2802.3-3, 2802.3-4, 2802.3-5 and 2802.3-6 are removed in their entirety and § 2802.3 is revised as follows:

§ 2802.3 Application content.

(a) Applications for right-of-way grants or temporary use permits shall be filed on a form approved by the Director. The application form shall contain instructions for the completion of the form and shall require the following information:

(1) The name and address of the applicant and the applicant's authorized agent, if appropriate;

(2) A description of the applicant's proposal;

(3) A map, USGS quadrangle, aerial photo or equivalent, showing the approximate location of the proposed right-of-way and facilities on public lands and existing improvements adjacent to the proposal, shall be attached to the application. Only the existing adjacent improvements which the proposal may directly affect need be shown on the map;

(4) A statement of the applicant's technical and financial capability to construct, operate, maintain and terminate the proposal;

(5) Certification by the applicant that he/she is of legal age, authorized to do business in the State and that the information submitted is correct to the best of the applicant's knowledge.

(b) The applicant may submit additional information to assist the authorized officer in processing the application. Such information may include, but is not limited to, the following:

(1) Federal or State approvals required for the proposal;

(2) A description of the alternative route(s) and mode(s) considered by the applicant when developing the proposal;

(3) Copies of or reference to similar applications or grants the applicant has submitted or holds;

(4) A statement of need and economic feasibility or the proposal;

(5) A statement of the environmental, social and economic effects of the proposal.

§ 2802.4 [Amended]

3. Section 2802.4 is amended by revising paragraph (h) to read:

(h) The authorized officer may include in his/her decision to issue a grant a provision that shall be included in a right-of-way grant requiring that no construction on or use of the right-of-way shall occur until a detailed construction, operation, rehabilitation and environmental protection plan has been submitted to and approved by the authorized officer. This requirement may be imposed for all or any part of the right-of-way.

§ 2802.5 [Amended]

4. Section 2802.5 is amended by:

(a) Inserting at the beginning of the first paragraph of the section the figure "(a)";

(b) Redesignating existing paragraphs (a), (b) and (c) as subparagraphs (1), (2) and (3); and

(c) Adding a new paragraph (b) to read:

(b) In order to facilitate management of the public lands, any person or State or local government which has constructed public highways under the authority of R.S. 2477 (43 U.S.C. 932, repealed October 21, 1976) may file a map showing the location of such public highways with the authorized officer. Maps filed under this paragraph shall be in sufficient detail to show the location of the R.S. 2477 highway(s) on public lands in relation to State or county highway(s) or road(s) in the vicinity. The submission of such maps showing the location of R.S. 2477 highway(s) on public lands shall not be conclusive evidence as to their existence. Similarly, a failure to show the location of R.S. 2477 highway(s) on any map shall not preclude a later finding as to their existence.

Subpart 2805—Applicants for Electric Power Transmission Lines of 66 KV or Above [Removed]

5. Subpart 2805—Applications for Electric Power Transmission Lines of 66 KV or Above—is removed in its entirety.

[FR Doc. 82-7803 Filed 3-22-82; 8:45 am]

BILLING CODE 4310-84-M

43 CFR Part 2880

[Circular No. 2501]

Amendment to the Rights-of-Way Under the Mineral Leasing Act Regulations

AGENCY: Bureau of Land Management, Interior.

ACTION: Final rulemaking.

SUMMARY: This final rulemaking will eliminate burdensome, outdated and unneeded provisions in the existing regulations for oil and gas right-of-way grants under the Mineral Leasing Act.

EFFECTIVE DATE: April 22, 1982.

ADDRESS: Inquiries or suggestions should be addressed to: Director (330), Bureau of Land Management, 1800 C Street, NW., Washington, D.C. 20240.

FOR FURTHER INFORMATION CONTACT: John Hafterson, (202) 653-8842 or Robert C. Bruce, (202) 343-8735.

SUPPLEMENTARY INFORMATION: The proposed rulemaking amending the regulations on Rights-of-Way Under the Mineral Leasing Act was published in the *Federal Register* on August 5, 1981 (46 FR 39964), with a 45-day comment period ending on September 21, 1981.

Forty-two comments were received on this proposed rulemaking and the proposed rulemaking on Rights-of-Way, Procedures and Principles, which was published the same date. Most of those making comments combined their comments and for the purposes of these two rulemakings, we have combined all of the comments and considered them as applying to both rulemakings. The comments came from the following sources: 22 from industry, 9 from Federal agencies, 8 from industry associations, 1 from an association of State governments and 1 from an individual.

The comments were unanimous in their praise of the effort of the Department of the Interior in reducing the impact of the right-of-way regulations on the affected public. As one comment pointed out, the Department of the Interior deserves praise for its efforts to reduce the paperwork burden imposed on the public by its regulations. The comments noted that the right-of-way regulations had been developed in close consultation with the affected public, but that these changes were an improvement to that effort. In addition to these general comments, comments were made on specific sections of the proposed rulemaking and will be discussed in connection with each of the sections.

The comments supported the change in the proposed rulemaking that is continued in the final rulemaking that allows the filing of a right-of-way application in any office of the Bureau of Land Management having jurisdiction over the lands and not just at a State Office, as is now required. This change will save time for the using public.

The comments praised the Department of the Interior for the streamlining of the application process and the reduction in the amount of information required of an applicant to an absolute minimum. The comments did make some suggestions for further reductions in the information required of an applicant and these have resulted in a further change in the final rulemaking that has reduced still further the required information, with the applicant being given the opportunity to submit additional information, if it is desired, that might be helpful to the authorized officer in reaching a decision on the right-of-way application. One significant change in the required information is a more specific paragraph on the maps that are to be submitted with the application. The information called for is a bare minimum and should be easily available to all applicants.

As a result of specific comments on ways of simplifying the regulations, two additional changes have been made in the final rulemaking. Section 2882.2-4, other data that may be required, has been removed from the regulations by the final rulemaking. A study of the regulations confirmed that this list of items was unneeded. Any additional information needed by the authorized officer could be specified in a notice to the applicant at the time it was needed. Further, much of the information listed in § 2882.2-4 might not ever be needed and an unsuspecting applicant might spend the time and effort gathering it in an effort to save time because it was listed in the regulations.

Several of the comments were concerned about the application form that will be used in the future for all right-of-way grants. Even though the form was initially designed for Alaska, the instructions that will accompany it will inform an applicant of which items on the form must be completed. We believe that the new application form will be a further step in reducing the paperwork burden on the public.

The second change made by the final rulemaking as a result of comments was a revision of paragraph (m) of § 2882.3. The change continues to give the authorized officer authority to include in the right-of-way grant a provision limiting activity on the right-of-way until the authorized officer has received and approved those documents needed to properly protect the public lands. The continuing authority will enable the authorized officer to obtain information needed to protect the public lands, a concern of one of the comments.

The principal author of this final rulemaking is John Hafterson, Division of Rights-of-Way and Project Review, assisted by the staff of the Office of Legislation and Regulatory Management, Bureau of Land Management.

The Department of the Interior has determined that this document is not a major rule under Executive Order 12291 and will not have a significant economic effect on a substantial number of small entities under the Regulatory Flexibility Act (Pub. L. 96-354).

The information collection requirements contained in 43 CFR Part 2880 have been approved by the Office of Management and Budget under 44

U.S.C. 3507 and assigned clearance numbers 1004-0060 and 1004-0107.

Under the authority of section 28 of the Mineral Leasing Act of 1920, as amended (30 U.S.C. 185), Part 2880, Subchapter B, Chapter II, Title 43 of the Code of Federal Regulations is amended as set forth below.

Garrey E. Carruthers,
Assistant Secretary of the Interior.
December 4, 1981.

PART 2880—RIGHTS-OF-WAY UNDER THE MINERAL LEASING ACT

§ 2882.1 [Amended]

1. Section 2882.2-1 is amended in paragraph (a) by removing the last two sentences thereof, removing paragraphs (b), (c), (d), (e), (f), (g), (h), (k), and (l), by redesignating paragraph (i) as paragraph (b) and removing the last sentence thereof, and by redesignating paragraph (j) as paragraph (c).

2. Section 2882.2-2(a) is revised as follows:

§ 2882.2-2 Application filing.

(a) Where the Federal lands involved are under the jurisdiction of the Bureau of Land Management, Department of the Interior, application for a right-of-way grant or temporary use permit or for a renewal of either shall be filed with either the Area Manager, the District Manager or the State Director of a Bureau of Land Management office having jurisdiction over the Federal lands involved.

3. Section 2882.2-3 is revised as follows:

§ 2882.2-3 Application content.

(a) Applications for right-of-way grants and temporary use permits shall be filed on a form approved by the Director. The application form shall contain instructions for completion of the form and shall require the following information:

- (1) The name and address of the applicant and the applicant's agent, if appropriate;
- (2) A description of the applicant's proposal;
- (3) A map, USGS quadrangle, aerial photo or equivalent, showing the approximate location of the proposed right-of-way and facilities on public lands and existing improvements

adjacent to the proposal, shall be attached to the application. Only the existing adjacent improvements which the proposal may directly affect need be shown on the map;

(4) A statement of the applicant's technical and financial capability to construct, operate, maintain and terminate the proposals;

(5) Certification by the applicant that he/she is of legal age, authorized to do business in the State and that the information submitted is correct to the best of the applicant's knowledge; and

(6) Disclose, to the extent applicable, the applicant's citizenship and the partnership, corporation, association and other business entity information required by § 2882.2-1 of this title.

(b) The applicant may submit additional information to assist the authorized officer in processing the application. Such information may include, but is not limited to, the following:

- (1) Federal or State approvals required for the proposal;
- (2) A description of the alternative route(s) and mode(s) considered by the applicant when developing the proposal;
- (3) Copies of or reference to similar applications or grants the applicant has submitted or holds;
- (4) A statement of need and economic feasibility or other proposal; and
- (5) A statement of the environmental, social and economic effects of the proposal.

§ 2882.2-4 [Removed]

4. Section 2882.2-4 is removed in its entirety.

§ 2882.3 [Amended]

5. Section 2882.3 is amended by revising paragraph (m) to read:

(m) At the discretion of the authorized officer, a provision may be placed in a right-of-way grant or temporary use permit requiring that no construction or use shall occur until a detailed construction, operation, rehabilitation and environmental protection plan has been submitted to the authorized officer and a notice to proceed has been issued. This requirement may be imposed for all or any part of the right-of-way.

[FR Doc. 82-7804 Filed 3-22-82; 8:45 am]

BILLING CODE 4310-84-M

Register

Tuesday
March 23, 1982

Part V

Department of Health and Human Services

Health Care Financing Administration

Medicare Program; Proposed Rule on
Ambulatory Surgical Services and List of
Covered Surgical Procedures for Certain
Ambulatory Surgical Services

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

42 CFR Parts 405 and 416

Medicare Program; Ambulatory Surgical Services

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Proposed rule.

SUMMARY: These regulations would implement, in part, section 934 of Pub. L. 96-499, the Omnibus Reconciliation Act of 1980, which adds to the benefits available under Part B of Medicare, facility services associated with certain surgical procedures provided in an independent ambulatory surgical center. That section also provides, under certain conditions, for Medicare reimbursement to physicians of 100 percent of the reasonable charges (rather than the usual 80 percent) for services provided in connection with certain surgical procedures performed on an ambulatory basis. These regulations would establish: (1) The standards an independent ambulatory surgical center must meet to be approved for participation in the Medicare program; (2) criteria for determining which surgical procedures would be included for purposes of reimbursing facilities and physicians under this provision; (3) the payment methodology and reimbursement procedures with respect to facility services; and (4) the requirements relating to agreements by the facility to furnish services under the program and by physicians with respect to accepting payments for procedures (agreements to accept "assignments").

The purpose of the legislation and these regulations is to encourage the performance in an ambulatory setting of certain surgical procedures that are now frequently furnished on an inpatient hospital basis. The regulations would assure that these procedures are only those that are appropriately and safely performed in an ambulatory setting, and that the cost to the Medicare program of services provided in that setting is lower than would have been incurred for services provided on an inpatient basis.

DATES: To assure consideration, comments should be mailed by April 22, 1982.

ADDRESS: Address comments in writing to: Administrator, Department of Health and Human Services, Health Care Financing Administration, P.O. Box 17073, Baltimore, Maryland 21235.

If you prefer, you may deliver your comments to Room 309-G Hubert H. Humphrey Building, 200 Independence Avenue SW., Washington, D.C., or to Room 789, East High Rise Building, 6325 Security Boulevard, Baltimore, Maryland.

In commenting, please refer to BPP-135-P. Agencies and organizations are requested to submit comments in duplicate.

Comments will be available for public inspection, beginning approximately two weeks after publication, in Room 309-G of the Department's office at 200 Independence Avenue SW., Washington, D.C. 20201 on Monday through Friday of each week from 8:30 a.m. to 5:00 p.m. (202-245-7890).

FOR FURTHER INFORMATION, CONTACT:

Anthony Lovecchio (Covered Procedures) 301-594-8561

Bernard Truffer (Reimbursement) 301-597-1369

Margaret Van Amringe (Health, Safety and other Facility Standards) 301-594-9712

Sheila Ryan (Assignment Agreements) 301-594-9437

SUPPLEMENTARY INFORMATION:

I. Background

Generally, there are two elements of the total charge for a surgical procedure—a charge for the facility services furnished, such as use of an operating room, and a charge for the physician's professional services for performing the procedure. Medicare covers the physician's professional services regardless of the setting. Coverage of facility services, however, varies somewhat between settings as described below. The Medicare program covered and provided reimbursement for facility services for surgical procedures performed in a hospital on an inpatient basis at 100 percent of the hospital's reasonable costs. Before the Omnibus Reconciliation Act of 1980, facility services associated with ambulatory surgery were covered and reimbursed only in a hospital-related ambulatory surgical setting; that is, on an outpatient basis in a hospital or in a hospital-affiliated ambulatory surgical center (HAASC). (An HAASC is an integral and subordinate part of a hospital, operated with other departments of the hospital under common licensure, governance and professional supervision, whether located on the hospital's premises or offsite.) These ambulatory surgical facility services were reimbursed at 80 percent of the hospital's reasonable cost, in accordance with the cost reimbursement principles of 42 CFR Part

405, Subpart D. The Medicare beneficiary was responsible for any unmet portion of the Part B deductible (the amount for which the beneficiary is responsible before Medicare begins to pay) and for the coinsurance (20 percent of the hospital's remaining customary charges) for the procedure.

Medicare law has not previously permitted coverage or payment for facility services associated with surgery furnished in an independent ambulatory surgical center (a freestanding center that is not related to a hospital) or made any special payment in addition to a physician's reasonable charge for surgical services furnished in a physician's office. (For the remainder of this preamble, unless otherwise noted, the term ASC refers to an independent ambulatory surgical center.) That is, facility costs (or overhead amounts in the case of physicians' offices) such as equipment, capital investments, supplies and medications, and staffing costs, for example, for nurses and operating room technicians, have not been reimbursable in the ASC. With regard to the physician's office settings, some overhead costs have been recognized by the Medicare program only to the extent they are considered "incident to" the service. Medicare reimbursement for the physician's charge for performing a surgical procedure is made at 80 percent of the reasonable charge for the service, without regard to the setting (inpatient hospital, hospital-related ambulatory setting, ASC or physician's office). In all settings, the beneficiary was responsible for the Part B deductible and coinsurance for the physician's services.

II. Legislation

A. Pub. L. 96-499—Introduction

Section 934 of P.L. 96-499, the Omnibus Reconciliation Act of 1980, amended sections 1832(a)(2), 1833, 1863 and 1864 of the Social Security Act (Act).

In considering this legislation, Congress recognized that the more limited coverage and reimbursement of ambulatory surgery, as compared to inpatient hospital surgery, has resulted in patients being admitted to hospitals for surgery that may have been safely and less expensively furnished on an ambulatory basis. (Report of the Committee on the Budget to Accompany H.R. 7766, H.R. Report No. 96-1167, pg. 390).

B. ASCs

1. *Procedures covered.* Section 934 authorizes Medicare coverage for ASC facility services under certain

conditions, and requires the Secretary to develop a list of the procedures that may be covered. The statute specifies that the procedures be those that are appropriately performed on an inpatient basis but that can, consistent with accepted medical practice, be safely done in certain ambulatory surgical settings. However, Congress specified that the list should not include procedures that have customarily been performed on an ambulatory basis in locations that have less elaborate surgical facilities than those found in ASCs, such as physicians' offices.

2. Reimbursement. For ASC facility services, the statute requires payment of a standard overhead amount based on the Secretary's estimate of a fair fee that is related to the cost of furnishing the service generally and is substantially less than the fee that would be paid if the procedure were performed on an inpatient hospital basis. Further, each amount must be reviewed periodically and may be adjusted by the Secretary to account for varying conditions in different areas.

3. Agreement to accept assignment. Under section 1832(a)(2)(F)(i) of the Act, the ASC must enter into an agreement with the Secretary to accept assignment of all Medicare claims for facility services as a condition for receiving payment for those services. This agreement would be included in the participation agreement that the ASC has with HCFA to participate in Medicare. Medicare payment would then be made at 100 percent of the established rate per procedure. There would be no beneficiary liability for coinsurance or the Part B deductible.

4. Standards. Legislative requirements for development of standards that an ASC must meet and for determining a facility's compliance with standards are discussed in part IV of this document.

C. Hospital-related ambulatory surgical facilities

Section 934 made no changes with respect to reimbursement for facility costs associated with surgical procedures performed in hospital-related ambulatory surgical settings. The costs would be included in the hospital's Medicare cost reports and reimbursed at the reasonable cost level. Medicare beneficiary deductible and coinsurance amounts would still apply.

D. Physician's professional services

With respect to reimbursement for physicians' services, including all pre- and post-operative services, the legislation provides for payment of 100 percent of the physician's reasonable charge for services provided in

connection with a listed surgical procedure performed in a hospital-related ambulatory surgical setting, an ASC, or a physician's office. If the physician performing the procedure accepts assignment of the claim, there would be no Part B deductible or coinsurance. If assignment is not accepted, the usual rules governing Medicare payments for the physician's services would apply.

E. Physicians' offices

Although section 934 includes a provision permitting payment of an overhead amount for surgical procedures performed in physicians' offices, these proposed rules do not address that part of the legislation for several reasons. First, under the statute, Medicare coverage of overhead costs associated with surgical procedures provided in this setting is contingent upon, among other things, review of the performance of those procedures by a Professional Standards Review Organization (PSRO). At this time, PSROs are not engaged in this type of review.

Moreover, even if PSRO review were now available, we would not be in a position to develop payment rates for surgical procedures performed in physicians' offices. Since Medicare currently reimburses physicians only for their professional fees, we have no charge data relevant to facility services. Also, since the statute requires that these rates take into account the additional costs that physicians incur in providing such services, it would be necessary for us to have sufficient cost data on which to base the rate calculations. Unlike the case with ASCs, we have not had the benefit of prior, detailed studies, or an existing source of data to use in rate development. Therefore, we thought it best to use the available resources to implement first the portion of the legislation applicable to ASCs and to physicians' professional services performed in settings other than the office. We would then use the experience gained under these regulations to assist us in resolving the issues necessary to develop rules to implement the physicians' office component of the legislation.

III. Implementation of the Legislation

A. Federal Register Notice

Section 934 requires the Secretary to consult with the National Professional Standards Review Council and appropriate medical organizations with respect to developing a list of surgical procedures covered under this provision. On May 22, 1981, we requested in a

Federal Register notice (46 FR 28013), information and suggestions from interested persons or groups, professional organizations, specialty societies and surgical facilities, to assist us in formulating appropriate policy that would be both consistent with the intent of Congress and responsive to the concerns of the public and the health care facilities and practitioners involved. In this notice we requested information to give us a sense of policies that would be acceptable to all parties concerned. Specifically, we asked for broad, generally acceptable criteria for determining what surgical procedures should be included on the list of covered procedures as well as specific procedures done on an inpatient basis that could be performed safely on an ambulatory basis. We also asked for suggestions concerning the facility characteristics and professional services needed to perform these surgical procedures safely in an ambulatory surgical facility. With respect to reimbursement, we requested information about those services usually included in an ASC's charge, those services billed separately, and the most feasible mechanism to relate costs incurred by a facility to a particular procedure. We requested information on the manner in which third party payors reimburse facility services. We also strongly encouraged facilities to submit copies of charge schedules and cost information to aid us in developing appropriate reimbursement rates.

We received 53 comments, representing the views of 10 professional organizations, 20 hospitals, 11 ASCs and 12 other interested parties. While the comments were substantial, responses to specific reimbursement questions were somewhat inadequate. However, we considered the comments received in the development of our policy implementing this provision and made every effort to accommodate suggestions received. Also, both before and after the publication of our May 22 Federal Register notice, we contacted or met with interested persons, professional organizations, and specialty societies in order to share our policy direction and obtain additional information to aid us in our policy development. In addition, we met twice with the National Professional Standards Review Council to discuss the development of our list. After we developed the list, we referred it to the Council for their review. When they meet this spring, we plan to consult with them once again. We believe that the policies set forth in these proposed regulations represent the general

consensus of the parties who responded to our public notice or were contacted by us.

B. Provisions of the Regulations

The following parts of the preamble deal with four major policy areas covered by the regulations: ASC health, safety, and other standard; coverage; reimbursement; and acceptance of assignment.

IV. HEALTH, SAFETY, AND OTHER STANDARDS FOR ASCs

A. Standards

Section 1832(a)(2)(F)(i) of the Act requires the Secretary to establish health, safety, and other standards that ASCs must meet to enter into an agreement for participation in Medicare. The intent of these standards is to establish acceptable criteria that would both protect beneficiaries and permit ASCs the greatest degree of flexibility in complying with the standards.

These standards would be contained in a new Part 416 established in Title 42 of the CFR:

Section 416.25, Basic requirements and procedures: This section sets forth general criteria concerning which facilities may participate as ASCs, and the procedures HCFA and ASCs will follow when a facility wishes to participate under Medicare. Also, if HCFA does not enter into or renew an agreement, the facility's appeal rights are referenced.

Sections 416.30 and 416.35, Agreements: These sections detail the contents and terms of the agreement between an ASC and HCFA and the procedures for termination of the agreement.

Section 416.40, Compliance with State licensure law: This section recognizes State licensure laws that apply to ambulatory surgical centers. Several comments have been received recommending that State licensure not be a requirement for Medicare coverage. However, HCFA requires of all providers and suppliers of health services participating in Medicare compliance with State licensure laws. If the State does not have licensing laws for ASCs, this section of the regulation would not apply.

Section 416.41, Governing body and management, is included as we consider centralization of authority and responsibility necessary to the provision of quality care and for meeting the facility's fiscal and other responsibilities under the Medicare program. The standard on hospitalization is included to assure beneficiary access to a hospital in the event of an emergency

requiring treatment beyond the capabilities of the ASC.

Section 416.42, Surgical services, deals with the actual provision of surgical services. Because anesthesia is a potentially dangerous aspect of any surgical procedure, two standards are included to assure that the patient is properly examined for risk prior to surgery, and that appropriately qualified individuals administer the anesthesia. We believe that whenever anesthesia is given these practices are crucial to insuring patient safety.

Section 416.43, Evaluation of quality, requires an ASC to evaluate, on an ongoing basis, the quality of care it provides. A comprehensive self-assessment of quality is considered the best method of assuring safe and effective health services. In addition, these regulations would allow us to provide substantial flexibility in the other standards.

Facilities customarily develop and implement policies and procedures designed to minimize avoidable risks. Frequently, through experience and vigilance, problems are identified requiring some modification of these policies and procedures. It is the responsibility of management, as well as of the medical staff, to maintain the necessary information base for the identification of problems so that the facility can easily correct situations that may threaten patients' well-being.

The critical aspect of determining compliance with this condition is not the specific findings of the self-assessment, but the degree to which the facility honestly and continually appraises itself. Our intention is not to require a regimented and massive evaluation program, but to formalize, to some extent, those processes that are ongoing in every well organized medical facility. These processes may include identification of problems (for example, surgical outcomes), analysis to determine the actual causes, and corrective action. Since the identification of a significant problem serves little purpose unless the problem is corrected, these regulations would require that a facility must, to comply with the condition, take appropriate remedial action. However, the specific approach used by the facility to formalize this process is best determined by the facility itself. Since we believe that self-assessment should be ongoing and regular, we would expect facilities to show that any substantial intervals without analysis were justified.

Although general findings from surveys performed by State agencies are considered public information, the

specific findings of the self-assessment conducted internally by the facility are considered confidential and would not be releasable to the general public.

Section 416.44, Environment, focuses on the physical aspects of the ASC including provision for infection control. Patient safety cannot be assured unless the building is properly constructed, equipped, maintained, and functional. With respect to fire safety standards developed by the National Fire Protection Association, HCFA would retain the authority to waive certain provisions on a case-by-case basis.

Section 416.45, Medical staff, contains general standards for surgeons and other practitioners providing services in the ASC. The purpose of the condition is to establish accountability. While the ASC must be established primarily for the purpose of providing outpatient surgery, other health services may be provided by practitioners other than surgeons. For this reason, Standard (b), Other Practitioners, is included which would require oversight of the clinical activities of other practitioners. These practitioners may or may not be members of the medical staff.

Section 416.46, Nursing services, contains general provisions for delineation of nursing responsibilities and the requirement for availability of a registered nurse in case of emergencies.

Section 416.47, Medical records, contains medical record service requirements for an ASC. Complete records of clinical services provided are necessary for good medical treatment and to support claims for payment. There are two standards: Organization; and Form and content of record.

Section 416.48, Pharmaceutical services, contains basic requirements for the provision of drugs and biologicals. This condition is based on a recognition that drugs and biologicals normally provided in an ASC setting are less varied than those in an organized pharmacy service of a hospital, but that certain minimal requirements are necessary to ensure that adverse patient reactions and risks are minimized.

Section 416.49, Laboratory and radiological services, provides general requirements for availability of these services. If either service is provided directly by the ASC, the conditions of participation for hospital laboratory or radiologic services, respectively, would be applied (42 CFR 405.1028 and 405.1029). The rationale for using the hospital conditions of participation is—

- The hazards and operational problems associated with the provision of laboratory and radiologic services are significant in any type of health facility.

- The current hospital regulations regarding laboratory and radiologic services are considered flexible, and are currently applied in other health facilities (for example, skilled nursing facilities).

A preliminary draft of the total set of standards was developed and compared to the standards of two national ambulatory care accreditation programs for ambulatory services as well as licensure laws of 23 States. That draft was generally comparable in all areas with the following exceptions.

- Section 416.43 (Evaluation of quality): Various elements of the condition are required under State licensure and by the accreditation associations. However, the States and the associations do not require a consolidated program of self-assessment as required by the draft regulations.

- Section 416.45 (Medical staff): The two accreditation associations have no requirements for medical staff. However, 19 (of 23 total) States have licensure laws for medical staff that are equal to or more stringent than the draft standards.

We have shared the preliminary draft of these standards (in the early stages of their development) with national organizations having a direct interest in ambulatory surgical centers. Detailed comments were received from these organizations. Generally, the comments on the preliminary draft were favorable but included suggestions and rationale for minor changes in wording or personnel requirements which we have incorporated into these proposed regulations where appropriate.

B. Implementation

State agencies would be authorized on behalf of HCFA to survey ASCs. The time interval between surveys would vary; that is, one, two or three years depending on the facility's degree of compliance with these regulations. This flexible approach would permit facilities having no deficiencies to undergo surveys only every two or three years, while facilities having significant, but correctable, deficiencies would receive yearly surveys until those deficiencies were corrected (within specified periods of time). Where deficiencies are serious, resulting in an ASC being found out of compliance with one or more conditions, the facility would be ineligible for participation.

The purposes of this implementation plan would be to provide the facility with an incentive (that is, less frequent surveys) to meet all requirements, and to allow the State agency to focus its survey activities on those facilities having difficulties meeting the

requirements. While the regulations are intended to be self-explanatory, interpretive guidelines would be provided to surveyors to assist in the survey process and to other interested parties upon request and would highlight areas where flexible interpretations are appropriate. These guidelines would include a further explanation of the intent of the regulations, examples, sources of information within facilities that would assist the surveyor, and general guidance for understanding how the survey findings should relate to the final approval.

C. Deemed Status

An ASC would be deemed to meet our standards for coverage if it is accredited by an approved national accrediting organization and licensed by the State when State law provides for that licensure. We propose to recognize the Accrediting Association for Ambulatory Health Care, Inc., as such an organization, since its accrediting standards are at least as rigorous as those we are proposing. If other national accrediting organizations desire similar recognition, they should submit a request and a copy of their accrediting standards as part of their comments on this proposal. As a condition of our granting deemed status, we would require that each facility release to HCFA the findings of its accreditation survey. As is the case for all governmental records not exempt from disclosure under the Freedom of Information Act, the findings would be available to the public. In connection with this deemed status, we would perform validation surveys on a sample basis as part of HCFA's validation process. We are also considering granting deemed status for any ASC that is licensed by the State in which it is located. We are particularly interested in comments related to our deemed proposals.

V. Coverage

A. Background

As noted above, section 1833(i)(1) requires the Secretary to develop, in consultation with the National Professional Standards Review Council an appropriate medical organizations, a list of surgical procedures that, while appropriately performed in an inpatient hospital setting, may also be performed in certain ambulatory settings. The report accompanying the legislation explained that Congress intended that procedures currently done on an ambulatory basis, especially in physicians' offices, that do not generally

require the more elaborate facilities of an ASC, should not be included in the list of covered procedures.

B. List of Covered Surgical Procedures

The list of covered procedures is the key element in defining the benefits available under these regulations to Medicare beneficiaries. If a given procedure is on the list, ASC facility services furnished in connection with that procedure would be reimbursed. However, if the procedure is not listed as a covered procedure, the beneficiary would either pay the ASC's facility charges out-of-pocket (or through a private insurer) or undergo the procedure in a covered setting such as a hospital. As under prior law, Medicare would still make reimbursement for the physician's professional services, but at 80 percent of the reasonable charge for such services rather than the 100 percent authorized for listed covered procedures when the physician agrees to accept assignment.

Criteria for list of covered surgical procedures.—The development of the list raised a number of questions regarding how and from whom information regarding possible procedures should be drawn, what criteria should be used to decide whether a given procedure should be listed, and how such procedures should be described. Further detail regarding those questions and some of the actions taken to answer them may be found in the preamble to the list of covered procedures, published as a proposed notice elsewhere in this issue of the Federal Register.

One question was whether the list of covered procedures would be incorporated directly into the body of these regulations, or whether we could find and incorporate broad, generally accepted criteria to describe and determine those kinds of procedures that should be covered, allowing the list to be published as a notice in the Federal Register.

Consequently, in the May 22, 1981 Federal Register notice (described in section III-A, above) we requested suggestions for " * * * Broad, generally accepted criteria for determining what surgical procedures, now done on an inpatient basis, may be safely performed in ambulatory surgical facilities." We decided that if such criteria could be developed, they would be helpful in two ways—first, they would permit us to incorporate criteria, rather than specific procedures in the codified Medicare regulations; and, second, they would be helpful in making decisions on specific procedures where no clear consensus

existed among ASCs or the medical profession as to whether or not they should be included on the list of covered procedures.

The comments we received in response to the notice resolved this issue. Of those who suggested criteria, there was a consensus as to both general and specific criteria that were consistent with the statute. (Some commenters suggested that no list be used, but the statute requires that a list be developed.) We propose to incorporate these general and specific criteria in the regulations as § 416.85, along with other requirements either specified in the statute or logically flowing from its provisions. HCFA would publish specific procedures covered as notices in the *Federal Register*. The proposed list of covered procedures is published elsewhere in this issue of the *Federal Register*.

1. *General Requirements.* Procedures to be listed would be of a type that require accommodations found in an ASC—an operating room (or rooms) equipped and staffed for surgical procedures of the types performed in the ASC, and some type of recovery room or convalescent room. We expect that ASCs may differ from one another with respect to the size, number and kind of areas and equipment they have, since the types of surgery done in such facilities vary from one facility to another. But, as the proposed conditions for coverage of these regulations provide, there is a basic set of standards all ASCs must meet to be covered under the program, and the procedures covered are those that would require a facility meeting such standards.

In addition, there are two requirements set by the law that define the range of covered procedures to be included on the list. At one end of the range, procedures that require the facilities of an inpatient hospital, and are not generally considered safe when performed on an ambulatory basis, whether in an ASC or on an outpatient basis in a hospital, would be excluded. At the opposite end are procedures that may safely be done in a physician's office and do not generally require the more sophisticated facilities of an ASC.

2. *Specific Requirements.*

a. *Length of time for procedures and recovery.* Generally, procedures covered would not be expected to exceed 90 minutes total operating time. This is not to imply that a given procedure done on a given patient would not be covered if it exceeds 90 minutes. Rather, the expectation is that the type of procedure, without complications, generally averages less than 90 minutes for most patients.

We are proposing that the recovery time for covered procedures, that is, the period following the procedure in which the patient must be kept in the recovery or convalescent room before being released, should not generally require more than 4 hours. Again, this is not a hard and fast case-by-case requirement, but only an average for most patients.

b. *Limits on types and duration of anesthesia.* The procedures that would be covered in ASCs may or may not require anesthesia. We propose that if anesthesia is required, it must be local or regional or, if general, its duration cannot exceed 90 minutes. Again, if a covered procedure on a given patient requires additional time, coverage would not be denied. This requirement is primarily intended as a method of screening procedures for coverage. As with the limits on operating and recovery time, this limit would be imposed in large part by the nature of an ASC—a facility with limited hours of operation, designed primarily for relatively short surgical procedures.

c. *Other limits.* Procedures would not be covered that are generally emergency or life-threatening in nature. Also, covered procedures would not generally be of a type that could be anticipated to result in extensive loss of blood, require major or prolonged invasion of body cavities, or directly involve major blood vessels. This requirement is a result of the comments we solicited in our *Federal Register* notice of May 22.

We wish to emphasize that inclusion of a procedure on the list of those suitable for performance in an ASC would not mean the procedure *must* be performed in that setting. In each case, the physician would determine when the patient's condition or characteristics required hospitalization for surgery.

C. *Definition of Covered Facility Services*

General definition.—The only statutory requirement regarding coverage for facility services is that they be services furnished by the ASC in connection with a covered procedure (sections 1832(a)(2)(F) and 1833(i)(2)(A) of the Act).

In attempting to define the term more fully, we requested information from representatives of ASCs regarding what services they currently include in their "facility fee" or charge. The responses were mixed and contained broader regional and specialty variations than we had expected. Moreover, defining services is complicated by the recent development of specialized ASCs that focus on a few types of procedures in one or two medical specialties, and by the structure and complexity of ASCs

that include on their premises more than a single type of facility recognized by the Medicare program. For example, the ASC may, in addition to the surgical facility portion itself, contain an independent laboratory, a radiology clinic, or some other entity that may be covered under other provisions of the Medicare program. In short, there is only limited uniformity among all the various types of ASCs which can be covered under the law.

Consequently, the definition of facility services in the regulations would specify both what are and are not facility services. Generally, facility services would be defined as those items and services furnished in connection with listed covered procedures that would be covered under Medicare if furnished on an inpatient or outpatient basis in a hospital. Excluded from the term would be physician services and medical and other health services for which payment can be made under other Medicare provisions.

Examples of covered ASC facility services would include:

- (1) The use by the patient of the ASC's facilities;
- (2) Nursing services, technician services, and other related services;
- (3) Drugs, biologicals, surgical dressings, supplies, splints, casts, appliances and equipment directly related to the provision of surgical procedures;
- (4) Diagnostic or therapeutic items and services directly related to the surgical procedure (see section on diagnostic tests for further explanation);
- (5) Administrative, recordkeeping and housekeeping items and services;
- (6) Materials for anesthesia.

Examples of services not included in the term "facility services" would be:

- (1) Physicians' services;
- (2) The sale, lease or rental of durable medical equipment to ASC patients for use in their homes;
- (3) Prosthetic devices;
- (4) Ambulance services;
- (5) Leg, arm, back and neck braces; and
- (6) Artificial legs, arms and eyes.

Diagnostic tests.—Many ASCs perform simple diagnostic tests just before surgery, primarily urinalysis and blood hematocrit, which are generally included in their facility charges. To the extent that such simple tests are directly related to a procedure and included in the charges for covered procedures, they would be considered facility services. However, under Part B of the Medicare program, diagnostic tests may not be covered in laboratories independent of a physician's office, rural health clinic, or

a hospital unless those laboratories meet the requirements of 42 CFR Part 405, Subpart M, the conditions for coverage of services of independent laboratories. Therefore, diagnostic tests, other than simple tests discussed above, performed by the ASC would not be covered under this provision. The ASC may, of course, have its laboratory approved as meeting the conditions of Subpart M, but then the laboratory itself would bill the Medicare Part B carrier (or the beneficiary) for the tests performed. The ASC may also have agreements with an independent or other laboratory to perform diagnostic tests, which would be billed for by that laboratory.

VI. Reimbursement

A. Summary of Reimbursement Provisions

1. Participating ASCs would be paid a prospectively determined rate per procedure for facility services.

2. A physician's reasonable charge for furnishing his or her professional services in connection with a covered surgical procedure performed in a hospital-related ambulatory surgical setting or an ASC would be billed separately and reimbursed at 100 percent of the reasonable charge for that service if the physician accepts assignment of the claim. If assignment is not accepted, the usual rules governing Medicare payments would prevail.

3. Other medical services (as defined in section 1861(s) of the Act) furnished in connection with but not directly related to the performance of the covered procedures performed in hospital-related ambulatory surgical settings or ASCs would be billed separately under the usual payment procedures.

4. A beneficiary (or an ASC as his or her assignee) dissatisfied with reimbursement for services provided would be entitled to dispute the determination under existing Medicare procedures.

B. Legislative Basis

The Report of the Senate Committee on Finance to accompany H.R. 934 (Senate Report No. 96-471, pg. 35) states: "The overhead factor is expected to be calculated on a prospective basis (and periodically updated) utilizing sample survey and similar techniques to develop reasonable estimated overhead allowances for each of the listed procedures which take account of volume (within reasonable limits).

Although the statute authorizes use of an optional all-inclusive rate covering the facility overhead and all related

services, such as physician's professional services, we do not propose to implement that option at this time because there is very little interest in the all-inclusive method of payment within the industry.

C. ASC Payment Methodology

Our review of payment methods currently used by ASCs disclosed that generally, most ASCs use either a pre-established rate (not including physicians' services for performing a procedure) or a charge based on surgical time and materials used. The statutory language requires that Medicare reimbursement be made at a standard rate per procedure. We propose to base the Medicare payment system on the pre-established rate method because it allows the center to know the payment before the service is furnished and it is more widely supported by the ASC industry.

1. *Data Resources.* At the time of passage of the ambulatory surgery legislation, HCFA had little available current information on costs or charges in ASCs. A study by a professional research firm, which evaluated the effects of alternative surgical settings, produced a considerable volume of data on the facilities which participated in the demonstration project. However, due to the limited number of facilities and procedures studied and the age of the data collected (1976-1978), the results of the project were of little practical use in establishing actual payment rates.

In order to obtain more current data on ASC facility costs and charges, we asked the Freestanding Ambulatory Surgical Association (FASA) to assist us by conducting a survey of its members. This survey produced a significant sampling (35 charge schedules, 40 completed questionnaires on billing practices and frequency data, and 19 financial reports) of 1979 and 1980 cost and charge information, as well as data on procedure time and frequency. We also used the survey information and data received in response to our Federal Register Notice of May 22, 1981, to establish the classification of procedures and calculate national group rates.

2. *Classification.* The proposed reimbursement methodology would use a four group classification system. All procedures within each group would be reimbursed at a single rate, adjusted for geographic variations. We propose to use a group classification system rather than a separate rate for each procedure for payment to ASCs for two reasons:

- Administrative simplicity for both the ASCs and HCFA. A grouping system

significantly reduces both the analytical work in computing and updating rates and, to some extent, the claims processing work.

- Limited data available for our initial rate setting. The sampling of centers' charge schedules resulted in only one or two charge entries for some procedures, which was too limited to use in establishing separate rates for each procedure.

In establishing a classification system for ASC reimbursement, we developed an indexing method for ranking each procedure based on a facility's charge for an individual procedure as compared to its average charge for all procedures offered. In this way we could determine how a facility values a given procedure in relationship to the other procedures it offers. (For example, if a facility charges \$200 for a myringotomy and the average charge for all procedures provided at the facility is \$250, this would yield an index value of .8000 for the myringotomy.) We calculated the average of the index numbers (for all facilities) for each procedure, and then arrayed the procedures by this national average index number. After determining the national average index for each procedure, we then classified the covered procedures into four groups by that value. We used interval points to establish group breaking points as follows:

- Group 1—index greater than 1.1
- Group 2—index between 1.0 and 1.1
- Group 3—index between .9 and 1.0
- Group 4—index less than .9

The index value is used exclusively for classification purposes. When determining the actual reimbursement rate for a group, as described below, we used actual charge and cost information as reported by the facilities.

We propose to use an indexing method for classification in an effort to purify the data to some extent. In our analysis of the raw charge data, we discovered wide variances in charges among facilities making a particular service available. By indexing procedures, we would be able to remove the effects of geographic differences and facility specific variations, such as those related to cost and efficiency differences and determine the value a particular facility places on a procedure in relationship to other procedures, which is needed for a group classification system.

3. *Rate Setting.* In order to establish a rate for each of the four groups, we propose to use a four-step procedure; that is, we would (a) adjust actual charges to remove the effects of area

wage differences; (b) calculate the average charge for each procedure in the group; (c) calculate the relationship of costs and charges for ASCs; and (d) select a rate for the group that would result in ASCs being paid the average approximate cost for the procedures in each group. The rate setting mechanism is discussed below.

a. Wage Adjustments. In calculating the payment rates, it is necessary to remove any variations in facilities' charges which are due solely to area differences in labor costs. For each charge we would separate the charge into labor and non-labor components. Analysis of the financial reports available revealed that, on the average, wages composed approximately one-third of facilities' total costs. Assuming facilities' charges to be similarly related to costs, we would adjust one third of the charge for each procedure.

For this purpose, we would use the area wage index that appears in the schedule of Medicare limits on hospital inpatient general routine operating costs that is authorized by 42 CFR 405.560. (The index we used was published on June 30, 1981 [46 FR 33641]). This index, which reflects the different wage levels in areas in which centers are located, would relate the wage levels in each State Standard Metropolitan Statistical Area (SMSA), New England County Metropolitan Area (NECMA), or rural area to a national norm of 1.0. The effect of this calculation would be to adjust the labor portion of each facility's charges to remove the effect of State-to-State wage differences. We would then add the adjusted labor portion of the charge to the nonlabor portion.

b. Average Charge per Procedure. To determine the average charge per procedure, we would sum the wage adjusted charges for all facilities furnishing a given procedure and divide the result by the number of facilities in our sample providing the service.

c. Cost/Charge Adjustment. The statute requires that Medicare payments to ASCs be cost-related. In order to implement this mandate, it is necessary to determine the relationship of ASC cost and charges. In determining this relationship, we relied on financial statements supplied voluntarily by 19 ASCs. Because the statements did not contain sufficient detail to permit application of the Medicare reasonable cost principles contained in 42 CFR Part 405, Subpart D, we propose to use estimates to come extent. (Although we use the term "reasonable costs" in this preamble, we do so not in the technical sense authorized under section 1861(v) of the Act and Subpart D of 42 CFR Part 405, but in its plain meaning in common

speech.) In reviewing cost data submitted, we identified some expenses that would be excluded under the Medicare reimbursement principles, such as entertainment, advertising, gifts, and similar expenses. Additionally some other cost items appeared unusually large. Therefore, in making an estimate of reasonable levels of other costs, we determined that the average level of administrative and general expenses incurred by the sample facilities was 42.1 percent of total costs. We believe there is a strong possibility that the reported costs were overstated, when viewed against costs that are allowable under Medicare reasonable cost principles. This would be true particularly with respect to use of accelerated depreciation methods (use restricted under Medicare) and costs included for obtaining services and supplies from organizations related by control or ownership to the facility (these costs are also restricted under Medicare). Therefore, we propose to round the allowable administrative and general expenses to 40 percent and used this as an upper limit on reasonable administrative and general costs.

Using this process, the average cost/charge ratio would be 0.95 for the 19 facilities. However, one facility in the sample had experienced an extremely large loss (cost/charge ratio in excess of 1.8). This was a new facility experiencing large start-up costs and low initial volume. We do not believe that it is proper for the Medicare program to subsidize such atypical heavy losses, regardless of their cause. Therefore, we propose to eliminate this facility from the data when calculating the aggregate cost/charge ratio. The resultant ratio equals 0.897, which we propose to round to 0.90.

d. Group Rates. To determine the group rate for each class of procedures, we would array the average wage-adjusted charge for the procedures included in the class and calculate the charge at the 60th percentile. We selected the 60th percentile because our analysis of data submitted by the facilities indicated that, on the average, they would recover their reasonable costs through the payment mechanism if we set the target rate at this point. In this way, we hope to provide incentives and promote efficiencies among centers by making reimbursement at the national reasonable cost levels.

In considering the appropriate percentile to select as the group rate, we examined centers' charges and potential Medicare reimbursement for the 35 most commonly furnished surgical procedures. We evaluated the effects of Medicare reimbursement at several

alternative points within the array of wage-adjusted group charges, such as the median, 60th percentile, 75th percentile and 110 percent of the median. This analysis showed that at the 60th percentile, centers should recover 90.83 percent of their charges for the procedures evaluated. Since we had determined that on the average ASC costs equaled approximately 90 percent of their charges (see c. above), Medicare reimbursement at the 60th percentile of the group charges should reasonably approximate national average reasonable cost levels.

4. Inflation Factor. The charge data used in calculating facility reimbursement rates were almost entirely from calendar year 1980. In order to account for inflation that occurred between the time of establishment of the facilities' charge structures and the time of making payment to these centers, we have adjusted the initial rates calculated through the above procedure.

5. Group Rates. The four group rates resulting from the above methodology would be \$231—Group 4, \$275—Group 3, \$296—Group 2, and \$336—Group 1.

6. Individual Payment Rates. To determine the payment rate for each individual ASC, the national payment group rates would be readjusted to allow for the area variations attributable to local wages. Therefore, each carrier would divide the group reimbursement rate just described into labor and non-labor portions, multiply the labor portion (one third) by the area wage index, and add that figure to the non-labor portion to determine the individual facility's payment rate.

7. Periodic Update. We expect that the first years of this reimbursement method would provide us with experience in prospective reimbursement ratesetting. We propose to monitor the impact of the payment method closely by reviewing claims data and conducting sample surveys of ASC costs and charges (see section 8 immediately following). If, based on our experience and more extensive data, we believe that changes in the methodology of the ratesetting process or recalculations of the group payment rates are indicated, we would publish proposed changes for public comment.

In the meantime, we propose to account for new procedures that might be added to the list from time to time by developing an average index number from our existing charge data (in the same fashion as was done in the initial classification) and assigning the procedure to its appropriate group.

8. *Cost Reporting.* The ambulatory surgery legislation does not specifically address the issue of cost reporting. However, the Conference Report to accompany H.R. 7765 (H. Report No. 96-1479) states, " * * * This overhead factor is expected to be calculated on a prospective basis (and periodically updated) utilizing sample survey or similar techniques to establish reasonable estimated overhead allowances for each of the listed procedures * * *".

In establishing the initial overhead allowances, we relied on a sample survey of voluntarily submitted information from ASCs wishing to participate in the data base since the legislation did not explicitly authorize an audit of individual financial records. There are a number of problems inherent in using voluntarily submitted survey materials for this purpose, such as lack of randomness of sample, lack of control over sample size, no standard format or definitions of terms.

In an effort to overcome these problems in future updates of the ASC payment rates, we would make participation in the sample survey of cost and charge information a mandatory requirement in order to participate in the program. We would develop a simplified form of annual cost and charge reporting, to be completed by a random selection of ASC's each time we begin a re-evaluation of the reimbursement system or update payment rates. This would provide a uniform base to be used for program analysis and planning and to assist in establishing future payment rates.

Since we have not yet scheduled such reviews and since not all facilities will be asked to participate in each review, it is impossible to predict how often an individual facility would be required to complete the report. However, in no instance would such requests be more often than annually.

9. *Payment Limit.* Section 1833(i)(2)(A)(ii) of the Act places a limit on the amount of Medicare payment for ASC facility charges. This section requires that payment rates for ASC facility services " * * * result in substantially less amounts paid under this title than would have been paid if the procedure had been performed on an inpatient basis in a hospital".

Since hospitals are reimbursed for inpatient services on a reasonable cost basis, it is extremely difficult to apply this payment limit on a procedure-by-procedure basis. However, from our review of average length of stay data and per diem costs of routine nursing service for the most frequently performed surgical procedures in

ambulatory surgical facilities, we are convinced that payments to ASCs would be substantially less than the amount that would have been paid had all the procedures been provided in an inpatient setting.

For example, a statistical sampling summary of Medicare discharge data shows the average length of stay for iridectomy to be 4.51 days when the procedure is performed on an inpatient basis. Even assuming a low hospital per diem cost of \$130, and even if the Medicare beneficiary had not yet met the Part A deductible, (\$204 in calendar year 1981) the program would be responsible for \$382.30 plus ancillary costs (for example operating room charges, medications, etc.) for the inpatient procedure. If the procedure were performed on an ambulatory basis in an ASC with the reimbursement rate we have developed, Medicare would pay \$336 (plus or minus the wage adjustment) for the same procedure.

Therefore, because of the great difficulty of developing limits on a procedure-by-procedure basis and because available data indicate payments for ASC services can be expected to be less than for inpatient services, we are not proposing to include specific limits in our methodology at this time.

10. *Public Comments.* While the reimbursement methodology we propose to use in developing ASC payment rates is consistent with the majority of the feedback we have received from our discussions with concerned parties, we do not propose to include provision for return on equity capital, bad debts or an exception process which were suggested by some commenters.

a. *Return on Equity Capital.* We did not include a provision for return on equity capital in developing this reimbursement methodology. The purpose of allowing a return on equity capital as an allowable cost under Medicare reasonable cost reimbursement principles (42 CFR 405.429) is to permit payment of an amount above costs to proprietary providers to allow a profit. The reimbursement system contemplated for ASCs would be an incentive type system. As such, it is designed to establish a standard payment rate for a service regardless of an individual facility's costs of providing the service. The purpose of this type of system would be to provide an incentive for facilities to hold down costs by allowing the facility to keep the entire payment rate even if its costs of providing the service is less than the rate, thus permitting facilities a profit. Therefore, it would not be appropriate to include an

additional provision for profit by including a return on equity capital provision.

b. *Bad Debts.* Medicare reimbursement principles permit as an allowable cost bad debts resulting from uncollectible Medicare deductible and coinsurance amounts. However, under the ambulatory surgery benefit, Medicare reimbursement for facility services in an ASC would be made at 100 percent of the payment rate. Since the beneficiary has no deductibles or coinsurance to pay, there can be no Medicare bad debts.

c. *Exceptions.* Some Medicare incentive payment systems and cost limitations provide a process for exceptions to the payment maximum. No such exception process is contemplated in the ASC reimbursement methodology. The basis for existing exceptions is beneficiary-centered, in that a service may no longer be available to a beneficiary if an exception were not granted. Such a situation is unlikely in the case of surgery in an ASC, since there are available alternative settings. Additionally, there is no statutory authority for such exceptions as the legislation explicitly requires reimbursement at a standard rate.

11. *Other Non-selected Options.* a. *Specific Charge Per Procedure.* We considered setting a specific charge for each covered procedure on the list. We did not select this alternative primarily because of unavailability of data. Since we used only a sampling of ASC charges in developing the payment methodology, there were several procedures for which we had only one or two charge entries. We did not believe it would be reasonable to base Medicare payments on such limited data. Another factor that influenced our decision not to pursue this option was the increased administrative costs in rate calculation and claims processing associated with a series of payment rates specific to each procedure over the group rate system we have selected.

b. *Charge Related to Time.* We had considered developing a payment method based on a standard rate per unit of facility use time (operating room and recovery room time). However, our analysis of available data relating time to facilities' charges for a given procedure revealed a poor statistical correlation between the two. Consequently, we have not implemented this alternative.

c. *Weighted Percentile.* In selecting the charge within each group array to be used as the group rate, each procedure was treated equally, regardless of the

actual frequency of the individual procedures' performance. We realize that the reimbursement methodology possibly could have more accurately reflected ASC actual costs had we used a weighting factor. However, ASCs, for the most part, have not been furnishing services to Medicare beneficiaries because they have not been covered by the program. Therefore, we cannot base the group rate on a weighted percentile at this time because there are no data available.

d. Adjustment for Large Volume Facilities. The Conference Report accompanying the legislation anticipated an adjustment of the standard reimbursement rate to account for volume differences among facilities. We believe that facilities furnishing a large volume of procedures should be able to achieve economies (by buying supplies in bulk, for example) and that it might be reasonable to make adjustments in the rates to account for and encourage such economies. Our current data do not provide an adequate basis for such a proposal. We would, however, continue to consider means to account for volume variations in future updates of the group rates.

D. ASC Facility Costs-Inapplicability of Deductible and Coinsurance

Section 934 of Pub. L. 96-499 provides for 100 percent Medicare reimbursement to ASCs rather than the 80 percent generally payable for Part B benefits. As a requirement for payment under section 1832(a)(2)(F)(i), the ASC must agree to accept assignment for all its Medicare claims. Therefore, total payment for facility services would be made directly to the facility. The Medicare beneficiary would not have any deductible or coinsurance to pay; that is, no portion of the payment rate would be applied against any unmet portion of the deductible and no coinsurance payment would be made by the beneficiary. (The beneficiary must fully satisfy the \$75 deductible before any other Part B benefits are payable by the program.)

E. Reimbursement Appeals

A beneficiary (or an ASC as his or her assignee) dissatisfied with reimbursement for services would be entitled to an administrative appeal under the existing Medicare procedures established in 42 CFR Part 405, Subpart H. These appeal procedures provide for a review of disputed claims. Additionally, the beneficiary or ASC would be able to request a hearing on the review determination.

F. Physician Reimbursement—ASC and Hospital-Related Surgical Facilities

Medicare payments for physicians' professional services in connection with covered surgical procedures performed in an ASC or a hospital-related ambulatory surgical setting would be made at 100 percent of the reasonable charge for the service (the Medicare beneficiary would incur no deductible or coinsurance). In order to qualify for that payment, the physician would have to accept assignment of the Medicare claim (including all pre- and post-operative services), and perform the procedure in one of these settings. The physician's decision whether to accept assignment, and thus take advantage of this benefit, would not impact upon the Medicare reimbursement to the facility for services furnished by the facility.

VIII. Assignment Provisions

A. Physician's Professional Services

When a beneficiary receives a covered medical service for which he or she may receive direct payment under Part B, the beneficiary may assign the right to that payment to the physician or other person who furnished the services if the physician or other person agrees to the assignment. Under the terms of the assignment, a physician agrees to accept the Medicare reasonable charge as payment in full for services provided (section 1842(b)(3)(B)(ii) of the Act and 42 CFR 405.1675).

Medicare would pay a physician as described in section VI. F, above. To receive 100 percent of the reasonable charges, a physician would not be required to agree to accept assignment for all listed surgical procedures to all beneficiaries, but if the physician accepts assignment for services in connection with a covered surgical procedure in an individual case, the physician would also be required to accept assignment with respect to any pre-operative and post-operative services he or she furnishes in connection with the procedure in the particular case.

Under section 1870(f) of the Act and 42 CFR 405.1684, if a beneficiary dies before he or she assigns the right of payment for an unpaid Part B service, payment may be made to the physician if he or she agrees to accept the reasonable charge as payment in full. This procedure is similar to an assignment and would be treated as an assignment under these regulations.

Section 1842(b)(5) of the Act and 42 CFR 405.1680(d) prohibit the Medicare program from making Part B payment for physician services to anyone other than the beneficiary or the physician,

with certain limited exceptions. An entity such as an employer, facility, or health care delivery system described in 42 CFR 405.1680(d)(1) (2), or (3) may submit claims and receive Medicare Part B payment for a physician's services if the entity has entered into an employment or other contractual arrangement with the physician authorizing the entity to accept assignment on the physician's behalf. Under these regulations, therefore, the Medicare Part B program would pay the entity 100 percent of the reasonable charges for physicians' services (including all pre-operative and post-operative services) in connection with a covered surgical procedure performed in a hospital-related ambulatory surgical setting or an ASC if the entity agrees on the physician's behalf to accept assignment for those services in the individual case.

B. ASC Facilities

As detailed earlier, the Medicare Part B program would pay an ASC a prospectively determined standard overhead amount for the center's facility services furnished in connection with covered surgical procedures performed in the facility if it has in effect an agreement with HCFA to accept assignment for all those services. Again, no deductible or coinsurance would be applicable to those services. This assignment provision is incorporated into the ASC's agreement with the Secretary required under section 1832(a)(2)(F) of the Act. Under the law, facilities may not accept assignment on a case-by-case basis as is the situation with the physician assignment provision described earlier.

While Medicare Part B usually makes payment on the basis of a reasonable charge determined by the Medicare carrier, and while that is the full charge for the service when assignment is accepted, section 934 provides instead for payment of a standard overhead amount that is cost related. Since the facility must agree to accept assignment in all cases, the standard overhead amount constitutes full payment for the facility's services. For purposes of the assignment provisions in these regulations, we are proposing to treat the standard overhead amount in the same manner as a reasonable charge. Thus the ASC, in accepting assignment, would agree to accept the standard overhead amount as full payment for the facility services.

With respect to ASC assignment agreements, when a beneficiary dies before he or she assigns the right of payment for an unpaid Part B service,

we would treat as assignment for purposes of section 934, payment to the facility after the death of the beneficiary, on the basis of its agreement to accept the reasonable charge as the full charge.

VIII. Competition

These proposed regulations would permit a new class of facilities, ASCs, to compete with hospitals in providing ambulatory surgical services to Medicare beneficiaries. Previously, Medicare coverage and reimbursement for facility services furnished in connection with surgical procedures were available only to hospitals. These regulations would remove a barrier to entry into the market for such services, and would thus encourage competition.

It appears that ASCs are able to provide services of at least equal quality and at less cost than either the hospital inpatient or hospital ambulatory surgical settings. It should be recognized, however, that Medicare beneficiaries, at present, comprise a small fraction of ASCs' patients. Consequently, while extension of Medicare coverage to ASCs will clearly affect the competition between ASCs and hospitals, it is not expected that this effect would be substantial.

We do believe, however, that the extension of coverage and reimbursement to ASCs will give beneficiaries and their physicians important additional options in their selection of sites for surgery. Those options in turn will enhance the competition between ASCs and hospitals.

IX. Impact Analysis

A. Executive Order 12291

The Secretary has determined that these proposed rules do not meet the criteria for a "major rule" as defined by section 1(b) of Executive Order 12291 because they do not have an economic effect of \$100 million or otherwise meet threshold criteria of the Executive Order.

Our actuaries have estimated a \$2 million savings in FY 1983 attributable to the ambulatory surgical benefit. We anticipate the amount of savings to substantially increase in subsequent years as the number of participating ASCs and the volume of services delivered to Medicare beneficiaries in ASCs continues to grow.

In making cost comparisons, we did not predict that extending Medicare coverage to ASCs will significantly affect the number of surgical procedures performed on Medicare beneficiaries, although we have allowed for a small

increase in elective procedures performed because of the convenience afforded by coverage being extended to this setting. What we do expect is a transfer of appropriate surgical procedures from the inpatient setting to the less costly ambulatory surgical setting. However, because of the general health conditions and advanced age of much of the Medicare population, we would not expect a very large shift in the total number of Medicare inpatient surgical cases to the ambulatory setting. In comparing costs of inpatient surgery to ASC facility reimbursement expected under these regulations, we considered national average routine inpatient costs and costs of ancillary services, as well as average ASC facility reimbursement and increased physician payments on assigned claims.

The legislation extending Medicare coverage for surgery in ASCs provides for 100 percent reimbursement of the payment rate for such surgical procedures. The Medicare beneficiary would not have to pay the Part B deductible and 20 percent coinsurance for these services. Also, the cost for the Part A deductible may not have to be incurred by the beneficiary if he or she can take advantage of undergoing surgery in an ambulatory setting rather than an inpatient setting. Consequently, the Medicare beneficiary population would also experience savings through these regulations.

This regulation would promote competition, and benefit Medicare beneficiaries, the ASC industry and the Medicare program trust fund. Some minor adverse effects of this program may be experienced by hospitals who may now feel the effects of competition through a decrease in absolute number of short term inpatient stays associated with surgical procedures. Some hospitals are concerned that this regulation may cause an increase in unused beds and unused operating room time. This is of particular concern among hospitals already experiencing low occupancy rates. However, because of the anticipated relatively low utilization of ASCs by Medicare beneficiaries and because the decrease in utilization would be spread among the hospitals serving the ASC's service area, we do not expect any significant adverse effects on a hospital's total Medicare reimbursement.

B. Regulatory Flexibility Act

The Secretary certifies, pursuant to section 605(b) of the Regulatory Flexibility Act, that these regulations would not have a significant economic impact on substantial number of small entities. With respect to hospitals, most

of which are small entities as defined by the Act, we do not anticipate a significant economic impact for the reasons given above. As to ASCs, all those of which we are presently aware can be considered to be "small entities" within the meaning of section 601(6) of Pub. L. 96-354. That section defines "small entities" as small business, not-for-profit enterprises independently owned and operated and not dominant in their fields, and government jurisdictions serving less than 50,000 persons. We estimate that there are approximately 125 potentially participating ASCs throughout the country at this time. We do not believe, however, that this represents a substantial number of small businesses.

Further, we do not believe that these regulations would have a significant economic impact on these potentially participating ASCs. Based on a study by a professional research firm, which evaluated the effects of alternative surgical settings, we estimate that Medicare beneficiaries would comprise only approximately 10 percent of an ASC's total patient load. Also, we have actively sought to keep the costs of compliance with these regulations minimal by permitting as much flexibility as possible in the certification standards, developing a simplified payment system, and reducing reporting requirements by using only sample surveys. Finally, these regulations would serve to increase revenue for these small entities by providing Medicare coverage and reimbursement where it was not previously available. For these reasons we do not anticipate these regulations would significantly affect a substantial number of small businesses.

C. Reporting Recordkeeping Requirements

Section 416.30(d) of these regulations contains reporting requirements and §§ 416.43 and 416.47(b) contain recordkeeping requirements which have not yet been approved by the Executive Office of Management and Budget (EOMB) but are subject to the Paperwork Reduction Act (Pub. L. 96-511). Since the information required to be reported under § 416.30(d) would be used to evaluate the payment methodology and update payment rates, this information would not be gathered until centers have obtained some experience with the program.

X. Response to Comments

Because of the large number of comments we receive, we cannot acknowledge or respond to them individually. However, in preparing the

final rule we will consider all comments and will respond to them in the preamble to the rule.

XI. List of Subjects¹

42 CFR Part 405

Administrative practice and procedure
Certification of compliance
Clinics
Contracts (Agreements)
End-Stage Renal Disease (ESRD)
Health care
Health facilities
Health maintenance organizations (HMO)
Health professions
Health suppliers
Home health agencies
Hospitals
Inpatients
Kidney diseases
Laboratories
Medicare
Nursing homes
Onsite surveys
Outpatient providers
Reporting requirements
Rural areas
X-rays

42 CFR Part 416

Ambulatory surgical centers
Assignment
Contracts (Agreements)
Medicare
Physicians
Reporting Requirements
Surgical Procedures

42 CFR Chapter IV is amended as set forth below.

A. The Table of Contents is amended by adding a new Part 416 to Subchapter B to read as follows:

CHAPTER IV—HEALTH CARE FINANCING ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

* * *

SUBCHAPTER B—MEDICARE PROGRAMS

* * *

PART 416—AMBULATORY SURGICAL SERVICES

* * *

¹ Health Care Financing Administration is providing this list in compliance with 1 CFR 18.20. That regulation requires agencies to include a list of index terms for each CFR part affected in Rules and Proposed Rules documents published in the Federal Register beginning April 1, 1982.

PART 405—FEDERAL HEALTH INSURANCE FOR THE AGED AND DISABLED

Supplementary Medical Insurance Benefits; Enrollment, Coverage, Exclusions and Payment

B. Subpart B of Part 405 is amended as follows:

1. The authority citation for Subpart B is amended to read as follows:

Authority: Secs. 1102, 1831–1843, 1861, 1862, 1866, 1871; 49 Stat. 647, as amended, 79 Stat. 301–312, 313, 325, 327, 331; 42 U.S.C. 1302, 1395j–1395v, 1395x, 1395y, 1395cc, and 1395hh.

2. In § 405.230 the introductory language for paragraph (a) is reprinted, a new paragraph (a)(6) is added and paragraph (b) is revised as follows:

§ 405.230 Supplementary medical insurance benefits.

(a) *Benefits provided.* Any individual who is enrolled under the supplementary medical insurance plan established by Part B of title XVIII of the Act is, subject to the conditions, limitations, and exclusions described in this Part 405, entitled to have:

(6) Payment made on his or her behalf for covered ambulatory surgical center facility services, as described in § 416.61 of this chapter, that are furnished in connection with surgical procedures described in § 416.65 of this chapter, and performed in a participating ambulatory surgical center.

(b) *Reimbursable expenses.* In order to be considered incurred expenses, expenses for physicians' services, home, health services, ambulatory surgical center facility services, and for other medical and health services covered under the supplementary medical insurance plan must be for services furnished to an individual during his or her coverage period. (See as described in §§ 405.221 through 405.223.)

3. In § 405.240 the introductory paragraph is revised, paragraphs (i) and (j) are added and reserved and new paragraphs (k) and (l) are added to read as follows:

§ 405.240 Payment of supplementary medical insurance benefits; amounts payable.

In the case of an individual who incurs expenses during his or her coverage period under the supplementary medical insurance plan, payment with respect to the total amount of such expenses incurred during a calendar year shall, subject to the provisions of §§ 405.243–405.246, be made as follows:

* * *

(i) [Reserved]

(j) [Reserved]

(k) One hundred percent of the reasonable charges for physicians' services (including all pre- and post-operative services) furnished in connection with surgical procedures as specified in § 416.65 of this chapter, if the following conditions are met:

(1) The procedures are performed in a participating ambulatory surgical center, on an outpatient basis in a hospital, or in a hospital-affiliated ambulatory surgical center.

(2) The physician accepts assignment with respect to payment for those services furnished in connection with the procedures. For purposes of this section:

(i) Assignment means an assignment under § 405.1675 of the right to receive payment under the Medicare Part B program and payment under § 405.1684 (when an individual dies before assigning payment).

(ii) A physician may authorize an entity specified in § 405.1680(d)(1), (2), or (3) to accept assignment on his or her behalf.

(l) One hundred percent of a standard overhead amount as specified in § 416.120(c) of this chapter, for ambulatory surgical center facility services, as described in § 416.61 of this chapter, that are furnished in connection with surgical procedures described in § 416.65 of this chapter and performed in a participating ambulatory surgical center.

4. Section 405.244–1 is amended by revising the section title, designating a portion of the section as paragraph (a), and adding new paragraphs (b) and (c). As amended, § 405.244–1 reads as follows:

§ 405.244–1 Payment of supplementary medical insurance benefits; kidney donor services and ambulatory surgical services.

Notwithstanding any other provisions in this title, there are no deductible or coinsurance requirements with respect to—(a) Services furnished to an individual in connection with the donation of a kidney for transplant surgery;

(b) Physicians' services (including all pre- and post-operative services) when the physician accepts assignment, as described in § 405.240(k)(2), and provides services in connection with a covered surgical procedure, as specified in § 416.65 of this chapter, performed in a participating ambulatory surgical center, on an outpatient basis in a hospital or in a hospital-affiliated ambulatory surgical facility; or

(c) Facility services, as described in § 416.65 of this chapter, furnished in

connection with surgical procedures as specified in § 416.65 of this chapter, when those procedures are performed in a participating ambulatory surgical center.

5. Section 405.250-2 is amended by revising the section title, redesignating the undesignated introductory paragraph as paragraph (a), redesignating current paragraphs (a) and (b) as (a)(1) and (a)(2), and adding a new paragraph (b) to read as follows:

§ 405.250-2 Procedures for payment; rural health clinic and ambulatory surgical center facility services furnished by a rural health clinic or an ambulatory surgical center.

(a) Payment for covered rural health clinic services shall be made if:

(1) The services are furnished by a rural health clinic in accordance with the requirements of Subpart X of this part and Subpart A of 481 of this chapter; and

(2) A written request for payment is filed by the clinic on the form and in the manner prescribed by HCFA.

(b) Payment for facility surgical services furnished by an ambulatory surgical center shall be made if—

(1) The services are furnished in accordance with the requirements of Part 416 of this chapter; and

(2) A written request for payment is filed by the ambulatory surgical center on the form and in the manner prescribed by HCFA.

Subpart O—Providers of Services, Emergency Service Hospitals, Independent Laboratories, Suppliers of Portable X-Ray Services, End-Stage Renal Disease Treatment Facilities, and Persons; Determinations and Appeals Procedures

The authority citation for Subpart O reads as follows:

Authority: Secs. 1102, 1866, 1869, 1871, 1872, 49 Stat. 647, as amended; 79 Stat. 327; 79 Stat. 330-332; 42 U.S.C. 1302, 1395 et seq., unless otherwise noted.

C. Subpart O of Part 405 is amended as follows:

1. The Table of Contents is amended by revising the subpart title and the title of § 405.1501 to read as follows:

Subpart O—Providers of Services, Emergency Service Hospitals, Independent Laboratories, Suppliers of Portable X-Ray Services, Independent Ambulatory Surgical Centers, End-Stage Renal Disease Treatment Facilities, and Persons; Determinations and Appeals Procedures

405.1501 Providers of services, emergency service hospitals, independent laboratories, suppliers of portable X-ray services, independent ambulatory surgical centers, end-stage renal disease

treatment facilities and persons; determinations and appeals procedures.

2. In § 405.1501 the section title is revised, the introductory language for paragraph (a) is reprinted without (change), and paragraphs (a)(5) and (c) are revised as follows:

§ 405.1501 Providers of services, emergency service hospitals, independent laboratories, suppliers of portable X-ray services, independent ambulatory surgical centers, end-stage renal disease treatment facilities and persons; determinations and appeals procedures.

(a) The provisions contained in this Subpart O shall govern the procedure for making and reviewing determinations with respect to:

(5) Whether an independent laboratory, supplier of portable X-ray services, independent ambulatory surgical service center, or end-stage renal disease treatment facility meets the appropriate conditions for coverage of its services (see Subparts M and N of this Part 405, Subpart B of this Part 416 of this Chapter, and Appendix to Subpart B of this Part 405); and

(c) Any independent laboratory, supplier of portable X-ray services, independent ambulatory surgical service center, or any end-stage renal disease treatment facility which is dissatisfied with an initial determination (see § 405.1502) that the services subject to the determination do not meet the conditions for coverage (see Subparts M and N of this Part 405, Subpart B of Part 416 of this chapter, and Appendix to Subpart B of this Part 405) may request a reconsideration of that determination (§ 405.1510). If dissatisfied with the reconsidered determination or where a determination had been made that an independent laboratory's, portable X-ray supplier's independent ambulatory surgical center's, or end-stage renal disease treatment facility's services met the respective conditions for coverage, with an initial determination thereafter that the services subject to the determination no longer meet the respective conditions for coverage, a laboratory, portable X-ray supplier, independent ambulatory surgical center, or end-stage renal disease treatment facility may request a hearing thereon (see § 405.1530), and if dissatisfied with the decision of the Administrative Law Judge may request Appeals Council review. The statute does not offer a laboratory, portable X-ray supplier, independent ambulatory surgical center, or end-stage renal disease treatment facility a judicial

review of the Secretary's final decision after such hearing and review.

3. In § 405.1502, the introductory paragraph is reprinted without change and paragraphs (b)(1) and (b)(2) are revised to read as follows:

§ 405.1502 Initial determinations.

The Secretary will make findings, setting forth the pertinent facts and conclusions, and an initial determination with respect to:

(b)(1) Whether an independent laboratory, supplier of portable X-ray services, independent ambulatory surgical center, or end-stage renal disease treatment facility meets the respective conditions for coverage (see Subparts M and N of this Part 405, Subpart B of Part 416 of this chapter, and Appendix to Subpart B of this Part 405). If the laboratory, portable X-ray supplier, independent ambulatory surgical center, or end-stage renal disease treatment facility has filed a written request for such a determination; or

(2) Whether the services of an independent laboratory, supplier of portable X-ray services independent ambulatory surgical center, or an end-stage renal disease treatment facility continue to meet their respective conditions for coverage of the services subject to the determination; and

§ 405.1503 [Amended]

4. Section 405.1503 is amended by inserting the words "independent ambulatory surgical center," following "portable X-ray supplier," each time it appears.

§ 405.1505 [Amended]

5. Section 405.1505(a)(2) is amended by inserting the words "independent ambulatory surgical center," following "supplier of portable X-ray services,"

§ 405.1510 [Amended]

6. Section 405.1510 is amended by inserting the words "independent ambulatory surgical center," after "supplier of portable X-ray services," or "portable X-ray supplier," each time they appear and by removing the words "M, N," where they appear and inserting in their place, "M and N of this Part 405, Subpart B of Part 416 of this chapter,"

§§ 405.1511-405.1513, 405.1515-405.1516 and 405.1519 [Amended]

7. Sections 405.1511(a), 405.1512, 405.1513, 405.1515, 405.1516, and 405.1519 are amended by inserting the words "independent ambulatory surgical

center," following "portable X-ray supplier," each time it appears.

§ 405.1520 [Amended]

8. Section 405.1520 is amended by inserting the words "independent ambulatory surgical center," after "portable X-ray supplier," or "supplier of portable X-ray services," each time they appear and by removing the words "M, N," where they appear and inserting, in their place, "M and N of this Part 405, Subpart B of Part 416 of this chapter,".

§ 405.1530 and 405.1531 [Amended]

9. Sections 405.1530 and 405.1531 are amended by inserting the words "independent ambulatory surgical center," following "portable X-ray supplier," each time it appears.

10. Section 405.1532 is revised to read as follows:

§ 405.1532 Parties to the hearing.

The parties to the hearing shall be the institution, agency, clinic, laboratory, portable X-ray supplier, independent ambulatory surgical center, end-stage renal disease treatment facility, or person which was a party to the prior determination (see §§ 405.1502(b)(2), (c), (d)(2), and (e), 405.1514, and 405.1519) and HCFA as representing the Secretary. HCFA shall be represented at the hearing (see § 405.1543).

§ 405.1534, 405.1536-405.1537 and 405.1542 [Amended]

11. Sections 405.1534, 405.1536, 405.1537, and 405.1542 are amended by inserting the words "independent ambulatory surgical center," after "portable X-ray supplier," where it appears.

12. Section 405.1543 is revised to read as follows:

§ 405.1513 Joint hearings.

When two or more institutions, agencies, clinics, laboratories, portable X-ray suppliers, independent ambulatory surgical centers, end-stage renal disease treatment facilities, or persons have requested hearings and the same or substantially similar matters are in issue, the Administrative Law Judge may, if all parties agree, fix the same times and places for each prehearing conference or hearing and conduct all such proceedings jointly. Where joint hearings are held, a single record of the proceedings shall be made and a separate decision issued with respect to each institution, agency, clinic, laboratory, portable X-ray supplier, independent ambulatory surgical center, end-stage renal disease treatment facility, or person.

§ 405.1545 [Amended]

13. Section 405.1545 is amended by inserting the words "independent ambulatory surgical center," after "portable X-ray supplier," where it appears.

§ 405.1550 [Amended]

14. Section 405.1550 is amended by inserting the words "independent ambulatory surgical center," after "portable X-ray supplier," each time it appears and by removing the words "the Medicare Bureau (as well as the Health Standards and Quality Bureau in the case of a determination regarding an end-stage renal disease treatment facility)" where they appear and inserting, in their place, "HCFA".

§§ 405.1551-405.1554 [Amended]

15. Sections 405.1551, 405.1552, 405.1553, and 405.1554 are amended by inserting the words "independent ambulatory surgical center," after "portable X-ray supplier," each time it appears.

16. Section 405.1563 is revised to read as follows:

§ 405.1563 Action by the Appeals Council on request for review.

The review or denial of the Administrative Law Judge's decision shall be conducted by a panel of at least two members of the Appeals Council designated by the Chairman or Deputy Chairman and one person from the U.S. Public Health Service designated by the Secretary. Except as provided in § 405.1568, the Appeals Council shall review the Administrative Law Judge's decision or dismissal where an institution, agency, clinic, laboratory, portable X-ray supplier, independent ambulatory surgical center, end-stage renal disease treatment facility, or person, files a request for review. The Appeals Council may dismiss, deny, or grant a request for review filed by HCFA as representing the Secretary. If the review is granted, the Appeals Council may either modify, affirm, or reverse the Administrative Law Judge's decision. Notice of the action by the Appeals Council shall be mailed to the institution, agency, clinic, laboratory, portable X-ray supplier independent ambulatory surgical center, end-stage renal disease treatment facility, or person and HCFA.

17. Section 405.1567 is revised to read as follows:

§ 405.1567 Effect of the Appeals Council decision.

The decision of the Appeals Council shall be final and binding unless a civil action (see § 405.1501 (b), (e) and (f)) is

filed by the institution, agency, clinic, or person in a district court of the United States as authorized by section 1862(d)(3) or 1869(c) of the Act, as appropriate, or unless the decision is revised in accordance with § 405.1570. (Section 1869(c) of the Act does not grant judicial review of the Secretary's decision with respect to whether an independent laboratory, supplier of portable X-ray services, independent ambulatory surgical center, or end-stage renal disease treatment facility meets the conditions for coverage, as required by Subparts M and N of this Part 405, Subpart B of Part 416 of this chapter, or Appendix to Subpart B of this Part 405.)

§ 405.1569 [Amended]

18. Section 405.1569 is amended by inserting the words "independent ambulatory surgical center," after "portable X-ray supplier," or "supplier of portable X-ray services," where they appear.

§ 405.1590 [Amended]

19. Section 405.1590 is amended by inserting the words "independent ambulatory surgical center," after "portable X-ray supplier," where it appears.

20. Section 405.1592 is revised to read as follows:

§ 405.1592 Fees for services.

Fees for any services provided by a representative appointed and qualified as in §§ 405.1590 and 405.1591 on behalf of any institution, facility, agency, clinic, laboratory, portable X-ray supplier, or independent ambulatory surgical center shall not be subject to the provisions of section 206 of title II of the Social Security Act.

D. A new Part 416 is added as set forth below.

PART 416—AMBULATORY SURGICAL SERVICES

Subpart A—General Provisions and Definitions

Sec.

- 416.1 Scope.
- 416.2 Definitions.
- 416.3 Expenses not subject to deductible or coinsurance.

Subpart B—Ambulatory Surgical Centers: Coverage and Benefits.

416.20 Basis and purpose.

Conditions for Coverage

- 416.25 Basic requirements and procedures.
- 416.30 Terms of agreement with HCFA.
- 416.35 Termination of agreement.
- 416.39 Conditions for coverage—General provisions.
- 416.40 Condition for coverage—Compliance with State licensure law.

Sec.

- 416.41 Condition for coverage—Governing body and management.
- 416.42 Condition for coverage—Surgical services.
- 416.43 Condition for coverage—Evaluation of quality.
- 416.44 Condition for coverage—Environment.
- 416.45 Condition for coverage—Medical staff.
- 416.46 Condition for coverage—Nursing services.
- 416.47 Condition for coverage—Medical records.
- 416.48 Condition for coverage—Pharmaceutical services.
- 416.49 Condition for coverage—Laboratory and radiologic services.

Scope of Benefits

- 416.60 Reimbursable services: General provision.
- 416.61 ASC facility services: Scope.
- 416.65 Covered surgical procedures.
- 416.75 Performance of listed surgical procedures on an inpatient hospital basis.

Subpart C—Payment for Ambulatory Surgical Services

- 416.100 Basis and purpose.
- 416.110 Payment for physicians' services furnished in connection with covered surgical procedures.
- 416.120 Payment for facility services.
- 416.125 ASC facility services payment rate.
- 416.130 Publication of revised payment methodologies.
- 416.140 Reporting requirements.
- 416.150 Beneficiary appeals.

Authority: Secs. 1102, 1832(a)(2), 1833, 1863 and 1864 of the Social Security Act (42 U.S.C. 1302, 1395k(a)(2), 1395l, 1395z and 1395aa)

Subpart A—General Provisions and Definitions

§ 416.1 Scope.

This part establishes the requirements for coverage and reimbursement of certain ambulatory surgical services under the Medicare program, authorized under sections 1832(a)(2) and 1833 of the Act.

§ 416.2 Definitions.

As used in this part:

"Ambulatory surgical center" or "ASC" means a facility that is not part of a hospital ("Part of a hospital" means an integral and subordinate part of a hospital, operated with other departments of the hospital under common licensure, governance, and professional supervision, and located either on the hospital premises or offsite); is designed to operate primarily for the purpose of providing surgical services to patients not requiring hospitalization; and meets the conditions set forth in Subpart B of this part.

"Covered surgical procedures" means those surgical and other medical

procedures which meet the criteria specified in this part and are published by HCFA in the Federal Register.

§ 416.3 Expenses not subject to deductible or coinsurance.

Notwithstanding any other provisions in this chapter, expenses for services covered under this part are not subject to the supplementary medical insurance benefits deductible or coinsurance requirements for—

(a) Physicians' services (including pre- and post-operative services), when the physician accepts assignment as described in § 405.240(k)(2) of this chapter and provides services in connection with a covered surgical procedure, as specified in § 416.65, performed in a participating ASC, on an outpatient basis in a hospital or in a hospital-affiliated ambulatory surgical center; or

(b) Facility services as described in § 416.61 furnished in connection with surgical procedures as specified in § 416.65 when those procedures are performed in a participating ASC.

Subpart B—Ambulatory Surgical Centers: Coverage and Benefits.

§ 416.20 Basis and purpose.

This subpart implements sections 1832(a)(2) and 1833 of the Act, with respect to—

(a) The conditions that an ASC must meet to participate in the Medicare program (conditions for coverage); and

(b) The scope of benefits covered in an ASC.

Conditions for Coverage

§ 416.25 Basic requirements and procedures.

(a) *Eligible facilities.* Participation as an ASC is limited to those facilities that meet the definition in § 416.2.

(b) *Survey by the survey agency.* (1) Unless the ASC is deemed to be in compliance with the conditions for coverage (see § 416.39(b) for deemed compliance), the ASC must be surveyed to ascertain compliance with the requirements in §§ 416.40–416.49.

(2) We would survey deemed ASCs on a sample basis as part of HCFA's validation process.

(c) *Acceptance of the ASC as qualified to furnish ambulatory surgical services.* If HCFA determines, after reviewing the survey agency recommendation and other evidence relating to the qualification of the ASC, that the facility meets the requirements of this subpart, it will send to the ASC—

- (1) Written notice of the determination; and
- (2) Two copies of the ASC agreement.

(d) *Filing of agreement by the ASC.* If the ASC wishes to participate in the program, it must—

(1) Have both copies of the ASC agreement signed by its authorized representative; and

(2) File them with HCFA.

(e) *Acceptance by HCFA.* If HCFA accepts the agreement filed by the ASC, it will return to the ASC one copy of the agreement, with a notice of acceptance specifying the effective date.

(f) *Appeal rights.* If HCFA refuses to enter into an agreement or if HCFA terminates an agreement, the ASC is entitled to a hearing in accordance with Part 405, Subpart O of this chapter.

§ 416.30 Terms of agreement with HCFA.

As part of the agreement under § 416.25(d), the ASC must agree to the following:

(a) *Compliance with coverage conditions.* The ASC agrees to meet the requirements regarding conditions for coverage as specified in § 416.39 and to report promptly to HCFA any failure to do so.

(b) *Charges to beneficiaries.* The ASC agrees not to charge the beneficiary or any other person for items or services for which the beneficiary is entitled to have payment made under the provisions of this subpart (or for which the beneficiary would have been entitled if the ASC had filed a request for payment in accordance with § 405.250–2 of this chapter).

(c) *Refunds to beneficiaries.* (1) The ASC agrees to refund as promptly as possible any money incorrectly collected from beneficiaries or from someone on their behalf.

(2) As used in this section, "money incorrectly collected" means sums collected in excess of those specified in paragraph (b) of this section. It includes amounts collected for a period of time when the beneficiary was believed not to be entitled to Medicare benefits if—

(i) The beneficiary is later determined to have been entitled to Medicare benefits; and

(ii) The beneficiary's entitlement period falls within the time the ASC's agreement with HCFA is in effect.

(d) *Furnishing information.* The ASC agrees to furnish to HCFA, if requested, information necessary to establish payment rates specified in §§ 416.120–416.130 in the form and manner that HCFA requires.

(e) *Acceptance of assignment.* The ASC agrees to accept assignment for all facility services furnished in connection with covered surgical procedures as specified in 416.65. For purposes of this section, assignment means an

assignment under § 405.1675 of the right to receive payment under Medicare Part B and payment under § 405.1684 (when an individual dies before assigning payment).

(f) *Additional provisions.* The agreement may contain any additional provisions that HCFA finds necessary or desirable for the efficient and effective administration of the Medicare program.

§ 416.35 Termination of agreement.

(a) *Termination by the ASC—*

(1) *Notice to HCFA.* If the ASC wishes to terminate its agreement, it must file with HCFA a written notice stating the intended effective date of termination.

(2) *Action by HCFA.* HCFA may approve the date proposed for termination by the ASC, or set a different date no later than 6 months after the date of the ASC's notice if HCFA determines that termination on the latter date—

(i) Would not unduly disrupt services to the community serviced by the ASC; or

(ii) Would not otherwise interfere with the effective and efficient administration of the Medicare program.

(3) If an ASC ceases to furnish services to the community, that shall be deemed to be a voluntary termination of the agreement by the ASC, effective on the last day of business with Medicare beneficiaries.

(b) *Termination by HCFA—*(1) *Cause for termination.* HCFA may terminate an agreement if it determines that the ASC—

(i) No longer meets the conditions for coverage as specified under § 416.39; or

(ii) Is not in substantial compliance with the provisions of the agreement, the requirements of this subpart, and other applicable regulations of Subchapter B of this chapter, or any applicable provisions of title XVIII of the Act.

(2) *Notice of termination.* HCFA will send notice of termination to the ASC at least 15 days before the effective date stated in the notice.

(3) *Appeal by the ASC.* An ASC may appeal the termination of its agreement in accordance with the provisions set forth in Part 405, Subpart O of this chapter.

(c) *Effect of termination.* Payment will not be available for ASC services furnished on or after the effective date of termination.

(d) *Notice to the public.* Prompt notice of the date and effect of termination shall be given to the public, through publication in local newspapers by—

(1) The ASC, after HCFA has approved or set a termination date; or
(2) HCFA, when it has terminated the agreement.

(e) *Conditions for reinstatement after termination of agreement by HCFA.*

When an agreement with an ASC is terminated by HCFA, the ASC may not file another agreement to participate in the Medicare program unless HCFA—

(1) Finds that the reason for the termination of the prior agreement has been removed; and

(2) Is assured that the reason for the termination will not recur.

§ 416.39 Conditions for coverage—General provisions.

(a) Except as provided for in paragraph (b) of this section, as ASC must maintain compliance with the conditions set forth in §§ 416.40–416.49.

(b) The ASC is deemed to be in compliance with the conditions set forth in §§ 416.40–416.49 if—

(1) The ASC is accredited by the Accrediting Association for Ambulatory Health Care, Inc.;

(2) Where State law requires ASC licensure, the ASC is licensed by the State; and

(3) The ASC releases to HCFA the findings of the accreditation survey.

§ 416.40 Condition for coverage—Compliance with State licensure law.

The ASC must be licensed when State law provides for licensure of ambulatory surgical centers.

§ 416.41 Condition for coverage—Governing body and management.

The ASC must have a governing body, or an individual, that assumes full legal responsibility for determining, implementing, and monitoring policies governing the ASC's total operation and for ensuring that these policies are administered so as to provide quality health care in a safe environment. When services are provided through a contract with an outside resource, the ASC must assure that these services are provided in a safe and effective manner.

Standard: Hospitalization. The ASC must have a written procedure for the immediate transfer to a hospital of patients requiring emergency medical care beyond the capabilities of the ASC.

§ 416.42 Condition for coverage—Surgical services.

Surgical procedures must be performed in a safe manner by qualified physicians who have been granted clinical privileges, and in accordance with approved policies and procedures of the ASC.

(a) *Standard: Anesthetic risk.* A physician must examine the patient immediately before surgery to evaluate the risk of anesthesia and of the procedure to be performed.

(b) *Standard: Administration of anesthesia.* Anesthesia must be administered by anesthesiologists, physician anesthesiologists, nurse anesthetists, anesthesia assistants, or supervised trainees in an approved educational program.

§ 416.43 Condition for coverage—Evaluation of quality.

The ASC, with the active participation of the medical staff, must conduct an ongoing, comprehensive self-assessment of the quality of care provided and use findings, when appropriate, in the revision of center policies and consideration of clinical privileges.

§ 416.44 Condition for coverage—Environment.

The ASC must have a safe and sanitary environment, properly constructed, equipped, and maintained to protect the health and safety of patients.

(a) *Standard: Physical environment.* The ASC must provide a functional and sanitary environment for the provision of surgical services.

(1) Each operating room must be designed and equipped so that the types of surgery conducted can be performed in a manner that protects the lives and assures the physical safety of all individuals in the area.

(2) The ASC must have a separate recovery room and waiting area.

(3) The ASC must establish a program for identifying and preventing infections, maintaining a sanitary environment, and reporting the results to appropriate authorities.

(b) *Standard: Safety from fire.* The ASC must meet the provisions of the Life Safety Code of the National Fire Protection Association (NFPA-1981 edition) that are applicable to ambulatory surgical centers, with the following exception. In consideration of a recommendation by the State survey agency, HCFA may waive, for periods deemed appropriate, specific provisions of that code which, if rigidly applied, would result in unreasonable hardship upon an ASC, but only if the waiver will not adversely affect the health and safety of the patients.

(c) *Standard: Emergency equipment.* Emergency equipment available to the operating rooms must include at least the following:

(1) Emergency call system.

(2) Oxygen.

(3) Mechanical ventilatory assistance equipment including airways, manual breathing bag, and ventilator.

(4) Cardiac defibrillator.

(5) Cardiac monitoring equipment.

- (6) Thoracostomy set.
- (7) Tracheostomy set.
- (8) Laryngoscopes and endotracheal tubes.
- (9) Suction equipment.
- (10) Emergency drugs and supplies specified by the medical staff.

§ 416.45 Condition for coverage—Medical staff.

The medical staff of the ASC must be accountable to the governing body or the individual responsible for governing the ASC's total operation.

(a) *Standard: Membership and clinical privileges.* Members of the medical staff must be legally and professionally qualified for the positions to which they are appointed and privileges granted.

(b) *Standard: Other practitioners.* If the ASC assigns patient care responsibilities to practitioners other than physicians, it must have established policies and procedures, approved by the governing body, for overseeing and evaluating their clinical activities.

§ 416.46 Condition for coverage—Nursing services.

The nursing services of the ASC must be directed and staffed to assure that the nursing needs of all patients are met.

(a) *Standard: Organization and staffing.* Patient care responsibilities must be delineated for all nursing service personnel. Nursing services must be provided in accordance with recognized standards of practice. There must be a registered nurse available for emergency treatment whenever there is a patient in the ASC.

§ 416.47 Condition for coverage—Medical records.

The ASC must maintain complete, comprehensive, and accurate medical records to ensure adequate patient care.

(a) *Standard: Organization.* The ASC must develop and maintain a system for the proper collection, storage, and use of patient records.

(b) *Standard: Form and content of record.* The ASC must maintain a medical record for each patient. Every record must be accurate, legible, and promptly completed. Medical records must include at least the following:

- (1) Patient identification.
- (2) Significant medical history and results of physical examination.
- (3) Pre-operative diagnostic studies (entered before surgery), if performed.
- (4) Findings and techniques of the operation.
- (5) Any allergies and abnormal drug reactions.
- (6) Discharge diagnosis.

§ 416.48 Condition for coverage—Pharmaceutical services.

The ASC must provide drugs and biologicals in a safe and effective manner, in accordance with accepted professional practice, and under the direction of an individual designated responsible for pharmaceutical services.

(a) *Standard: Administration of drugs.* Drugs must be prepared and administered according to established policies and acceptable standards of practice.

(1) Adverse reactions must be reported to the physician responsible for the patient and must be documented in the record.

(2) Blood, blood products, and parenteral solutions must be administered only by physicians, anesthesiologists, or registered nurses.

(3) Verbal orders for drugs and biologicals must be followed by a written order, signed by the prescribing physician.

§ 416.49 Condition for coverage—Laboratory and radiologic services.

The ASC must have written policies that provide for routine and emergency laboratory and radiologic services to meet the needs of the patients.

(a) *Standard: Provision of services.* Laboratory and radiologic services, may be furnished by the ASC or through agreement with Medicare approved outside resources. If the ASC provides its own laboratory or radiologic services, it must meet the applicable requirements in §§ 405.1028 and 405.1029 of this chapter.

Scope of Benefits

§ 416.60 Reimbursable services: General provision.

Ambulatory surgical center services reimbursable under this subpart are facility services, furnished in connection with covered surgical procedures, to Medicare beneficiaries by an ASC that has an agreement with HCFA.

§ 416.61 ASC facility services: Scope.

(a) ASC facility services are items and services furnished by an ASC in connection with a covered surgical procedure as specified under § 416.65, furnished to a Medicare beneficiary. These items and services are those which would otherwise be covered under Medicare if furnished on an inpatient or outpatient basis in a hospital in connection with the covered surgical procedure.

(b) ASC facility services do not include items and services for which payment may be made under other provisions of Part 405 of this chapter, such as physicians' services, laboratory,

X-ray of diagnostic procedures (other than those directly related to performance of the surgical procedure), prosthetic devices, ambulance services, leg, arm, back and neck braces, artificial limbs, and durable medical equipment for use in the patient's home.

(c) ASC facility services include, but are not limited to—

- (1) Nursing, technician, and related services;
- (2) Use of ASC facilities;
- (3) Drugs, biologicals, surgical dressings, supplies, splints, casts and appliances and equipment directly related to the provision of surgical procedures;
- (4) Diagnostic or therapeutic services or items directly related to the provision of a surgical procedure;
- (5) Administrative, recordkeeping and housekeeping items and services;
- (6) Materials for anesthesia.

§ 416.65 Covered surgical procedures.

Covered surgical procedures are those procedures that meet the standards described in paragraphs (a) and (b) of this section and are included in the list published in accordance with paragraph (c) of this section.

(a) *General standards.* Covered surgical procedures are those surgical and other medical procedures that—

- (1) Are commonly performed on an inpatient basis in hospitals, but may be safely performed in an ASC;
- (2) Are not of a type that are commonly performed, or that may be safely performed, in physicians' offices;
- (3) Are limited to those requiring a dedicated operating room (or suite), and generally requiring a post-operative recovery room or short-term (not overnight) convalescent room; and
- (4) Are not otherwise excluded under § 405.310 of this chapter.

(b) *Specific standards.* (1) Covered surgical procedures are limited to those that do not generally exceed—

- (i) A total of 90 minutes operating time; and
- (ii) A total of 4 hours recovery or convalescent time.
- (2) If the covered surgical procedures require anesthesia, the anesthesia must be—
 - (i) Local or regional anesthesia; or
 - (ii) General anesthesia of 90 minutes or less duration.
- (3) Covered surgical procedures may not be of a type that—
 - (i) Generally result in extensive blood loss;
 - (ii) Require major or prolonged invasion of body cavities;
 - (iii) Directly involve major blood vessels; or

(iv) Are generally emergency or life-threatening in nature.

(c) *Publication of covered procedures.* HCFA will publish in the Federal Register a list of covered surgical procedures and revisions as appropriate.

§ 416.75 Performance of listed surgical procedures on an inpatient hospital basis.

The inclusion of any procedure as a covered surgical procedure under § 416.65 does not preclude its coverage in an inpatient hospital setting under Medicare.

Subpart C—Payment for Ambulatory Surgical Services

§ 416.100 Basis and purpose.

This subpart implements sections 1832(a)(2) and 1833 of the Act with respect to Medicare payment for ambulatory surgical services furnished in connection with covered surgical procedures performed in a participating ASC, on an outpatient basis in a hospital or in a hospital-affiliated ambulatory surgical center.

§ 416.110 Payment for physicians' services furnished in connection with covered surgical procedures.

Payment for physicians' services (including all pre- and post-operative services) will be made at 100 percent of the reasonable charge for those services if—

(a) The services are furnished in connection with a covered surgical procedure as specified in § 416.65;

(b) The services are performed in a participating ASC, on an outpatient basis in a hospital or in a hospital-affiliated ambulatory surgical center; and

(c) The physician accepts assignment for those services (see § 405.240(k)(2) of this chapter).

§ 416.120 Payment for facility services.

Payment for facility services furnished in connection with surgical procedures as specified in § 416.65 will be made as follows:

(a) *Hospital outpatient department.* Payment will be in accordance with Part 405, Subpart D of this chapter.

(b) *Hospital-affiliated ambulatory surgical center.* Payment will be in accordance with Part 405, Subpart D of this chapter if—

(1) The ASC is an integral and subordinate part of a hospital; and

(2) The center is operated with other departments of the hospital under common licensure, governance and professional supervision.

(c) *Independent ASC.* Payment will be 100 percent of a prospectively determined rate per covered surgical procedure. This rate will cover the cost of services such as supplies, nursing services, equipment, etc., as specified in § 416.61. The rate will not cover physician's services, or other medical services covered under section 1861(s) of the Act, (for example, X-ray services or laboratory services) which are not directly related to the performance of the surgical procedure. These services will be billed separately and paid on a reasonable charge basis.

§ 416.125 ASC facility services payment rate.

(a) The payment rate will be equal to a prospectively determined standard overhead amount per procedure which is based on an estimate of the costs incurred by ambulatory surgical centers generally in providing services furnished in connection with the performance of that procedure.

(b) The payment rate must result in substantially less Medicare expenditures than would have been paid under the program had the procedure been performed on an inpatient basis in a hospital.

§ 416.130 Publication of revised payment methodologies.

Whenever HCFA proposes to revise the payment rate for ASCs, HCFA will publish a notice in the Federal Register describing the revision. The notice will also explain the basis on which the rates were established. After reviewing public comments, HCFA will publish a notice establishing the rates authorized by this section. In setting these rates, HCFA may adopt reasonable classifications of facilities and may establish different rates for different types of surgical procedures.

§ 416.140 Reporting requirements.

(a) HCFA will periodically conduct a sample survey of ASCs participating in the program to collect data for analysis or re-evaluation of the payment rates. Such a survey will be conducted no more frequently than annually. HCFA will notify the ASCs randomly selected to participate in each survey by mail or

their selection and the appropriate form and content of the report.

(1) If the facility does not submit an adequate report in response to HCFA's survey request, HCFA may terminate the agreement to participate under the Medicare ambulatory surgery program.

(2) HCFA may grant a 30-day postponement of the due date for the survey report if it determines that the facility has demonstrated good cause for the delay.

(b) Ambulatory surgical centers must—

(1) Maintain adequate financial records, in the form and containing the data required by HCFA, to allow determination of the payment rates for covered surgical procedures furnished to Medicare beneficiaries under this subpart.

(2) Within 60 days of a request from HCFA submit, in the form and detail as may be required by HCFA, a report of—

(i) Their operations, including the allowable costs actually incurred for the period and the actual number and kinds of surgical procedures furnished during the period; and

(ii) Their customary charges for each surgical procedure furnished for the period.

§ 416.150 Beneficiary appeals.

A beneficiary (or ASC as his or her assignee) may request a hearing by a carrier (subject to the limitations and conditions set forth in Part 405, Subpart H of this chapter) if the beneficiary or the ASC—

(a) Is dissatisfied with a carrier's denial of a request for payment made on his or her behalf by an ASC;

(b) Is dissatisfied with the amount of payment; or

(c) Believes the request for payment is not being acted upon with reasonable promptness.

(Catalog of Federal Domestic Assistance Program, No. 13.774, Medicare-Supplementary Medical Insurance)

Dated: January 15, 1982.

Carolyn K. Davis,
Administrator, Health Care Financing
Administration.

Approved: February 16, 1982.

Richard S. Schweiker,
Secretary.

[FR Doc. 82-7654 Filed 3-22-82; 8:45 am]
BILLING CODE 4120-03-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

Medicare Program; List of Covered Surgical Procedures for Certain Ambulatory Surgical Services

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Proposed Notice.

SUMMARY: Under the proposed rules published elsewhere in this issue of the *Federal Register*, reimbursement would be available under the Medicare Supplementary Insurance program (Part B) for independent ambulatory surgical center (ASC) facility services in connection with certain surgical procedures. For those same procedures, physicians would be reimbursed at 100 percent of their reasonable charges for providing services in connection with the procedure performed in a participating ASC, on an outpatient basis in a hospital or in a hospital-affiliated ambulatory surgical center (HAASC) if certain requirements are met. This notice contains the proposed list of the surgical procedures pertinent to these reimbursement provisions.

DATE: To assure consideration, comments should be received by April 22, 1982.

FOR FURTHER INFORMATION CONTACT: Anthony Lovecchio 301-594-8561.

ADDRESSES: Please address your comments in writing to: Administrator, Health Care Financing Administration, Department of Health and Human Services, P.O. Box 17073, Baltimore, MD 21235.

If you prefer, you may deliver your comments to Room 309-G, Hubert H. Humphrey Building, 200 Independence Avenue, SW., in the District; or to Room 789, East High Rise Building, 6325 Security Boulevard, in Baltimore.

In commenting, please refer to file code BPP-194-PN.

Comments will be available for public inspection, beginning approximately 2 weeks from today in Room 309-G of the Department's offices at 200 Independence Avenue, SW., in Washington, D.C., on Monday through Friday of each week from 8:30 a.m. to 5:00 p.m. (telephone 202-245-7890).

Because of the large number of comments we receive, we cannot acknowledge or respond to them individually. However, in preparing the final notice, we will consider all comments and will respond to them in the preamble to that notice.

SUPPLEMENTARY INFORMATION:

Background

Section 934 of Pub. L. 96-499, the Omnibus Reconciliation Act of 1980, amended title XVIII of the Social Security Act, to authorize Medicare Part B coverage for facility services furnished in connection with certain surgical procedures performed in an independent ambulatory surgical center (ASC). For the same procedures, physician reimbursement at 100 percent of their reasonable charge is authorized if certain requirements are met. (Under the usual procedures, Medicare pays 80 percent of the physician's reasonable charge; the beneficiary is responsible for the remainder.)

With respect to the surgical procedures covered under this provision, the statute requires the Secretary to develop, in consultation with the National Professional Standards Review Council and appropriate medical organizations, a list of surgical procedures that, although appropriately performed in an inpatient hospital setting, may also be performed safely in certain ambulatory settings. The report accompanying the legislation (Report of the Committee on the Budget to Accompany H.R. 7766, H.R. Report No. 96-1167, pg. 390) explained that Congress intended that procedures currently done on an ambulatory basis, especially in physicians' office, that do not generally require the more elaborate facilities of an ASC, should not be included in the list of covered procedures.

The development of the proposed list posed several questions. Among these were:

- What kind of information regarding covered procedures should be gathered, and from whom;
- How should the test of " * * * appropriately performed on an inpatient basis * * * " be applied; and
- What criteria should be used to decide whether a given procedure should be included?

With respect to the first question, the statute requires, as noted above, that the National Professional Standards Review Council and appropriate medical organizations be consulted. In addition, there were several other possibilities we could pursue. First, existing ASCs could be asked to list those procedures they perform, together with any recommendations they might have for additional procedures. Second, a review could be undertaken of lengths of stay in hospitals of fewer than 2 or 3 days, which would pinpoint procedures that have potential for performance in an ambulatory setting. A related approach

would be to compare the relative proportions of inpatient to outpatient utilization for surgical procedures. Yet another method would be to develop consensus lists from State and local medical societies as well as local Professional Standards Review Organizations, in addition to the consultation required by the statute.

All these approaches were used, although to varying degrees, in gathering information and resolving the questions posed. We began by meeting with representatives of the Free-Standing Ambulatory Surgical Association (FASA), a group which represents a number of existing ASCs. We asked them for information they had concerning procedures currently being done by ASCs, and an indication of what procedures were being performed on Medicare beneficiaries. Our purpose was to focus attention on procedures likely to generate a substantial claims volume. We also sought to assure that the list would be a useful one in terms of covering procedures actually being done.

We then addressed the question of how to obtain additional information from sources other than FASA and ASCs, particularly from interested members of the medical community who were not aware of the legislative provision or who knew of it, but were uncertain as to whom to contact to give input. We therefore published a Notice in the *Federal Register* on May 22, 1981 to solicit information, not only on possible procedures for the list, but on some of the other questions as well. One item we specifically requested was information concerning broad, general criteria that could help us decide whether a given procedure should be included in the list. The notice resulted in a number of helpful suggestions, both on criteria as well as specific procedures. We also directly contacted several specialty societies and insurance carriers with experience with ambulatory surgery for suggestions and approaches to the issues involved. By late summer 1981 we had developed our list and then referred it to the National Professional Standards Review Council for their review. (We met twice with the Council before developing the list.) In addition, when they meet this spring, we plan to consult with them on our list once again.

In order to apply the legislative requirement of "appropriately performed on an inpatient basis" we obtained from the Office of Data Services of HCFA's Office of Research, Demonstrations and Statistics a list of inpatient surgical procedures showing lengths of stay. This information proved useful for two

purposes—assuring that a given procedure was being done on an inpatient basis as well as identifying surgical procedures with relatively short lengths of stay (1–3 days) which might be suitable for ambulatory surgery and thus for inclusion on the list, even if not currently being done on a widespread basis in ASCs.

Definition of Surgical Procedure

Another issue that arose during the development of the list was the definition of the term "surgical procedure". The statute, in describing the procedures to be covered, refers to "surgical procedure * * * which * * * can be performed safely on an ambulatory basis in an ambulatory surgical center * * *". A surgical procedure is commonly thought of as one involving an incision of some type, whether done with a scalpel or, more recently, a laser, followed by removal of repair of an organ or other tissue. In recent years the development of fiberoptic technology, together with new surgical instruments using that technology, has resulted in surgical procedures that, while invasive and manipulative, do not require incisions. Instead, the procedures are performed without an incision through various body openings. In reviewing the various lists submitted, we found that these procedures are being done to a varying degree in ASCs and, we believe, meet the definition of "surgical procedures" commonly accepted by the medical profession.

Nature and Applicability of the List

The resulting proposed list published in this notice meets not only statutory requirements, but also our objective of producing a list which closely conforms to the procedures that are commonly being performed on the aged in ASCs and which consists of procedures about which there was widespread agreement in the comments we received. Once the list is published as a final, we would publish additions to the list of procedures as necessary. We welcome suggestions as to specific procedures or classes of procedures that should be considered.

It is important to note that the inclusion of a surgical procedure on this list would not mean it may be performed only in an ambulatory surgical setting. The choice of operating site would remain a matter of the professional judgment of the patient's physician. Reimbursement would continue to be available without any special justification or review for these procedures performed on a hospital

inpatient basis for Medicare beneficiaries.

This list of procedures would apply to facility services furnished by ASCs; that is, those not part of a hospital. Coverage of ambulatory surgical facility services furnished in hospital-related ambulatory surgical settings (that is, on an outpatient basis in a hospital or in an HAASC) would not be affected. However, this list would apply to 100 percent reimbursement for physician's professional services in connection with a listed procedure performed in hospital-related ambulatory surgical settings or ASCs.

To the extent possible, we have used the most common name or term to describe a given procedure. Where there are major regional or other differences in the commonly recognized name of a given procedure, we have listed that procedure under each name used.

The procedures are grouped by body system to help reduce confusion in the case of a procedure, such as tenotomy, that may be performed at a variety of body sites or on different body systems.

The procedures are also arranged into four groups that refer to the facility payment amount that would be available under the Medicare program. The four group rates are Group 1—\$336, Group 2—\$296, Group 3—\$275, and Group 4—\$231. Thus a given ASC would receive the same payment for all of the group 3 procedures performed on Medicare beneficiaries at that facility. The payment rates would first be calculated on a nationwide basis; then adjusted to account for regional factors, such as wage differentials, to arrive at the rate applicable to each ASC. A more detailed explanation of the reimbursement methodology is contained in the Supplementary Information section of the proposed ambulatory surgical regulations published in this Federal Register issue.

List of Covered Procedures

Integumentary System

- Group 1:
 - Cyncomastasia excision, uni- and bilateral
- Group 2:
 - Breast biopsy (incision, excision, uni- or bilateral)
 - Mandible cyst excision, simple
 - Pilonidal cyst excision, simple, extensive
 - Skin graft
- Group 4:
 - Benign lesion, excision (lipoma)
 - Fingernail, toenail removal
 - Malignant lesion, excision (Basal cell, Melanoma)

Musculoskeletal System

- Group 1:
 - Hammertoe Repair
 - Boutonniere repair

- Bunionectomy
- Ligament repair
- Neurectomy
- Osteotomy
- Synovectomy
- Arthroscopy
- Fasciectomy/Fasciotomy
- Arthrodesis
- Arthroplasty
- Tendon Repair with graft, implant or transfer

Group 2:

- Bursectomy
- Capsulectomy/capsulotomy (metacarpophalangeal and interphalangeal)
- Ganglionectomy (wrist)
- Neuroma excision (Morton's and cutaneous and digital nerves)
- Osteotomy metatarsal (metatarsal head excision)
- Tendon repair without graft, implant or transfer

Group 3:

- Phalangectomy (amputation, fingers and toes)
- Sequestrectomy
- Tendon Sheath Release (De Quervains)
- Zygoma (Zygomatic arch) Reduction

Group 4:

- Closed Reduction of Nasal Fracture
- Tenotomy, hands, fingers, ankle, feet and toes
- Trigger Finger Release (tendon sheath incision for)

Respiratory System

- Group 1:
 - Septal Reconstruction
 - Submucous Resection (turbinate and nasal septum)
- Group 2:
 - Ethmoidectomy
- Group 3:
 - Nasal Polypectomy
 - Antral Window (puncture) (Sinusotomy)
- Group 4:
 - Bronchoscopy
 - Excision turbinate
 - Laryngoscopy

Cardiovascular System

- Group 1:
 - Varicose Vein Ligation
- Group 4:
 - Temporal Artery, Ligation or biopsy

Hemic and Lymphatic System

- Group 3:
 - Cervical Node (lymph node) biopsy

Digestive System

- Group 1:
 - Peritoneoscopy (mini-laparotomy)
 - Herniorrhaphy
- Group 2:
 - Colostomy Revision (simple)
 - Wedge Resection of Lip
 - Hemorrhoidectomy
- Group 3:
 - Branchial Arch Appendage Excision
 - Liver Biopsy, percutaneous
 - Vermilionectomy (Lip peel)
 - Fistulotomy
- Group 4:
 - Esophagoscopy

Gastroscopy
Rectal Dilation
Tongue Biopsy

Urinary System

Group 2:
Transurethral Resection of Bladder Tumor
(Cystourethroscopy w/operative procedure)

Group 4:
Cystourethroscopy
Urethral Dilation

Male Genital System

Group 1:
Varicocele repair

Group 2:
Hydrocele excision
Spermatocele excision

Group 3:
Orchiectomy

Group 4:
Prostate Biopsy

Femal Genital System

Group 1:
Laparoscopy

Group 2:
Colpotomy, with exploration
Dilation and curettage, diagnostic and/or therapeutic (nonobstetric)

Group 3:
Bartholin cystectomy

Hysterosalpingogram
Perineoplasty
Vaginal tumor (cyst) excision

Group 4:
Vulva (labia) biopsy
Examination under Anesthesia (pelvic)
Vaginal Stenosis Release (Dilation of Vagina under Anesthesia)
Culdoscopy (Culdocentesis)

Endocrine System

Group 2:
Thyroglossal Duct Cyst Removal

Nervous System

Group 1:
Ulnar Nerve Repair
Ulnar Nerve Transfer

Group 2:
Neurolysis (including carpal tunnel decompression)

Eye and Ocular Adnexa System

Group 1:
Cataract extraction
Enucleation, with and without implant
Iridectomy
Eye Muscle Operation (extraocular muscles, strabismus procedure)

Group 2:
Ectropion/Entropion repair

Group 3:
Canthoplasty

Tarsorrhaphy

Group 4:
Chalazion excision
Discission lens (needling of lens)
Foreign Body Removal
Pterygium (excision or transposition)
Lacrimal duct probing or reconstruction

Auditory

Group 1:
Mastoidectomy, simple (transmastoid antrotomy)
Myringoplasty
Stapedectomy
Tympanoplasty (without mastoidectomy)

Group 4:
Myringotomy (including aspiration and/or eustachian tube inflation)

(Sec. 1833(i)(1), of the Social Security Act (42 U.S.C. 1395f))

(Catalog of Federal Domestic Assistance Program No. 13.774, Medicare—Supplementary Medical Insurance Program)

Dated: January 15, 1982.

Carolyne K. Davis,
Administrator, Health Care Financing Administration.

[FR Doc. 7655 Filed 3-22-82; 8:45 am]

BILLING CODE 4120-03-M

Best is Great Federal Forest

Tuesday
March 23, 1982

Part VI

Department of the Interior

Office of Surface Mining Reclamation and
Enforcement

Surface Coal Mining and Reclamation
Permanent Program Regulations;
Revegetation

DEPARTMENT OF THE INTERIOR

Office of Surface Mining Reclamation and Enforcement

30 CFR Parts 816 and 817

Surface Coal Mining and Reclamation Permanent Program Regulations: Revegetation

AGENCY: Office of Surface Mining Reclamation and Enforcement, Interior.

ACTION: Proposed rule.

SUMMARY: The Office of Surface Mining (OSM) proposes to modify the revegetation sections of the permanent regulatory program. The revised rules are proposed in order to reduce the burden of existing rules, minimize duplication, and provide internal consistency. This proposed rule would (1) delete the requirement for use of field trials to demonstrate that introduced species are desirable and necessary, (2) delete the requirements for grazing during the last years of responsibility for pasture or rangelands, (3) broaden the approaches acceptable for determining the success of revegetation, (4) provide for the use of success standards that reflect local and regional recommendations on tree and shrub stocking, (5) permit tree and shrub planting, maintenance work, and normal husbandry practices during the period of responsibility for revegetation success, and (6) revise the standards relating to the responsibility period for areas receiving more than 26 inches average annual precipitation.

DATES: *Written comments:* Accepted until 5 p.m. (eastern time) on April 22, 1981.

Public hearings: Held on request only, on April 16, 1982, at 9:00 a.m.

Public meetings: Scheduled on request only.

ADDRESSES: *Written comments:* Hand-deliver to the Office of Surface Mining, U.S. Department of the Interior, Administrative Record (TSR 14.14), Room 5315, 1100 L Street, NW., Washington, D.C.; or mail to the Office of Surface Mining, U.S. Department of the Interior, Administrative Record (TSR 14.14), Room 5315L, 1951 Constitution Avenue, NW., Washington, DC 20240.

Public hearings: Washington, D.C.—Department of the Interior Auditorium, 18th and C Streets, NW.; and Denver, Colo.—Brooks Tower, 2d Flood Conference Room, 1020 15th Street. Pittsburgh, PA—Wm. S. Moorehead Federal Bldg., 1000 Liberty Ave., Room 2212.

Public meetings: OSM offices in Washington, D.C.; Charleston, W. Va.;

Knoxville, Tenn.; Indianapolis, Ind.; and Denver, Colo.

FOR FURTHER INFORMATION CONTACT:

Public hearings: Arlo Dalrymple, Division of Technical Assistance, Office of Surface Mining, U.S. Department of the Interior, 1951 Constitution Avenue, NW., Washington, DC 20240; 202-343-5864.

Public Meetings: Jose del Rio, 202-343-4022.

SUPPLEMENTARY INFORMATION:

- I. Public Commenting Procedures.
- II. Background.
- III. Discussion of Proposed Rules.
- IV. Procedural Matters.

I. Public Commenting Procedures

Written comments.—Written comments should be specific, pertain only to the issues proposed in this rulemaking, and include explanations in support of the commenter's recommendations. Commenters are requested to submit five copies of their comments (see "ADDRESSES"). Comments received after the time indicated under "DATES" or at locations other than Washington, D.C., will not necessarily be considered or be included in the Administrative Record for the final rulemaking.

Public hearings.—Persons wishing to comment at the public hearings should contact the person listed under "FOR FURTHER INFORMATION CONTACT" by the close of business *three working days* before the date of the hearing. If no one requests to comment at a public hearing at a particular location by that date, the hearing will not be held. If only one person requests to comment, a public meeting, rather than a public hearing, may be held and the results of the meeting included in the Administrative Record.

Filing of a written statement at the time of the hearing is requested and will greatly assist the transcriber. Submission of written statements in advance of the hearing will allow OSM officials to prepare appropriate questions.

Public hearings will continue on the specified date until all persons scheduled to comment have been heard. Persons in the audience who have not been scheduled to comment and wish to do so will be heard following those scheduled. The hearing will end after all persons scheduled to comment, and persons present in the audience who wish to comment, have been heard.

Public meetings.—Persons wishing to meet with OSM representatives to discuss these proposed rules may request a meeting at any of the locations listed in "ADDRESSES" by contacting the

person listed under "FOR FURTHER INFORMATION CONTACT."

All such meetings are open to the public and, if possible, notices of meetings will be posted in advance in the Administrative Record room (1100 L St. office). A written summary of each public meeting will be made a part of the Administrative Record.

II. Background

These proposed rules are intended to amend, remove, or revise OSM's permanent program rules for revegetation, currently set forth at 30 CFR 816.111 through 816.117 and 817.111 through 816.117. The revegetation rules were originally published at 44 FR 15312 (March 13, 1979). A preproposal draft of these amendments was provided to State regulatory authorities and other interested parties. Following distribution of this preproposal draft, meetings were held with representatives of State regulatory authorities on July 21, 22, and 23, 1981, at which time the preproposal draft of the revegetation rules was a topic of discussion. Summaries of these discussions are in the Administrative Record. Other comments were also received, and all comments received on the preproposal draft will continue to be considered during the course of this rulemaking.

Section 515(b)(2) of the Surface Mining Control and Reclamation Act, 30 U.S.C. 1201 *et seq.* (the Act), requires the operator as a minimum to restore the land affected to a condition capable of supporting the uses which it was capable of supporting prior to any mining, or higher or better uses of which there is a reasonable likelihood.

Furthermore, section 515(b)(19) of the Act requires the operator to establish, on all affected lands, a "diverse, effective, and permanent vegetative cover of the same seasonal variety native to the area of land to be affected and capable of self-regeneration and plant succession at least equal in extent of cover to the natural vegetation of the area * * *." Section 516(b)(6) imposes a similar requirement for underground mining permitted under the Act. Section 515(b)(19) also permits the use of introduced species in the revegetation process where desirable and necessary to achieve the approved postmining land use. Section 515(b)(20) of the Act requires the operator to assume responsibility for successful revegetation for 5 or 10 full years after the last year of augmented seeding, fertilizing, irrigation, or other work to assure compliance with section 515(b)(19). The 5-year period of responsibility is applicable to areas or

regions receiving an annual average precipitation greater than 26 inches and the 10-year period is applicable to areas or regions where the annual average precipitation is 26 inches or less.

The rules proposed today would govern revegetation to reclaim areas affected by surface mining, §§ 816.111-816.117, and to reclaim areas affected by underground mining, §§ 817.111-817.117. While separate rules govern these different types of mining and revegetation, most of the changes proposed are substantially the same. Accordingly, in this preamble, OSM will discuss changes to Part 816, with the understanding that the discussion will also apply to Part 817. Where the proposed changes for the two parts are not the same, differences will be noted.

III. Discussion of Proposed Rules

A. General Requirements

The general requirements for revegetation and the use of introduced species are set forth in §§ 816.111 and 816.112. OSM is proposing to amend and reword these sections by combining the requirements under § 816.111 and deleting § 816.112. This restructuring is intended to emphasize the statutory criteria set forth in section 515(b)(19) of the Act and to clarify rules which were perceived to be awkward and confusing. Section 516(b)(6) of the Act, pertaining to surface effects of underground coal mining, lacks the criteria that require a vegetative cover of the same seasonal variety native to the area of land to be affected and the provision that relates to the use of introduced species. The differences in wording of proposed §§ 816.111 and 817.111 reflect those distinctions.

The intent of section 515(b)(19) of the Act may be inferred from the meaning of the words "diverse, effective, and permanent" which describe the type of vegetative cover to be achieved. *Diverse* means sufficiently varied amounts and types of vegetation to achieve ground cover and support the postmining land uses. The precise numbers required to achieve this diversity should be determined by regional climatic and soil conditions. However, the ultimate test will be the sufficiency of the plant communities to assure survival of adequate number and varieties to achieve the postmining land use and the required extent of ground cover. Diversity does not necessarily mean that every species or variety of premining grass, shrubs, or trees be reestablished in identical numbers and ratios after mining. *Effective* means, as Congress has stated, "both the productivity of the planted species concerning its utility to

the intended postmining land use (e.g., nutritional value for livestock) as well as its capability of stabilizing the soil surface with respect to reducing siltation to normal premining background levels." H. Rep. No. 95-218, 95th Cong., 1st Sess. 106 (1977). *Permanent* means that the plant community as a whole must be capable of providing the necessary amount of ground cover over time through natural plant succession, and not necessarily that every individual plant species will propagate itself in identical numbers and ratios throughout the future.

As proposed, § 816.111(a) would closely follow the Act and would require the operator to establish on all affected land a diverse, effective, and permanent vegetative cover that is comprised of species native to the area, or introduced species where approved by the regulatory authority. The permanent vegetative cover must be at least equal in extent of cover to the natural vegetation of the area and must achieve productivity levels compatible with the approved postmining land use. Proposed § 816.111(a) would also allow the use of introduced species but would not require that their use be approved by the regulatory authority since § 516(b)(6) of the Act does not contain that requirement for underground mines.

Proposed § 816.111(b) would provide that the reestablished species be desirable and necessary to achieve the approved postmining land use and be capable of self-regeneration and plant succession. The requirement of comparability with other plant and animal species contained in existing § 816.112(c) would be retained in proposed §§ 816.111(b) (3).

In addition, the proposal would require the reestablished species to have the same seasonal characteristics of growth as the original vegetation. This requirement is based on language in section 515(b)(19) of the Act which specifies that the vegetative cover must be of the same seasonal variety native to the area of land to be affected. OSM believes that "seasonal variety" in section 515(b)(19) of the Act and "seasonal characteristics of growth" discussed on page 106 in House Report 95-218, *supra*, have essentially the same meaning. The term "seasonal characteristics of growth," which is more easily understood than the language in existing § 816.111(b)(3), refers to the major season of growth for herbaceous species.

In general, herbaceous species can be grouped into cool season and warm season species (Cook, Hyde, and Sims, 1974, and Raftall and Vogel, 1978). Cool

season species grow mostly in the spring and fall, but are nearly dormant or grow poorly in the summer. In contrast, warm season species grown primarily during late spring and summer but are dormant in early spring and fall.

Note.—Full citations of reference texts will be provided at the end of the discussion of the proposed rules.

Species useful in achieving a quick and temporary cover may not have the same seasonal characteristics of growth as the original vegetation and may not be capable of self-regeneration and plant succession. For this reason, proposed § 816.111(c) provides an exception that allows regulatory authorities to approve their use whenever measures to establish permanent vegetation are included in an approved permit and reclamation plan. Since the seasonal growth characteristics provision does not apply to Part 817, the exception in Part 817 pertains only to the self-regeneration and plant succession requirement.

Water area and road surface exception.—The exception from revegetation requirements for water areas and road surfaces contained in existing § 816.111(b)(1) is proposed for deletion. Because regulatory authorities, operators, and the public recognize that such areas and surface would not normally be seeded to a permanent vegetative cover, this deletion would not change operator responsibility for any performance standard with respect to areas covered by water and road surfaces.

Erosion control.—Several commenters on the preproposal draft objected to language that required the vegetative cover to control erosion. It was argued that complete control of erosion was impossible. Others contended that the Act's requirements for water impoundments, protection of topsoil, or other strata suitable for vegetation, contemporaneous reclamation, and roads were all intended to minimize erosion. It was further noted that, while other sections of the Act have specific erosion control requirements, sections 515(b) (19) and (20) of the Act do not explicitly address erosion.

Although sections 515(b) (19) and (20) do not specifically reference erosion control, section 515(b)(4) of the Act imposes a general erosion control requirement. However, this requirement will continue to be satisfied by other regulations under the Act. For instance, the existing regulations for topsoil distribution specifically require in § 816.24(b)(3) that topsoil and other materials have to be redistributed in a

manner that protects the topsoil from wind and water erosion before and after it is seeded and planted. In addition, possible topsoil rule changes that OSM is considering would explicitly continue this requirement.

Thus, OSM is proposing to delete the requirement for erosion control that is currently contained in §§ 816.111(b)(2), 816.113, and 816.116(b)(3). It should be emphasized that the requirement contained in proposed § 816.111(a)(3) would be intended to require the operator to achieve a ground cover that is equal to or greater than the ground cover that existed before mining. Effectively then, the reestablished vegetation would provide the reclaimed soils with protection from erosion equal to the protection provided prior to disturbance of the site. Furthermore, it can be more easily ascertained whether a ground cover success standard had been achieved than whether an erosion control standard is met.

Cropland exception.—The requirements of existing § 816.111(b)(4) for cropland have been reworded and are proposed as § 816.111(d).

Proposed § 816.111(d) would provide an exception from the requirements of permanent vegetative cover, diverse species, seasonal characteristics, and self-regeneration and plant succession when the approved postmining land use is cropland.

permanent vegetation would not necessarily be desirable when the postmining vegetative use is to be cropland, because most cropland is used to produce annual rather than the more permanent biennial or perennial species. This provision is based on section 515(b)(20) of the Act that provides "that when the regulatory authority issues a written finding approving a long-term, intensive, agricultural postmining land use as part of the mining and reclamation plan, the authority may grant exception to the provisions of Paragraph (19) * * *" of the Act.

B. Introduced Species

Existing § 816.112, entitled "Revegetation: Use of Introduced Species" is proposed for deletion. From the existing rules it can be inferred that the use of introduced species is discouraged or strictly limited, while in fact, their use in the revegetation process is permitted in section 515(b)(19) of the Act when desirable and necessary to achieve the postmining land use. Proposed § 816.111(b)(1) would incorporate this standard and broaden its application to also include native species.

Section § 816.112(a) of the present rule allows introduced species to be

substituted for native species only after field trials have shown that introduced species are desirable and necessary to achieve the approved postmining land use. Introduced species of trees, shrubs, grasses, and legumes have been widely and successfully used in surface mine reclamation for a considerable length of time. Many of these introduced species have become naturalized. OSM believes that in most cases the respective regulatory authorities would be aware of research findings and characteristics of species that are desirable for use in a revegetation plan and may approve such species without the necessity of field trials. Hence, the requirement for field trials is proposed for deletion. This proposed deletion of a field trial requirement is not intended to preclude the regulatory authority from establishing field trial requirements in particular instances when the operator proposes using a species (native or introduced) that has not been proven suitable for the proposed postmining land use under similar growing conditions. The proposed retention of the requirement in § 816.111 that plant species shall be "effective" and "desirable and necessary to achieve the approved postmining land use" is thought to provide adequate authority for regulatory authorities in individual circumstances to question the use of a plant species and to require the operator to demonstrate that a species is effective and desirable. The regulatory authority could request such a demonstration in those instances where there is not sufficient past experience with a species under similar growing conditions.

OSM is proposing to retain the requirements of § 816.112(d) regarding compliance with applicable State and Federal laws regulating seed and introduced species and to redesignate it as § 816.111(b)(5) and § 817.111(b)(4). The phrase "and are not poisonous or noxious" presently found in § 816.112(d) is proposed for deletion. OSM believes that compliance with the phrases "species that meet applicable State and Federal statutes" and "desirable and necessary" would limit the use of noxious species.

C. Timing

Existing § 816.113 could be interpreted to require the planting of vegetation during the interim between backfilling and grading and the replacement of topsoil. OSM is proposing to reword § 816.113 to specify that seeding or planting is not expected to occur until backfilling and grading are complete and topsoil or substitute materials are in place.

Proposed § 816.113 would continue to require that there be no major time lag between completion of regrading and the planting and seeding of the area to be revegetated. The time of seeding will depend upon the method of land preparation and the species used (Sampson, 1952). Some sites may require the use of annuals such as small grains, grasses, or legumes to stabilize the area while perennials become established (Plass, 1978). In many locations, suitable species are available and climatic conditions are favorable for seeding during a major portion of the year (Rafail and Vogel, 1978). Under the proposal, the operator also would be permitted to use mulches or other cultural practices to control erosion until permanent species are adequately established.

D. Mulching

Section 816.114 of the existing rules requires that mulching and other soil stabilizing practices be used on all regraded and topsoiled areas except where the permittee can demonstrate that alternative procedures will achieve successful revegetation. It provides that the regulatory authority may, on a case-by-case basis, suspend the mulching requirement.

OSM is proposing to amend § 816.114 to eliminate the mandatory mulching requirement and to give the regulatory authority complete flexibility as to requiring mulches and soil stabilizers. As proposed, the regulatory authority could require the application of suitable mulch or use of other soil stabilizing practices where deemed necessary.

When developing the proposed rules, OSM considered deleting all mulching requirements of § 816.114. It was thought that the bond release requirements would insure successful revegetation of the affected area with or without mulching. Commenters to the preproposal draft disagreed and argued that the deletion would be too dependent on the performance bond as a guarantee of successful reclamation. Commenters contended that failure to require mulching could result in excessive erosion during the period of responsibility. They felt that this could result in erosion losses that could have been prevented if the regulatory authority had required mulching or other soil stabilizing practices. Other commenters recommended proposing a rule that provided for the regulatory authority to require the application of mulch or use of other soil stabilizing practices when deemed necessary. The alternative has been proposed.

E. Grazing

The requirements of § 816.115 are being proposed for deletion because of a judicial ruling that section 515 (b)(19) of the Act does not require that proposed postmining pasture or grazing land must actually be subjected to grazing activities. These provisions have been suspended by OSM following an order of the U.S. District Court *In re: Permanent Surface Mining Regulation Litigation*, No. 79-1144 (D.D.C., February 26, 1980), a case currently on appeal. (See 45 FR 51549, August 4, 1980.) In light of the current litigation, OSM will at this time refrain from proposing requirements for § 816.115.

F. Standards of Success

OSM believes that standards of success for revegetation can best be developed on a State level. The proposed regulations would require the regulatory authority to develop standards that reflect the capabilities of local soils and climatic conditions. Minimum standards and acceptable sampling techniques would become parts of State programs and would be subject to approval by OSM. OSM believes this arrangement will enable States to tailor success standards to local conditions and at the same time will assure that, regardless of State, all selected standards will provide similar degrees of proof that adequate reclamation has been achieved.

General success criteria.—Section 816.116(a) of the existing rules requires that revegetation success be measured by techniques approved by the regulatory authority after consultation with appropriate State and Federal agencies. It also provides that comparisons of the ground cover and productivity be made only on the basis of reference areas or through the use of technical guidance procedures published by the U.S. Department of Agriculture (USDA) or the Department of the Interior (DOI). In addition, existing § 816.116(b)(1) requires ground cover and productivity to be equal to the ground cover and productivity of an approved reference area or to the standards in technical guides approved by the Director for use in the regulatory program.

Proposed § 816.116(a) would contain the general requirements that the success of revegetation be judged on the effectiveness of the vegetation for the approved postmining land use and on the extent of cover compared to the cover of naturally occurring vegetation in the area. It would also incorporate the general requirements of § 816.111. It would differ from the existing rule by

not requiring technical standards for evaluating ground cover and productivity to have been published by the USDA or DOI. Instead, the rule would permit the regulatory authority to select technical standards from any source or, if desirable, to develop new standards. Reference areas could continue to be used for determining the success of revegetation when deemed appropriate by the regulatory authority. The requirement for consultation with appropriate State and Federal agencies would be retained.

As proposed, § 816.116(a) would require that success standards contain criteria for evaluating ground cover, production, or tree stocking. Furthermore, cover diversity, seasonal growth characteristics, and the regenerative capacity would have to be evaluated by methods determined by the regulatory authority.

Measurement techniques and tests.—OSM believes that, whenever practical, quantitative techniques should be used for evaluating revegetation success. The ocular technique was found to be the most common method used for determining release of revegetation performance bonds in the Eastern and Interior coal provinces. (See U.S. Bureau of Mines, 1978.) This technique is one whereby the inspector visually inspects the site and decides whether success has been achieved. The method is highly dependent upon the training, experience, and objectivity of the inspector. Mine operators interviewed for this Bureau of Mines report indicated that there was considerable variability among inspectors when making performance bond release inspections and that more standardized inspection techniques would be desirable.

Proposed § 816.116(a)(1) would require the use of statistically valid sampling techniques for measuring success. Under the proposal, the sampling procedures would be chosen by the regulatory authority. OSM believes that the use of statistically valid sampling techniques would aid regulatory authorities in making consistent decisions regarding performance bond release and provide standardized inspection techniques sought by mine operators.

Existing § 816.116(b)(3) allows ground cover and productivity to be considered equivalent to that of a reference area or a technical standard whenever 90 percent of the ground cover and productivity of the standard or reference area is achieved. Proposed § 816.116(a)(2) would not set a standard which could be met with a 90 percent equivalency. Under the proposed rules,

the three vegetation parameters—ground cover, production, or tree stocking—would only be considered equal to the success standard approved by the regulatory authority when the parameters are fully equivalent with 90 percent statistical confidence.

Cook and Bonham (1977) suggest that since a sample represents a part or portion of a population and is presented as evidence of some character of the whole population, perhaps the best approach is to sample with an intensity that yields an acceptable confidence interval to detect a 10 to 20 percent difference at probability levels of 0.10 and 0.20 for premining and postmining conditions. The confidence level requirement of the proposal would yield quantitative information that the reclamation has in fact been accomplished at a given level of certainty.

Management practices.—OSM is proposing to delete the requirements in existing § 816.116(c) requiring operators to maintain fences, use proper management practices, and conduct periodic measurements of vegetation, soils, and water. OSM believes these rules are not specifically required by the Act and can be provided for by the regulatory authority, if appropriate, based on local conditions.

Periods of responsibility.—As a result of the February 26, 1980, district court decision, cited *supra*, the requirements of existing §§ 816.116(b)(1) (i) and (ii) and the corresponding sections in Part 817, which require that the period of responsibility begins when the ground cover or productivity equals the approved standard, were suspended (45 FR 51548, August 4, 1980). The court suggested that the period of responsibility should begin after the last year of augmented seeding, fertilization and irrigation.

The 5 and 10 year periods of responsibility required by the Act would be retained in proposed § 816.116(c). Proposed § 816.116(c) would start the period of responsibility after the last year of augmented seeding, fertilization, irrigation or other work which ensures revegetation success. The period would continue for not less than 5 years in areas of more than 26 inches average annual precipitation. In areas of 26 inches or less annual precipitation, the operator responsibility would continue for not less than 10 years.

As to practices permitted during the responsibility periods, the proposal would permit tree and shrub planting, maintenance work, and normal husbandry practices essential for plant establishment, as well as those

nonaugmentative practices that can be expected to continue as part of the postmining land use. This is proposed because planting stock of the necessary age and species may not always be available and it is sometimes impractical to require trees and shrubs to be planted during late summer and fall when herbaceous cover is established (Rafaill and Vogel, 1978). It is possible that limited maintenance work will be needed to fill rills and gullies and to reseed and fertilize small spots where the vegetation has failed. Under proposed rule § 816.116(c) these activities would not cause a restarting of the period of responsibility. Normal husbandry practices would be permitted during the period of responsibility so long as they can reasonably be expected to continue after bond release.

In areas of less than or equal to 26.0 inches average annual precipitation, proposed § 816.116(c)(3) would allow interseeding and supplemental fertilizing during the first 5 years of the responsibility period even though they may not be maintenance work or husbandry practices that can be expected to continue. These practices would be permitted only when necessary for the establishment of a diverse, effective, and permanent vegetative cover. This provision was added in order to make it possible to achieve greater age and species diversity, especially on western rangeland (Cook, Hyde, and Sims, 1974).

Under proposed § 816.116(c)(3) the use of supplemental irrigation to reestablish vegetation would also be a permissible cultural practice that can be used during the first 2 years of the responsibility period. This is believed necessary to establish suitable perennial communities that support the postmining land use. OSM does not believe that this limited practice would be considered augmentative under section 515(b)(20) of the Act (Dollhopf, DePuit, and Klages, 1980; Packer and Aldon, 1978; Thornburg and Fuchs, 1978; and Ries and Day, 1978).

The present rule, in § 816.116(b)(1)(i), requires that the vegetation on the mined area must equal the approved success standard for the last two consecutive years of the responsibility period for areas of more than 26.0 inches average annual precipitation. Proposed § 816.116(c)(2) would require the vegetation to be equal to the success standard only during the growing season of the last year of the responsibility period unless 2 years would be required by the regulatory authority. The change is proposed to reduce the burden of recordkeeping and inspection. OSM

request comments and support data related to the need for a specific 1- or 2-year test. The requirement of the last two consecutive years was retained for areas of less than 26.0 inches average annual precipitation, because the greater variability in climatic conditions, especially precipitation, in these western States makes it difficult to base success on a single year's data.

Determination of annual precipitation.—Existing § 816.116(b)(2) lists data sources and specifies procedures for determining average annual precipitation. OSM is proposing deletion of this section since it is primarily a listing of informational sources and is not deemed necessary to the understanding of the regulatory requirements.

Remined areas and areas developed for residential, commercial or industrial use.—To clarify that existing § 816.116(b)(3)(i) is applicable to previously mined areas which had not been reclaimed under the Act but are being remined, the words "previously mined" would be changed to "remined" in the corresponding proposed § 816.116(b)(5). In addition, OSM is proposing to delete the language in proposed § 816.116(b)(5) "and shall be adequate to control erosion." As previously discussed, other sections of the rules should be adequate to protect the plant growth media from erosion.

Existing § 816.116(b)(3)(ii) allows the ground cover of living plants to be not less than that required to control erosion for areas to be developed for industrial or residential use less than 2 years after regrading is completed. Proposed § 816.116(b)(4) would extend the 2-year period to a 5-year period or such lesser period specified by the regulatory authority. It would also apply explicitly to commercial uses such as retail sales and service establishments. If the approved postmining land use would not be achieved during the specified period, the general revegetation success standards would apply (other than competitiveness with the approved, but unachieved, postmining land use). Comments are specifically requested as to whether the regulatory authority should have complete flexibility in setting the period for achievement of the postmining land use.

Deletion of alternative fixed standard.—OSM is proposing to delete existing § 816.116(d). That section provides an alternative fixed standard for determining the success of revegetation when permit areas are 40 acres or less in size and in locations with an average annual precipitation of more than 26 inches. The flexibility

generally provided to regulatory authorities by proposed § 816.116(a) obviates the need for a special fixed standard for small permit areas.

Wildlife and forest land success standards.—The proposed rules would delete § 816.117. Existing § 816.117 sets standards for reforestation and requires that woody plants be of sufficient number for adequate use of the available growing space. Section 816.117(a) specifies that for a tree or shrub to be counted towards meeting the stocking requirements it must have been in place at least two growing seasons, be alive and healthy, and have at least one-third of its length in live crown. Existing § 816.117(b) requires a minimum stocking of 450 trees or shrubs per acre when commercial forest land is the postmining land use. A minimum of 75 percent of the countable trees and shrubs must be commercial tree species. Under existing rules the period of responsibility is to begin when the ground cover is 70 percent of the ground cover of the reference area with 90-percent statistical confidence or when the regulatory authority determines that ground cover is adequate to control erosion and the stocking is equal to or greater than 450 trees or shrubs per acre.

Moreover, existing § 816.116(c) sets forth minimum standards for areas where woody plants are used for wildlife management, recreation, shelter belts, or forest uses other than commercial forest land. An inventory of woody plants in a reference area is required. Local and regional recommendations regarding species composition, spacing, and planting arrangements are to be used and stocking must be equal to or greater than 90 percent of the stocking of woody plants of the same life form on the reference area.

The proposed rule provides that minimum stocking and planting arrangement would be specified by the regulatory authority, based on local and regional conditions and after consultation with the State agencies responsible for the administration of forestry and wildlife programs. On Federal lands, concurrence would have to be obtained from the land management agency.

Proposed § 816.116(b)(3) would require that the success of revegetation on areas developed for fish and wildlife habitat, recreation, shelter belts, or forest products be based on tree and shrub stocking and ground cover. For purposes of determining the success of stocking and the adequacy of plant arrangement, the proposed rule would require that countable trees and shrubs

have utility for the postmining land use and, at time of bond release, be healthy and in place for at least two growing seasons. The ground cover could not be less than required to achieve the postmining land use.

G. Reference Materials

Reference materials used to develop these proposed rules are as follows:

Aldon, E. F., 1975, Techniques for establishing native plants on coal mine spoils in New Mexico, in Third symposium on surface mining and reclamation: National Coal Association, Washington, D.C., vol. 1, pp. 21, 26.

Aldon, E. F., 1978, Reclamation of coal-mined land in the Southwest: Journal of Soil and Water Conservation, vol. 33, no. 2, pp. 75-79.

Aldon, E. F., and Springfield, H. W., 1975, Reclaiming coal mine spoils in the Four Corners, in Reclamation and use of disturbed land in the Southwest: University of Arizona Press, Tucson, p. 234.

Armiger, W. H., Jones, J. N., and Bennett, O. L., 1976, Revegetation of land disturbed by strip mining of coal in Appalachia: U.S. Department of Agriculture, Agricultural Research Service, p. 8.

Cook, W. C., Hyde, R. M., and Sims, P. L., 1974, Revegetation guidelines for surface mined areas: Science Series No. 16, Colorado State University.

Cook, W. C., and Bonham, C. D., 1977, Techniques for vegetation measurements and analysis for a pre- and postmining inventory: Science Series No. 28, Colorado State University.

Dollhopf, D. J., DePuit, E. J., and Klages, M. G., 1980, Chemical amendment and irrigation effects on sodium migration and vegetation characteristics in sodic mines in Montana: Reclamation Research Technology Bulletin 736, Montana Agricultural Experiment Station, Montana State University, Bozeman, Mont.

Grandt, A. F., 1978, Mined-land reclamation in the Interior Coal Province: Journal of Soil and Water Conservation, vol. 33, no. 2, pp. 22-68.

Grim, E. C., and Hill, R. D., 1974, Environmental protection in surface mining of coal: U.S. Environmental Protection Agency, EPA-670/2-74-093, pp. 189-190.

Heady, H. F., 1975, Rangeland management: McGraw-Hill Book Co., New York, pp. 350-351.

Holton, H. N., 1972, A concept for disfiltration estimates in watershed engineering: U.S. Department of Agriculture ARS Report, pp. 23, 24, and 25 (figs. 6, 7, and 8).

Kranz, B. W., 1974, Benefits in cost and effectiveness of liquid materials used in hydroseeding operations, in Second research and applied technology symposium on mined-land reclamation: National Coal Association, Washington, D.C., p. 163.

Merkel, D. L., 1974, Revegetation in the Southwest—its hazards and successes, in Second research and applied technology symposium on mined-land reclamation: National Coal Association, Washington, D.C., pp. 189-190.

Packer, P. E., and Aldon, E. F., 1978, Revegetation techniques for dry regions, in Proceedings of a symposium on reclamation of drastically disturbed lands: American Society of Agronomy, pp. 425-450.

Plass, W. T., 1978, Reclamation of coal-mined land in Appalachia: Journal of Soil and Water Conservation, vol. 33, no. 2, pp. 56-61.

Power, J. F., 1978, Reclamation research on strip-mined lands in dry regions, in Proceedings of a symposium on reclamation of drastically disturbed lands: American Society of Agronomy, pp. 521-535.

Power, J. F., Ries, R. E., and Sandoval, F. M., 1978, Reclamation of coal-mined land in the Northern Great Plains: Journal of Soil and Water Conservation, vol. 33, no. 2, pp. 69-74.

Rafail, B. L., and Vogel, W. G., 1978, A guide for vegetating surface-mined lands for wildlife in Eastern Kentucky and West Virginia: U.S. Fish and Wildlife Service, FWS/OBS-78/84.

Ries, R. E., and Day, A. D., 1978, Use of irrigation in reclamation in dry regions, in Proceedings of a symposium on reclamation of drastically disturbed lands: American Society of Agronomy, pp. 505-520.

U.S. Bureau of Mines, 1978, Development of new bond release criteria for surface coal mines in the Eastern and Interior Coal Provinces of the United States: (Prepared by HRB Singer.) U.S. Bureau of Mines contract J0177024, pp. 9-11, 90-92, 171-188.

Sampson, A. W., 1952, Range management, principles and practices: John Wiley and Sons, Inc., New York, pp. 226, 229, and 232.

Stoddart, L. A., Smith, A. D., and Box, T. W., 1975, Range management, third edition: McGraw-Hill, New York, p. 483.

Thornburg, A. A., and Fuchs, S. H., 1978, Plant materials and requirements for growth in dry regions, in Proceedings of a symposium on reclamation of drastically disturbed lands: American Society of Agronomy, pp. 411-423.

U.S. Bureau of Indian Affairs, 1961, Methods of applying land and grass management principles, in Handbook for making resources inventories: Chapter III, p. 14.

U.S. Congress, 1977, House Report 95-218: 95th Congress, 1st session, 199 pp.

U.S. Environmental Protection Agency, 1973, Processes, procedures, and methods to control pollution from mining activities: EPA 430/9-73-011, p. 151.

U.S. Environmental Protection Agency, 1976, Erosion and sediment control—Surface mining in the eastern United States: Vol. 2, Design: EPA 625/3-76-006, pp. 81-87.

Valentine, J. F., 1971, Range development and improvements: Brigham Young University Press, Provo, Utah, p. 279.

Vogel, W. G., 1973, The effect of herbaceous vegetation on survival and growth of trees planted on coal-mine spoils, in Research and applied technology symposium on mined-land reclamation: Bituminous Coal Research, Inc., Monroeville, Pa., pp. 175-178, tables 1, 3, 4, and 5.

Vogel, W. G., 1975, Requirements and use of fertilizer, lime, and mulch for vegetating acid mine spoils, in Third symposium on surface mining and reclamation: National Coal Association, Washington, D.C., pp. 152-171, tables 1, 2, and 7.

Vogel, W. G., and Berg, W. A., 1973, Fertilizer and herbaceous cover influence

establishment of direct-seeded black locust on coal mine spoils, in R. J. Hutnik and Grant Davis, editors, Ecology and reclamation of devastated land: Gordon and Breach, New York, vol. 2, pp. 189-198, table 1.

Wahlquist, B. T., Dressler, R. L., and Sowards, W., 1975, Mined-land revegetation without supplemental irrigation in the arid Southwest, in Third symposium on surface mining and reclamation: National Coal Association, Washington, D.C., vol. 1, pp. 29-39.

Woodward, L. W., 1943, Infiltration capacities of some plant soil complexes of Utah range watershed lands: American Geophysical Union Transactions, part II, pp. 468-473.

IV. Procedural Matters

The Department of the Interior (DOI) has examined these proposed rules according to the criteria of Executive Order 12291 (February 17, 1981). OSM has determined that these are not major rules and do not require a regulatory impact analysis because they will impose only minor costs on the coal industry and coal consumers. In addition, the proposed rules emphasize the use of performance standards instead of design criteria, which will allow operators to utilize the most cost-effective means of achieving the performance standards.

The DOI has also determined, pursuant to the Regulatory Flexibility Act, 5 U.S.C. 601 *et seq.*, that these rules will not have a significant economic impact on a substantial number of small entities. The proposed rules will allow small coal operators increased flexibility in meeting performance standards and should especially ease the regulatory burden on small coal operators in Appalachia.

OSM has prepared a draft environmental assessment (EA) on this proposed rule and has made an interim finding that it would not significantly affect the quality of the human environment. The draft EA is on file in the OSM Administrative Record at the address listed in the "Addresses" section of this preamble. A final EA will be completed and a final conclusion reached on the significance of any resulting impacts before issuance of the final rule. OSM also is preparing an EA of the cumulative impacts on the human environment of this rulemaking and related rulemakings under the Act. This cumulative EA also will be completed before this rule is made final.

Accordingly, 30 CFR Parts 816 and 817 are proposed to be amended as set forth herein.

Dated: February 26, 1982.

William P. Pendley,

Acting Assistant Secretary, Energy and Minerals.

PART 816—PERMANENT PROGRAM PERFORMANCE STANDARDS— SURFACE MINING ACTIVITIES

1. Section 816.111 is revised to read as follows:

§ 816.111 Revegetation: General requirements.

(a) The permittee shall establish on all affected land, in accordance with the approved permit and reclamation plan, a vegetative cover that is—

- (1) Diverse, effective, and permanent;
- (2) Comprised of species native to the area or of introduced species where approved by the regulatory authority;
- (3) At least equal in extent of cover to the natural vegetation of the area; and
- (4) Capable of achieving productivity levels compatible with the approved postmining land use.

(b) Whether introduced or native, the reestablished plant species are to—

- (1) Be desirable and necessary to achieve the approved postmining land use;
- (2) Have the same seasonal characteristics of growth as the original vegetation;
- (3) Be capable of self-regeneration and plant succession;
- (4) Be compatible with the plant and animal species of the area; and
- (5) Meet the requirements of applicable State and Federal statutes regulating seed and introduced species.

(c) The regulatory authority may grant exception to the requirements of paragraphs (b)(2) and (b)(3) of this section when the species are necessary to achieve a quick, temporary, and stabilizing cover and measures to establish permanent vegetation are included in the approved permit and reclamation plan.

(d) When the regulatory authority approves a cropland postmining land use, the regulatory authority may grant exception to the requirements of paragraphs (a)(1), (a)(3), (b)(2), and (b)(3) of this section. The requirements of 30 CFR Part 823 apply for areas designated as prime farmland.

§ 816.112 [Removed]

2. Section 816.112 is removed.
3. Section 816.113 is revised to read as follows:

§ 816.113 Revegetation: Timing.

Seeding and planting of disturbed areas are to be conducted during the first normal period for favorable planting conditions after replacement of

the plant growth medium. The normal period for favorable planting is that planting time generally accepted locally for the type of plant materials selected. To effectively control erosion, disturbed areas may be seeded and planted with temporary cover species or otherwise protected until permanent vegetation is adequately established.

4. Section 816.114 is revised to read as follows:

§ 816.114 Revegetation: Mulching.

The regulatory authority may require the application of suitable mulch or use of other soil stabilizing practices where deemed necessary.

§ 816.115 [Removed]

5. Section 816.115 is removed.
6. Section 816.116 is revised to read as follows:

§ 816.116 Revegetation: Standards for success.

(a) Success of revegetation is to be judged on the effectiveness of the vegetation for the approved postmining land use, the extent of cover compared to the cover occurring in natural vegetation of the area, and the other general requirements of § 816.111.

(1) Standards for success and statistically valid sampling techniques for measuring success are to be selected by the regulatory authority after consultation with appropriate State and Federal agencies and specified in a regulatory program approved by the Office of Surface Mining in accordance with the procedures of Subchapter C of this chapter.

(2) Standards for success are to include criteria to evaluate the appropriate vegetation parameters of ground cover, production, or tree stocking. Ground cover, production or stocking are to be considered equal to the approved success standard when they are equivalent with 90-percent statistical confidence.

(b) Standards for success are to be applied in accordance with the approved postmining land use and at a minimum are to satisfy the following conditions:

(1) For areas developed for use as grazing land or pasture land, the ground cover and production of living plants on the revegetated area are to be at least equal to that of a reference area or such other success standards selected by the regulatory authority.

(2) For areas developed for use as cropland, crop production on the mined area is to be at least equal to that of a reference area or such other success standards selected by the regulatory authority.

(3) For areas to be developed for fish and wildlife habitat, recreation, shelter belts, or forest products, success of vegetation is to be determined on the basis of tree and shrub stocking and ground cover.

(i) Minimum stocking and planting arrangement are to be specified by the regulatory authority on the basis of local and regional conditions and after consultation with the State agencies responsible for the administration of forestry and wildlife programs. On Federal land concurrence must be obtained from the land management agency.

(ii) Trees and shrubs and will be used in determining the success of stocking and the adequacy of plant arrangement are to have utility for the approved postmining land use and at the time of bond release are to be healthy and have been in place for at least two growing seasons.

(iii) Ground cover of living plants is not to be less than required to achieve the postmining land use.

(4) For areas to be developed for industrial, commercial, or residential use, the ground cover of living plants is not to be less than that required to control erosion. In the event the permittee does not achieve the approved postmining land use within 5 years after regarding is completed, or such lesser period as may be specified by the regulatory authority, the general revegetation success standards of paragraph (a) of this section are to apply (other than compatibility with the approved, but unachieved, postmining land use).

(5) For remined areas that were not reclaimed to the requirements of this subchapter, as a minimum the ground cover of living plants is not to be less than the cover that can be supported by the best available topsoil or other suitable material in the redisturbed area and is not to be less than the ground cover existing before redisturbance.

(c)(1) The period of extended responsibility under the performance bond requirements of Subchapter J of this chapter begins after the last year of augmented seeding, fertilizing, irrigation, or other work, excluding tree and shrub planting, maintenance work, and husbandry practices that can be expected to continue as part of the postmining land use.

(2) In areas of more than 26.0 inches average annual precipitation the period of responsibility is to continue for a period of five full years. Vegetation parameters identified in paragraph (b) of this section are to equal the approved success standard during the growing

season of the last year of the responsibility period or, if required by the regulatory authority, during the growing season of the last 2 years of the responsibility period.

(3) In areas of less than or equal to 26.0 inches average annual precipitation, the period of responsibility is to continue for a period of ten full years. Interseeding and supplemental fertilizing may be allowed during the first 5 years of the responsibility period, and supplemental irrigation may be allowed during the first 2 years of the responsibility period when these practices are necessary for establishment of a diverse, effective, and permanent vegetative cover. Vegetation parameters identified in paragraph (b) of this section are to equal the approved success standard for at least the last two consecutive years of the responsibility period.

§ 816.117 [Removed]

7. Section 816.117 is removed.

PART 817—PERMANENT PROGRAM PERFORMANCE STANDARDS—UNDERGROUND MINING ACTIVITIES

8. Section 817.111 is revised to read as follows:

§ 817.111 Revegetation: General Requirements.

(a) The permittee shall establish on all lands affected, in accordance with the approved permit and reclamation plan, a vegetative cover that is—

- (1) Diverse and permanent;
 - (2) At least equal in extent of cover to the natural vegetation of the area; and
 - (3) Capable of achieving productivity levels compatible with the approved postmining land use.
- (b) Whether introduced or native, the reestablished plant species are to—
- (1) Be desirable and necessary to achieve the approved postmining land use;
 - (2) Be capable of self-regeneration and plant succession;
 - (3) Be compatible with the plant and animal species of the area; and
 - (4) Meet the requirements of applicable State and Federal statutes regulating seed and introduced species.

(c) The regulatory authority may grant exception to the requirements of paragraph (b)(2) of this section when the species are necessary to achieve a quick, temporary, and stabilizing cover and measures to establish permanent vegetation are included in the approved permit and reclamation plan.

(d) When the regulatory authority, by written finding, approves a cropland postmining land use, the regulatory authority may grant exceptions to the

requirements of paragraphs (a)(1), (a)(2), and (b)(2) of this section. The requirements of 30 CFR 823 apply for areas designated as prime farmland.

§ 817.112 [Removed]

9. Section 817.112 is removed.

10. Section 817.113 is revised to read as follows:

§ 817.113 Revegetation: Timing.

Seeding and planting of disturbed areas are to be conducted during the first normal period for favorable planting conditions after replacement of the plant growth medium. The normal period for favorable planting is to be that planting time generally accepted locally for the type of plant materials selected. To effectively control erosion, disturbed areas may be seeded and planted with temporary cover species or otherwise protected against erosion until permanent vegetation is adequately established.

11. Section 817.114 is revised to read as follows:

§ 817.114 Revegetation: Mulching.

The regulatory authority may require the application of suitable mulch or use of other soil stabilizing practices where deemed necessary.

§ 817.115 [Removed]

12. Section 817.115 is removed.

13. Section 817.116 is revised to read as follows:

§ 817.116 Revegetation: Standards for success.

(a) Success of revegetation is to be judged on the effectiveness of the vegetation for the approved postmining land use, the extent of cover compared to the cover occurring in natural vegetation of the area, and the general requirements of § 817.111.

(1) Standards for success and statistically valid sampling techniques for measuring success are to be selected by the regulatory authority after consultation with appropriate State and Federal agencies and specified in a regulatory program approved by the Office of Surface Mining in accordance with the procedures of Subchapter C of this chapter.

(2) Standards for success are to include criteria to evaluate the appropriate vegetation parameters of ground cover, production, or tree stocking. Ground cover, production or stocking are to be considered equal to the approved success standard when they are equivalent with 90-percent statistical confidence.

(b) Standards for success are to be applied in accordance with the approved postmining land use and at a

minimum are to satisfy the following conditions:

(1) For areas developed for use as grazing land or pasture land, the ground cover and production of living plants on the revegetated area are to be at least equal to that of a reference area or such other success standards selected by the regulatory authority.

(2) For areas developed for use as cropland, crop production on the mined area is to be at least equal to that of a reference area or such other success standards selected by the regulatory authority.

(3) For areas to be developed for fish and wildlife habitat, recreation, shelter belts, or forest products, success of vegetation is to be determined on the basis of tree and shrub stocking and ground cover.

(i) Minimum stocking and planting arrangement are to be specified by the regulatory authority on the basis of local and regional conditions and after consultation with the State agencies responsible for the administration of forestry and wildlife programs. On Federal land concurrence must be obtained from the land management agency.

(ii) Trees and shrubs that will be used in determining the success of stocking and the adequacy of plant arrangement are to have utility for the approved postmining land use and at the time of bond release are to be healthy and have been in place for at least two growing seasons.

(iii) Ground cover of living plants is not to be less than required to achieve the postmining land use.

(4) For areas to be developed for industrial, commercial, or residential use, the ground cover of living plants is not to be less than that required to control erosion. In the event the permittee does not achieve the required postmining land use within 5 years after regrading is completed, or such lesser period as may be specified by the regulatory authority, the general revegetation success standards of paragraph (a) of this section apply (other than compatibility with the approved, but unachieved, postmining land use).

(5) For remined areas that were not reclaimed to the requirements of this subchapter, as a minimum, the ground cover of living plants is not to be less than the cover that can be supported by the best available topsoil or other suitable material in the redisturbed area and is not to be less than the ground cover existing before redisturbance.

(c)(1) The period of extended responsibility under the performance

bond requirements of Subchapter J of this chapter begins after the last year of augmented seeding, fertilizing, irrigation, or other work, excluding tree and shrub planting, maintenance work, and husbandry practices that can be expected to continue as part of the postmining land use.

(2) In areas of more than 26.0 inches average annual precipitation the period of responsibility is to continue for a period of five full years. Vegetation parameters identified in Paragraph (b) of this section are to equal the approved success standard during the growing

season of the last year of the responsibility period, or, if required by the regulatory authority, during the growing season of the last 2 years of the responsibility period.

(3) In areas of less than or equal to 26.0 inches average annual precipitation, the period of responsibility is to continue for a period of ten full years. Interseeding and supplemental fertilizing may be allowed during the first 5 years of the responsibility period, and supplemental irrigation may be allowed during the first 2 years of the responsibility period when these

practices are necessary for establishment of a diverse and permanent vegetative cover. Vegetation parameters identified in Paragraph (b) of this section are to equal the approved success standard for at least the last two consecutive years of the responsibility period.

§ 817.117 [Removed]

14. Section 817.117 is removed.

(Pub. L. 95-87; 30 U.S.C. Section 1201 *et seq.*)

[FR Doc. 82-7762 Filed 3-22-82; 8:45 am]

BILLING CODE 4310-05-M

Reader Aids

Federal Register

Vol. 47, No. 56

Tuesday, March 23, 1982

INFORMATION AND ASSISTANCE

PUBLICATIONS

Code of Federal Regulations

CFR Unit	202-523-3419
General information, index, and finding aids	523-3517
Incorporation by reference	523-5227
Printing schedules and pricing information	523-4534
	523-3419

Federal Register

Corrections	523-5237
Daily Issue Unit	523-5237
General information, index, and finding aids	523-5227
Privacy Act	523-5237
Public Inspection Desk	523-5215
Scheduling of documents	523-3187

Laws

Indexes	523-5282
Law numbers and dates	523-5282
	523-5266

Slip law orders (GPO)

	275-3030
--	----------

Presidential Documents

Executive orders and proclamations	523-5233
Public Papers of the President	523-5235
Weekly Compilation of Presidential Documents	523-5235

United States Government Manual

	523-5230
--	----------

SERVICES

Agency services	523-4534
Automation	523-3408
Library	523-4986
Magnetic tapes of FR issues and CFR volumes (GPO)	275-2867
Public Inspection Desk	523-5215
Special Projects	523-4534
Subscription orders (GPO)	783-3238
Subscription problems (GPO)	275-3054
TTY for the deaf	523-5229

FEDERAL REGISTER PAGES AND DATES, MARCH

8547-8748	1
8749-8976	2
8977-9184	3
9185-9386	4
9387-9804	5
9805-9980	8
9981-10198	9
10199-10502	10
10503-10762	11
10763-11000	12
11001-11242	15
11243-11494	16
11495-11640	17
11641-11814	18
11815-12124	19
12125-12326	22
12327-12604	23

CFR PARTS AFFECTED DURING MARCH

At the end of each month, the Office of the Federal Register publishes separately a list of CFR Sections Affected (LSA), which lists parts and sections affected by documents published since the revision date of each title.

1 CFR

Proposed Rules:	
Ch. III	11024

3 CFR

Administrative Orders:	
Presidential determination:	
No. 82-7 of	
February 10, 1982	9805
Proclamations:	
2416 (See PLO	
6214)	11668
3279 (Amended by	
Proc. 4907)	10507
4707 (Amended by	
Proc. 4904)	8753
4768 (Amended by	
Proc. 4904)	8753
4801 (See Proc.	
4904)	8753
4884 (See Proc.	
4904)	8753
4887 (See Proc.	
4904)	8753
4902	8549
4903	8751
4904	8753
4905	8977
4906	9807
4907	10507
4908	10763
4909	10765
4910	12127

Executive Orders:

September 22, 1866	
(Revoked by	
PLO 6171)	9838
March 14, 1878	
(Revoked in part	
by PLO 6205)	11665
March 12, 1884	
(See PLO 6214)	11668
June 13, 1902	
(Revoked by	
PLO 6184)	10213
July 2, 1910	
(Revoked in part	
by PLO's 6177,	
6215, 6228)	9840,
	11669, 11871
July 2, 1910	
(Revoked by	
PLO 6229)	12172
December 1, 1910	
(Revoked in part	
by PLO 6222)	11674
January 23, 1911	
(Revoked by	
PLO 6229)	12172
April 29, 1912	
(Revoked in part	
by PLO 6216)	11669
April 12, 1913	
(See PLO 6213)	11668
April 3, 1914	
(Revoked in part	
by PLO 6207)	11666
June 30, 1916	
(Revoked in part	
by PLO 6208)	11666
April 28, 1917	
(Revoked by	
PLO 6204)	11664
August 15, 1919	
(Revoked in part	
by PLO 6224)	11675
March 29, 1922	
(Revoked by	
PLO 6175)	9839
November 9, 1923	
(Revoked in part	
by PLO 6206)	11665
October 30, 1924	
(Revoked in part	
by PLO 6201)	11662
April 17, 1926	
(Revoked in part	
by PLO's 6173,	
6210)	9838, 11667
November 6, 1926	
(Revoked in part	
by PLO 6201)	11662
September 20, 1927	
(Revoked in part	
by PLO 6206)	11665
February 13, 1929	
(Revoked in part	
by PLO 6206)	11665
808 (Revoked by	
PLO 6214)	11668
923 (See	
PLO 6214)	11668
3655 (Revoked by	
PLO 6175)	9839
3893 (See PLO	
6171)	9838
4060 (Revoked by	
PLO 6214)	11668
4170 (Revoked by	
PLO 6226)	11675
5327 (See	
PLO 6202)	11663
5650 (Revoked in part	
by PLO 6206)	11665
5683 (Revoked by	
PLO 6193)	10214
7799 (Revoked in part	
by PLO 6227)	11676
7993 (See	
PLO 6214)	11668
8009 (Revoked in part	
by PLO 6206)	11665
11888 (Amended by	
EO 12349)	8749

11954 (Revoked by EO 12348).....	8547
12074 (Revoked by EO 12350).....	10503
12193 (See EO 12531).....	10505
12295 (See EO 12351).....	10505
12348.....	8547
12349.....	8749
12350.....	10503
12351.....	10505
12352.....	12125

5 CFR

Ch. XIV.....	9185
737.....	9694
2430.....	11243

Proposed Rules:

410.....	10855
831.....	9470

7 CFR

Ch. IV.....	11642
0.....	10509, 12327
29.....	8979
51.....	9185
53.....	12327
54.....	11641
285.....	10767
273.....	11815
301.....	8982, 12328
425.....	11645
719.....	9981
724.....	10770
725.....	10772
726.....	10773
907.....	9188, 10509, 11650
910.....	9188, 9387, 10724, 11816
928.....	10775
959.....	8551
981.....	9809
982.....	10775
1093.....	11495
1094.....	10510
1421.....	9188
1435.....	9194
1446.....	8553
1475.....	9981
1701.....	9387
1823.....	11609

Proposed Rules:

210.....	11877
272.....	11878
273.....	11878
729.....	9972, 10045
985.....	8784
1004.....	10230
1006.....	10203
1007.....	10053, 10203
1011.....	10203, 11679
1012.....	10203
1030.....	11283
1046.....	10203
1094.....	10203
1096.....	10203
1098.....	10203
1425.....	11284
1701.....	8785, 10057, 11285
1861.....	11521
1944.....	10566
1951.....	11521
2900.....	8786

8 CFR

204.....	12129
----------	-------

212.....	12129
214.....	12129
223.....	12129
237.....	12129
242.....	12129
245.....	12129
248.....	12129
238.....	8759, 9982
265.....	12129
316a.....	10776
328.....	10776
332.....	10776
332a.....	10776
334.....	10776
335.....	10776
335b.....	10776
336.....	10776
339.....	10776
344.....	10776

9 CFR

72.....	11001
82.....	11243
92.....	11509
112.....	8759
303.....	12134
318.....	10779
319.....	10779
381.....	10779, 12134

Proposed Rules:

92.....	9854
309.....	10856
317.....	9471
381.....	9471, 10856

10 CFR

1.....	9983, 11816
2.....	9983, 9987
14.....	8983
25.....	9194
50.....	11651
73.....	11511
95.....	9194
440.....	9014
705.....	12135
790.....	8555
1004.....	9995

Proposed Rules:

Ch. I.....	8788
463.....	11178
508.....	10589
600.....	12038
794.....	9017

12 CFR

204.....	8987
207.....	8988
211.....	11817
217.....	8987
220.....	8988
221.....	8988
224.....	8988
303.....	9810
308.....	9811
407.....	12136
545.....	10785
546.....	10788
555.....	10785
561.....	10785
576.....	10788
584.....	10785
611.....	12136
613.....	12136
614.....	12136
615.....	12136

616.....	12136
617.....	12136
618.....	12136
701.....	10199
1204.....	11246

Proposed Rules:

Ch. II.....	9017
207.....	8788
220.....	8788
221.....	8788
545.....	9472, 9855
561.....	10858
563.....	9472, 10511
564.....	10858
615.....	11536
701.....	10232, 10234

13 CFR

105.....	12332
120.....	8990

14 CFR

39.....	8555-8561, 9196, 9812-9815, 10511, 11002-11008, 11652, 12151, 12152
47.....	12153
71.....	8562, 9816, 9817, 10512, 10513, 11009, 11653, 12154-12156
73.....	8563, 11010, 11653, 11654, 12156
75.....	9200, 9817, 12156
91.....	10514
97.....	9818, 12157
99.....	12324
121.....	10515
202.....	10516
208.....	9819
213.....	10517
241.....	9744
314.....	9744, 11819
385.....	9200, 10200, 10517
389.....	10518

Proposed Rules:

Ch. I.....	11026, 12186, 12320
21.....	9360, 9859
23.....	9360
36.....	9360
39.....	10591, 11034-11037, 12186-12190
71.....	8595, 9222, 9224, 9860, 10592-10594, 11038, 12191-12193
73.....	11700
75.....	8596, 9222
91.....	9360
121.....	9360, 10748
135.....	9360, 10748
139.....	9360

15 CFR

370.....	11247
371.....	11247
373.....	11247
376.....	9201, 11247
379.....	9201, 11247
385.....	9201, 11247
386.....	11247
399.....	9201, 11247
904.....	9820, 10200
970.....	11512
2301.....	11228

Proposed Rules:

904.....	9861
----------	------

16 CFR

13.....	9388, 9821
1700.....	10201

Proposed Rules:

13.....	11285
1700.....	10235
1306.....	12353

17 CFR

155.....	11250
200.....	11380, 11819
201.....	11380, 11819
211.....	10789, 11475
229.....	11380, 11819
230.....	11251, 11380, 11819
231.....	11476
239.....	11251, 11380
240.....	9388, 11476, 11819
241.....	10792, 11380
249.....	11380, 11819
250.....	11380, 11819
260.....	11380, 11819
271.....	10518
274.....	10518, 11380, 11819

Proposed Rules:

1.....	12353
12.....	9225
180.....	9225
190.....	8789
230.....	11482, 11701, 11704
239.....	11288, 11482
240.....	11482, 11704

18 CFR

35.....	8991
260.....	10202
271.....	8564, 8565, 10203
410.....	9206

Proposed Rules:

141.....	10237
271.....	8596, 10237-10242
273.....	8596
274.....	8596
711.....	12296
713.....	12296
714.....	12296
716.....	12296

19 CFR

10.....	12159
212.....	9389

Proposed Rules:

10.....	9225, 11706
18.....	9225
19.....	9225
24.....	9225
113.....	9225
125.....	9225
132.....	9225
142.....	9225
143.....	11706
144.....	9225
177.....	10058, 12194

20 CFR

404.....	12161
----------	-------

Proposed Rules:

404.....	8789
----------	------

21 CFR

5.....	8761, 11269
14.....	8763
20.....	10804
73.....	10804

74.....11819	660.....10525	520.....12338	Proposed Rules:
81.....10804	668.....10529	535.....12339	775.....10859
101.....11820	712.....10529		
102.....11820	Proposed Rules:		
103.....11820	628.....9247		
114.....11820			
122.....11820			
131.....11270, 11820			
133.....11820			
135.....11820			
136.....11820			
137.....11820			
139.....11820			
145.....9997, 11820			
146.....11820			
150.....11820			
155.....11820			
160.....11820			
161.....11820			
163.....11820			
164.....11820			
166.....11820			
168.....11820			
169.....11820			
170.....11835			
172.....8763, 11835			
173.....11835			
175.....9395, 11835			
176.....9998, 11835			
177.....11835			
178.....9999, 11835			
179.....11835			
180.....11835			
181.....11835			
184.....11835			
186.....11835			
189.....11835			
211.....9395			
331.....9395			
436.....9395, 11856			
442.....11856			
450.....9395			
520.....9395, 10805			
522.....9398, 10805, 10806			
524.....10807			
556.....9395			
558.....8764, 8765, 9394, 9398, 10807, 10808, 12338			
573.....9395			
610.....9395			
630.....9395			
701.....9395			
801.....9395			
1308.....11513			
Proposed Rules:			
Subch. F.....12358			
333 (2 documents).....12430, 12480			
862.....11879			
866.....11879, 11880			
868.....11880			
874.....11879			
878.....11879			
880.....11880			
892.....11879			
22 CFR			
22.....9999			
201.....8766			
606.....11858			
Proposed Rules:			
41.....12359			
23 CFR			
12.....10522			
24 CFR			
111.....8991			
200.....9206			
201.....10204			
203.....10205			
213.....10205			
234.....10205			
420.....11655			
570.....9822			
885.....9206			
25 CFR			
700.....11858			
26 CFR			
1.....11515			
31.....11275			
35.....11275			
26.....8995			
150.....8995			
Proposed Rules:			
1.....11296, 11882, 12361			
51.....9018			
27 CFR			
Proposed Rules:			
4.....11884			
5.....11884			
7.....11884			
28 CFR			
0.....9822, 10809			
13.....11516			
570.....9755, 10206			
571.....9755			
29 CFR			
511.....11865			
1401.....10530			
1402.....10530			
1404.....9823			
1410.....10530			
1420.....10530			
1425.....10530			
2704.....10000			
Proposed Rules:			
1910.....12092			
30 CFR			
19.....11368			
23.....11369			
36.....11371			
910.....10372			
Proposed Rules:			
Ch. VII.....10058			
55.....10190			
57.....10190			
415.....9862			
716.....12310			
785.....12082, 12310			
816.....10501, 10742, 12088, 12596			
817.....10501, 10742, 12596			
819.....12088			
931.....12361			
948.....11885			
31 CFR			
209.....9823			
32 CFR			
1 through 39.....9399			
41.....10162			
199.....12163			
Proposed Rules:			
199.....11707			
230.....11708			
231.....11717			
299.....8791			
632.....8790			
33 CFR			
84.....10531			
85.....10531			
86.....10531			
117.....8566, 9825, 10532, 11010			
140.....9366			
141.....9366			
142.....9366			
143.....9366, 11011			
144.....9366, 10533			
146.....9366			
147.....9366			
149.....10533			
175.....10533			
Proposed Rules:			
100.....9863			
117.....8597-8599, 9864, 10595, 12194			
147.....11719			
157.....11724			
159.....9248			
165.....11719			
401.....11039			
34 CFR			
645.....9158			
646.....9150			
648.....11866			
776.....9786			
35 CFR			
10.....9207			
36 CFR			
7.....11011			
907.....8767			
Proposed Rules:			
1.....11598			
2.....11598			
3.....11598			
4.....11598			
5.....11598			
6.....11598			
7.....11598			
12.....11598			
50.....11725			
38 CFR			
1.....11279, 12340			
3.....11012, 11655			
6.....11656			
8.....11656			
17.....10809			
36.....9826, 12346			
Proposed Rules:			
3.....12362			
21.....11041, 12363			
39 CFR			
111.....10206			
40 CFR			
6.....9827, 9831			
52.....8566, 8772, 9462, 9463, 9832-9836, 10206, 10208, 10534, 10535, 10813, 11013, 11280, 11661, 11866, 12164, 12166			
61.....11662			
62.....10004, 10535			
81.....10208, 11014, 11870			
122.....10006			
123.....12347			
141.....8997, 10998			
180.....8998-9001, 10210- 10212, 10536			
256.....9002-9005			
260.....9007			
264.....10006			
265.....9802, 10006, 12316			
Proposed Rules:			
Ch. I.....9477, 9864			
33.....8960			
52.....9019, 9478-9481, 10058, 10860, 11042, 11045, 12195, 12364			
80.....11536			
81.....8791, 9019, 10243			
85.....8606			
86.....8606, 11538, 12366			
122.....8792, 10861, 11538			
123.....8792, 9336, 9865, 10861, 10862, 11538			
124.....8792, 10861, 11538			
141.....9350			
142.....9796			
146.....8792, 10861			
180.....9025, 10244, 10596			
260.....9336, 9865			
262.....9336, 9865			
265.....8606, 10059			
300.....10972			
799.....10597			
1510.....10862			
41 CFR			
1-4.....8774			
8-1.....8777			
5-53.....11017			
5-63.....11019			
5A-53.....11017, 11019			
5B-15.....11019			
5B-63.....11019			
29-1.....11374			
101.....12167			
101-11.....11281			
101-26.....8779			
101-37.....8777			
101-41.....11281			
Proposed Rules:			
101-41.....11296			
42 CFR			
447.....8567			
Proposed Rules:			
405.....12574			
416.....12574			
43 CFR			
1820.....12292			
2800.....12568			
2880.....12570			
3420.....9008			

Public Land Orders:

30 (Revoked by PLO 6214).....	11668
548 (Revoked in part by PLO 6201).....	11662
648 (Revoked in part by PLO 6185).....	10825
1314 (Revoked by PLO 6179).....	9840
1368 (Revoked in part by PLO 6220).....	11671
1421 (Revoked in part by PLO 6220).....	11671
1529 (Revoked in part by PLO 6220).....	11671
1609 (Revoked by PLO 6221).....	11673
1642 (Revoked by PLO 6186).....	10213
1653 (Revoked by PLO 6220).....	11671
2278 (Revoked in part by PLO 6220).....	11671
2565 (Revoked in part by PLO 6220).....	11671
2845 (Revoked in part by PLO 6220).....	11671
2978 (Revoked in part by PLO 6220).....	11671
3250 (Revoked in part by PLO 6220).....	11671
3282 (Revoked in part by PLO 6220).....	11671
3310 (Revoked in part by PLO 6220).....	11671
3500 (Revoked in part by PLO 6194).....	10215
3633 (Revoked by PLO 6191).....	10214
3777 (Revoked in part by PLO 6220).....	11671
3841 (Revoked in part by PLO 6220).....	11671
3964 (Revoked by PLO 6178).....	9840
4265 (Revoked in part by PLO 6220).....	11671
4788 (See PLO 6220).....	11671
4839 (Revoked by PLO 6195).....	10215
4448 (Revoked in part by PLO 6198).....	11282
5140 (Revoked in part by PLO 6220).....	11671
5490 (See PLO 6178).....	9840
5844 (See PLO's 6020 and 6196).....	10826
5992 (Corrected by PLO 6197).....	11022
6020 (Corrected by PLO 6196).....	10826
6044 (Corrected by PLO 6212).....	11668
6098 (Corrected by PLO 6199).....	11517
6127.....	11022
6149.....	8779
6143.....	10537
6171.....	9838
6172.....	9838
6173.....	9838
6174.....	9839
6175.....	9839

6176.....	9839
6177.....	9840
6178.....	9840
6179.....	9840
6180.....	9841
6181.....	9841
6182.....	9842
6183.....	9842
6184.....	10213
6185.....	10825
6186.....	10213
6187.....	10213
6188.....	10825
6189.....	10826
6190.....	10214
6191.....	10214
6192.....	10826
6193.....	10214
6194.....	10215
6195.....	10215
6196.....	10826
6197.....	11022
6198.....	11282
6199.....	11517
6200.....	11282
6201.....	11662
6202.....	11662
6203.....	11664
6204.....	11664
6205.....	11665
6206.....	11665
6207.....	11666
6208.....	11666
6209.....	11667
6210.....	11667
6211.....	11667
6212.....	11668
6213.....	11668
6214.....	11668
6215.....	11669
6216.....	11669
6217.....	11669
6218.....	11670
6219.....	11670
6220.....	11671
6221.....	11673
6222.....	11674
6223.....	11674
6224.....	11675
6225.....	11675
6226.....	11675
6227.....	11676
6228.....	11871
6229.....	12172
Proposed Rules:	
3140.....	8734, 9026
3800.....	12197
5440.....	12078
5450.....	12078
5460.....	12078
44 CFR	
2.....	12172
64.....	10827, 10829
65.....	10006, 10215, 10538, 10830
67.....	10006, 10540
70.....	10007-10018
205.....	10553
312.....	11297
351.....	10758
Proposed Rules:	
67.....	9865, 10059-10063, 10245
312.....	11297

45 CFR

13.....	10834
46.....	9208
301.....	8568
400.....	10841
401.....	10841
500.....	10850
531.....	11850
605.....	8570
Proposed Rules:	
46.....	12276
1050.....	10598
1067.....	10598
1068.....	10598
46 CFR	
25.....	10558
33.....	10558
67.....	8581
75.....	10558
94.....	10558
108.....	10558
160.....	10558
162.....	10558
164.....	10558
180.....	10558
192.....	10558
524.....	10217
530.....	10851
Proposed Rules:	
Ch. IV.....	10600
10.....	11046
536.....	10862
549.....	12367
47 CFR	
1.....	9208, 10852
2.....	9464, 11022
21.....	10852
22.....	10018
23.....	10852
25.....	10852
42.....	10559
43.....	10852
67.....	9170
68.....	10219
73.....	8583, 8779-8782, 9208-9214, 10219, 10560, 10852, 11023, 11872-11874
74.....	9214
76.....	8783
78.....	10852
83.....	10220
87.....	10852
90.....	10852, 11022
94.....	10852
99.....	11022
Proposed Rules:	
Ch. I.....	10863
1.....	10871, 11886
2.....	9249
15.....	9249
43.....	10871
73.....	8792-8797, 9249, 9482, 10259-10261, 10601, 10603, 11046, 11727-11733, 11901-11909
74.....	9251
81.....	9249
83.....	9249
90.....	10064, 11731
97.....	8798
48 CFR	
Proposed Rules:	
32.....	10878

49 CFR

1.....	11676
192.....	9842
670.....	11677
1011.....	9466
1033.....	9010, 11518
1065.....	12349
1100.....	9011
1111.....	9844, 11875
1201.....	9466, 12349
1206.....	9466, 12349
1207.....	9466, 12349
1241.....	10041
1249.....	9468
Proposed Rules:	
171.....	9346, 9865
172.....	9346, 9865
387-399.....	10066, 10610
391.....	9256
571.....	9865
1137.....	8801
1201.....	11539, 11910
1244.....	11541
1263.....	11910
1310.....	8801
50 CFR	
611.....	10227
619.....	12181
671.....	10043, 10044, 10228, 10853, 11677, 12184
Proposed Rules:	
17.....	9483, 9867
18.....	9869
228.....	9027
285.....	12367
611.....	11299
640.....	10878
651.....	10605

AGENCY PUBLICATION ON ASSIGNED DAYS OF THE WEEK

The following agencies have agreed to publish all documents on two assigned days of the week (Monday/Thursday or Tuesday/Friday).

This is a voluntary program. (See OFR NOTICE 41 FR 32914, August 6, 1976.)

Monday	Tuesday	Wednesday	Thursday	Friday
DOT/SECRETARY	USDA/ASCS		DOT/SECRETARY	USDA/ASCS
DOT/COAST GUARD	USDA/FNS		DOT/COAST GUARD	USDA/FNS
DOT/FAA	USDA/REA		DOT/FAA	USDA/REA
DOT/FHWA	USDA/SCS		DOT/FHWA	USDA/SCS
DOT/FRA	MSPB/OPM		DOT/FRA	MSPB/OPM
DOT/MA	LABOR		DOT/MA	LABOR
DOT/NHTSA	HHS/FDA		DOT/NHTSA	HHS/FDA
DOT/RSPA			DOT/RSPA	
DOT/SLSDC			DOT/SLSDC	
DOT/UMTA			DOT/UMTA	

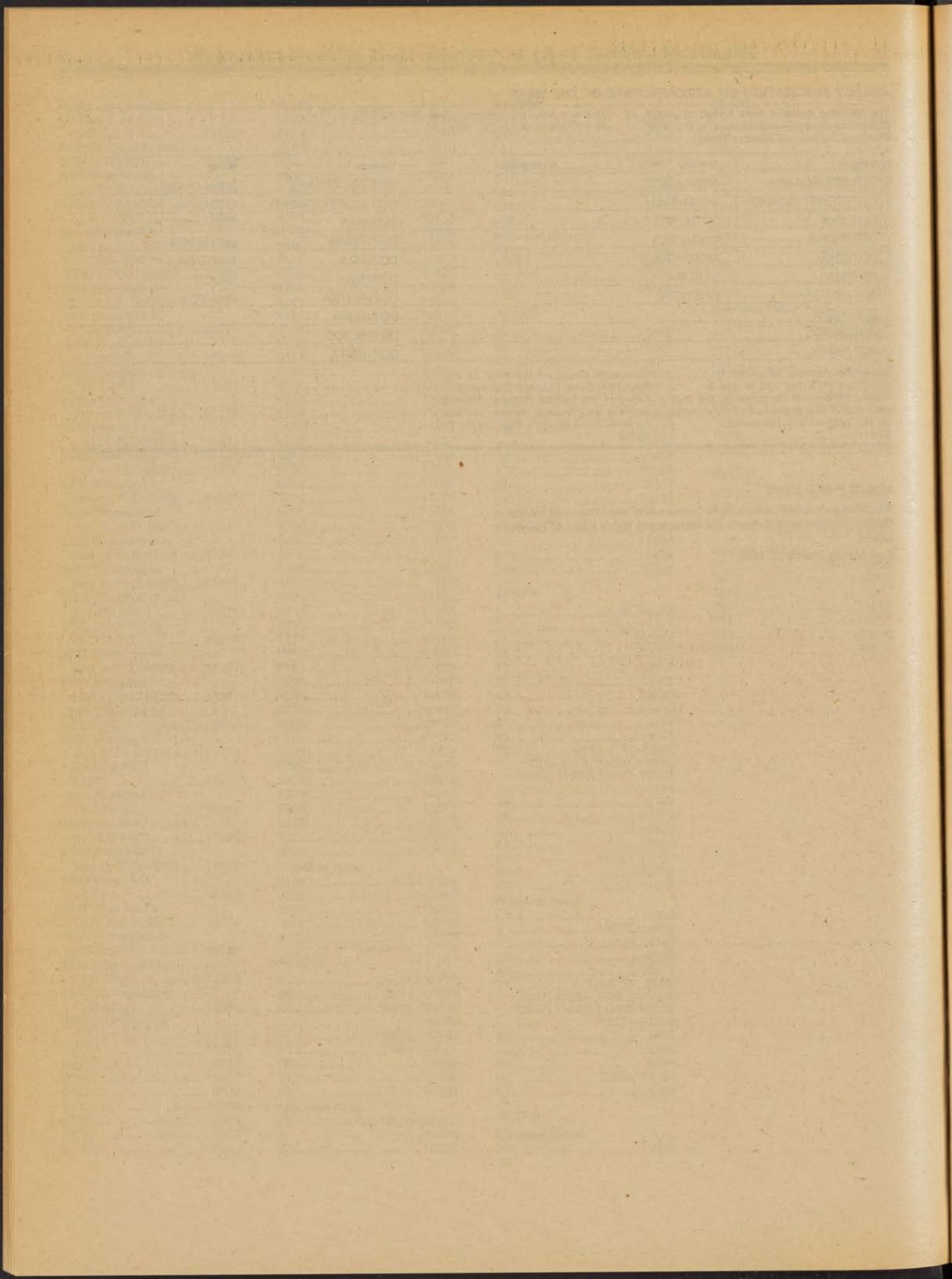
Documents normally scheduled for publication on a day that will be a Federal holiday will be published the next work day following the holiday. Comments on this program are still invited.

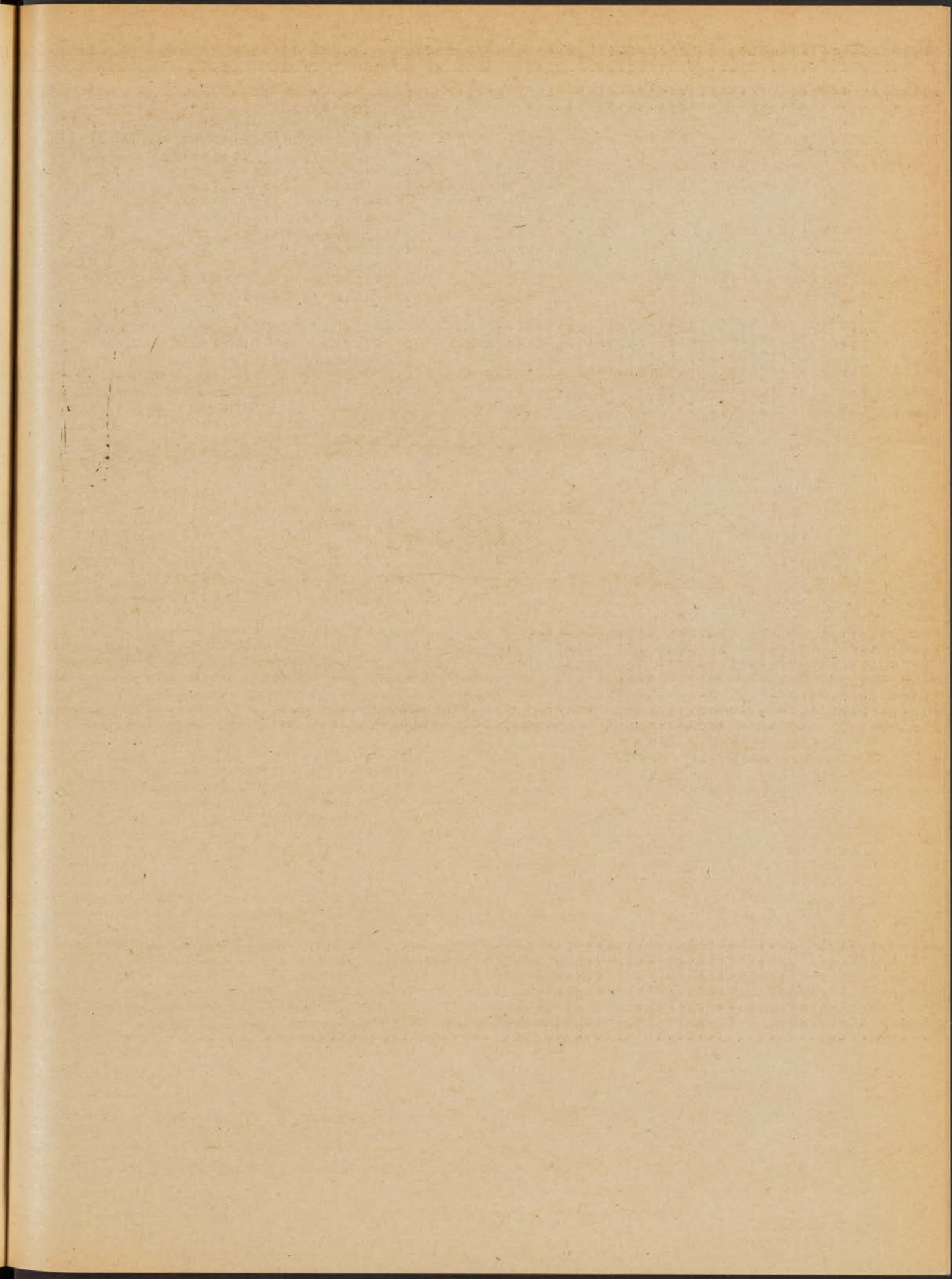
Comments should be submitted to the Day-of-the-Week Program Coordinator, Office of the Federal Register, National Archives and Records Service, General Services Administration, Washington, D.C. 20408.

List of Public Laws

Note: No public bills which have become law were received by the Office of the Federal Register for inclusion in today's List of Public Laws.

Last Listing March 22, 1982





THE HISTORY OF THE CITY OF BOSTON

FROM THE FIRST SETTLEMENT
TO THE PRESENT TIME
BY
JOHN B. BOWEN

BOSTON
PUBLISHED BY
J. B. BOWEN

THE HISTORY OF THE
CITY OF BOSTON
FROM THE FIRST SETTLEMENT
TO THE PRESENT TIME
BY
JOHN B. BOWEN

BOSTON
PUBLISHED BY
J. B. BOWEN

THE HISTORY OF THE
CITY OF BOSTON
FROM THE FIRST SETTLEMENT
TO THE PRESENT TIME
BY
JOHN B. BOWEN

BOSTON
PUBLISHED BY
J. B. BOWEN

THE HISTORY OF THE
CITY OF BOSTON
FROM THE FIRST SETTLEMENT
TO THE PRESENT TIME
BY
JOHN B. BOWEN

BOSTON
PUBLISHED BY
J. B. BOWEN

THE HISTORY OF THE
CITY OF BOSTON
FROM THE FIRST SETTLEMENT
TO THE PRESENT TIME
BY
JOHN B. BOWEN

BOSTON
PUBLISHED BY
J. B. BOWEN

THE HISTORY OF THE
CITY OF BOSTON
FROM THE FIRST SETTLEMENT
TO THE PRESENT TIME
BY
JOHN B. BOWEN

BOSTON
PUBLISHED BY
J. B. BOWEN

THE HISTORY OF THE
CITY OF BOSTON
FROM THE FIRST SETTLEMENT
TO THE PRESENT TIME
BY
JOHN B. BOWEN

BOSTON
PUBLISHED BY
J. B. BOWEN

would you like to know

if any changes have been made in certain titles of the CODE OF FEDERAL REGULATIONS without reading the Federal Register every day? If so, you may wish to subscribe to the LSA (List of CFR Sections Affected), the "Federal Register Index," or both.

LSA (List of CFR Sections Affected)
\$10.00
per year

The LSA (List of CFR Sections Affected) is designed to lead users of the Code of Federal Regulations to amendatory actions published in the Federal Register, and is issued monthly in cumulative form. Entries indicate the nature of the changes.

Federal Register Index **\$8.00**
per year

Indexes covering the contents of the daily Federal Register are issued monthly in cumulative form. Entries are carried primarily under the names of the issuing agencies. Significant subjects are carried as cross-references.

A finding aid is included in each publication which lists Federal Register page numbers with the date of publication in the Federal Register.

Note to FR Subscribers: FR Indexes and the LSA (List of CFR Sections Affected) will continue to be mailed free of charge to regular FR subscribers.

Mail order form to:
Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402

There is enclosed \$_____ for _____ subscription(s) to the publications checked below:

..... LSA (LIST OF CFR SECTIONS AFFECTED) (\$10.00 a year domestic; \$12.50 foreign)

..... FEDERAL REGISTER INDEX (\$8.00 a year domestic; \$10.00 foreign)

Name _____

Street Address _____

City _____ State _____ ZIP _____

Make check payable to the Superintendent of Documents