

✓4
Sm 1/2
D 84/7

96th Congress }
1st Session }

1049

DOCUMENTS

COMMITTEE PRINT

MAY 23 1979

FARRELL LIBRARY
KANSAS STATE UNIVERSITY

COMPETITIVE PROBLEMS IN THE
DRUG INDUSTRY

Fixed-Dose Combination Antibiotic Drugs

SUMMARY AND ANALYSIS

SELECT COMMITTEE ON SMALL BUSINESS
UNITED STATES SENATE

SUBCOMMITTEE ON MONOPOLY, ECONOMIC
CONCENTRATION AND ANTICOMPETITIVE
ACTIVITIES

PREPARED BY THE
CONGRESSIONAL RESEARCH SERVICE
LIBRARY OF CONGRESS

A SUMMARY ANALYSIS AND DISCUSSION OF ISSUES HIGHLIGHTED DURING THE 1969 HEARINGS ON FIXED-DOSE COMBINATION ANTIBIOTIC DRUGS (COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY—VOLUME 12) AND THE 1972 HEARINGS ON MISUSE OF ANTIBIOTICS (ADVERTISING OF PROPRIETARY MEDICINES—VOLUME 3), WITH A REVIEW OF SUBSEQUENT GOVERNMENT ACTIONS AND THE CURRENT STATUS OF THESE DRUG PRODUCTS



MAY 1, 1979

Printed for the use of the Select Committee on Small Business

U.S. GOVERNMENT PRINTING OFFICE

44-041 O

WASHINGTON : 1979

DOCUMENTS
MAY 23 1979
FARRIS STATE UNIVERSITY
LIBRARY

SELECT COMMITTEE ON SMALL BUSINESS

GAYLORD NELSON, Wisconsin, *Chairman*

SAM NUNN, Georgia
JOHN C. CULVER, Iowa
WALTER D. HUDDLESTON, Kentucky
DALE BUMPERS, Arkansas
ROBERT MORGAN, North Carolina
JAMES R. SASSER, Tennessee
DONALD W. STEWART, Alabama
MAX BAUCUS, Montana
CARL LEVIN, Michigan

LOWELL P. WEICKER, JR., Connecticut
BOB PACKWOOD, Oregon
ORRIN G. HATCH, Utah
S. I. HAYAKAWA, California
HARRISON H. SCHMITT, New Mexico
RUDY BOSCHWITZ, Minnesota
LARRY PRESSLER, South Dakota

WILLIAM B. CHERKASKY, *Executive Director*
GERALD D. STURGES, *Professional Staff Member*
ROBERT J. DOTCHIN, *Minority Staff Director*

SUBCOMMITTEE ON MONOPOLY, ECONOMIC CONCENTRATION AND
ANTICOMPETITIVE ACTIVITIES

JAMES R. SASSER, Tennessee, *Chairman*

CARL LEVIN, Michigan
GAYLORD NELSON, Wisconsin

LARRY PRESSLER, South Dakota
BOB PACKWOOD, Oregon

(II)

LETTER OF SUBMITTAL



The Library of Congress

Congressional Research Service

Washington, D.C. 20540

March 30, 1979

Honorable Gaylord Nelson
Chairman, Subcommittee on Monopoly and
Anticompetitive Activities
Senate Select Committee on Small Business
United States Senate
Washington, D.C. 20510

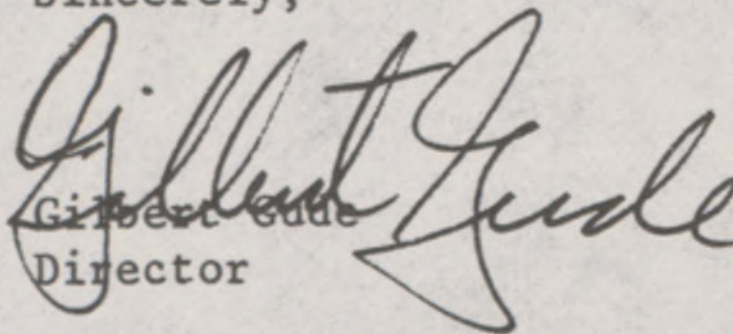
Dear Senator Nelson:

I am pleased to submit this analysis and review of the fixed-dose combination antibiotic drug hearings that were conducted before your subcommittee in 1969 and 1972. This summary report, prepared at your request, is particularly timely in light of the continuing controversy over the efficacy requirements for drug marketing.

The hearings summary was prepared by Ms. Renée Ford, a private consultant, under a Congressional Research Service contract (CRS 78-62-5). It was reviewed and edited by Ms. Vikki Zegel, Analyst in Life Sciences, of the CRS Science Policy Research Division. The report provides an analytical review of testimony presented during the 1969 and 1972 hearings, as well as an update of what has been learned since those hearings with regard to the safety and efficacy of fixed-dose combination antibiotic drugs. The actions of the Federal Government since the hearings relating to these drug products are also highlighted.

May I express my appreciation for this opportunity, on the part of the Congressional Research Service, to cooperate with your subcommittee in the preparation of this timely and most useful report.

Sincerely,


Gilbert S. Eide
Director

(III)

CONTENTS

	Page
Letter of submittal.....	III
I. Introduction.....	1
A. Purpose.....	1
B. Background.....	1
C. Policy issues.....	5
II. Fixed-dose combination drugs.....	7
A. Antibiotic combinations.....	7
B. Antibiotics combined with other drugs.....	9
C. Rationale for the development and use of fixed-combination antibiotics.....	11
D. Justification for fixed-dose combinations.....	12
E. The current status of fixed-dose combinations.....	14
III. Drug advertising and physician information about drugs.....	16
A. The influence of advertising on the use of fixed-dose combination antibiotics.....	16
B. The AMA's role in the advertising of fixed-dose combination antibiotics.....	19
C. Drug advertising and physician information.....	21
D. Improving physician information about drugs.....	22
IV. The Federal Government's actions.....	24
A. The drug efficacy study and drug efficacy study implementation (DESI).....	24
B. The FDA's response to the drug efficacy study.....	26
C. FDA's progress in withdrawing drugs from the market.....	28
D. Improving FDA's withdrawal procedure.....	29
V. The current status of fixed-dose combination antibiotic drugs.....	31
A. The status of antibiotic drugs found to be ineffective as a fixed combination.....	31
B. Fixed-dose combinations that are effective.....	31
C. Continuing questions.....	33

APPENDIXES

Appendix A—Witness List:	
Alphabetical list of witnesses who presented statements during the 1969 and 1972 hearings on fixed combination antibiotic drugs.....	35
Appendix B—FDA Announcements:	
FDA announcements of intention to revoke certificates of safety and effectiveness for certain combination drugs.....	36
Appendix C—FDA Brief, "Achrocidin Case":	
<i>American Cyanamid Company, Petitioner v. Elliot R. Richardson, Secretary of Health, Education, and Welfare, and Charles C. Edwards, Commissioner of Food and Drugs, Respondents</i> ; United States Court of Appeals for the First Circuit, No. 71-1388.....	45
Appendix D—Correspondence re FDA compliance with 1972 Court Order:	
1. Michael C. Harper, Esq., Center for Law and Social Policy, to Donald Kennedy, Commissioner of Food and Drugs, July 6, 1977.....	48
2. Draft of reply by Donald Kennedy to above letter, Aug. 17, 1977.....	50
3. Donald Kennedy to Michael C. Harper, Aug. 30, 1977.....	53

Appendix D—Continued	
4. J. Richard Crout, M.D., Director of Bureau of Drugs, to Michael C. Harper, Esq., Dec. 7, 1977-----	Page 58
Appendix E—Court Order: <i>APHA v. Veneman</i> , No. 1847-70 (D. DC., Oct. 10, 1972)-----	61
Appendix F—Physician Information: Physician information as provided in the 1978 Physicians' Desk Ref- erence (PDR) for certain still-marketed "ineffective" fixed combina- tion antibiotic drug products: Achrostatin V, Declostatin, Terrasta- tin, and Mysteclin-F, capsules and syrup-----	70
Appendix G—Physician Information: Physician information as provided in the 1978 PDR for four approved fixed-combination drug products: one synthetic antibacterial com- bination product, Bactrim; and three antibiotic combination prod- ucts, Rifamate, Rimactazid, and Polycillin-PRB-----	79
Appendix H—FDA Announcement: Drug implementation followup notice-----	92

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

FIXED-DOSE COMBINATION ANTIBIOTIC DRUGS

I. INTRODUCTION

A. PURPOSE

This report has a four-fold purpose: (1) To review the major issues raised during the subcommittee's 1969 and 1972 hearings on the advertising, marketing, and use of fixed combination drugs, with particular focus on fixed-dose combination antibiotic drug products;^{1 2} (2) to examine these and related issues in light of current knowledge about the physiologic actions and effects of fixed-dose combination antibiotic drugs in the human body; (3) to discuss Federal Government actions relating to the marketing of this class of drug products; and (4) to bring the status of fixed-dose combination antibiotic drug products up-to-date.

B. BACKGROUND

As part of its continuing series of hearings on competitive problems in the drug industry and on the advertising of proprietary medicines, this subcommittee heard testimony in 1969 and in 1972 from expert witnesses in the medical field. They discussed the status of knowledge about fixed combinations of antimicrobial agents and the potential health effects associated with their use.

In stating the purpose of these hearings, the Subcommittee Chairman, Senator Gaylord Nelson, pointed out that

The two official compendia, the U.S. Pharmacopeia and the National Formulary do not even list these (fixed combination) drugs because it is their judgment that there is no therapeutic basis for giving drugs in a fixed combination. The American Medical Association's Council on Drugs has for years opposed the use of combination drugs. This raises the question: On what basis does the Journal of the AMA or any other medical journal accept advertisements that promote bad medical practice?³

* * * * *

Could the reason be that advertising these drugs provides an important source of revenue? If so, is this a proper consideration for a professional medical society?

¹ U.S. Congress. Senate. Select Committee on Small Business. Subcommittee on Monopoly. Competitive Problems in the Drug Industry. Hearings, 91st Congress, 1st Session on the Present Status of Competition in the Pharmaceutical Industry; Drug Combinations-Antibiotics (Volume 12). Hearings held May 6, 7, 20, and 27, 1969. Washington, U.S. Govt. Print. Off., 1969; 1 volume (pp. 4999-5272). [Hereinafter referred to as The 1969 Drug Combinations-Antibiotics Hearings.]

² U.S. Congress. Senate. Select Committee on Small Business. Subcommittee on Monopoly. Advertising of Proprietary Medicines. Hearings, 92nd Congress, 2nd Session on the Effect of Promotion and Advertising of Over-The-Counter Drugs on Competition, Small Business, and the Health and Welfare of the Public; Misuse of Antibiotics (Volume 3). Hearings held December 5, 6, 7, 8, 13, and 14, 1972. Washington, U.S. Govt. Print. Off., 1973; 1 volume (pp. 939-1351). [Hereinafter referred to as The 1972 Misuse of Antibiotics Hearings.]

³ The 1969 Drug Combinations-Antibiotics Hearings, p. 4999.

These are some of the questions to be explored in depth during the subcommittee's hearings this month. The issues involved are of grave importance to the health and welfare of the American people. It is our hope that the study we are making will shed some light on these perplexing problems so that we may find the means for correcting them.⁴

Fixed combination antibiotic drugs refer to either mixtures of antibiotics or mixtures of an antibiotic with another pharmacologically active drug such as a steroid, a sulfonamide, an antifungal agent, an antihistamine, an analgesic, a decongestant, or a vasoconstrictor.⁵

Witnesses noted the "curious paradox" that despite condemnation by the leading authorities on infectious diseases, there has been continued "widespread usage" by the medical profession of fixed combination drugs.⁶

Twelve years before the 1969 subcommittee hearings, nine leading infectious disease authorities, one of whom, Dr. Harry F. Dowling, was chairman of the AMA Council on Drugs, signed an editorial in the April 1957 issue of the *Archives of Internal Medicine*, a publication of the American Medical Association, in which they concluded:

There are no data or experience which would justify the employment of any fixed combination of two antibiotics in a single ampule or a single tablet or capsule for systemic use. It is our firm conviction that the promotion and sale of such combinations should be discouraged until and unless adequate data from controlled clinical investigation justify this practice, and then only with respect to definite combinations for specific purposes.⁷

In the same year, one of the signers of the above editorial, Dr. Maxwell Finland, wrote this statement, which was cosigned by the "leading experts in antimicrobial therapy at that time."

Considerable caution is warranted in accepting the trend to fixed antibiotic combinations as inevitable or in lending support to a trend that may not be desirable. We would be remiss in our duties as physicians, teachers, and investigators were we to encourage, adopt, and recommend the use of new agents that we cannot consider to be as good as, or no better than, those previously shown to be good, even if they are legally certified. It is particularly incumbent on us to be very circumspect about the use of drugs of any sort in fixed combinations that do not offer the physician discretion as to the choice of components, or of the ratios in which they are used. The presence in any combination of a new or unproved components, or of a substance that may be inferior to others that might well be used instead, should make us even more cautious. They should be recommended and adopted, if at all, only after adequate, carefully controlled, and critically evaluated, study shows them definitely to be useful and superior.⁸

In response to Chairman Nelson's query about whether experts on the use of fixed combination antibiotics hadn't concluded "a good many years ago" that they "were not efficacious," Dr. Herbert L. Ley, Jr., then the Commissioner of Food and Drugs, testified that

There were many members of the scientific community who concluded and spoke very vigorously that fixed combination antibiotics were an illogical and irrational therapeutic tool as early as 1952. (Emphasis added.)⁹

It was also pointed out by Chairman Nelson that "the AMA Journal itself has editorialized very strongly against fixed combinations over a period of years."¹⁰

⁴ The 1969 Drug Combinations-Antibiotics Hearings, p. 5000.

⁵ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5002, 5013, 5020, and 5080.

⁶ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5008 and 5025.

⁷ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5251-2.

⁸ The 1969 Drug Combinations-Antibiotics Hearings, p. 5026.

⁹ The 1969 Drug Combinations-Antibiotics Hearings, p. 5147.

¹⁰ The 1969 Drug Combinations-Antibiotics Hearings, p. 5147.

Nevertheless, by 1966 when the National Academy of Sciences-National Research Council (NAS/NRC) under contract to the Food and Drug Administration undertook a study of the efficacy of drugs put on the market between 1938 and 1962 (as a result of the enactment of the Kefauver-Harris Amendments of 1962), it was estimated that combination drugs constituted 40 percent of the most frequently prescribed drugs. This was in spite of published cautionary statements questioning their safety and efficacy by respected medical experts for almost 15 years.

In the NAS/NRC Drug Efficacy Study, attention was focused on the efficacy of combination drugs. In its 1969 Final Report to the Commissioner of Food and Drugs, the NAS/NRC report stated:

It is a basic principle of medical practice that more than one drug should be administered for the treatment of a given condition only if the physician is persuaded that there is substantial reason to believe that each drug will make a positive contribution to the effect he seeks. Risks of adverse drug reactions (sic) should not be multiplied unless there be overriding benefit. Moreover, each drug should be given at the dose level that may be expected to make its optimal contribution to the total effect, taking into account the status of the individual patient and any synergistic or antagonistic effects that one drug may be known to have on the safety or efficacy of the other.

On these grounds, multiple therapy using fixed dose ratios determined by the manufacturer and not by the physician is, in general, poor practice.¹¹

At the time of the subcommittee's hearings there were a number of fixed combination antibiotic drugs on the market. The NAS/NRC reviewed more than 80 of them. All were judged to be ineffective.

On June 13, 1969, the FDA published a notice in the Federal Register announcing that as a result of its evaluation of the reports received from the NAS/NRC Drug Efficacy Study Group "the certificate of safety and effectiveness heretofore issued for the combination drugs [containing penicillin, tetracycline, or chlortetracycline] should be revoked on the basis of unwarranted hazards."¹²

To date, most of the combination drug products cited in the June 1969 Federal Register announcement as ineffective for their prescribed uses have been withdrawn from the market. One of these drug products still being marketed is Mysteclin-F, a combination of tetracycline and an antifungal antibiotic, amphotericin B.

During his testimony, Dr. Ley discussed this combination drug:

In 1960, tetracycline and amphotericin-B were combined and marketed under the trade name Mysteclin-F. This drug was represented to provide simultaneous antimicrobial therapy and antifungal prophylaxis.

And again, for general awareness, a fungus is an infectious disease organism somewhat like bread mold capable of causing infections in man, but a little different than the ordinary bacteria and the streptococcus or staphylococcus.

Senator NELSON. Is there anything to be gained from a therapeutic standpoint in administering these two drugs in fixed combinations in administrative dosages?

Dr. LEY. No, in my opinion there is not any justification for a fixed combination of these two products. There may be on occasion justification for separate administration of such drugs as amphotericin-B in the control and treatment of functional combinations of antibiotic therapy. But as a fixed combination, no.

The immediate commercial success of many of these antibiotic combinations was remarkable. Mysteclin-F and Panalba have been among the 200 most prescribed drugs since 1961.¹³

¹¹ FDA Drug Bulletin, The Drug Efficacy Study, Fixed Combination Prescription Drugs, Oral Hypoglycemic Agents, June 23, 1971.

¹² Drugs. Federal Register, v. 34, No. 113, Parts 141a, 146a, 141c, 146a: June 13, 1969: pp. 9333-38. [Hereinafter referred to as the Federal Register Statement, June 13, 1969. See also Appendix B.]

¹³ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5142-3.

In November 1969, another notice was published in the Federal Register announcing the intent to revoke the certification of a number of other combination drug products because the NAS-NRC study had found them to be ineffective for their prescribed uses. These were all combinations of some form of tetracycline, an antibiotic, with one or more of the sulfa drugs: sulfamethizine, sulfadiazine, sulfamerazine, or sulfamethizole, or with nystatin, which like amphotericin-B is an antifungal agent.¹⁴

In response to objections by the manufacturers of these drug products and a request to have additional time to submit data, the FDA Commissioner extended the effective date of the order to repeal the provisions for certification of these drug products until "March 23, 1970 unless stayed by the Commissioner."¹⁵

Although it has been 9 years since the original Federal Register announcements, the status of these presumably unsafe and ineffective combinations drug products has not been finally determined. They have, therefore, remained on the market. Their FDA-approved product labeling contains a statement enclosed in a box similar to that shown below for Mysteclin-F.

MYSTECLIN-F® CAPSULES

(Tetracycline-Amphotericin-B Capsules)

MYSTECLIN-F SYRUP

(Tetracycline-Amphotericin B Syrup)

Recently, a panel of the National Academy of Sciences—National Research Council has stated that in its informed judgment Mysteclin-F is ineffective as a fixed combination. Further, it stated, "The Panel is not aware of evidence of proved efficacy of this combination in the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished. It should be noted that the apparent reduction of organisms in the feces may be an artifact due to residual antibiotic activity and thus may not reflect the true state in the patient. It is preferable, in the Panel's opinion, to prescribe antifungal drugs when clinically indicated, rather than to use them indiscriminately as 'prophylaxis' against an uncommon clinical entity seen during therapy with tetracyclines and other antibiotics."¹⁶

The still-marketed ineffective fixed-combination antibiotic drug products are listed and described in Table 1-1. The final section of this report will discuss the current status of fixed-dose combination drugs: (1) The FDA's actions with respect to the antibiotic combination drug products considered ineffective for their prescribed uses that were not withdrawn; and (2) antibiotic drug combinations that have been approved since 1970 as effective for their specific purposes.

¹⁴ Drugs. Federal Register, v. 34, No. 218, Parts 141c, 146c, 148n; November 13, 1969: 18161. Hereinafter referred to as the Federal Register Statement, November 13, 1969. See also Appendix B.

¹⁵ Drugs. Federal Register, v. 34, No. 249, Parts 141c, 146c, 148n; December 31, 1969: 20427. Hereinafter referred to as the Federal Register Statement, December 31, 1969. See also Appendix B.

¹⁶ Physicians Desk Reference, 32nd edition. New Jersey, Medical Economics Company, 1978; 1603. See also Appendix F.

C. POLICY ISSUES

A key issue that emerged during the subcommittee's consideration of fixed-dose combination antibiotic drugs centered around the source of physician information about drug products. According to the testimony presented at the 1969 hearings, it comes, to a large extent, from the drug manufacturing companies via their advertising in medical journals.

As the history of the combination drug products shows, this is not a reliable source. One of the least effective but most heavily advertised of these drugs, Panalba, was, before its withdrawal, one of the 200 most frequently prescribed drugs in this country.¹⁷ In 1968, it generated \$16,860,000 in revenue.¹⁸ One of the witnesses observed that "the demand was created by misleading advertising and by the inability of many physicians to evaluate the claims made * * *" ¹⁹

Repeatedly, the theme of the relation of advertising to drug use was raised. The chairman noted that most medical journals depend on the drug companies for half their income and the nonsubscription medical press depends on them for their entire income. He questioned whether these publications showed much responsibility for the content of the advertising they accepted.²⁰

The patient who pays both in health and in dollars for the drugs prescribed has a right to expect that the doctors's choice of drugs is based on the most reliable information. Dr. Calvin M. Kunin, chairman of the department of medicine at the University of Virginia, suggested that clinical pharmacologists from medical centers or similarly trained persons could be used to keep physicians informed about the latest developments. He called it a "counterpropaganda operation." ²¹

Another possible issue concerns the adequacy of procedures followed by the FDA for revoking the certification of those drugs that are ineffective for their prescribed uses. The combination drug, Mysteclin-F, for example, is still on the market 9 years after the then Commissioner of Food and Drugs, Dr. Ley, testified at the 1969 hearings that "we have received and reviewed additional data and have concluded that substantial evidence still is lacking to support claims in the labeling." ²²

Patients have the right to feel assured that their physicians will prescribe only the safest and most effective drugs. This assurance has a two-fold dependence: (1) Only safe and effective drugs should be on the market; and (2) doctors must be correctly informed about them.

¹⁷ The 1969 Drug Combinations-Antibiotics Hearings, p. 5000.

¹⁸ The 1969 Drug Combinations-Antibiotics Hearings, p. 5057.

¹⁹ The 1969 Drug Combinations-Antibiotics Hearings, p. 5017.

²⁰ The 1969 Drug Combinations-Antibiotics Hearings, p. 5047.

²¹ The 1969 Drug Combinations-Antibiotics Hearings, p. 5046.

²² The 1969 Drug Combinations-Antibiotics Hearings, p. 5174.

TABLE 1-1.—CERTAIN FIXED COMBINATION ANTIBIOTIC DRUG PRODUCTS CONCLUDED TO BE "INEFFECTIVE AS A FIXED-COMBINATION" THAT ARE STILL ON THE MARKET

DESI No.: ¹ Trade name (dose form)	Ingredients	Manufacturer	Number of products	Comments to date (December 1978)
11409:				
Achrostatin V (capsule)-----	Tetracycline hydrochloride, nystatin.	Lederle-----	1	Not requesting a hearing but affected by another hearing request.
Achrostatin V (powder)-----	Tetracycline, nystatin-----	do-----	1	Do.
Comycin (capsule)-----	Tetracycline phosphate complex, nystatin.	Upjohn-----	2	Hearing request not resolved.
Declostatin (capsule)-----	Demeclocycline ² hydrochloride, nystatin.	Lederle-----	1	Not requesting a hearing but affected by another hearing request.
Declostatin (powder)-----	Demeclocycline, nystatin-----	do-----	1	Do.
Mysteclin V (capsule)-----	Tetracycline phosphate complex, nystatin.	Squibb-----	1	Do.
Terrastatin (capsule)-----	Oxytetracycline hydrochloride, nystatin.	Pfizer-----	1	Hearing request not resolved.
Terrastatin (powder)-----	Oxytetracycline, nystatin-----	do-----	1	Do.
Tetrastatin (capsule)-----	Tetracycline hydrochloride, glucosamine hydrochloride, nystatin.	Roerig-----	1	Do.
Tetrastatin (powder)-----	Tetracycline, glucosamine nystatin.	do-----	1	Do.
50213:				
Azotrex (capsule)-----	Tetracycline phosphate complex, sulfamethizole, phenazopyridine hydrochloride.	Bristol Labs-----	1	Not requesting a hearing but affected by another hearing request.
Azotrex (syrup)-----	Tetracycline, sulfamethizole.	do-----	1	Do.
Polycline with Triple Sulfa (suspension).	Tetracycline calcium, sulfamethazine, sulfadiazine, sulfamerazine.	do-----	1	Do.
Tetrex Triple Sulfa (syrup).	Tetracycline, sulfamethazine, sulfadiazine, sulfamerazine.	do-----	1	Do.
50230:				
Mysteclin F (capsule)-----	Tetracycline hydrochloride, amphotericin B.	Squibb-----	1	Hearing request not resolved.
Mysteclin F-125 (capsule)-----	do-----	do-----	1	Do.
Mysteclin F (drops)-----	Tetracycline, amphotericin B.	do-----	1	Do.
Mysteclin F (syrup)-----	do-----	do-----	1	Do.
50248: Aureomycin Triple Sulfa (tablets).	Chlortetracycline hydrochloride, sulfamethazine, sulfadiazine, sulfamerazine.	Lederle-----	1	Do.
Total-----			20	

¹ DESI—The acronym for "Drug Efficacy Study Implementation Project." DESI No.—An identifying number used to group 1 or more drug products usually by pharmacological activity.

² Also called demethylchlortetracycline.

Source: As compiled by the DESI project. Antibiotic products reviewed by DESI FDA printout, Sept. 1, 1978.

II. FIXED-DOSE COMBINATION DRUGS

A. ANTIBIOTIC COMBINATIONS

Fixed combinations of anti-infective drugs "refer to mixtures of antibiotics or of an antibiotic with another drug in the same package. They were first marketed during the period 1938-62 when the FDA was charged with passing upon the safety of drugs but not on their efficacy".²³

As stated in a standard reference work in pharmacology:

Combination therapy with antimicrobial agents began almost as soon as two such agents became available. Shortly after streptomycin was developed, it was mixed with penicillin and the combination recommended for clinical use, especially in situations in which the definitive etiology was not readily apparent. The advent of other antimicrobial agent, the appearance of increasing numbers of drug-resistant bacterial species, and the reports of enhanced antibacterial activity *in vitro* led to the development of a number of other combinations in which the ratios of the compounds were fixed on the basis of *in vitro* determinations. These are known as "fixed-dose" combinations.²⁴

According to a leading pharmacology review, there was an incentive to develop fixed combinations of two or more antibiotics because:

For 3 decades physicians have been so justifiably impressed with the efficacy and the relative harmlessness of the antimicrobial drugs that many were tempted to reason that, "If one drug is good, 2 should be better, and 3 should cure almost anybody of almost anything."²⁵

In his testimony, Dr. William L. Hewitt (Professor of Medicine, University of California School of Medicine, Los Angeles), presented the development of antibiotic combination drugs in historical perspective. First, he discussed the "logic of broad spectrum activity" that underlay the development of the first fixed-combination antibiotic drug product, penicillin with streptomycin, in the early 1950's.

Initial reports of its clinical use appeared to be favorable. However, subsequent carefully controlled studies coupled with increased insight into the importance and significance of infections of mixed bacterial flora and advances in chemotherapy that led to new antibiotic discoveries, raise doubts about the rationale for fixed-combinations of antibiotic drugs. These factors appeared to imply that narrow spectrum antibiotics may be more beneficial than a broad-spectrum combination of antibiotics.²⁶

The next part of Dr. Hewitt's statement placed the responsibility for departing from "sound principles of chemotherapy" (with regard to the antibiotic combinations) on Dr. Henry Welch, who was then the Director of the FDA's Division of Antibiotics.

The next portent of things to come and the initial departure from sound principles of chemotherapy appeared under the advocacy of Dr. Henry Welch, then Director of the Division of Antibiotics of the Food and Drug Administration.

²³ The 1969 Drug Combinations-Antibiotics Hearings, p. 5002.

²⁴ Goodman, Louis S. and Alfred Gilman. The Pharmacological Basis of Therapeutics; New York, Macmillan Publishing Company, 1975; 1095.

²⁵ Meyers, Frederick H., Ernest Jawetz, and Alan Goldfien, Review of Medical Pharmacology, Los Altos California, Lange Medical Publications, 1976; 583.

²⁶ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5054-78.

This was first documented in his opening remarks at the Fourth Symposium on Antibiotics and later published in *Antibiotics Annual*. By this time over 20 antibiotic agents had been described indicating this would be a fertile field for the discovery of agents beneficial in the treatment of disease. Already the ingenuity of the clinical investigators as well as the pharmaceutical industry was stimulated by speculation concerning the effect of various antibiotic combinations, particularly in connection with the agents in which they were individually involved. Dr. Welch specifically mentioned twelve combinations of antibiotics, a number of which fortunately have never found their way to the market place. No allusion was made to fixed combinations of antibiotics but these had already appeared and received the tacit approval of the Food and Drug Administration.

Mr. GORDON. Dr. Hewitt, is it true that Dr. Welch was the FDA official responsible for the approval of the marketing of these fixed combinations?

Dr. HEWITT. I think that at this time Dr. Welch's title was director of the division of antibiotics of the FDA. I don't think he was the administrator, but I think he was the one that was responsible for the approval of such—or at least let's say certifying—I would presume as to their safety.

Mr. GORDON. His activities had something to do with popularizing them too.

Dr. HEWITT. Oh, yes. His opening statements at this particular meeting were very dramatic ones. And it was immediately recognized by all the clinical investigators and medical people present at this meeting that this was a distinct policy which was now being promulgated. And at this time it was recognized by him, if not the majority of the people, that it was a very bad policy.

Senator NELSON. When was this?

Dr. HEWITT. The reference is given here 1956.²⁷

He then went on to point out that the purpose of fixed-combinations of antibiotics was seen by many of those physicians and clinical investigators most experienced in the field of infectious diseases to be essentially "a shotgun approach to the treatment of undiagnosed disease," although the concept has initially been presented as "a calculated rational method of attacking the problem of resistant organisms."²⁸

In this regard, Dr. Hewitt inserted in the record comments made by Dr. Harry F. Dowling (Department of Medicine, University of Illinois and past chairman of the AMA Council on Drugs), in which, by reasoning from a chemotherapeutic standpoint, Dr. Dowling points out the fallacy of using two antibiotics together. Essentially his argument was that if an organism is resistant to one of the antibiotics, that antibiotic will be ineffective; and if the organism is sensitive to both antibiotics then one only of them need be used.

Therefore, one takes the chance in every case that (the bacteria causing an infection) is resistant to a certain antibiotic when he uses it. If he tests against two antibiotics and finds that the organism is sensitive to both, then he can get just as good a result with one. Why use two? If he finds it is resistant to one and not to the other, then he is not going to get any effect by using the antibiotic to which it is resistant. Then we return to the fact that it may be sensitive to both. Is the patient any better off if we use two antibiotics? We may delay—and our work certainly does not show that we delay to any great extent—the appearance of resistant strains in these cases. Would the patient not be better off if we used good doses of one antibiotic and concentrated on that? If this fails, then we can use another antibiotic. We know exactly what we are doing. We know exactly where we are going and I doubt whether we do when we use more than one antibiotic.²⁹

Dr. Hewitt observed that the principles enunciated by Dr. Dowling were ignored by the pharmaceutical industry "because of the economic rewards of pharmaceutical gimmickery and the tremendous impact on promotional activities by the industry."³⁰

²⁷ The 1969 Drug Combinations-Antibiotic Hearings, p. 5055.

²⁸ The 1969 Drug Combinations-Antibiotics Hearings, p. 5055.

²⁹ The 1969 Drug Combinations-Antibiotics Hearings, p. 5056.

³⁰ The 1969 Drug Combinations-Antibiotics Hearings, p. 5056.

B. ANTIBIOTICS COMBINED WITH OTHER DRUGS

Similar reasoning also appears to have led to combining antibiotics with a diversity of other pharmacologically active drugs. Dr. Ley and Dr. Heinz F. Eichenwald (University of Texas Southwestern Medical School) both discussed these combinations in their testimony.

Dr. LEY. In 1952 penicillin was marketed in combination with APC and antihistamines. For those who have not had close contact with the medical profession, APC is aspirin, phenacetin and caffeine—a sort of glorified aspirin. This combination was recommended for the relief of symptoms and the prevention of complications of the common cold and other acute upper respiratory infections.

In 1955, tetracycline was combined with vitamins.

Senator NELSON. What was the rationale of that combination?

Dr. LEY. I have no information which would lead to any statement of rationale for this combination, Mr. Chairman.³¹

* * * * *

Dr. LEY. In 1956, tetracycline appeared in combination with APC and the antihistamine, chlorothen citrate. The original labeling for the product read:

* * * for the palliation and treatment of the common cold and for the relief of the symptoms such as headache, muscular aches and pains, prevention of secondary bacterial infections, and relief of mucus and nasal discharge accompanying such a cold.

Later that year, a competitor combined tetracycline with glucosamine, APC, and the antihistamine, buclizine hydrochloride.³²

* * * * *

Dr. EICHENWALD. I would not wish to end this statement without commenting on combinations which include an antimicrobial agent, as well as a variety of other drugs. One example of this type that might be cited is Tain, which consists of triacetyl-oleandomycin plus an aspirin-like compound, an oral nasal decongestant, and an antihistaminic drug. One might wonder why the manufacturer did not include vitamins, sex hormones, a contraceptive, and corticosteroids to cover all other eventualities.³³

* * * * *

I am citing Tain to bring to your attention the fact that antibiotics are not only combined with each other but also with other pharmacologically active ingredients. Occasionally, these situations are reduced to the point of utter absurdity when an antimicrobial agent, ineffective against the organisms producing the syndrome for which its use is recommended, is combined with a substance that is a placebo, devoid of any useful pharmacologic activity. An example of this situation is the combination of streptomycin with a kaolin-pectin material, resulting in a mixture recommended, and used, for the treatment of diarrhea. Streptomycin administered orally is not useful in the treatment of any bacterial diarrhea and the value of the kaolin-pectin material, while no doubt harmless, has, in my judgment, never been adequately established.³⁴

Dr. Hewitt, in presenting his history of the development of fixed-combination drugs, proposed an interesting explanation for the proliferation of "a variety of antibiotic and nonantibiotic substances" in combination with the broad spectrum antibiotic, tetracycline, (See testimony below.) He noted the curious fact that "chloramphenicol with a spectrum of activity quite similar to that of tetracycline was never considered to benefit by fixed combination with other antibiotics." He speculated that since chloramphenicol was manufactured by only one company, there was no need to develop additional products in order to ensure its market. Tetracycline, on the other hand, was manufactured by several companies in an essentially identical form. Consequently, there was an incentive for each of its manufac-

³¹ The 1969 Drug Combinations-Antibiotics Hearings, p. 5141.

³² The 1969 Drug Combinations-Antibiotics Hearings, p. 5142.

³³ The 1969 Drug Combinations-Antibiotics Hearings, p. 5019.

³⁴ The 1969 Drug Combinations-Antibiotics Hearings, p. 5020.

urers to capture a larger share of the potential market for tetracycline by developing novel forms of this drug product.

Dr. HEWITT. Chloramphenicol was discovered, patented, and marketed solely by Parke, Davis and Co. to whom these rights belonged. Tetracycline, on the other hand, was available and was marketed by at least four major ethical pharmaceutical houses. The urge for survival in such a climate would be sufficient to stimulate the utmost ingenuity among these competitors in the drug industry.

* * * * *

[Therefore,]

* * * tetracycline appeared in combination with a variety of antibiotic and non-antibiotic substances, depending upon the pharmaceutical company responsible for its marketing and design, to provide promotional material which would convince physicians to use one tetracycline rather than another.

You understand, of course, that all these tetracyclines are identical.³⁵

Three years later (1972) at subsequent antibiotics hearings held by the subcommittee, Dr. Henry Simmons, then the director of the FDA's Bureau of Drugs, discussed antibiotic combination drugs developed for colds and other respiratory ailments. He noted that in 1963 an FDA panel had concluded that antibiotics were ineffective against colds and the majority of viral infections. Nevertheless, it took 8 years, until December 1971, to finally remove from the market drug preparations in which antibiotics were combined with "antihistamines and/or analgesics and/or decongestants." Even the AMA protested the FDA's proposal to discontinue the certification of antibiotic-containing cold medications. Dr. Simmons noted:

However, antibiotic combination drugs for head colds and other respiratory ailments have been widely used for many years. In such drugs the antibiotic is combined with nonantibiotic cold remedies such as antihistamines and analgesics. FDA has removed a number of these fixed combinations from the market. The first such product appeared on the market in 1952, and was a mixture of penicillin G, aspirin, phenacetin, caffeine, and an antihistamine. The labeling said, among other things, "Bristapen treatment should be initiated at the appearance of the first symptoms of coryza * * *." A few years later, tetracycline was manufactured in combination with phenacetin, caffeine, salicylamide, and chlorothen citrate. The original labeling for this drug (Achrocidin) read "for the palliation and treatment of the common cold and for the relief of the symptoms such as headache, muscular aches and pains, prevention of secondary bacterial infections, and relief of mucous and nasal discharge accompanying such a cold."

In 1963, an FDA panel was convened to consider the prophylactic use of antimicrobial agents in combination with analgesics, antihistamines, and other drugs. This panel concluded that there is no acceptable evidence that any antimicrobial agent is of value in the treatment of the common cold or of any viral infection; infections due to certain large viruses were excepted. They also concluded that antimicrobial agents are of no value in preventing bacterial complications in patients with common colds who are otherwise healthy. The panel further determined that when prophylactic therapy of respiratory infection is justified, the antimicrobial agent that may be used must be one that is relatively free of inherent toxicity. This would preclude the use of chloramphenicol, triacetyloleandomycin, and/or sulfonamide products.

However, the efforts of the FDA, in 1963, to discontinue certification of antibiotics in combination with cold medications were misunderstood and strongly opposed by a number of associations, manufacturers, and physicians.

Mr. GORDON. Would you please expand on this point: the FDA plans to remove the antibiotic-containing cold medications from the market. Then what happened? Was the opposition organized? What did organized medicine do about it?

Dr. SIMMONS. Well, there were comments sent to the agency by many physicians, several hundred, I believe, and I believe the American Medical Association also opposed such a move. I wasn't here at the time and I am not completely familiar with the nature of their objections, but they did come.

³⁵ The 1969 Drug Combinations-Antibiotics Hearings, p. 5056.

Mr. GORDON. The AMA opposed the move by the Food and Drug Administration; is that correct?

Dr. SIMMONS. That is correct.

Mr. GORDON. And were these letters from doctors organized or just spontaneous?

Dr. SIMMONS. We think there is some evidence they were organized at least to some extent.

Mr. GORDON. Thank you.

Dr. SIMMONS. Subsequently, in September 1970, the FDA did initiate action to discontinue certification of the combinations based on an evaluation by the National Academy of Sciences-National Research Council panel as "Ineffective as a Fixed Combination." Nonetheless, it was not until December 1971, after a series of legal proceedings culminating in two Supreme Court Justices independently denying a stay of our withdrawal order, that antibiotics in combination with antihistamines and/or analgesics and/or decongestants were finally removed from the market.³⁶

An excerpt from the statement submitted to the subcommittee by Dr. Charles C. Edwards, then the Commissioner of Food and Drugs, highlights the enormous commercial value of these medications which were judged to be ineffective and perhaps even unsafe.

The most widely prescribed of these combinations removed from the market was Achrocidin, a product containing tetracycline. In support of this product, the manufacturer had submitted a "survey" of 274 physicians, qualified as specialists, most of whom considered this product to be safe and effective. Of those surveyed, 6.9 percent were pediatricians; none of their comments mentioned the inappropriateness of using tetracycline in children with developing teeth. Also, 11.6 percent of those surveyed were obstetricians, none of whom mentioned the hazard to the fetus of using tetracycline in the latter part of pregnancy. Some of the comments of the specialists referred to the effectiveness of the particular product for influenza and colds, despite the fact that both are caused by viruses for which tetracycline is ineffective. Several of the physicians commented that the availability of the product avoided the need for having to write more than one prescription.

In the last six months in which this product was marketed, June-December 1971, 41,208,800 tablets were certified in this country. This is more than enough for a complete course of treatment for 1.3 million patients.

This product represented a class of drugs about which the AMA Drug Evaluations said:

These remedies are irrational mixtures, the value of which has not been established since the usefulness of anti-infectives to treat the common cold has been proved to be fallacious. Accordingly, their use is not recommended. Yet an estimated 1.3 million Americans were treated with these drugs in the six months before they were removed from the market.³⁷

C. RATIONALE FOR THE DEVELOPMENT AND USE OF FIXED-COMBINATION ANTIBIOTICS

As was noted above, "*in vitro* (test-tube) determinations," which appeared to show "enhanced antibacterial activity", led to the development of a number of fixed-combination antibiotics. Apparently, however, "the results of *in vitro* tests have correlated very poorly with the clinical results and mixtures of antimicrobial agents have been demonstrated to be superior to a single agent only in a few instances."³⁸

According to Dr. William M. Kirby (University of Washington School of Medicine):

In theory, fixed combinations of antimicrobial agents would appear to offer some therapeutic advantages, but in actual practice these are difficult to demonstrate. Test tube experiments about 15 years ago showed that two antibiotics sometimes acted synergistically against various bacteria, and this observation led to the marketing of a number of fixed combinations. More extensive studies sub-

³⁶ The 1972 Misuse of Antibiotics Hearings, pp. 1044-5.

³⁷ The 1972 Misuse of Antibiotics Hearings, pp. 1094, 1095.

³⁸ Goodman and Gilman, op. cit., p. 1095.

sequently showed that with most combinations the action was only occasionally synergistic, more often it was indifferent, and in some instances it was antagonistic. Tests to demonstrate these effects are available in only a few laboratories, so that the physician who gives a patient a fixed combination cannot be certain whether the action is likely to be synergistic, indifferent, or antagonistic. Furthermore, clinical studies purporting to confirm laboratory synergism were poorly conducted and controlled, and provided no real evidence that fixed combinations were more effective than when either of the antimicrobial agents was used alone.

Another reason advanced for the use of fixed combinations is that they are likely to be effective in infections caused by a mixture of bacteria, some of which are susceptible to one of the antibiotics and the rest to the other. In actual practice, however, one organism is usually chiefly responsible, for clinical infections and the best results are obtained by concentrating on this major pathogen. In the instances where a second antibiotic is likely to be helpful, it is best to obtain cultures and to determine the susceptibility of the micro-organisms to a number of antibiotics. Clinical studies demonstrating the superiority of fixed combinations in infections involving mixtures of bacteria are not available.

Delaying the emergence of antibiotic-resistant bacteria is still another reason given for prescribing antibiotic combinations, but there is no substantial evidence that this objective has been accomplished by the fixed combinations now on the market. Rather, the evidence indicates that bacteria are likely to become resistant to both of the antibacterial agents present in the combination. Finally, by broadening the spectrum of bacteria affected, fixed combinations are frequently administered to increase the likelihood of providing effective therapy. However, in the infections where fixed combinations are commonly used it has not been proven by clinical comparisons that the results are better than when one of the antibiotics is given alone. In seriously ill patients where the infecting organism has not yet been determined, it is indeed proper to administer more than one antibiotic. When this is done, each antibiotic should be selected carefully on the basis of the most likely diagnosis, and they should be administered separately, with dosages being adjusted according to the patient's needs. This involves assessing many factors, including the function of vital organs such as the liver and kidneys.³⁹

D. JUSTIFICATION FOR FIXED-DOSE COMBINATIONS

In his testimony, Dr. Eichenwald gave the justifications used by the pharmaceutical manufacturers as a basis for their production of these mixtures.

The pharmaceutical houses have provided several justifications which, to them provide a basis for the commercial preparation of these mixtures:

- (1) They are useful in the treatment of mixed bacterial infections.
- (2) There is enhancement of antibacterial activity from the use of combinations.
- (3) Because combinations "widen the spectrum of activity," they provide for satisfactory treatment of infections before etiology is known or in cases when it is impossible to determine the etiology.
- (4) Antibiotic combinations were used extemporaneously by physicians prior to the introduction of the fixed dosage commercially available drugs.
- (5) Combinations are cheaper than the sum of the price of the individual ingredients.
- (6) Combinations are easier to administer and thus more convenient.
- (7) Physicians demanded combinations and the pharmaceutical houses simply followed the demand.
- (8) Following their introduction, combinations were used widely, some of them in fact becoming "best sellers." Thus, the acceptance by physicians indicates that these preparations must be useful and have filled a so-called therapeutic gap.

He then commented, in detail, on each one. (See also Table 2-1.)

First, the problem of mixed bacterial infections. The sort of situation, where several microbial organism work together to cause disease is relatively uncommon but may occur in such illnesses as bronchiectasis, peritonitis, urinary tract infections, chronic otitis media, and occasionally in burns. Many different species of bacteria are associated with these conditions and patterns of antimicrobial sensitivity are very variable. Thus, it is unlikely that any given fixed combination would contain either the proper drugs or the proper amounts of each drug to be effective

³⁹ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5003-4.

in even a relatively modest proportion of cases. Additionally, it has been demonstrated that while under some rather prescribed circumstances a "broad spectrum" effect may be produced by the combination of two antimicrobial agents, the degree of antibacterial activity is generally quite unpredictable and under other circumstances antimicrobial effectiveness may be decreased by combination therapy.

Furthermore, in the case of several of the available combinations (such as Panalba, Albamycin T, Signemycin, erythromycin-sulfa, et cetera), the dosage formulation is such that in some instances, if the manufacturer's recommendations are followed, the patient would receive too little of both drugs for maximal effectiveness, in other instances, too little of one of the two drugs in the combination, and in the case of some erythromycin-sulfa combinations, if the physician wishes to administer even moderately large doses of erythromycin the patient will receive an excessive and potentially dangerous amount of sulfonamides.

Let me comment next on possible enhancement of antibacterial activity by two drugs. It is true that in three unusual circumstances combinations of drugs are more effective than single drugs alone. The best example is perhaps tuberculosis; bacterial and endocarditis due to group D streptococci and occasional endocarditis due to streptococcus viridans are treated more effectively by a combination than by single drugs. However, it must be emphasized that these are rare and very serious infections where dosage of each drug is usually individually adjusted on the basis of many considerations.

* * * * *

The third theoretical argument for combinations is that they permit more ready treatment of infections before etiology is known and are useful in instances where it is impossible to determine etiology.

It is true that at times it is necessary to treat patients with severe infections before the etiology has been determined. There are indeed valid indications for the use of drug combinations in such instances. However, in all cases the drugs used should be given at least initially by the parenteral route. With one exception, penicillin-streptomycin, all fixed combinations on the market can only be given orally. Furthermore, the combinations that are useful in these limited circumstances, at least in my field of medicine, are not the drugs available in combinations. The limitation imposed upon the physician by a combination consisting of fixed amounts of drugs are again obvious, particularly in pediatrics where careful dosage control is essential. Furthermore, at the present moment there are single drug entities available which are highly effective and reasonably free of toxicity so that the so-called "broad spectrum" argument for combinations has become progressively less valid.

The fourth argument is that physicians used combinations before the pharmaceutical houses introduced them. Again, this is true but only for a very limited series of conditions. In most cases, the physicians tailored the use of two drugs to the patient's specific condition, something not possible with fixed combinations.

* * * * *

Furthermore, some of the more popularly used oral combinations such as penicillin and sulfa and erythromycin and sulfa, which have been employed in the past in the treatment of middle ear infections in children have subsequently been shown to be more effective than either penicillin or erythromycin alone. However, the important point is that a physician, in those limited instances when he did use combinations in the past, adjusted the dosages of the different components to the specific needs of the patient.

The claims of greater convenience and lower expense should be considered. Since combinations are clinically only very rarely indicated and then only in adjustable dosage, this argument for the existence of combinations is silly. This whole business involves a type of circular reasoning which totally avoids the issue of effectiveness and safety.

* * * * *

The last two reasons given by the pharmaceutical industry for the existence of drug combinations can be considered together. It is claimed that the physicians demanded them and their usefulness is shown by the fact that they are widely used. This, again, involves some circuitous reasoning because the pharmaceutical houses point to the admittedly widespread use of combinations to state that physicians must, therefore, demand them. In fact, the opposite is true, the demand was

created by misleading advertising and by the inability of many physicians to evaluate the claims made for these agents.⁴⁰

TABLE 2-1.—*Summary of arguments against the use of fixed-dose combination antibiotic drugs*¹

1. There is lack of indications for prefixed combinations of anti-infective agents.
2. There is lack of controlled clinical studies to prove indications for prefixed combinations of anti-infective agents.
3. When a prefixed combination of anti-infective agents is used, there is a limitation of dose of one ingredient because of the toxic concentrations of the other.
4. In most infections there is a lack of therapeutic advantage of prefixed combinations over one specific antibiotic.
5. If one ingredient is unnecessary, there is hazard of increased unnecessary adverse drug reactions including the development of resistant strains of micro-organisms.
6. When a prefixed combination of antibiotics is chosen empirically, there may be interference with further diagnostic techniques.
7. Specific narrow spectrum antibiotics may be more advantageous than a "wide spectrum" combination of antibiotics.
8. None of the combinations has any effect against viruses, which cause most of the infections in the United States.

E. THE CURRENT STATUS OF FIXED-DOSE COMBINATIONS

At this writing, the approval of almost all fixed-dose combinations on the market at the time of the 1969 Hearings, has been withdrawn by the FDA for several reasons.

These antibiotic combinations encourage inadequate treatment because there is an inevitable tendency to employ the same total dose of the mixture as of a single agent. Such a dose does not necessarily provide an effective amount of any single agent in the combination, particularly of the superior drug. Mixtures provide a false sense of security with regard to a wider coverage or "broad spectrum" of activity. In fact they supply a narrower effective coverage by substituting less effective agents and smaller amounts of individual drugs than if the antimicrobial agents were selected individually, each for its own value, and administered in the proper dose for the purpose intended. They reduce the therapeutic effectiveness that would be anticipated from proper doses of individual drugs or from proper choice of extemporaneous concurrent therapy according to specific requirements, especially when care is taken to choose only agents that may be expected to be most effective against the causative micro-organism.⁴¹

Even though when first developed, fixed-combination drugs were produced and marketed indiscriminately and the majority of the original preparations are no longer on the market, the concept itself still may have validity as pointed out by Dr. Kunin.

I would like to mention to you that there are some examples of combinations which might be rationale. The reason I say this is that I had the opportunity to be in Uganda for the past month, and observed two combinations that might be of value.^{41a}

The point I am trying to get across is that one doesn't necessarily have to make a blanket statement that all fixed combinations are bad. It just so happens that many are. But on occasion one can find a combination that might be valuable. I think we ought to have an open mind and judge each on its merits.

* * * * *

⁴⁰ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5014-17.

¹ Source: Testimony of Dr. Robert I. Wise, Chairman, Department of Medicine, Jefferson Medical College Philadelphia, Pa., The 1969 Drug Combinations-Antibiotics Hearings, pp. 5077-8.

⁴¹ Goodman and Gilman, op.cit., pp. 1104-5.

^{41a} See chapter V-B for a further discussion of the current status of these drugs.

All I am trying to say is that, as we review all of the combinations of antimicrobial agents used in the United States today, one cannot make a good case for their continued use. However, one should keep an open mind and say, if one can demonstrate the efficacy of a combination which is greater than any one of the ingredients, and which has some economic or sociological advantage, we should be prepared to accept that combination provided that the evidence for efficacy is presented. Our charge is efficacy. Here we find all of these compounds not be effective as fixed combinations. But there may be some exceptions.

I want to keep the door open just a little bit.

Senator NELSON. If I understand what you are saying thus far, the panel has not reviewed any fixed combination that they felt met the statutory standard of efficacy.

Dr. KUNIN. That is right. We want to be prepared, however, for any new evidence that the companies may have, any new development that may occur, so that we don't become so fixed and inflexible that we cannot be prepared to accept new advances that might be of advantage.⁴²

⁴² The 1969 Drug Combinations-Antibiotics Hearings, pp. 5024-5.

III. DRUG ADVERTISING AND PHYSICIAN INFORMATION ABOUT DRUGS

A. THE INFLUENCE OF ADVERTISING ON THE USE OF FIXED-DOSE COMBINATION ANTIBIOTICS

A recurrent theme in the hearings was the influence of the advertising and promotion of fixed-dose combination antibiotics on their use by practicing physicians.

As stated by Dr. Eichenwald:

I cannot overemphasize the fact that the demand for these agents was created by advertising which made claims which are still, a decade or so later, unsubstantiated on the basis of controlled observations. Thus, the guillible physician was lulled into a sense of security which substituted a "miracle combination" for his own diagnostic judgment or laboratory work. The pressures went something like this:

You can treat nearly everything you encounter with one of these combinations, then why bother to make exact diagnoses or perform laboratory work required for the identification of a specific bacterial agent causing the disease in question.⁴³

Dr. Kirby specifically commented about the extensive advertising of the drug Panalba (tetracycline phosphate complex with novobiocin) in the Journal of the American Medical Association (JAMA), even though this drug as well as other fixed-dose combination antibiotics had been cited as ineffective by experts on antibiotic drugs. He noted:

Why, it may be asked, if fixed combinations have these deficiencies and are opposed by the experts, have they been so widely used in the treatment of patients? The chief motive of the individual physician is to do his best for the patient, and I am not accusing him of negligence or incompetence. The answer lies, I think, in the education provided by the drug companies, otherwise known as advertising, including elaborate displays in medical journals and at medical meetings, visits by detail men, et cetera. I would like to show an example. I have with me here a recent issue of the Journal of the American Medical Association, the entire back cover of which is an advertisement for Panalba.⁴⁴

* * * * *

It is well known that the American Medical Association has an advertising department, presumably with high standards, and it can reasonably be assumed that a display of the name Panalba in such a prominent fashion is not only a reminder but is in a sense an endorsement of the product. In comparison with the occasional negative statements made by antibiotic experts, the positive message of this advertisement is brought repeatedly to the attention of the practicing physician, and with the additional incentive of an implied endorsement it is not surprising that the product is widely used. Doctors do not like to admit that they are influenced by advertising but it seems to me that the facts speak for themselves. Whenever doctors tell me that they depend on the experts, I remind them of the fixed combinations such as Panalba. Here is a product that is opposed by all the experts in the field, but it still is used widely in clinical therapy. This message is apparently very clear to the pharmaceutical houses, who spend several hundred million dollars a year in advertising their products to the medical profession. These expenditures would not be likely to continue if they did not bear results.⁴⁵

The minority counsel, James P. Duffy, pursued the question of advertising further by asking Dr. Kunin if he thought drug advertising was responsible for the fact that the medical profession had

⁴³ The 1969 Drug Combinations-Antibiotics Hearings, p. 5017.

⁴⁴ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5009-5010.

⁴⁵ The 1969 Drug Combinations-Antibiotics Hearings, p. 5011.

largely ignored the warnings in the literature, over a 15-year period, that certain fixed-combination antibiotics might be more harmful than beneficial.

Dr. KUNIN. There is no question that physicians are swayed intensively by advertising, and that they are intensively swayed by the very effective representatives of the pharmaceutical industry that call upon them. The problem here is to discern the wheat from the chaff.

Very often an advertisement does have some value, it does inform physicians of the development, and so does the representative. Unfortunately it is extremely difficult to dissect out what part of the advertisement and what part of the material that is presented by the representative is valid. In many ways the material is colored.

Most of the postgraduate education today is done by the pharmaceutical industry. I believe personally that the medical schools and medical institutions should have a greater opportunity to indulge in postgraduate medical education.⁴⁶

Chairman Nelson continued the discussion by raising the question of the chief source used by doctors for their information about combination drugs. He expressed misgivings about the responsibility shown by medical journals when they print ads that would be unacceptable in the text.

Senator NELSON. The minority counsel raises a question that we have been examining, and on which we have comments and testimony from a variety of distinguished medical witnesses. It is this:

If you went to a doctor, or to a medical student, and said, "Now here is the infecting agent, go ahead and do the research and come back and report what drug, if any, you would use." If he looked in the U.S. Pharmacopeia or the National Formulary, he would not find any fixed combination listed because they don't list them, for the very reason that your panel rejects them. If they looked in the literature that distinguished people have written he would find a negative response to fixed combinations. He would come back with that answer.

Dr. KUNIN. That is right.

Senator NELSON. So, therefore, the interesting question is, Why is it that the fixed combination is so widely used? Or, for example, why has it been that, contrary to all the experts who have written on the matter, chloramphenicol is still widely prescribed for nonindicated cases? We have raised the questions—from what source do doctors get their information on combination drugs? It has to come from some place. In other words, the doctor didn't look in USP because he couldn't find the fixed combination there, he didn't look to the experts who authored the best papers written and the best articles, but he got the information some place. I think it is quite obvious that he began to use it and does use it based upon advertising and promotion.

This brings us to the question which we have raised here, that most of the journals rely for 50 percent of their income upon drug company advertising, and the medical press 100 percent, those that don't have subscriptions, just 100 percent. And then they carry in their own journals ads that are very cleverly done that promote the use of the drug which the magazine—the journals in their text, will say is not a proper use. And this is one aspect of the hearings that we are pursuing and will continue to pursue, because it seems to me that the journals ought to be responsible in respect to what they are willing to accept. My own conclusion is, from what I have seen, that they aren't very responsible in that particular respect. However, they are very responsible, the journals, in terms of what they will accept as a scientific paper in the text of the very journal in which they accept an ad that they would reject in the text.⁴⁷

Chairman Nelson pursued the question of the advertising of fixed combinations in the AMA Journal with another witness, Dr. John Adriani (Charity Hospital, New Orleans, La.), by asking whether the AMA could justify running ads for these drugs when it had been recommended that they be withdrawn from the market as inefficacious and unsafe.

⁴⁶ The 1969 Drug Combinations-Antibiotics Hearings, p. 5045.

⁴⁷ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5046, 5047.

In view of the position of the drug council and the editorial in the AMA Journal for 1957, and then in view of the appearance before the Kefauver committee in which the council again criticized the use of fixed combinations, and the fact that the AMA witness testified that the AMA Journal expected to phase out any advertising of fixed combinations in some relatively brief period of time, and in view of the position of the National Research Council recommending that all fixed combinations be taken off the market on the grounds of either inefficacy or a health hazard, how can the AMA justify running ads that promote fixed combinations in the journal at the same time its physicians, all the scientific community in this country as well as the council agree that these drugs are inefficacious and in many respects expose the patient to a health hazard since simultaneously he is being exposed to a drug that he doesn't need.

Dr. ADRIANI. I do not think the AMA can justify it. The procedure for preparing the journal is for certain people to take care of certain aspects. The advertising is handled by a different department. None of the advertising is in any way supervised by the Council on Drugs. I do not want to go into details because I do not want to speak for the council on that point. But there are various persons in medical circles and on the council who are unhappy about the advertising.

Now, the American Medical Association derives a good part of its income from advertising.⁴⁸

After pointing out that advertising provides a large part of the AMA's income, Dr. Adriani noted "that the AMA needs every dollar it can get to remain in the black."⁴⁹

Chairman Nelson then remarked on the paradox of advertising and promotion's greater success in "persuading doctors to use" antibiotic combination drugs than "text material in the JAMA or other journals" has in "dissuading them."

Senator NELSON. I raised this question before with the editor of the New England Journal of Medicine, Dr. Ingelfinger, and Dr. Annis, and others. It still seems to me to raise a puzzling credibility issue when one of the most distinguished medical associations in the country, maybe in the world, maintains that not only are the antibiotic combinations inefficacious but that there is also a health hazard in prescribing them. Yet, they are, at the same time, willing to accept ads that promote them. As a matter of fact the advertising and promotion is more successful in persuading doctors to use them than the text material in the JAMA or the other journals in dissuading them. Doesn't that seem to you to raise a kind of a credibility question? Isn't there a great distinction given to an ad advertised in the journal? Isn't that a kind of an imprimatur of the approval in effect to the physician who sees the ad?

Dr. ADRIANI. Well, the only answer that one could give to a question like that is that the position taken in doing this is indefensible. One cannot defend it. All I can say is that if you have the scientific members of your association writing and saying that fixed combinations of drugs are bad, and you have the management particularly the lay people accepting advertising, and there is no consultation between the scientific groups in the association and those who pass on advertising and what they are publishing scientifically for their physicians is in conflict with what is in the advertising—this is indefensible.

I could not defend this for the American Medical Association. I am however not speaking for them. But you are perfectly right. This is ironical.⁵⁰

Chairman Nelson went on to raise the question about the close relationship existing between the drug industry and medical societies. In this regard he pointed out "that the AMA is an associate member of the Pharmaceutical Manufacturers Association," which came as a surprise to the witness, Dr. Adriani.⁵¹

Senator NELSON. I have raised this question before. But it seems to me the acceptance of an ad which is contrary to the scientific evidence and known position of the Drug Council compromises them in a way that they really ought not to be. And I raise the question about this close relationship between the manufacturers of drugs and the medical societies through the advertising they take. It seems to

⁴⁸ The 1969 Drug Combinations-Antibiotics Hearings, p. 5110.

⁴⁹ The 1969 Drug Combinations-Antibiotics Hearings, p. 5111.

⁵⁰ The 1969 Drug Combinations-Antibiotics Hearings, p. 5111.

⁵¹ The 1969 Drug Combinations-Antibiotics Hearings, p. 5113.

me that in subtle ways it takes away from medical societies the responsibility they have for being tough critics of bad medical practice when they are in effect endorsing in a magazine the drugs that they know shouldn't be used. I don't know whether you want to comment on that or not.

Dr. ADRIANI. I was on the editorial board of our specialty journal, *Anesthesiology*, for 9 years. The advertising was policed by one of the members of the editorial committee. There was a period when something happened. I think right after the Kefauver-Harris amendments went into effect, when the advertising fell off substantially in all journals, including ours. We as editors did not care. But our board of directors did. They were concerned that the income was falling off. And I said, "well, you will have to get it from some other source." And that was the attitude I took about that journal.

There is no question about the fact that an advertiser can cancel out an ad. If they are the ones that are providing your income—if I am paying you a salary, I have control over you. I hold the aces and you hold the deuces. In this particular case if a pharmaceutical firm does not like what someone does, and they have an ad, they can say, we will cancel the ad. And this means a loss of income. I feel personally that this is a bad position to be in. I would get out of such a position in some way.⁵²

Dr. Dowling summarized the problem doctors face in becoming correctly informed about drugs, in the written statement of his "views on the uses of fixed combinations of antibiotics," submitted in response to Senator Nelson's request.

The provisions of the Drug Amendments Act of 1962 make it possible for the Food and Drug Administration to disallow claims for efficacy of most fixed combinations of antibiotics on the basis that the effectiveness of each ingredient has not been proved and because the adverse effects of the combination outweigh any possible benefits.

The same Act also allows the FDA to insist upon truth in the advertising of drugs to physicians. But the FDA cannot do the job alone. I believe that medical societies and editors of journals should: (1) Aid the FDA in devising regulations regarding advertising; (2) become familiar with the regulations as they are made; (3) interpret the regulations; (4) set their own standards even higher, and (5) screen advertisements in the journals they control. Just as important is the job of interpreting to the practicing physician what he should look for and what he can expect to derive from advertisements. Also we must find out how the doctor is using these advertisements and what information he is getting from them under the new system of regulation. The drug companies will study the ability of these advertisements to sell drugs, we may be sure. Who will study how they improve (or worsen) the practice of medicine? Here is a clear challenge to the medical profession.

* * * * *

* * * it is necessary for the organized medical profession to help the Food and Drug Administration implement the law requiring proper advertising of drugs to physicians and to go even further than the FDA can, in improving the quality of these advertisements.⁵³

In effect, Dr. Dowling called on the AMA to act more responsibly both with respect to the quality of the advertising it publishes and with respect to its role in helping physicians improve the way they practice medicine.

B. THE AMA'S ROLE IN THE ADVERTISING OF FIXED-DOSE COMBINATION ANTIBIOTICS

The drug advertising that reaches most doctors and has the greatest influence on them is carried by *JAMA*, a weekly journal, which "is sent to almost all practicing physicians in the United States."⁵⁴

⁵² The 1969 Drug Combinations-Antibiotics Hearings, p. 5112.

⁵³ The 1969 Drug Combinations-Antibiotics Hearings, p. 5271.

⁵⁴ The 1969 Drug Combinations-Antibiotics Hearings, p. 5011.

As Dr. Kirby pointed out to the subcommittee, JAMA continued to run large, prominently-displayed ads for fixed-dose combination drugs even after an editorial opposing their use, signed by 9 leading authorities on infectious diseases, was published in another AMA journal, *The Archives of Internal Medicine*.⁵⁵

Chairman Nelson then called attention to the AMA's own stated principles of advertising on the title page of JAMA.

Advertising principles. Advertisements in this issue have been reviewed to comply with the principles governing advertising in AMA scientific publications. A copy of these principles is available upon request from the Office of Advertising Evaluation.

Then, we have here the principles that they say guide the Journal in the acceptance of ads, the full statement of principles. I would simply like to point out for the hearing record, because as I say, we have raised this issue with representatives of each of the medical journals that has appeared before the committee, that the AMA principles describe the type of data needed to support an ad.

Data should include pertinent reports published and unpublished, favorable and unfavorable, of clinical and laboratory investigations covering the efficacy and relative safety of the product under consideration—They include the word efficacy themselves.

These data should be based upon sound studies and should be sufficiently comprehensive to permit a critical evaluation of the subject matter. While the quantity of the scientific data required will depend upon the type of product, the nature of the medical problem involved, and the claims made in the advertising copy, the quality of the evidence is regarded as highly important; in this respect the importance of suitable controls is emphasized. Compilations of subjective individual case reports and testimonials are not considered acceptable evidence.

Then in another part of the AMA principles it is stated:

Mixtures of drugs. Clinical and laboratory data should be submitted for review by the Office of Advertising Evaluation. Clearance depends primarily on showing justifications for the rationality of the combination.⁵⁶

He continued by noting that the AMA was, in fact, violating its own principles by running ads for drugs of questionable efficacy.

I simply point out for the record that here is the most distinguished, largest professional medical organization in the country, that is consistently violating the standards it has established for itself and is contrary to the editorial that they ran in their own publication in 1957 and contrary to the position of the Drug Council of the AMA. I raise this not for any comments by you, Doctor, but because I have raised the issue of the propriety of professional journals permitting the advertising and promotion of drugs that promote bad medical practice, and here is a case where the AMA is clearly violating its own standards as well as running contrary to the judgment of—in running the ad, to the judgment of all the scientific expertise in this country on fixed combinations.⁵⁷

During the course of Dr. Kunin's testimony, as well as in his written statement, he mentioned that a white paper had been prepared jointly by the NAS/NRC panel he had chaired and the one chaired by Dr. Hewitt. The purpose of this paper was to explain to practicing physicians why the panels had judged fixed combinations of penicillin with streptomycin and penicillin with sulfonamides to be ineffective. In Dr. Kunin's words:

We felt that the issues involved were so important that white papers were prepared to present our thoughts in some detail. We also felt that it would be most important for practicing physicians to be aware of our arguments, since the judgment recently taken by the FDA to remove them from the market would

⁵⁵ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5251, 5252.

⁵⁶ The 1969 Drug Combinations-Antibiotics Hearings, p. 5010.

⁵⁷ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5010, 5011.

affect their practice. To this end the paper was prepared for publication in the New England Journal of Medicine which will appear in the May 22, 1969, issue.⁵⁸

Chairman Nelson inquired why such an important advisory to the medical community was not being published by the American Medical Association. Dr. Kunin's reply was that it had been rejected without reason by JAMA.

Dr. KUNIN. It was submitted by the National Academy of Science, not by myself personally, but by the executive officer of the National Academy of Science to the Journal of the American Medical Association. It was not accepted that journal. I informed Dr. Inglefinger, the editor of the New England Journal of Medicine, of this rejection, and he accepted it for publication. In his letter he said:

As much as I regret taking a paper that has been rejected by the JAMA, I am delighted to take this one for the New England Journal.⁵⁹

Chairman Nelson then observed that rejecting a paper "submitted by a distinguished scientific panel" in which a drug, Panalba, that was being heavily advertised in JAMA, was condemned as not meeting "the statutory requirement of efficacy," * * *.

"throws some kind of cloud over the question of the objectivity of JAMA itself."⁶⁰

Senator NELSON. I noticed that as far back as 1961 before the Kefauver committee in the hearings on S. 1552, part one, on page 69, that Dr. Hussey, who was then chairman of the board of trustees of the AMA, in answer to a question by Senator Kefauver, said:

I am proposing essentially that this is mainly a mob of education, and that this resolves itself into a problem of communication. The physician who has available to him on the market a drug which in extended usage turns out to be inefficacious, although originally thought to be effective, or which turns out to be dangerous, although originally thought to be safe, the physician must learn the facts about that drug. It is a matter of delivering to him information quickly and in a form that he will interpret accurately. To my mind, this is something that the profession, especially the American Medical Association, has an obligation to do.

And it strikes me that they are not living up to their own standards when they reject a paper, prepared by panels of distinguished authorities, stating that drugs that they are advertising are not efficacious.

And it strikes me as strange that the most distinguished and widely known medical journal in this country would decline to accept a scientific paper done by a group of scientists that convened to review the efficacy of drugs in the market place, among the most important at least, if not the most important, scientific papers on drugs in the market place ever presented in this country. Their scientific judgments should be made known so as to educate the profession, yet the Journal of the American Medical Association declined to accept a paper by that panel.⁶¹

C. DRUG ADVERTISING AND PHYSICIAN INFORMATION

Chairman Nelson quoted a statement made by Bernard Hirsch, the general counsel of the American Medical Association, during his testimony before the House Ways and Means Committee. In that statement, Hirsch attributed educational value to drug advertising.

* * * drug advertisements often provide an important step in the process through which the physician becomes educated in the therapeutic value and risks of new drugs * * *⁶²

The noted physicians who appeared before the subcommittee testified to the contrary, however. They maintained that the advertisements for fixed-dose combination antibiotic drugs published in the

⁵⁸ The 1969 Drug Combinations-Antibiotics Hearings, p. 5038.

⁵⁹ The 1969 Drug Combinations-Antibiotics Hearings, p. 5038.

⁶⁰ The 1969 Drug Combinations-Antibiotics Hearings, p. 5038.

⁶¹ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5038, 5039.

⁶² The 1969 Drug Combinations-Antibiotics Hearings, p. 5000.

AMA's journals, rather than educating, served to mislead and misinform practicing physicians about both the safety and efficacy of these drugs.

Dr. KIRBY. Why, it may be asked, if fixed combinations have these deficiencies and are opposed by the experts, have they been so widely used in the treatment of patients? * * * the answer lies, I think, in the education provided by the drug companies, otherwise known as advertising, including elaborate displays in medical journals and at medical meetings * * * ⁶³

Dr. EICHENWALD. I cannot overemphasize the fact that the demand for these agents was created by advertising which made claims which are still, a decade or so later, unsubstantiated on the basis of controlled observations. ⁶⁴

Dr. KUNIN. There is no question that physicians are swayed intensively by advertising * * * ⁶⁵

Dr. WISE. * * * advertisements containing statements that would not be acceptable in a scientific manuscript are printed in the same [medical] journals. ⁶⁶

Dr. ADRIANI. * * * what they [JAMA] are publishing scientifically for their physicians is in conflict with what is in advertising—this is indefensible. ⁶⁷

D. IMPROVING PHYSICIAN INFORMATION ABOUT DRUGS

Dr. Kunin suggested a way to present physicians with objectively evaluated up-to-date information about drugs.

There was meeting at the National Academy of Science, with discussion of the problem of what I call counter detail men, or medical center representatives, in whom we would be able to have a group of individuals whose opinion, based upon the judgments of our drug and formulary committees, should be presented individually to physicians as friends in court, so to speak, visiting physicians, in the same way that a pharmaceutical representative visits a physician. ⁶⁸

He also described a successful experiment in which a University of Virginia medical student visited many physicians in the central part of Virginia to inform them about the evaluation of two new drugs.

We did a study last summer in which we had one of our medical students visit over 200 physicians in the central area of Virginia. He was extremely well received by these physicians. He presented information on two new drugs that had been evaluated by our drug and formulary committee. They were willing to have him come back. They wanted to see him at least once every 5 weeks at least 15 to 20 minutes to provide them with up-to-date information. ⁶⁹

Dr. Kunin requested financial support so that medical centers can provide needed reliable postgraduate medical education on a continuous basis.

So in a sense I am applying for a grant to do this.

There are many groups of clinical pharmacologists in this country which are fully qualified to do this very thing.

This isn't the same thing as having a man stand in the drugstore and tell the patient all about what drug he has. This is a direct representative of a responsible medical center going to physicians and telling them the latest findings and giving them information. This man does not have to be an expert. He is simply a means of communication from a responsible committee to the physicians in the area that that medical center serves.

I think we can go a long way here in advancing the kind of information and postgraduate medical education which is needed. It is not an expensive enterprise, because you don't need a very highly trained individual. There are other things that he can do as well. He can determine some special need of the physician, and bring this back to the medical centers and modify the program from time to time.

⁶³ The 1969 Drug Combinations-Antibiotics Hearings, p. 5010.

⁶⁴ The 1969 Drug Combinations-Antibiotics Hearings, p. 5017.

⁶⁵ The 1969 Drug Combinations-Antibiotics Hearings, p. 5045.

⁶⁶ The 1969 Drug Combinations-Antibiotics Hearings, p. 5072.

⁶⁷ The 1969 Drug Combinations-Antibiotics Hearing p. 5111.

⁶⁸ The 1969 Drug Combinations-Antibiotics Hearings, p. 5045.

⁶⁹ The 1969 Drug Combinations-Antibiotics Hearings, p. 5046.

I think we have done a poor job in postgraduate medical education, because all we have done is send a man out to see physicians and give them a little talk, and then he goes away. We have to have someone who maintains a continuous contact with physicians, so he has an area that he serves, and a group of physicians that relies upon him for information.⁷⁰

This approach would counteract the effective techniques for presenting information used by the pharmaceutical industry, and would return the responsibility for postgraduate medical education to medical institutions.

Improving the amount and accuracy of physician information while at the same time preventing the receipt of misinformation was also discussed by Dr. Harry F. Dowling of Great Falls, Va., during the 1972 hearings:

The accuracy of information reaching the physician has improved considerably since the 1962 Act. Much worth-while information can now be obtained from advertisements themselves; journal articles are more informative since clinical studies are better, and the A.M.A. Council on Drugs has published an excellent book, *AMA Drug Evaluations*, which gives the consensus of experts in each field of drug therapy in straight-shooting language which the physician can understand and also evaluates the commoner mixtures. Yet from the evidence presented, many physicians either do not refer to *AMA Drug Evaluations* or read the *Medical Letter* or the informative journal articles; or else the counterpressures for poor prescribing are too great. This leads to the second item, preventing misinformation.

Much of the misinformation in the past came from printed advertisements in journals or sent by direct mail. The FDA is doing a good job of monitoring these; today they are factual rather than depending on suggestion to sell their product. The editors of the better journals are serving as an additional defense against improper advertisements. When companies have made misleading statements, the FDA has sometimes required that a corrective letter be sent to all members of the prescribing professions. Theoretically, these should be effective in combating false impressions; actually I know of no studies to determine their impact upon prescribing. I would strongly recommend that the FDA make such a study.

One large loophole is still present: the activities of detail men are being affected very little if at all by the new law. One reason for this is that it would be impossible to monitor adequately the hundreds of conversations that take place between detail men and doctors every day. Second, it is not clear whether the present law gives the FDA control over oral presentations. And yet the detail man can negate much of the good influence of the improved information that is reaching physicians today. In my book *"Medicines for Man"* (pp. 273-275) I reviewed all the studies I could find in the literature on the influence of detail men on prescribing habits of physicians and found that the detail man was the source of the first information about a new drug for 31 to 52 percent of doctors in the different studies.

Also, detail men were responsible for persuading doctors to use a new drug from 21 to 67 percent of the time. From testimony given before this committee (Hearings, Part 8, pp. 3482-3517) there is good evidence that therapeutic claims are exaggerated and toxic reactions minimized by detail men. Obviously, something should be done to prevent this subversion of the intent of Congress. I would suggest that the FDA require that all printed material transmitted from a company or its representative to its detail men, or used in presentations to the detail men, or used by detail men in presentations to physicians, should be subject to monitoring by that Agency. If the present law does not allow this, an amendment to the 1962 Act should be considered.⁷¹

But as Dr. A. G. Macgregor, a Scottish physician, made clear in presenting his views on combination drugs at a symposium:

In the long run it is the doctor, not the industry, who is responsible for any prescription for a patient and there is no point in some doctors saying they are harassed and importuned to use drugs of which they do not approve. The remedy is in their own hands, for they need not prescribe.⁷²

⁷⁰ The 1969 Drug Combinations-Antibiotics Hearings, p. 5046.

⁷¹ The 1972 Misuse of Antibiotics Hearings, pp. 1117-19.

⁷² Macgregor, A. G. Are Drug Combinations Necessary. *Journal Mondial de Pharmacie*, 12: 281-286 (July-Sept.) 1969.

IV. THE FEDERAL GOVERNMENT'S ACTIONS

A. THE DRUG EFFICACY STUDY AND DRUG EFFICACY STUDY IMPLEMENTATION (DESI)

Between 1938 and 1962 the FDA only has authority to review the safety of new drugs intended for marketing. In 1962, Congress amended the Food, Drug, and Cosmetic Act of 1938 adding the requirement that a new drug application should present substantial evidence that a drug is effective for the manufacturer's stated indications (or claims) for its use. Consequently, each new drug product that has received FDA approval for entry into the market since 1962 has been cleared for both safety and efficacy. The FDA was also required to review for efficacy all those drug products approved only on the basis of safety that had been marketed between 1938 and the passage of the 1962 amendments. This resulted in the Drug Efficacy Study Implementation (DESI) project.⁷³

In the FDA's own words:

The DESI program stems directly from requirements of the Federal Food, Drug, and Cosmetic Act. Beginning in 1938, this law required preclearance of new drugs by FDA for safety. The Drug Amendments of 1962 (Kefauver-Harris) required that effectiveness as well as safety of drugs be established prior to marketing. The amendment provided that this proof of efficacy be in the form of "substantial evidence." This evidence was defined by the Congress as "* * * adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have."⁷⁴

Over 3,500 prescription drug formulations having a total of about 16,000 claims (an average of 5 per drug) had to be reviewed for efficacy under this retroactive ruling. In addition, for every approved drug there were five sold without FDA approval. These comprised two categories: drugs that were chemically identical to previously approved drugs, known as "me-too" drugs; and combinations of approved drugs, the subject of this report.⁷⁵

In 1966, when it appeared that the FDA did not have the resources to complete the reviewing task within a reasonable period of time, the commissioner requested assistance from the Division of Medical Sciences of the National Academy of Sciences-National Research Council (NAS/NRC). A contract between FDA and the Academy was signed for carrying out what became known as the Drug Efficacy Study of the NAS/NRC.

In order to conduct the study, the area of drug usage was divided into 30 subdivisions. A panel of experts, predominantly physicians with academic affiliations, was organized for each of the subdivisions.

⁷³ Bryan, Paul A. Desi Who? FDA Consumer, October, 1972, Reprint, DHEW Publication No. (FDA) 73-3013.

⁷⁴ FDA Drug Bulletin, The Drug Efficacy Study, Fixed Combination Prescription Drugs, Oral Hypoglycemic Agents, June 23, 1971.

⁷⁵ Bryan, Paul A., op.cit.

Each panel consisted of a chairman and five additional members. A 22-member Policy Advisory Committee provided policy guidance.

According to the FDA:

To accomplish this task within a reasonable time, FDA went to the National Academy of Science for assistance. The Academy assembled 30 panels with some 200 medical and scientific specialists described in its 1969 report as "predominantly physicians with academic affiliations for the obvious reason that these best met the legal qualification of 'experts qualified by scientific training and experience to evaluate the effectiveness of the drug(s) involved.' "

The National Research Council—research arm of the National Academy of Sciences—developed guidelines for the study. In the course of its work, NRC consulted manufacturers, professional and scientific organizations and other interested parties.

The 30 study panels of the Academy considered information gathered from all these sources, including FDA files and the scientific literature. On the basis of this information, panel members were able to make informed judgments.⁷⁶

Dr. Paul A. Bryan, who has headed the DESI project since its inception, described the classification system used by the panels in making their judgments.

Each claim for each drug was judged in one of six ways:

Effective.—Which meant the evidence was adequate to justify the claim.

Effective with reservations.—The claim might be effective, but some change had to be made, such as in labeling or in ingredients.

Probably effective.—More evidence was needed to support the claim, but the likelihood was that the evidence could be gathered.

Possibly effective.—The claim needed more study, but the chances that evidence could be gathered to prove its effectiveness were only moderate.

Lacking substantial evidence of effectiveness.—There was no scientific evidence to support the claim.

Ineffective as a fixed combination.—Although each of several ingredients in a combination might be effective, combining them did not make the drug any more useful than if one or more of the ingredients were used separately.⁷⁷

The initial development of the report on fixed combinations of antimicrobial agents was carried out by two panels, one chaired by Dr. William L. Hewitt and the other by Dr. Calvin M. Kunin. These panels focused particular attention respectively on fixed combinations of penicillin-sulfonamides and penicillin-streptomycin. However, the report in its final form received the unanimous concurrence of the three other panels on anti-infective drugs chaired by Dr. Heinz Eichenwald, Dr. William M. Kirby, and Dr. William B. Tucker, respectively.⁷⁸

Dr. Eichenwald stated the conclusion of this report in his testimony.

As you gentlemen are aware, the National Academy of Sciences-National Research Council undertook a drug efficacy study in 1966 under contract with the Food and Drug Administration. Essentially, the organization agreed to review the claims for effectiveness of drugs approved between 1938 and 1962. The study was conducted by a group of 30 panels, each consisting of a chairman and five additional members. Five of the panels concerned themselves with antimicrobial agents and each had occasion to consider the claims for efficacy of several products containing fixed combinations of antimicrobial drugs. I was chairman of the Antibiotics Panel No. 1.

It is of interest that all five panels, consisting of a total of 30 recognized experts in the field of antimicrobial therapy, concluded unanimously that there was no place in the medical armamentarium for fixed antimicrobial drug combinations or for products consisting of antibiotics combined with other pharmacologically

⁷⁶ FDA Drug Bulletin, The Drug Efficacy Study, Fixed Combination Prescription Drugs, Oral Hypoglycemic Agents, June 23, 1971.

⁷⁷ Bryan, Paul A., op. cit.

⁷⁸ Drug Efficacy Study, Final Report to the Commissioner of Food and Drugs, FDA, from the Division of Medical Sciences, NAS/NRC, Washington, D.C., 1969: 1-12.

active drugs. There are few instances in medicine when so many experts have agreed unanimously and without reservation.⁷⁹

Put in numerical terms by Dr. Bryan:

Of the 16,573 drug claims evaluated by the NAS/NRC, 3,493 or 21.1 percent were found to be lacking in substantial evidence of effectiveness or where found *ineffective as a fixed combination*. [Emphasis added.]⁸⁰

B. THE FDA'S RESPONSE TO THE DRUG EFFICACY STUDY

What did the FDA do with the results of the NAS/NRC study?
Dr. Bryan described the procedure:

The NAS/NRC reports started coming to FDA in late 1967 and were all in by mid-1969. In January 1968 FDA formed a Task Force to implement the NAS/NRC reports. This was the beginning of DESI.

DESI coordinates the physicians, pharmacologists, and chemists who carefully study the NAS/NRC recommendations and other available evidence. Most often, FDA's experts have agreed with the NAS/NRC panelists.

Once FDA reaches its conclusions for each drug, legal experts write the recommendations into language for publication. If a drug has no claims evaluated higher than "lacking in substantial evidence of effectiveness," it must be withdrawn from the market unless positive information is submitted by the manufacturer within 60 days. Manufacturers of drugs that are rated "possible effective" have six months to submit evidence of effectiveness, although this can be extended if bona fide studies are planned or underway. Manufacturers of "probably effective" drugs have a year to conduct tests, with reasonable extension of time when necessary.

All "me-too" drugs get the same treatment.⁸¹

In his testimony, during the 1969 hearings, Dr. Ley reported on what actions the FDA actually took with respect to specific fixed combination drug products on receipt of the Academy's findings.

On December 24, 1968, FDA announced in the Federal Register its concurrence with the Academy's conclusions that Mysteclin-F, Albamycin-T (G.U.), Panalba, and Achromycin Nasal Spray were ineffective as fixed combinations. Early in January both E.R. Squibb & Sons, Inc., which markets Mysteclin-F, and the Upjohn Co., which markets the Panalba and Albamycin combinations, requested additional time to assemble and to submit additional evidence of efficacy. I granted both firms an additional 120 days to collate and submit new clinical data.

I subsequently notified both firms that we were considering cancellation of the time extensions granted in January, and directed them to immediately submit any substantial medical evidence they had that would be relevant to the efficacy of the drugs. Additional data were provided, but these were not adequate to demonstrate the effectiveness of the fixed combinations. Upjohn presented a proposed protocol to develop the type of evidence required by law, but explained that it would be quite costly and would require about 2 years for completion.⁸²

* * * * *

On May 15, 1969, we published an order in the Federal Register repealing the antibiotic regulations for Panalba and Albamycin-T and decertifying outstanding stocks. These preparations will be subject to seizure when the order becomes effective on June 14, 1969. We set the effective date 30 days after publication to allow the firm to make objections, to show reasonable grounds for a hearing if it has such grounds, and to give the firm time enough to recall stocks of these products. Upjohn has not initiated these recalls to date.

The firm's position is that these products should not be removed from the market without a public hearing. If reasonable grounds are presented, we would be required to grant a hearing on the efficacy of the preparations—but we do not believe they should remain on the market during the course of a hearing and any subsequent litigation that might ensue. In the light of the hazards involved and the NAS/NRC finding that the products are ineffective as fixed combinations, continued marketing cannot be justified.

⁷⁹ The 1969 Drug Combinations-Antibiotics Hearings, p. 5013.

⁸⁰ Bryan, Paul A., op. cit.

⁸¹ Bryan, Paul A., op. cit.

⁸² The 1969 Drug Combinations-Antibiotics Hearings, p. 5167.

I have described in some detail the Agency's actions affecting novobiocin, and combinations including novobiocin, because we intend to follow the same pattern in dealing with other antibiotic preparations received by NAS/NRC.

The committee should understand that reports on other antibiotic combinations were coming to my office from the Bureau of Medicine task force headed by Dr. Bryan during this same period of time. And on April 2, 1969, we announced in the Federal Register our intention to start action to end the marketing of 78 additional antibiotic-contained combination drugs which academy panels had found ineffective as fixed combinations. We included this large number of drugs in one "package" quite deliberately; we wanted to give the medical profession, the industry, and the public a clear signal of the academy's thinking, and FDA's thinking, on these combination preparations. The products involved included antibiotic-sulfa combinations, penicillin-streptomycin preparations, and other combinations including erythromycin, neomycin, tetracycline, chlortetracycline, nystatin, oxytetracycline, oleandomycin, and triacetyloleandomycin. Some of the formulations also included analgesics, vitamins, or other ingredients.

Two groups of these products, the penicillin-sulfa and the penicillin-streptomycin combinations, present the same kind of problem as Panalba. They pose a hazard to the patient, which is not offset by any therapeutic benefit that cannot be achieved by using these drugs singly.

The April 2, 1969, announcement gave interested parties 30 days to submit any data relevant to the efficacy of the products listed. It is significant, Mr. Chairman, that only three of the 23 firms listed as marketing penicillin-sulfa and penicillin-streptomycin combinations responded to that invitation.

Wyeth and Pfizer submitted material on the pen-strep combinations, but no new clinical data were included. Squibb proposed labeling changes on its pen-sulfa preparations and also submitted data from a controlled study of this combination in pediatric use. After review of the study, we concluded that it did not provide substantial evidence of the effectiveness and safety of the penicillin-sulfa combination.

I have signed orders to end the marketing of both the penicillin-streptomycin and penicillin-sulfa preparations. Regulations under which these combinations were certified will be repealed. Outstanding stocks will be decertified. These orders will be published in the Federal Register later this week, or very early next week, if the holiday interferes, and will become effective 40 days later.

This will allow 30 days for the companies to file objections and to seek a hearing, 10 days for our review of the objections, and time for recalls to be completed.

Anyone who may be adversely affected by these actions may file objections within 30 days after publication and request a hearing. Such requests must state reasonable grounds for a hearing, identifying any claimed errors in the NAS/NRC evaluation or any adequate, well controlled investigations which may be offered as evidence of safety and effectiveness. As in the case of Panalba, however, we do not intend to permit the continued marketing of the pen-sulfa and pen-strep combinations during any hearing proceedings that may take place.

I also have signed an order to repeal the regulation and revoke certificates for Mysteclin-F, Squibb's combination of tetracycline and amphotericin-B. Since our announcement in December 1968 that this fixed combination is ineffective, we have received and reviewed additional data and have concluded that substantial evidence still is lacking to support claims in the labeling. The order regrading Mysteclin-F will take effect 40 days after publication in the Federal Register unless stayed by proper objections.⁸³

* * * * *

I hope that these examples have given the committee some indication of how we are proceeding with the challenging task of carrying out the NAS/NRC recommendations.⁸⁴

* * * * *

When safety is not an issue, we do not plan to remove a drug from distribution while a hearing is in progress. But in those cases we will insist that all promotional material for such products state the academy's finding, and FDA's concurrence, regarding the drug's lack of efficacy. The physician is entitled to this information and we intend to see that he gets it.

⁸³ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5173, 5174.

⁸⁴ The 1969 Drug Combinations-Antibiotics Hearings, p. 5174.

When new labeling is required as a result of academy recommendations, we will require the firms involved to publicize the changes in their advertising and other promotional material. Their detail men also will be required to provide this information to physicians and to others with whom they deal.⁸⁵

C. FDA'S PROGRESS IN WITHDRAWING DRUGS FROM THE MARKET

In his testimony during the 1972 hearings, Dr. Simmons, the Director of the Bureau of Drugs, recounted the FDA's efforts to discontinue certification of drug products containing antibiotics in combination with analgesics, antihistamines, and other drugs.

Subsequently, in September 1970, the FDA did initiate action to discontinue certification of the combinations based on an evaluation by the National Academy of Sciences-National Research Council panel as "Ineffective as a Fixed Combination." Nonetheless, it was not until December 1971, after a series of legal proceedings culminating in two Supreme Court Justices independently denying a stay of our withdrawal order, that antibiotics in combination with antihistamines and/or analgesics and/or decongestants were finally removed from the market. I am submitting a copy of that for the record.⁸⁶

(See Appendix C for the document referred to above.)

The FDA was ultimately successful in removing these combinations drugs products from the market, but only after two Justices of the Supreme Court refused the request of the companies involved (Bristol-Myers and American Cyanamid) to stay the withdrawal order.⁸⁷

This case is illustrative of the obstacles the FDA reports it encounters under the current statutory provisions when action is initiated to withdraw a previously approved drug from the market for inefficacy. (The current statute only allows suspension if an approved drug is found to be an "imminent hazard.")⁸⁸

The publication in The Federal Register in 1969 and 1970 of the FDA announcements of its intention to start action to end the marketing of all drug products found ineffective by the Academy triggered hundreds of hearing requests.

The FDA realized it could not grant all the requested hearings. For this reason a "summary judgment" procedure was developed. With this procedure, if the FDA determined that there was no factual issue (issue of fact) because the submitted studies in support of the hearing request failed to meet the statutory and regulatory standards,^{88a} then a ruling could be made against the hearing application and the drug could be withdrawn without a hearing.

The "summary judgment" mechanism, which was outside the statutory provisions, was contested by industry up to the Supreme Court. In June 1974, the Supreme Court upheld "summary judgment" as a lawful mechanism but also said that the FDA had to demonstrate that there was indeed no "issue of fact" in turning down a hearing request.

Subsequent to the Supreme Court's decision several of the FDA's summary judgment documents were rejected by lower courts on the basis that they did not fit the Supreme Court's ruling.

⁸⁵ The 1969 Drug Combinations-Antibiotics Hearings, p. 5175.

⁸⁶ The 1972 Misuse of Antibiotics Hearings, p. 1045.

⁸⁷ The 1972 Misuse of Antibiotics Hearings, p. 1052.

⁸⁸ This information and the subsequent material in this chapter concerning the FDA was provided via telephone communication with two FDA representatives on December 13, 1978.

^{88a} i.e., the pharmaceutical manufacturers did not submit data that were directly related to the efficacy question; see appendix D.

By 1970 there were still a large number of ineffective drugs on the market. There was much dissatisfaction in the health community with FDA's failure to implement the NAS/NRC drug efficacy study in a timely way.

Consequently, in 1970, the American Public Health Association (APHA) and the National Council of Senior Citizens "brought suit against the then Acting Secretary of the Department of Health, Education and Welfare and the then Commissioner of the Food and Drug Administration to enforce the implementation of the 1962 Amendments to the Food, Drug and Cosmetic Act of 1938 requiring that all marketed drugs be shown effective for their suggested use." A summary judgment was granted in 1972. "Judge Bryant explained that the FDA had been delinquent in discharging its responsibilities to implement the 1962 amendments."⁸⁹

By an accompanying unpublished order, the court required the FDA to complete the job of removing the ineffective drugs from the market by October 10, 1976.⁹⁰ Under this order the FDA had to file a progress report with the court every six months. These reports, which have been filed semiannually since March 1973, include: the number of man hours committed to the task, what has and hasn't been accomplished in the time period, and what problems have been encountered.⁹¹

According to Michael C. Harper, counsel for the two organizations that brought suit, as of July, 1977 "the FDA is still far from complying with the 1972 court order. The 1962 efficacy amendments to the Act remain substantially unimplemented, and the efforts of our clients to insure compliance with the amendments remain frustrated."⁹²

D. IMPROVING FDA'S WITHDRAWAL PROCEDURE

In his response to Harper's letter, the Commissioner of Food and Drugs, Donald Kennedy, cited the considerable resources and time of both FDA's legal and medical staffs to either conduct or deny a hearing:

I am deeply concerned about the resources needed to complete this portion of the DESI program, and am presently exploring ways to determine how we can efficiently reduce the number of pending hearing requests consistent with our other legal obligations.⁹³

According to an FDA representative, the present statutory provisions set forth by Congress to remove a previously approved ineffective drug from the market are very cumbersome. An enormous amount of medical and scientific data has to be reviewed. Holding a hearing is similar to a full-blown trial with witnesses and cross-examination. The resources, medical and legal, to do this are exceptionally high and the procedure is time-consuming. The FDA does not believe that even if the necessary resources were available the issues to be weighed warrant the procedure presently mandated.

⁸⁹ Letter from Michael C. Harper, counsel for the Center for Law and Social Policy, to Donald Kennedy, Commissioner, Food and Drug Administration, July 6, 1977. [See Appendix D for complete text.]

⁹⁰ *APHA v. Veneman*, No. 1847-70 (D.D.C. October 10, 1972). [See Appendix E for complete text.]

⁹¹ These reports entitled, Semiannual Reports to the U.S. District Court in Compliance with the Order of the Court in *APHA v. Veneman*, are available on request from Robert Wetherell, Associate Commissioner of Legislative Affairs, FDA Office of Legislative Affairs.

⁹² Letter from Michael C. Harper, counsel for the Center for Law and Social Policy, to Donald Kennedy Commissioner, Food and Drug Administration, July 6, 1977. [See Appendix D for complete text.]

⁹³ Letter from Donald Kennedy to Michael C. Harper, Esq., August 30, 1977. [See Appendix D for complete text.]

An additional drain on FDA's resources caused by these current statutory regulations results from the provision that previously approved drugs can continue to be marketed while their efficacy is in question. If it is economically advantageous to the pharmaceutical manufacturers to continue to market a product (i.e., it doesn't cost too much to appeal an FDA decision in court), they will fight FDA's efforts to remove a drug. In many cases it has taken 8 or 9 years to get ineffective drugs off the market.

The remedy, according to the FDA, would be for Congress to substitute section 111 of the Drug Regulation Reform Act, which was proposed but not passed in 1978, for the current statute (the Food, Drug and Cosmetic Act of 1938, 21 USC 355 as amended in 1962).⁹⁴

Section 111 would substitute a less formal decisionmaking process for the present procedure. This would be more expeditious and less costly. At the same time the interests of the various concerned parties—patients, physicians, drug manufacturers, and the FDA—would be assured fair treatment.

The following excerpt sets forth the FDA's position on this issue:

The process for withdrawing a drug from the market has been changed from a trial-type proceeding to a public hearing. The need for cross examination in deciding whether a monograph should be revoked is no greater than in deciding whether a monograph may be issued. The issues are virtually the same as at the time of approval and, once again, involve legislative rather than adjudicative facts. In addition, the current hearing procedures required under section 505(e) of the FD&C Act have proven extraordinarily cumbersome and time-consuming. The time from a proposal to withdraw a drug to a final administrative decision on the matter is at least 12 months, even if the Department and the affected drug manufacturers commit themselves to expedite the proceeding. More commonly, drug withdrawal proceedings extend much longer. In all drug evaluation proceedings under the FD&C Act, the persons most directly affected by the delays and lack of decisions—the patients and their physicians—are generally unable to participate or to demand a prompt resolution. These defects would be remedied by section 111.⁹⁵

The FDA's resources must be allocated to deal first with high priority drug-related issues such as imminent hazard and evaluation of new drugs that might save lives. Consequently, a mechanism like section 111, which would deal fairly but expeditiously with efficacy, would help to resolve the problem of the ineffective drugs still on the market 17 years after the passage of the 1962 efficacy amendments. A number of these ineffective still-marketed drug products are fixed-combination antibiotics.

⁹⁴ Information provided via telephone communication with two FDA representatives, December 13, 1978.

⁹⁵ Department of Health, Education and Welfare, The Administration Proposal, Drug Regulation Reform Act of 1978: Section-by-Section Analysis H.R. 11611 and S. 2755, 95th Congress, Second Session pp. 51-2.

V. THE CURRENT STATUS OF FIXED-DOSE COMBINATION ANTIBIOTIC DRUGS

A. THE STATUS OF ANTIBIOTIC DRUGS FOUND TO BE INEFFECTIVE AS A FIXED COMBINATION

As of December 1978, all but 20 fixed-dose combination antibiotic drugs evaluated as ineffective by the NAS/NRC drug efficacy study, have been withdrawn from the market. In each case, a hearing has been requested or the drug is affected by another hearing request. (See table 1-1.) The status of these drugs has, therefore, not been altered appreciably since the 1969 subcommittee hearings. It was not possible to ascertain from the FDA whether or not a timetable exists for their ultimate disposition.

The FDA claims that in the case of Mysteclin-F, they are currently reviewing new data from a large company-run study.⁹⁶ This is 9 years after Dr. Ley told the subcommittee:

I also have signed an order to repeal the regulation and revoke certificates for Mysteclin-F, Squibb's combination of tetracycline and amphotericin-B. Since our announcement in December 1968 that this fixed combination is ineffective, we have received and reviewed additional data and have concluded that substantial evidence still is lacking to support claims in the labeling. The order regarding Mysteclin-F will take effect 40 days after publication in the *Federal Register* unless stayed by proper objections.⁹⁷

B. FIXED-DOSE COMBINATIONS THAT ARE EFFECTIVE

In 1971, the FDA issued the following policy statement on combination drug products.

The FDA is not opposed to combination drug products; it recognizes that many are safe and effective and provide important advantages to patient and physician.

For a combination to be approved under the law there must be substantial evidence that each active component contributes to the claimed effect of the product, a requirement since 1962. If this requirement is satisfied, two or more drugs may be combined in a single dosage form when, in good medical practice, they would be given concurrently and when putting them together in the same product in no way detracts from their safety and efficiency. Such combination product should provide appropriate dosage for a significant patient population that can be defined in the labeling. A special case of this general rule is the addition of an ingredient that enhances the safety or effectiveness of the principal active component or minimizes its abuse potential.⁹⁸

In this report, the discussion of fixed-combination antibiotics has referred to drug products that are either taken orally or injected (i.e., systemic drugs—the types of drugs discussed in the 1969 and 1972 hearings.) It is, however, of interest to note that certain otic (for the ear) fixed-combination preparations containing antibiotics, which were originally evaluated as ineffective by the NAS/NRC drug efficacy

⁹⁶ Information received via telephone communication with an FDA representative, October 2, 1978.

⁹⁷ The 1969 Drug Combinations-Antibiotics Hearings, p. 5183.

⁹⁸ FDA Drug Bulletin, the Drug Efficacy Study, Fixed Combination Prescription Drugs, Oral Hypoglycemic Agents, June 23, 1971.

study, were subsequently upgraded to effective for specific indications as set forth in their labeling guidelines.⁹⁹

Dr. Kunin observed in his testimony that—

* * * on occasion one can find a combination that might be valuable * * * if one can demonstrate the efficacy of a combination which is greater than any one of the ingredients, and which has some economic or sociological advantage, we should be prepared to accept that combination provided that the evidence for efficacy is presented.¹⁰⁰

He discussed two promising fixed-combination antibiotics he had observed in Uganda, neither of which had as yet received FDA approval.

Finally this last paragraph—I would like to leave a little disclaimer here—there may be special instances where fixed combinations are of value—and this is what I alluded to before. They include the combined use of isoniazid and thiacetazone in the treatment of tuberculosis because of great convenience.

Senator NELSON. In this country?

Dr. KUNIN. No. I don't believe that these drugs are used in this country at this time—but if evidence were to be provided that would be satisfactory to an expert panel, or to the Food and Drug Administration, that there was an advantage to this particular combination, then I think the Food and Drug Administration, for the benefit of the American public, should accept evidence of that kind. That is why I am leaving this door open. I mentioned that such combinations are particularly useful in underdeveloped nations where it is much more preferable to give a single dose each day. In addition, evidence is accumulating—and here is the second example—that antimicrobial synergy—that is the effectiveness of the combination is greater than the sum of the individual activities of the ingredients exists when a drug called trimethoprim is combined with a sulfonamide.

This particular combination is undergoing extensive evaluation in the United Kingdom and other parts of the world. Actually it is licensed in the United Kingdom, and it is being used fairly widely.

Senator NELSON. What is the drug?

Dr. KUNIN. It is a combination of trimethoprim, which blocks the synthesis of a particular metabolite at one site, and sulfonamide blocks the same pathway at another site, so that the two together appear to have synergy or an effect greater than the sum of the two. It looks very promising.

Now, "promising" doesn't mean necessarily that it should be approved or accepted by our Food and Drug Administration. Nevertheless, there has been a fair amount of work with this, and it has been released in the United Kingdom. We will just have to look at the data and the evidence for this particular combination.

Senator NELSON. Is it marketed in this Country?

Dr. KUNIN. It is not marketed in this country.

Senator NELSON. Is there any difference—if there is a synergistic effect—by combining two drugs, is this any difference (sic) from the synergistic effect that is achieved in a fixed combination versus individual administration of the drug at—

Dr. KUNIN. Theoretically you can give the two drugs separately. But the whole advantage of the combination is that they really do work together. It is nice to get the two drugs in at the same time, the one capsule. If the manufacturers can show evidence that this particular combination has great efficacy, then I believe we should accept it. But we should examine the data. Yes, it would be much more convenient to have them together.

Senator NELSON. But would you get a better effect.

Dr. KUNIN. Yes; you can get a better effect, you can be more sure that the patient took the two drugs at the same time in the appropriate way. One of the major problems that a physician always has in prescribing drugs is: Will the patient have the prescription filled and will he take his medicine properly? These are just small areas. I am just leaving a crack of the door open, so that we can have an open mind, and so that we don't, you might say, unnecessarily punish the pharmaceutical industry for past sins.

They may be able to offer us some fixed combinations that are good.

⁹⁹ Drugs for Human Use; Drug Efficacy Study Implementation Follow-up Notice. Federal Register, v. 38 No. 153, August 9, 1973. [See also Appendix H.]

¹⁰⁰ The 1963 Drug Combinations-Antibiotics Hearings, p. 5025.

Senator NELSON. What you are really saying is what the law states—if the FDA is presented adequate clinical and testing proof that the drug is safe and efficacious then it ought to be approved like any other drug?

Dr. KUNIN. Of course.¹⁰¹

One of the drugs described by Dr. Kunin, trimethoprim with sulfamethoxazole, has been approved, and the other, the antitubercular drug, has been approved with one different component. The physiological action of this drug is, however, similar to the one described by Dr. Kunin. In addition, a third drug for treating gonorrhea, which can be given orally (rather than by the usual parenteral route), has also received approval.

The three approved fixed-combination antibiotics are:

(1) Trimethoprim with sulfamethoxazole (Bactrim). This is a synthetic antibacterial drug. Both of its components act to block folic acid synthesis in bacteria, thereby exerting a strong synergistic antibacterial effect. It is used in oral form to treat chronic urinary infection;¹⁰²

(2) rifampin with isoniazid (Rifamate and Rimactazid). This combination drug contains two antitubercular agents. Bacteria resistant to one of the components may be destroyed by the other. In effect, the speed with which mutant resistant bacterial strains appear is reduced;¹⁰³ and

(3) ampicillin trihydrate with probenecid (Polycillin-PRB). This is an oral single dose medication for the treatment of uncomplicated gonorrhea. The probenecid blocks the excretion of the ampicillin (a form of penicillin) thus maintaining high blood levels of the antigonorrheal agent, ampicillin. A recent study found this drug's cure rate to be 94.2 percent, which is "nearly equal to any treatment now available."¹⁰⁴

According to an FDA representative, there are several other antibiotic combination drugs currently under review.

C. CONTINUING QUESTIONS

Important questions about this issue include:

1. Do consumers of still-marketed ineffective fixed combination antibiotic drug products know about the increased risk of adverse reactions when they take multiple drugs, particularly such potentially dangerous ones as tetracycline and the sulfonamides? Isn't a patient put in double jeopardy when a drug is prescribed that cannot cure his illness and may cause him to become dangerously ill?

2. Is there any way of ensuring that physicians know which drugs they should not be prescribing and why, even though the drugs are still being marketed?

3. Can the powerful influence of the drug manufactures be counteracted?

4. Shouldn't the protection of the patient-public's health and purse take precedence over any other consideration?

5. What can be done to prevent approved drugs whose efficacy is in question from being marketed until the question is resolved?

¹⁰¹ The 1969 Drug Combinations-Antibiotics Hearings, pp. 5031-5032.

¹⁰² Weinstein, A. J., *Newer Antibiotics—Guidelines For Use*, Postgraduate Medicine, October 1976: 75-80

¹⁰³ Meyers, F. H., E. Jawetz, and A. Goldfien, *Review of Medical Pharmacology*, Los Altos, California, Lange Medical Publications, 1976: 583.

¹⁰⁴ Kleris, G. S., S. W. Hall, and T. J. Hart, *Treatment of Uncomplicated Gonorrhea with Polycillin-PRB*, *Journal of the American Venereal Disease Association*, December 1976: 84-86.

6. Is the court the correct place to resolve medical and scientific questions such as whether a drug's efficacy has been adequately proven or disproven?

These and other questions related to the issues of consumer protection and information are not confined to fixed-dose combination antibiotic drugs. The FDA has a legal responsibility (statutory as well as court-ordered) to patients and their physicians to remove all ineffective drugs from the market as expeditiously as possible. Patients have a right to confidence that the drugs they are prescribed will provide maximum benefit with minimum risk, and that they are not wasting their money on useless medications.

APPENDIXES

APPENDIX A—WITNESS LIST

Alphabetical list of witnesses who presented statements during the 1969 and 1972 Hearings on Fixed Combination Antibiotic Drugs.

THE 1969 DRUG COMBINATIONS-ANTIBIOTICS HEARINGS

Statement of—	Page
Adriani, Dr. John, Charity Hospital, New Orleans, La.....	5085
Bryan, Dr. Paul, Director, Bureau of Medicine Task Force, Food and Drug Administration; accompanied Dr. Herbert L. Ley, Jr., Commissioner, FDA.....	5134
Eichenwald, Dr. Heinz F., William Buchanan professor and chairman, Department of Pediatrics, University of Texas Southwestern Medical School, Dallas, Tex.....	5013
Goodrich, William W., counsel, Office of General Counsel, U.S. Department of Health, Education, and Welfare; accompanied Dr. Herbert L. Ley, Jr., Commissioner, FDA.....	5134
Hewitt, Dr. William L., professor of medicine, University of California School of Medicine, Los Angeles, Calif.....	5048
Jennings, Dr. John, Acting Director, Bureau of Medicine, Food and Drug Administration; accompanied Dr. Herbert L. Ley, Jr., Commissioner, FDA.....	5134
Kirby, Dr. William M. M., professor of medicine, University of Washington School of Medicine, Seattle, Wash.....	5002
Kunin, Dr. Calvin M., chairman, Department of Preventive Medicine, University of Virginia, Charlottesville, Va.....	5023
Ley, Dr. Herbert L., Commissioner of Food and Drugs, Consumer Protection and Environmental Health Service, Public Health Service, U.S. Department of Health, Education, and Welfare; accompanied by William W. Goodrich, Counsel, Office of General Counsel; Dr. John Jennings, Acting Director, Bureau of Medicine, Food and Drug Administration; and Dr. Paul Bryan, Director, Bureau of Medicine Task Force, Food and Drug Administration.....	5134
Wise, Robert I., M.D., Ph. D., professor of medicine and chairman, Department of Medicine, Jefferson Medical College, 1025 Walnut Street, Philadelphia, Pa.....	5071

THE 1972 MISUSE OF ANTIBIOTICS HEARINGS

Dowling, Harry F., M.D., 208 Bliss Lane, Great Falls, Va. 22066.....	1103
Simmons, Henry E., M.D., Director, Bureau of Drugs, Food and Drug Administration; accompanied by Jean Lockhart, M.D., chief medical officer, Division of Anti-Infective Drugs; Barrett Scoville, M.D., Deputy Director, Division of Neuropharmacologic Drugs; Gene M. Pfeifer, Office of General Counsel; and Gerald F. Meyer, Office of Legislative Services.....	1040, 1238

APPENDIX B—FDA ANNOUNCEMENTS

FDA announcements of intention to revoke certificates of safety and effectiveness for certain combination drugs.

Federal Register, June 13, 1969.

Federal Register, November 13, 1969.

Federal Register, December 31, 1969.

Federal Register, April 9, 1970.

RULES AND REGULATIONS

9333

Title 21—FOOD AND DRUGS

Chapter I—Food and Drug Administration, Department of Health, Education, and Welfare

SUBCHAPTER C—DRUGS

PART 141a—PENICILLIN AND PENICILLIN-CONTAINING DRUGS; TESTS AND METHODS OF ASSAY

PART 146a—CERTIFICATION OF PENICILLIN AND PENICILLIN-CONTAINING DRUGS

Certain Human-Use Penicillin-Streptomycin Combination Products for Injection

In the FEDERAL REGISTER of April 2, 1969 (34 F.R. 6006), the Commissioner of Food and Drugs announced the conclusions of the Food and Drug Administration following evaluation of reports received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on the following preparations:

1. Durycin F.A. (for aqueous injection); contains procaine penicillin G, buffered penicillin G crystalline-sodium, and streptomycin sulfate; marketed by Eli Lilly & Co., Post Office Box 618, Indianapolis, Ind. 46206.
2. Durycin A.S. (aqueous suspension); contains procaine penicillin G and streptomycin sulfate; marketed by Eli Lilly & Co.
3. Mycillin; contains procaine penicillin G and streptomycin sulfate; marketed by Maury Biological Co., Inc., 6109 South Western Avenue, Los Angeles, Calif. 90047.
4. PenStrep 4:1 and PenStrep 4:½; contain procaine penicillin G, penicillin G potassium, and streptomycin sulfate; marketed by Merck & Co., Inc., Rahway, N.J. 07065.
5. Strep-Combiotic Aqueous Suspension (multidose); contains procaine penicillin G and streptomycin sulfate; marketed by Charles Pfizer & Co., Inc., 235 East 42d Street, New York, N.Y. 10017.
6. Strep-Combiotic for Aqueous Suspension (single dose); contains procaine penicillin G, potassium penicillin G, and streptomycin sulfate; marketed by Charles Pfizer & Co., Inc.
7. Strep-Combiotic Aqueous Suspension—Isojet; contains procaine penicillin G and streptomycin sulfate; marketed by Charles Pfizer & Co., Inc.
8. Streptomycin-Bipenicillin; contains procaine penicillin G, sodium penicillin

G, and streptomycin sulfate; by Pure Laboratories, Inc., 50 Intervale Road, Parsippany, N.J. 07054.

9. Pentocin; contains procaine penicillin G, potassium penicillin G, and streptomycin sulfate; marketed by Pure Laboratories, Inc.

10. Procaine Penicillin in Streptomycin Sulfate Solution; contains procaine penicillin G and streptomycin sulfate; marketed by Roehr Products Co., Inc., A Subsidiary of Brunswick Corp., 2010 New Daytona Road, De Land, Fla. 32720.

11. Strep-Dicrysticin, Strep-Dicrysticin-800, Strep-Dicrysticin Fortis, and Strep-Dicrysticin Fortis-800 (four strengths, for suspension); contain procaine penicillin G, sodium penicillin G, and streptomycin sulfate; marketed by E. R. Squibb & Sons, Inc., Georges Road, New Brunswick, N.J. 08903.

12. Strep-Districillin A.S. (sterile suspension); contains procaine penicillin G and streptomycin sulfate; marketed by E. R. Squibb & Sons, Inc.

13. Penicillin-Streptomycin Readmixed Sterile Aqueous Suspension; contains procaine penicillin G and streptomycin sulfate; marketed by The Upjohn Co., 7171 Portage Road, Kalamazoo, Mich. 49002.

14. Cer-O-Strep—ONE-HALF and Cer-O-Strep—ONE (sterile powders); contain chlorprocaine penicillin O, sodium penicillin O, and streptomycin sulfate; marketed by The Upjohn Co.

15. Bicillinmycin All-Purpose Injection; contains benzathine penicillin G, potassium penicillin G, procaine penicillin G, and streptomycin sulfate; marketed by Wyeth Laboratories, Inc., Post Office Box 8299, Philadelphia, Pa. 19101.

16. Wycillin SM Injection 400 and Wycillin SM Injection 600; contain procaine penicillin G and streptomycin sulfate; marketed by Wyeth Laboratories, Inc.

The announcement stated that the Academy found these products to be ineffective or ineffective as a fixed combination for those indications in the labeling that were specific enough to be evaluated and that the Food and Drug Administration concurred that there is a lack of substantial evidence that each drug will have the effects it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling. All interested persons were invited to submit within 30 days pertinent data bearing on the proposal to amend the antibiotic drug regulations where necessary to delete the above antibiotic combinations from the list of drugs acceptable for certification.

Wyeth and Pfizer submitted responses to the announcement, and these have been reviewed. These submissions contained no new clinical data. It has been concluded that they do not provide substantial evidence of the effectiveness of such combination drugs.

Accordingly, the Commissioner concludes that in the absence of substantial evidence of effectiveness for the fixed combinations of drugs and in recognition of the known hazards associated with the use of each component of such

combination, e.g., deafness from streptomycin and allergenicity from penicillin, the regulations for certification of antibiotic drugs should be amended as follows to delete the above-listed antibiotic combinations, and all other parenteral dosage forms for human use containing penicillin and streptomycin, from the list of drugs acceptable for certification. The Commissioner further concludes that the certificates of safety and effectiveness heretofore issued for the combination drugs should be revoked on the basis of unwarranted hazards.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-51, as amended, 59 Stat. 463, as amended; 21 U.S.C. 352, 357) and under authority delegated to the Commissioner (21 CFR 2.120), the antibiotic drug regulations are amended as follows to remove provision for certification of such drugs for human use, and certificates previously issued for such drugs for human use under these regulations are revoked. Accordingly, Parts 141a and 146a are amended:

1. In § 141a.38, by changing the section heading to read as follows:

§ 141a.38 Procaine penicillin and streptomycin in oil veterinary; procaine penicillin and dihydrostreptomycin in oil veterinary.

2. In § 141a.39, by changing the section heading to read as follows:

§ 141a.39 Penicillin-streptomycin veterinary; penicillin-dihydrostreptomycin veterinary.

3. In § 141a.46, by changing the section heading to read as follows:

§ 141a.46 Procaine penicillin in streptomycin sulfate solution veterinary; procaine penicillin in dihydrostreptomycin sulfate solution veterinary.

4. In § 141a.67, by changing the section heading to read as follows:

§ 141a.67 Procaine penicillin and benzathine penicillin G in streptomycin sulfate solution veterinary; procaine penicillin and benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary (procaine penicillin and benzathine penicillin G in crystalline dihydrostreptomycin sulfate solution veterinary).

5. In § 141a.68, by changing the section heading to read as follows:

§ 141a.68 Benzathine penicillin G and streptomycin veterinary; benzathine penicillin G and dihydrostreptomycin veterinary.

6. In § 141a.71, by changing the section heading to read as follows:

§ 141a.71 Penicillin-streptomycin powder veterinary; penicillin-dihydrostreptomycin powder veterinary.

7. In § 141a.74, by changing the section heading to read as follows:

APPENDIX B (cont.)

9334

RULES AND REGULATIONS

§ 141a.74 Dibenzylamine penicillin and streptomycin in oil veterinary; dibenzylamine penicillin and dihydrostreptomycin in oil veterinary.

8. In § 141a.80, by changing the section heading to read as follows:

§ 141a.80 Benzathine penicillin G-procaine penicillin G-streptomycin in oil veterinary; benzathine penicillin G-procaine penicillin G-dihydrostreptomycin in oil veterinary.

9. By revising § 141a.88 to read as follows:

§ 141a.88 Benzathine penicillin G in streptomycin sulfate solution veterinary; benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary (benzathine penicillin G in crystalline dihydrostreptomycin sulfate solution veterinary).

Proceed as directed in § 141a.68 (a), (b), and (d).

§§ 141a.113, 141a.114 [Revoked]

10. By revoking § 141a.113 *Clemizole penicillin G* and § 141a.114 *Clemizole penicillin G-streptomycin sulfate aqueous suspension*.

§§ 146a.4, 146a.5 [Revoked]

11. By revoking § 146a.4 *Clemizole penicillin G* and § 146a.5 *Clemizole penicillin G-streptomycin sulfate aqueous suspension*.

12. In § 146a.57, by revising the section title and the introductory text of paragraph (a) to read as follows:

§ 146a.57 Procaine penicillin and streptomycin in oil veterinary; procaine penicillin and dihydrostreptomycin in oil veterinary.

(a) Procaine penicillin and streptomycin in oil veterinary and procaine penicillin and dihydrostreptomycin in oil veterinary conform to all requirements and to all procedures prescribed in § 146a.45 for procaine penicillin in oil for udder instillations of cattle or subcutaneous infection in fowl, except that:

13. In § 146a.58:

a. By revising the section heading and paragraphs (a), (b), and (c) to read as follows.

§ 146a.58 Penicillin-streptomycin veterinary; penicillin-dihydrostreptomycin veterinary.

(a) *Standards of identity, strength, quality, and purity.* Penicillin-streptomycin veterinary and penicillin-dihydrostreptomycin veterinary are procaine penicillin, crystalline sodium penicillin, potassium penicillin, *l*-phenamine penicillin G, or diethylaminoethyl ester penicillin G hydriodide, or a mixture of two or more such salts and streptomycin sulfate or dihydrostreptomycin sulfate, with or without suitable and harmless buffer substances and suspending or dispersing agents. Each drug is sterile, nontoxic, and nonpyrogenic. Its moisture content is not more than 3.5 percent, except if it contains procaine penicillin its

moisture content is not more than 4.2 percent. When prepared for injection as directed in its labeling, its pH is not less than 5.0 and not more than 7.5. The penicillin used conforms to the requirements of § 146a.24(a), § 146a.44(a), § 146a.64(a), or § 146a.74(a). The streptomycin sulfate used conforms to the requirements prescribed for streptomycin sulfate by § 146b.101(a) of this chapter. The dihydrostreptomycin sulfate used conforms to the requirements prescribed for dihydrostreptomycin sulfate by § 146b.103 of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium. Penicillin-streptomycin is also the drug described in § 146a.84 of this chapter if it conforms to all requirements of that section and of § 141a.60 of this chapter, except that it contains streptomycin in lieu of a mixture of streptomycin and dihydrostreptomycin.

(b) *Packaging.* In all cases the immediate containers shall be tight containers as defined by the U.S.P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards except that minor changes so caused that are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of transparent glass, closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness. Each such container may be packaged in combination with a container of a solvent consisting of water for injection U.S.P., dextrose injection U.S.P., or sodium chloride injection U.S.P.

(c) *Labeling.* (1) *It is packaged for dispensing.* In addition to the labeling requirements prescribed by § 1.106(c) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container and the immediate container, the statement "Expiration date _____", the blank being filled in with the date that is 48 months after the month in which the batch was certified, except that the blank may be filled in with the date that is 60 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section, and except that in no case shall the blank be filled in with the date that is more than 24 months after the month in which the batch was certified if it contains diethylaminoethyl ester penicillin G hydriodide.

(ii) In lieu of the statement "Caution: Federal law restricts this drug to sale by or on the order of a licensed veterinarian," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(iii) If it does not contain diethylaminoethyl penicillin G hydriodide and is intended for use in the treatment of food-producing animals, the labeling shall bear the statement "Warning—The use of this drug must be discontinued for 30 days before treated animals are slaughtered for food," and, if the drug is intended for use in animals producing milk for human consumption, the labeling shall also bear the statement required by § 148.5 of this chapter.

(iv) If it contains diethylaminoethyl penicillin G hydriodide, the labeling shall bear the statement "Warning—Not for use in animals which are raised for food production."

(2) *It is packaged solely for manufacturing use and/or repackaging.* Each package shall bear on its outside wrapper or container and the immediate container the following:

(i) The number of units of each salt of penicillin in each gram.

(ii) The number of milligrams of streptomycin or dihydrostreptomycin in each gram.

(iii) The statement "Caution: Federal law prohibits dispensing without prescription."

(iv) The statement "For manufacturing use," "For repackaging," or "For manufacturing use or repackaging."

(v) The information required by subparagraph (1)(i) of this paragraph.

b. Paragraph (d)(1) is amended by inserting the word "veterinary" after the word "streptomycin" in the first place it occurs.

14. In § 146a.67, by revising the section heading, the introductory text of paragraph (a), paragraph (b), and paragraph (c) (1) and (2) to read as follows:

§ 146a.67 Procaine penicillin in streptomycin sulfate solution veterinary; procaine penicillin in dihydrostreptomycin sulfate solution veterinary (procaine penicillin in crystalline dihydrostreptomycin sulfate solution veterinary).

(a) *Standards of identity, strength, quality, and purity.* Procaine penicillin in streptomycin sulfate solution veterinary is procaine penicillin G suspended in an aqueous solution of streptomycin sulfate. Procaine penicillin in dihydrostreptomycin sulfate solution veterinary is procaine penicillin suspended in an aqueous solution of dihydrostreptomycin sulfate or crystalline dihydrostreptomycin sulfate. Such solution shall contain one or more suitable and harmless buffer substances, preservatives, and suspending or dispersing agents, and it may contain one or more suitable and harmless stabilizing agents, procaine hydrochloride in a concentration not exceeding 2 percent, a suitable antihistaminic, a suitable anticholinergic and cortisone, or

APPENDIX B (cont.)

RULES AND REGULATIONS

9335

a suitable derivative of cortisone. It is purified that:

(b) *Packaging.* In all cases the immediate container shall be a tight container as defined by the U.S.P., shall be sterile at the time of filling and closing, shall be so sealed that the contents cannot be used without destroying such seal, and shall be of such composition as will not cause any change in the strength, quality, or purity of the contents beyond any limit therefor in applicable standards, except that minor changes so caused which are normal and unavoidable in good packaging, storage, and distribution practice shall be disregarded. In case it is packaged for dispensing, it shall be in immediate containers of transparent glass closed by a substance through which a hypodermic needle may be introduced and withdrawn without removing the closure or destroying its effectiveness, unless it is packaged to contain a single dose. Each such container shall contain not less than 1.0 milliliter, and each shall be filled with a volume in excess of that designated, which excess shall be sufficient to permit the withdrawal and administration of the volume indicated, whether administered in either single or multiple dose.

(c) *Labeling.*—(1) *It is packaged for dispensing and it contains an antihistaminic, and anticholinergic, or cortisone or a derivative of cortisone.* In addition to the labeling requirements prescribed by § 1.106(c) of this chapter (regulations issued under section 502(f) of the act), each package shall bear on the label or labeling, as hereinafter indicated, the following:

(i) On the outside wrapper or container, the statement "Store in refrigerator not above 15° C. (59° F.)."

(ii) On the outside wrapper or container and the immediate container, the statement "Expiration date _____," the blank being filled in with the date that is 12 months after the month during which the batch was certified, except that the blank may be filled in with the date that is 18 months, 24 months, or 36 months after the month during which the batch was certified if the person who requests certification has submitted to the Commissioner results of tests and assays showing that after having been stored for such period of time such drug as prepared by him complies with the standards prescribed by paragraph (a) of this section.

(iii) On the label and the labeling, the statement "For use only in cats, dogs, and horses; not for use in horses to be slaughtered for human consumption."

(iv) After the name "procaine penicillin in streptomycin sulfate solution veterinary," or "procaine penicillin in dihydrostreptomycin sulfate solution veterinary," wherever such name appears, the words "with _____," in juxtaposition with such name, the blank being filled in with the established name of the antihistaminic, the anticholinergic, the cortisone, or the derivative of cortisone.

(2) *It is packaged for dispensing and it does not contain an antihistaminic,*

an anticholinergic, or cortisone or a derivative of cortisone. It shall comply with the requirements of subparagraph (1) of this paragraph, except:

(i) In lieu of the statement "Caution: Federal law restricts this drug to sale by or on the order of a licensed veterinarian," each package shall include information containing directions and warnings adequate for the veterinary use of the drug by the laity.

(ii) If it contains dihydrostreptomycin, an expiration date of 48 months or 60 months may be used if data have been submitted as described in subparagraph (1) (ii) of this paragraph.

(iii) In lieu of the statement required by subparagraph (1) (iii) of this paragraph, the labeling shall bear the statement "Warning—The use of this drug must be discontinued for 30 days before treated animals are slaughtered for food," and, if the drug is intended for use in animals producing milk for human consumption, the labeling shall also bear the statement required by § 148.5 of this chapter.

15. In § 146a.90, by revising the section heading and the introductory text of the section to read as follows:

§ 146a.90 Procaine penicillin and benzathine penicillin G in streptomycin sulfate solution veterinary; procaine penicillin and benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary (procaine penicillin and benzathine penicillin G in crystalline dihydrostreptomycin sulfate solution veterinary).

Procaine penicillin and benzathine penicillin G in streptomycin sulfate solution veterinary and procaine penicillin G and benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary, or "procaine penicillin in and are subject to all procedures prescribed by § 146a.67 for procaine penicillin in streptomycin sulfate solution veterinary and procaine penicillin in dihydrostreptomycin sulfate solution veterinary, except that:

16. In § 146a.91, by revising the section heading and the introductory text of the section to read as follows:

§ 146a.91 Benzathine penicillin G and streptomycin veterinary; benzathine penicillin G and dihydrostreptomycin veterinary.

Benzathine penicillin G and streptomycin veterinary and benzathine penicillin G and dihydrostreptomycin veterinary conform to all requirements prescribed by § 146a.77 for the dry mixture of benzathine penicillin G for aqueous injection and are subject to all procedures prescribed by that section for benzathine penicillin G for aqueous injection, except that:

17. In § 146a.93, by revising the section heading and the introductory text of the section to read as follows:

§ 146a.93 Penicillin-streptomycin powder veterinary; penicillin-dihydrostreptomycin powder veterinary.

Penicillin-streptomycin powder veterinary and penicillin-dihydrostreptomycin powder veterinary conform to all the requirements and are subject to all procedures by § 146a.88 for penicillin-streptomycin tablets and penicillin-dihydrostreptomycin tablets, except that:

18. By § 146a.96 to read as follows:

§ 146a.96 Dibenzylamine penicillin and streptomycin in oil veterinary; dibenzylamine penicillin and dihydrostreptomycin in oil veterinary.

Dibenzylamine penicillin and streptomycin in oil veterinary and dibenzylamine penicillin and dihydrostreptomycin in oil veterinary conform to all the requirements prescribed by § 146a.57 for procaine penicillin and dihydrostreptomycin in oil veterinary and are subject to all procedures prescribed by § 146a.57 for procaine penicillin and streptomycin in oil veterinary and procaine penicillin and dihydrostreptomycin in oil veterinary, except that dibenzylamine penicillin is used in lieu of procaine penicillin. The dibenzylamine penicillin used conforms to the requirements of § 146a.94 (a), except § 146a.94 (a) (2), (3) (unless it is intended for subcutaneous injection in fowl), and (4).

19. In § 146a.102, by revising the section heading and the introductory text of paragraph (a) to read as follows:

§ 146a.102 Benzathine penicillin G-procaine penicillin G-streptomycin in oil veterinary; benzathine penicillin G-procaine penicillin G-dihydrostreptomycin in oil veterinary.

(a) Benzathine penicillin G-procaine penicillin G-streptomycin in oil veterinary and benzathine penicillin G-procaine penicillin G-dihydrostreptomycin in oil veterinary conform to all requirements and are subject to all procedures prescribed by § 146a.101 for benzathine penicillin G and procaine penicillin G in oil, except that:

20. By revising § 146a.110 to read as follows:

§ 146a.110 Benzathine penicillin G in streptomycin sulfate solution veterinary; benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary (benzathine penicillin G in crystalline dihydrostreptomycin sulfate solution veterinary).

Benzathine penicillin G in streptomycin sulfate solution veterinary and benzathine penicillin G in dihydrostreptomycin sulfate solution veterinary conform to all requirements and are subject to all procedures prescribed by § 146a.67 for procaine penicillin in streptomycin sulfate solution veterinary and procaine penicillin in dihydrostreptomycin sulfate solution veterinary, except that benzathine penicillin G is used in lieu of procaine penicillin and the label and labeling shall bear the statement "Warning—Not for use in animals which

APPENDIX B (cont.)

9336

are raised for food production." The benzathine penicillin G used conforms to the requirements of § 146a.68(a).

Any person who will be adversely affected by the removal of any such drugs from the market may file, within 30 days of publication hereof in the *FEDERAL REGISTER*, objections to this order stating reasonable grounds and requesting a hearing on such objections. A statement of reasonable grounds for a hearing must identify the claimed errors in the National Academy of Sciences—National Research Council evaluation or the Administration conclusions and identify any adequate and well-controlled investigations on the basis of which it could reasonably be concluded that the combination drug would have the effectiveness claimed and would be safe for their intended uses.

Effective date. This order shall become effective 40 days after the date of its publication in the *FEDERAL REGISTER* to allow time for a recall to be completed. Certification of new stocks has been discontinued.

Dated: May 27, 1969.

HERBERT L. LEY, Jr.,
Commissioner of Food and Drugs.

[F.R. Doc. 69-6990; Filed, June 12, 1969;
8:46 a.m.]

PART 141c—CHLORTETRACYCLINE (OR TETRACYCLINE) AND CHLORTETRACYCLINE- (OR TETRACYCLINE-) CONTAINING DRUGS; TESTS AND METHODS OF ASSAY

PART 146c—CERTIFICATION OF CHLORTETRACYCLINE (OR TETRACYCLINE) AND CHLORTETRACYCLINE- (OR TETRACYCLINE-) CONTAINING DRUGS

Tetracycline-Amphotericin B Combination Drugs

In the *FEDERAL REGISTER* of December 24, 1968 (33 F.R. 19204), the Commissioner of Food and Drugs announced the conclusions of the Food and Drug Administration following evaluation of a report received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on the following preparations marketed by E. R. Squibb & Sons, Inc., Georges Road, New Brunswick, N.J. 08903, and containing tetracycline and amphotericin B: Mysteclin "F" Capsules, Mysteclin "F"—125 Capsules, Mysteclin "F" Syrup, and Mysteclin "F" Pediatric Drops.

The announcement stated that the Academy evaluated these drugs as ineffective as a fixed combination in the prevention of disease due to monilial organisms when used as a prophylaxis against the overgrowth of fungi; further, it stated that the Food and Drug Administration concurred in the views expressed by the Academy and concluded there is a lack of substantial evidence that the fixed combination products will have the effect which they purport or are represented to have.

All interested persons who might be adversely affected by removal of the drugs from the market were invited to submit, within 30 days of publication of the announcement, any pertinent data bearing on the proposal to amend the antibiotic drug regulations, where necessary, to delete from the list of drugs acceptable for certification those that contain the above-listed antibiotic combination.

E. R. Squibb & Sons, Inc., requested an extension of time to permit them to assemble, analyze, and submit in an orderly fashion additional material bearing on the effectiveness of the combinations. The firm was granted an additional 120 days to supply the data.

A submission was duly received and reviewed and the Food and Drug Administration concludes that there remains a lack of substantial evidence that the combination drugs containing tetracycline-amphotericin B will have the effect they purport or are represented to have for the prevention of disease due to monilial organisms when used as a prophylaxis against overgrowth of fungi.

In addition to the listed products, for which the conditions of certification are described in §§ 141c.260, 141c.262, 146c.260, and 146c.262, other sections, 141c.257 and 146c.257, describe the conditions for certification of other oral dosage forms of tetracycline with amphotericin B. The data submitted in support of these preparations, though not evaluated by the National Academy of Sciences, have been reviewed by the Food and Drug Administration and have been found to lack substantial evidence of effectiveness that the fixed combinations will have the previously stated effect.

Accordingly, the Commissioner concludes: (1) That the regulations for the certification of antibiotic drugs should be amended to delete combination preparations containing tetracycline and amphotericin B from the list of drugs acceptable for certification because of a lack of substantial evidence that such combinations have the clinical effect they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling; and (2) that all outstanding certificates heretofore issued for such combination drugs should be revoked.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-51, as amended, 59 Stat. 463, as amended; 21 U.S.C. 352, 357) and under the authority delegated to the Commissioner (21 CFR 2.120), Parts 141c and 146c are amended by repealing §§ 141c.257, 141c.260, 141c.262, 146c.257, 146c.260, and 146c.262 and all antibiotic certificates issued under those regulations are revoked.

Any person who will be adversely affected by the removal of any such drugs from the market may file, within 30 days of publication hereof in the *FEDERAL REGISTER*, objections to this order stating reasonable grounds and requesting a hearing on such objections. A statement of reasonable grounds for a hearing should identify the claimed errors

in the National Academy of Sciences—National Research Council evaluation and the Administration's conclusions as to the effectiveness of the combination drug and identify any adequate and well controlled investigations on the basis of which it reasonably could be concluded that the drug would have the effectiveness claimed for its intended uses. Objections should be filed, preferably in quintuplicate, with the Hearing Clerk, Department of Health, Education, and Welfare, Room 5440, 330 Independence Avenue SW., Washington, D.C. 20201, and may be accompanied by a memorandum or brief in support thereof.

If objections accompanied by reasonable grounds are received, the Commissioner will promptly announce a hearing. If a hearing is scheduled, it will be held under the provisions of section 507(f) of the Act, employing the hearing procedures set forth in Subpart F of Part 2 (21 CFR Part 2), as amended by § 146.1 of the regulations published April 8, 1969, in the *FEDERAL REGISTER*.

Effective date. This order will become effective 40 days from its date of publication in the *FEDERAL REGISTER* unless stayed by the filing of proper objections. The Commissioner will announce in the *FEDERAL REGISTER* whether or not requests for hearing with reasonable grounds have been received during the 30-day period. At that time the Commissioner will specify how the outstanding stocks of the affected drugs are to be handled.

(Secs. 502, 507, 52 Stat. 1050-51, as amended, 59 Stat. 463, as amended; 21 U.S.C. 352, 357)

Dated: May 27, 1969.

HERBERT L. LEY, Jr.,
Commissioner of Food and Drugs.

[F.R. Doc. 69-6990; Filed, June 12, 1969;
8:46 a.m.]

PART 146a—CERTIFICATION OF PENICILLIN AND PENICILLIN-CONTAINING DRUGS

Certain Penicillin-Sulfonamide Combination Products for Oral Administration

In the *FEDERAL REGISTER* of April 2, 1969 (34 F.R. 6006), the Commissioner of Food and Drugs announced the conclusions of the Food and Drug Administration following evaluation of reports received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on the following preparations:

A. Combination drugs containing potassium penicillin G and sulfisoxazole: Gantrisin "100" Tablets, Gantrisin "200" Tablets, and Gantrisin "300" Tablets; marketed by Hoffmann-La Roche, Inc., 340 Kingsland Avenue, Nutley, N.J. 07110.

B. Combination drugs containing potassium penicillin G, sulfadiazine, sulfamerazine, and sulfamethazine:

1. Neopenzine Suspension; marketed by Eli Lilly & Co., Indianapolis, Ind. 46206.

APPENDIX B (cont.)

RULES AND REGULATIONS

9337

2. Neopenzine "150" Tablets and Neopenzine "300" Tablets; marketed by Eli Lilly & Co.
3. Trisem-Pen Powder; marketed by S. E. Massengill Co., Bristol, Tenn. 37620.
4. Trisem-Pen Tablets; marketed by The S. E. Massengill Co.
5. Penicillin with Triple Sulfas Tablets; marketed by Biocraft Laboratories, Inc., 92 Route 44, East Paterson, N.J. 07407.
6. K-cillin Sulfas Powder for Syrup; by Biocraft Laboratories, Inc.
7. Sulfas-Sugracillin 125M Granules and Sulfas-Sugracillin 250M Fortified Granules; marketed by The Upjohn Co., Kalamazoo, Mich. 49002.
8. Flavocillin-CS Powder; marketed by Philadelphia Laboratories, Inc., 9815 Roosevelt Boulevard, Philadelphia, Pa. 19114.
9. Potassium Penicillin G with Triple Sulfonamides Tablets; Philadelphia Laboratories, Inc.
10. Biosulfas 125M and 250M Tablets; marketed by The Upjohn Co.
11. Penicillin-Biotic-250 Tablets; by Richlyn Laboratories, Inc., Castor Avenue at Kensington Avenue, Philadelphia, Pa. 19124.
12. Penicillin with Triple Sulfas No. 1, No. 2, and No. 3; marketed by Richlyn Laboratories, Inc.
13. Potassium Penicillin G Tablets with Triple Sulfonamides; by Vitamix Pharmaceuticals, Inc., 2900 North 17th Street, Philadelphia, Pa. 19132.
14. Penicillin 100,000 (also 200,000, 250,000, and 300,000) Units with Triple Sulfonamides Tablets; marketed by Zenith Laboratories, Inc., 180 South Dean Street, Englewood, N.J. 07631.
15. Penicillin with Triple Sulfas Tablets; marketed by Supreme Pharmaceutical Co., Inc., 354 Mercer Street, Jersey City, N.J. 07302.
16. Pentid-Sulfas Tablets; marketed by E. R. Squibb & Sons, Inc., Georges Road, New Brunswick, N.J. 08902.
17. Pentid-Sulfas for Syrup and Pentid "400" Sulfas for Syrup; marketed by E. R. Squibb & Sons, Inc.
18. Penicillin-Three Sulfonamide Tablets "100" and Penicillin-Three Sulfonamide Tablets "300"; marketed by Nyco Laboratories, Inc., 34-34 Vernon Boulevard, Long Island City, N.Y. 11104.
19. Buffered Potassium Penicillin G with 3 Sulfas Powder for Syrup; marketed by Nyco Laboratories, Inc.
- C. Combination drugs containing potassium penicillin G, sulfadiazine, sulfamerazine, and sulfacetamide:
 1. Flavored Penicillin G Powder with Triple Sulfonamides; by Vitamix Pharmaceuticals, Inc.
 2. Penicillin with Sulfonamides Powder for Solution; marketed by Biocraft Laboratories, Inc.
- D. Combination drugs containing phenoxymethyl penicillin (as the base or benzathine salt), sulfadiazine, and sulfamerazine:
 1. Pen-Vee Sulfas, Tablets; marketed by Wyeth Laboratories, Inc., Philadelphia, Pa. 19101.

2. Pen-Vee Sulfas, Suspensions; marketed by Wyeth Laboratories, Inc.

E. Combination drugs containing phenoxymethyl penicillin (as the base or potassium or benzathine salt), sulfadiazine, sulfamerazine, and sulfamethazine:

1. Compoicillin-VK with Sulfas Film-tab; marketed by Abbott Laboratories, North Chicago, Ill. 60064.

2. Compoicillin-VK with Sulfas Granules for Oral Suspension; marketed by Abbott Laboratories.

3. V-Cillin Sulfas Tablets; marketed by Eli Lilly & Co.

4. V-Cillin Sulfas Pediatric for Oral Suspension; marketed by Eli Lilly & Co.

5. V-Cillin K Sulfas Tablets; marketed by Eli Lilly & Co.

6. V-Cillin K Sulfas Pediatric for Oral Suspension; marketed by Eli Lilly & Co.

F. Combination drugs containing benzathine penicillin G, sulfadiazine, sulfamerazine, and sulfamethazine:

1. Bicillin-Sulfas Suspension; marketed by Wyeth Laboratories, Inc.

2. Bicillin-Sulfas Tablets; marketed by Wyeth Laboratories, Inc.

The announcement stated that the Academy found these products to be ineffective or ineffective as fixed combinations for those indications in the labeling that were specific enough to be evaluated and that the Food and Drug Administration concurred that there is a lack of substantial evidence that each drug will have the effects it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling. All interested persons were invited to submit within 30 days pertinent data bearing on the proposal to amend the antibiotic drug regulations where necessary to delete the above antibiotic combinations from the list of drugs acceptable for certification.

E. R. Squibb and Sons submitted material in response to the announcement and this has been reviewed. The submission proposed labeling changes and included one controlled study of the drug in pediatric use, but it has been concluded that it does not provide substantial evidence of the effectiveness and evidence of the safety of such combination drug.

Accordingly, the Commissioner concludes that in the absence of substantial evidence of effectiveness for the fixed combination drugs and in recognition of the known hazards associated with each component of such combinations, e.g., hypersensitivity and blood dyscrasias with sulfonamides and allergenicity with penicillin, the regulations for the certification of antibiotic drugs should be amended as follows to delete the above-listed antibiotic combinations, and other oral dosage forms for human use containing penicillin and any sulfonamide, from the list of drugs acceptable for certification. The Commissioner further concludes that the certificates of safety and effectiveness heretofore issued for the combination drugs should be revoked on the basis of unwarranted hazards.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-51, as amended, 59 Stat. 463, as amended; 21 U.S.C. 352, 357) and under authority delegated to the Commissioner (21 CFR 2.120), Part 148a of the antibiotic drug regulations is amended as follows to delete the provisions for the inclusion of sulfonamides, in so far as they apply to such drugs for human use, and certificates previously issued for such drugs for human use under these regulations are revoked:

1. In § 148a.27 *Penicillin tablets*, the second sentence of paragraph (a) is revised to read "They may also contain probenecid, and, if they are intended solely for veterinary use, they may contain one or more suitable sulfonamides."

2. In § 148a.28 *Crystalline penicillin G oral suspension, crystalline penicillin G sodium oral suspension, potassium penicillin G oral suspension*, the first sentence of paragraph (a) is amended by deleting "or one or more suitable sulfonamides".

3. In § 148a.51 *Buffered penicillin powder, penicillin powder with buffered aqueous diluent*:

- a. Paragraph (a) is amended in the first sentence by deleting "with or without one or more suitable sulfonamides".

- b. Paragraph (b) is amended by changing the last sentence to read "Each immediate container may be packaged in combination with a container of a suitable and harmless aqueous vehicle and with or without probenecid."

4. In § 148a.69 *Benzathine penicillin G oral suspension, benzathine penicillin G for oral suspension (benzathine penicillin G powder)*:

- a. Paragraph (a) is amended in the first sentence by deleting "with or without one or more suitable sulfonamides".

- b. Paragraph (c) (1) (ii) is deleted.

5. In § 148a.95 *Dibenzylamine penicillin and potassium penicillin powder, buffered*:

- a. Paragraph (a) is amended in the first sentence by deleting "with or without one or more suitable sulfonamides, and".

- b. Paragraph (c) (1) (ii) is deleted.

6. In § 148a.104 *Phenoxymethyl penicillin for oral suspension, potassium phenoxymethyl penicillin for oral solution*:

- a. Paragraph (a) is amended in the first sentence by changing the comma after "preservatives" to a period and by deleting "and with or without one or more suitable sulfonamides."

- b. Paragraph (c) (1) (ii) is deleted.

Any person who will be adversely affected by the removal of any such drugs from the market may file, within 30 days after publication hereof in the *FEDERAL REGISTER*, objections to this order stating reasonable grounds and requesting a hearing on such objections. A statement of reasonable grounds for a hearing must identify the claimed errors in the National Academy of Sciences-National Research Council evaluation or the Administration's conclusions and identify

APPENDIX B (cont.)

RULES AND REGULATIONS

9338

any adequate and well-controlled investigations on the basis of which it could reasonably be concluded that the combination drugs would have the effectiveness claimed and would be safe for their intended uses.

Effective date. This order shall become effective 40 days after the date of its publication in the FEDERAL REGISTER to allow time for a recall to be completed. Certification of new stocks has been discontinued.

(Secs. 502, 507, 52 Stat. 1050-51, as amended, 59 Stat. 468, as amended; 21 U.S.C. 352, 357)

Dated: May 27, 1969.

HERBERT L. LEY, Jr.,
Commissioner of Food and Drugs.

[F.R. Doc. 69-6961; Filed, June 12, 1969;
8:46 a.m.]

APPENDIX B (cont.)

RULES AND REGULATIONS

18161

Title 21—FOOD AND DRUGS

Chapter I—Food and Drug Administration, Department of Health, Education, and Welfare

SUBCHAPTER C—DRUGS

PART 141c—CHLORTETRACYCLINE (OR TETRACYCLINE) AND CHLORTETRACYCLINE- (OR TETRACYCLINE-) CONTAINING DRUGS; TESTS AND METHODS OF ASSAY

PART 146c—CERTIFICATION OF CHLORTETRACYCLINE (OR TETRACYCLINE) AND CHLORTETRACYCLINE (OR TETRACYCLINE-) CONTAINING DRUGS

PART 148n—OXYTETRACYCLINE

Certain Tetracycline-Nystatin, Oxytetracycline-Nystatin, and Demethylchlortetracycline-Nystatin Combination Preparations for Oral Use in Humans

In the FEDERAL REGISTER of April 2, 1969 (34 F.R. 6007), the Commissioner of Food and Drugs announced the conclusions of the Food and Drug Administration following evaluation of reports received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on the following preparations:

A. Combination drugs containing tetracycline, tetracycline hydrochloride, or tetracycline phosphate complex with nystatin:

1. Mysteclin-V Capsules; E. R. Squibb & Sons, Inc., Georges Road, New Brunswick, N.J. 08903.
2. Terrastatin for Oral Suspension; Chas. Pfizer & Co., Inc., 235 East 42d Street, New York, N.Y. 10017.
3. Terrastatin Capsules; Chas. Pfizer & Co., Inc.
4. Comycin Half-Strength Capsules; The Upjohn Co., 7171 Portage Road, Kalamazoo, Mich. 49002.
5. Comycin Capsules; The Upjohn Co.
6. Achrostatin V for Oral Suspension; Lederle Laboratories, Division of American Cyanamid Co., West Middletown Road, Pearl River, N.Y. 10965.
7. Achrostatin V Capsules; Lederle Laboratories, Division of American Cyanamid Co.

B. Combination drugs containing oxytetracycline and nystatin:

1. Terrastatin for Oral Suspension; Chas. Pfizer & Co., Inc.
2. Terrastatin Capsules; Chas. Pfizer & Co., Inc.

C. Combination Drugs containing demethylchlortetracycline and nystatin:

1. Declostatin for Oral Suspension; Lederle Laboratories, Division of American Cyanamid Co.
2. Declostatin Capsules; Lederle Laboratories, Division of American Cyanamid Co.

The Academy evaluated these drugs as ineffective as fixed combinations for simultaneous antimicrobial therapy and

monilial prophylaxis and found that adequate documented evidence is lacking that the fixed combinations are useful during therapy in preventing clinical disease due to monilial superinfection. The Food and Drug Administration concurred with the views expressed by the Academy and concluded that substantial evidence is lacking that each of these combination drugs will have the effect it purports or is represented to have.

All interested persons who might be adversely affected by removal of drugs containing any of the above-listed combinations from the market were invited to submit within 30 days, any pertinent data bearing on the proposal to amend the antibiotic drug regulations to delete from the list of drugs acceptable for certification, those that contain the above-listed antibiotic combinations.

Lederle Laboratories submitted responses to the announcement which have been reviewed and found to contain no new clinical data. The Food and Drug Administration concludes that the material submitted does not provide substantial evidence of effectiveness of such combination drugs.

In addition to the above-listed products, for which the conditions of certification are described in §§ 141c.224, 141c.225, 141c.229, 141c.236, 141c.259, 141c.263, 146c.224, 146c.236, 146c.259, 146c.263, 148n.9 and 148n.10, other sections, §§ 141c.271, 146c.225, 146c.229, and 146c.271, described the conditions for certification of other oral dosage forms of such combinations. Preparations currently marketed under these regulations in addition to those listed above are:

1. Tetrex-F Capsules (tetracycline phosphate complex-nystatin) and Tetrex-F for Oral Suspension (tetracycline-nystatin); Bristol Laboratories, Division of Bristol-Myers Co., Thompson Road, Syracuse, N.Y. 13201.

2. Declostatin 300 Tablets (demethylchlortetracycline-nystatin); Lederle Laboratories, Division of American Cyanamid Co.

The data submitted in support of these preparations, though not evaluated by the National Academy of Sciences—National Research Council, have been reviewed by the Food and Drug Administration and have been found to lack substantial evidence that the fixed combinations will have the effect they purport or are represented to have.

Accordingly, the Commissioner of Food and Drugs concludes (1) that the regulations for the certification of antibiotic drugs should be amended as follows to delete the above-listed antibiotic combinations of oral dosage forms for human use from the list of drugs acceptable for certification and (2) that all outstanding certificates heretofore issued for such combination drugs should be revoked.

Therefore, pursuant to the provisions of the Federal Food, Drug and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-51, as amended, 59 Stat. 463, as amended; 21 U.S.C. 352, 357) and under authority delegated to the Commissioner (21 CFR 2.120), Parts 141c, 146c and 148n are

amended by repealing §§ 141c.224, 141c.225, 141c.229, 141c.236, 141c.259, 141c.263, 141c.271, 146c.224, 146c.225, 146c.229, 146c.236, 146c.259, 146c.263, 146c.271, 148n.9, and 148n.10, and all antibiotic certificates issued under those regulations are revoked.

Any person who will be adversely affected by the removal of any such drugs from the market may file, within 30 days after publication hereof in the FEDERAL REGISTER, objections to this order stating reasonable grounds and requesting a hearing on such objections. A statement of reasonable grounds for a hearing (1) should identify the claimed errors in the National Academy of Sciences—National Research Council's evaluation and the Administration's conclusions as to the effectiveness of the combination drug and (2) should identify any adequate and well-controlled investigations on the basis of which it reasonably could be concluded that the drug would have the effectiveness claimed for its intended uses. Objections should be filed (preferably in quintuplicate) with the Hearing Clerk, Department of Health, Education, and Welfare, Room 5440, 330 Independence Avenue SW., Washington, D.C. 20201, and may be accompanied by a memorandum or brief in support thereof.

If objections accompanied by reasonable grounds are received, the Commissioner will promptly announce a hearing. If a hearing is scheduled, it will be held under the provisions of section 507 (f) of the Federal Food, Drug, and Cosmetic Act.

Effective date. This order shall become effective 40 days after its date of publication in the FEDERAL REGISTER unless stayed by the filing of proper objections. The Commissioner will announce in the FEDERAL REGISTER whether or not requests for hearing with reasonable grounds have been received during the 30-day period. At that time the Commissioner will specify how the outstanding stocks of the affected drugs are to be handled.

(Secs. 502, 507, 52 Stat. 1050-51, as amended, 59 Stat. 463, as amended; 21 U.S.C. 352, 357)

Dated: November 4, 1969.

HERBERT L. LEY, Jr.,
Commissioner of Food and Drugs.

[F.R. Doc. 69-13425; Filed, Nov. 12, 1969; 8:46 a.m.]

APPENDIX B (cont.)

RULES AND REGULATIONS

✓ PART 141c—CHLORTETRACYCLINE (OR TETRACYCLINE) AND CHLORTETRACYCLINE - (OR TETRACYCLINE-) CONTAINING DRUGS; TESTS AND METHODS OF ASSAY

PART 146c—CERTIFICATION OF CHLORTETRACYCLINE (OR TETRACYCLINE) AND CHLORTETRACYCLINE - (OR TETRACYCLINE-) CONTAINING DRUGS

PART 148n—OXYTETRACYCLINE

Certain Tetracycline-Nystatin, Oxytetracycline-Nystatin, and Demethylchlortetracycline-Nystatin Combination Preparations for Oral Administration; Postponement of Effective Date and Extension of Time for Submitting Data

An order was published in the FEDERAL REGISTER of November 13, 1969 (34 F.R. 18161), to become effective in 40 days, amending Parts 141c, 146c, and 148n of the antibiotic drug regulations to repeal provisions for certification of combination drugs containing tetracycline-nystatin, oxytetracycline-nystatin, and demethylchlortetracycline-nystatin for oral use. Thirty days were provided for filing proper objections to the order and requests for a hearing.

The Commissioner of Food and Drugs has received objections and a request for an extension of the effective date to allow time for the submission of additional data.

Good reason therefor appearing, the effective date of the order is hereby postponed, and an additional 40 days from December 23, 1969, will be allowed for the submission of pertinent data. The order

shall become effective March 23, 1970, unless stayed by the Commissioner.

(Federal Food, Drug, and Cosmetic Act, secs. 502, 507, 52 Stat. 1050-51, as amended, 59 Stat. 463, as amended; 21 U.S.C. 352, 357, and under authority delegated to the Commissioner, 21 CFR 2.120)

Dated: December 23, 1969.

CHARLES C. EDWARDS,
Acting Commissioner
of Food and Drugs.

[F.R. Doc. 69-15404; Filed, Dec. 24, 1969;
10:43 a.m.]

FEDERAL REGISTER, VOL. 34, NO. 249—WEDNESDAY, DECEMBER 31, 1969

APPENDIX B (cont.)

RULES AND REGULATIONS

SUBCHAPTER C—DRUGS

PART 141c—CHLORTETRACYCLINE (OR TETRACYCLINE) AND CHLORTETRACYCLINE- (OR TETRACYCLINE-) CONTAINING DRUGS; TESTS AND METHODS OF ASSAY**PART 146c—CERTIFICATION OF CHLORTETRACYCLINE (OR TETRACYCLINE) AND CHLORTETRACYCLINE- (OR TETRACYCLINE-) CONTAINING DRUGS****PART 148n—OXYTETRACYCLINE****Certain Tetracycline-Nystatin, Oxytetracycline-Nystatin, and Demethylchlortetracycline-Nystatin Combination Preparations for Oral Administration; Further Postponement of Effective Date**

An order was published in the *FEDERAL REGISTER* of November 13, 1969 (34 F.R. 18161), to become effective in 40 days, amending Parts 141c, 146c, and 148n, of the antibiotic drug regulations to repeal provisions for certification of combination drugs containing tetracycline-nystatin, oxytetracycline-nystatin, and demethylchlortetracycline-nystatin for oral use.

Having received objections and a request for an extension of the effective date to allow for the submission of additional data, the Commissioner of Food and Drugs postponed the effective date of the order to March 23, 1970. The postponement document was published in

the *FEDERAL REGISTER* of December 31, 1969 (34 F.R. 20427).

Additional material has been received and is being reviewed; however, the Commissioner concludes that the effective date of the order should be further postponed to allow time for completion of review of the objections and the material submitted. When this review is completed, the Commissioner will announce in the *FEDERAL REGISTER* whether or not requests for hearing with reasonable grounds have been received. Therefore, the effective date of the order of November 13, 1969 (34 F.R. 18161), is hereby postponed pending said review.

This action is taken pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-51, as amended, 59 Stat. 463, as amended; 21 U.S.C. 352, 357) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: March 30, 1970.

SAM D. FINE,
*Acting Associate Commissioner
for Compliance.*

[F.R. Doc. 70-4304; Filed, Apr. 8, 1970;
8:46 a.m.]

APPENDIX C—FDA BRIEF, "ACHROCIDIN CASE"

American Cyanamid Company, Petitioner v. Elliot R. Richardson, Secretary of Health, Education, and Welfare, and Charles C. Edwards, Commissioner of Food and Drugs, Respondents, United States Court of Appeals for the First Circuit, No. 71-1388. (Source: Advertising of Proprietary Medicines, Vol. 3, pp. 1046-51).

UNITED STATES COURT OF APPEALS FOR THE FIRST CIRCUIT

No. 71-1388

AMERICAN CYANAMID COMPANY, PETITIONER

v.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND
CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, RESPONDENTS

Respondents' Brief

RESPONDENTS' STATEMENT OF THE ISSUE PRESENTED

Whether the Commissioner of Food and Drugs may, without granting a formal hearing, enter an Order repealing regulations providing for the certification of Achrocidin Compound Tablets and Achrocidin Compound Syrup, when the manufacturer involved fails to comply with the Commissioner's regulations requiring a showing of reasonable grounds for a hearing.

STATEMENT OF THE CASE

This case involves the validity of an order of the Commissioner of Food and Drugs¹ repealing regulations providing for the certification of Achrocidin Compound Tablets and Achrocidin Compound Syrup,² fixed-ratio combination drugs consisting primarily of an antibiotic, an antihistamine, and analgesics. The Achrocidin combinations are prescription drugs offered for "treatment of tetracycline-sensitive bacterial infection which may complicate vasomotor rhinitis, sinusitis and other allergic diseases of the upper respiratory tract, and for the concomitant symptomatic relief of headache and nasal congestion". (App. 8, 10).

In October 1962, Congress passed the Drug Amendments of 1962, P.L. 87-781, in which the standard of proof of drug effectiveness was defined in terms of "evidence consisting of adequate and well-controlled investigation, including clinical investigations * * *", 21 U.S.C. 355(d).³ Thereafter, the Commissioner contracted with the National Academy of Sciences-National Research Council⁴ to assist the Agency by establishing a Drug Efficacy Study Group to review the claims of drug effectiveness for all drugs on the market and to make recommendations to the Commissioner with respect to these drugs and their promotional claims.⁵

¹ Acting under delegated authority from the Secretary of Health, Education, and Welfare, 21 CFR 2.120.

² These drugs first came on the market in 1956 and 1957.

³ This standard applies to antibiotic drugs certified under 21 U.S.C. 357. *Pfizer, Inc. v. Richardson*, 434 F.2d 536 (C.A. 2, 1970).

⁴ Hereinafter referred to as the "NAS-NRC".

⁵ Hereinafter referred to as "Lederle."

All manufacturers, including petitioner, were directed to submit a special report of "the best data available to support medical claims" for their drugs, including a "list of literature references most pertinent to an evaluation of the effectiveness of the drug[s] for the purposes for which [they were] offered," and any "unpublished articles or other data pertinent to an evaluation of the claims." [App. 393-4; 21 F.R. 13014, October 6, 1966].

The NAS-NRC found the Achrocin drugs to be "ineffective as a fixed combination" [App. 118, 127].⁶ The Commissioner concurred in this evaluation of Achrocin and identical evaluations of similar drugs and on September 12, 1969, gave notice of his intention to amend the antibiotic regulations to delete provisions for marketing drugs containing fixed dosages of antibiotics with antihistamines, and/or analgesics and/or decongestants. [App. 33; 34 F.R. 14342]. All persons adversely affected were invited to submit data, in the form of adequate and well controlled studies, bearing on the proposal. Lederle responded to the notice with a six page letter which failed to identify any controlled studies on its drugs [App. 34-39].

On May 8, 1970, the Commissioner promulgated interpretive regulations articulating the criteria for adequate and well-controlled clinical investigations, 21 CFR 130.12(a)(5)(ii).⁷ Companion procedural regulations delineating the requirements of "reasonable grounds" for a hearing on the proposed issuance, amendment, or repeal of any antibiotic regulation under 21 U.S.C. 357(f) were also promulgated, 21 CFR 146.1(d). The regulations provide that:

The statement of reasonable grounds and request for a hearing shall be made in writing * * * and shall state the reasons why the proposal should not be adopted, or should not be adopted as proposed, together with a well-organized and full factual analysis of the clinical and other investigational data the objector is prepared to prove in support of his objections. A request for hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data incorporated into or referred to by the objections and from the factual analysis in the request for a hearing that there is no genuine issue of fact which precludes the action taken on the proposal, e.g. no adequate and well controlled clinical investigations to support the claims identified, the Commissioner will enter an order on this data, making findings and conclusions on such data.

On September 12, 1970, the Commissioner published a proposal to amend the antibiotic regulations to delete provisions for certification of antibiotic, antihistamine, analgesic combinations drugs [App. 41-2; 35 F.R. 14392]. All those adversely affected were referred to applicable regulations and given 30 days to "file objections to this order, request a hearing, and show reasonable grounds for a hearing". All manufacturers adversely affected acquiesced in the order, save Lederle and Bristol Laboratories, both of whom filed objections and requested a hearing.

In its October 12, 1970, request for a hearing, Lederle did not submit or refer to any controlled clinical investigations of the Achrocin drugs [App. 43-350].⁸ What Lederle did submit were, among other things, an ad hoc survey of physicians who used Achrocin, data showing voluminous sales, affidavits of physicians testifying to the usefulness and convenience of the drugs, and affidavits stating that ineffectiveness and lack of safety had not been proved.

⁶ The NAS-NRC Drug Efficacy Study Group Final Report explained this finding as follows: [App. 405-6]: "The rating 'Ineffective as a fixed combination' was brought into use to deal rationally with certain combinations of drugs, notably of two or more antibiotics, one or more of which when administered alone is acknowledged to be effective for the cited indications. It is a basic principle of medical practice that more than one drug should be administered for the treatment of a given condition only if the physician is persuaded that there is a substantial reason to believe that each drug will make a positive contribution to the effect he seeks. Risks of adverse drug reactions should not be multiplied unless there be overriding benefit. Moreover, each drug should be given at the dose level that may be expected to make its optimal contribution to the total effect, taking into account the status of the individual patient any synergistic or antagonistic effects that one drug may be known to have on the safety or efficacy of the other. On these grounds multiple therapy using fixed dose ratios determined by the manufacturer and not by the physician is, in general, poor practice."

⁷ The regulations require, among other things, that the plan for a study include, a clear statement of the study objective as well as provisions for selection of a homogenous patient population, for assignment of patients to test groups, standards of comparison by which the test drug can be evaluated, and statistical evaluation. See *Pharmaceutical Manufacturers Association v. Richardson*, 318 F. Supp 301 (D.Del., 1970).

⁸ Indeed, petitioner so recognized its failure to produce reasonable grounds as called for by the regulations that it requested a waiver of the adequate and well-controlled clinical investigating requirement on its drugs [App. 351-63].

On February 18, 1971, the Commissioner proposed to formalize his approach to fixed combination drugs in a statement of policy [Pet. Addendum, p. 38-9; 36 F.R. 3126]. The proposal stated that each ingredient in a combination drug must contribute to the drug's total effect and that the "advantage of the combination drug must obtain for all conditions for which the [drug is indicated], for the various dose schedules recommended, for the duration of dosage suggested, and for most patients for which the [drug] is recommended." Lederle did not comment on the proposal although comments were received from 29 other drug manufacturers. The substance of the proposal, albeit phrased in slightly different language, was adopted in final form on October 15, 1971 [Pet. Addendum, p. 40-1].

The final order under attack here was published on November 17, 1971. [App. 367; 36 F.R. 21879].⁹ The Commissioner noted that no adequate and well-controlled clinical investigations of Achrocidin had been identified; that there had been no showing "that each drug in the combination provides an advantage, as combined, for all doses, for the duration suggested, and for a significant patient population"; and that a determination of effectiveness could not be based on the efficacy of each component when administered alone, or on widespread physician acceptance.

After the Commissioner denied Lederle's request for a stay, it sought a judicial stay of the effectiveness of the order which was denied by this Court, Coffin J., on December 16, 1971. The company's motion for reargument was denied December 17, 1971. The Supreme Court, by Justices Brennan and Blackmun separately, denied Lederle's applications for a stay on December 22, 1971.

ARGUMENT

Lederle's arguments have, for the most part, been made before in other cases arising out of the Commissioner's efforts to implement the NAS-NRC drug efficacy review; in every instance the courts which have considered these arguments have rejected them. See: *Upjohn Co. v. Finch*, 422 F. 2d 944 (C.A. 6, 1970); *CIBA-Geigy Co. v. Richardson*, 446 F. 2d 466 (C.A. 2, 1971); *Pfizer Inc. v. Richardson*, 434 F. 2d 536 (C.A. 2, 1970); *Pharmaceutical Manufacturer's Association v. Richardson*, *supra*; *Diamond Laboratories v. Richardson*, decided (No. 71-1163, C.A. 8, January 3, 1972).¹⁰

⁹ Bristol Laboratories filed a petition for review of the order in the Third Circuit. After that proceeding was transferred to this Court pursuant to 18 U.S.C. 2112, Bristol's application for a stay of the order was denied and the appeal abandoned.

¹⁰ The Slip Opinion is reproduced in the Addendum to this Brief.

APPENDIX D—CORRESPONDENCE RE FDA COMPLIANCE WITH 1972
COURT ORDER

1. MICHAEL C. HARPER, ESQ., CENTER FOR LAW AND SOCIAL POLICY, TO DONALD KENNEDY, COMMISSIONER OF FOOD AND DRUGS, JULY 6, 1977

JULY 6, 1977.

DONALD KENNEDY,
Commissioner, Food and Drug Administration,
5600 Fishers Lane, Rockville, Md.

DEAR COMMISSIONER KENNEDY: We are writing as counsel to the American Public Health Association (APHA) and the National Council of Senior Citizens (NCSC). In 1970 APHA and NCSC brought suit against the then Acting Secretary of the Department of Health, Education and Welfare and the then Commissioner of the Food and Drug Administration to enforce the implementation of the 1962 amendments to the Food, Drug, and Cosmetic Act of 1938 requiring that all marketed drugs be shown effective for their suggested use. In 1972 our clients were granted summary judgment. In an opinion entitled *A.P.H.A. v. Veneman*, 349 F. Supp. 1311 (D.D.C. 1972), Judge Bryant explained that the F.D.A. had been delinquent in discharging its responsibilities to implement the 1962 amendments. By an accompanying, unpublished order, *A.P.H.A. v. Veneman*, No. 1847-70 (D.D.C., Oct. 10, 1972) (order), the court required the F.D.A. to take a series of actions by staggered deadlines reaching to October 19, 1976. By meeting these deadlines the F.D.A. was to implement the 1962 amendments 14 years after their passage and 12 years after the 1964 effective date which Congress had prescribed.

We are writing you now because October 10, 1976 is long past and the F.D.A. is still far from complying with the 1972 court order. The 1962 efficacy amendments to the Act remain substantially unimplemented, and the efforts of our clients to insure compliance with the amendments remain frustrated.

In accord with the court order, the F.D.A. has prepared semi-annual reports detailing the extent of its compliance. Those reports, however, have not justified sufficiently to us various failures of the F.D.A. to meet the court's deadlines. At this juncture, we believe that it would be beneficial for you and other involved officials to meet with us during July, in an effort to answer several questions raised but not resolved by your reports. Perhaps we thereby will be able to reach an agreement concerning further F.D.A. action, while avoiding resort to additional litigation.

Your responses to our inquiries may require preparation prior to the meeting, so we will describe our general concerns here. Our understanding of the F.D.A.'s position might be enhanced by your staff composing written answers to some or all of our questions for distribution at the meeting.

One of our major concerns is the F.D.A.'s utilization of paragraph XIV of the court orders. Under paragraph XIV, the court allowed the F.D.A. to permit the continued marketing of a "limited number of drugs" pending "completion of scientific studies to determine effectiveness where there is a compelling justification of the medical need" for the drugs. According to the F.D.A.'s ninth semi-annual report, 303 drugs are now exempt under this provision. According to the F.D.A.'s own count, that amounts to over 30 percent of the 1,800-odd drugs originally subject to the court order. We question whether this number of exemptions can be considered "limited" and whether the extent of the utilization of paragraph XIV does not itself constitute a violation of the court order. Our concerns are compounded by the fact that for 252 of the 303 drugs, notices of hearings had not been issued before exemption. Thus, when and if exemptions are removed for most of the paragraph XIV drugs, the administrative process by which these drugs could be withdrawn from the market would extend far into the future.

Furthermore, we can detect from reading the semi-annual reports and Federal Register notices no consistently applied standard for exempting drugs under paragraph XIV and we would like you to explain what criteria the F.D.A. has

used. In some cases, the F.D.A. has seemed to base exemptions on the absence of alternative drugs, but certain drugs have been exempted when alternatives did exist. In some, but not all cases, exemption notices have stressed that the drugs are used for highly serious ailments. The F.D.A. has defended some exemptions on the ground that the drug poses no safety risk, but in other cases a risk is either admitted or the F.D.A. is completely silent about safety.

We are also concerned that the F.D.A. rarely has indicated when a manufacturer of an exempted drug will complete its "pending scientific studies." We wonder if the F.D.A. has generally placed deadlines on these studies, and if so, how the deadlines have been set.

The significance of the number of paragraph XIV exemptions turns in part on how the F.D.A. plans to proceed once it lifts a paragraph XIV exemption. Will it issue a notice for hearing, and then rule on a request for hearing if there is one, in timeframes congruent with those provided by the court for nonparagraph XIV-exempt drugs in the same categories? Will the completed "scientific studies" affect the original NAS-NRC classifications of drugs?

We also find it perplexing that the number of paragraph XIV exemptions, as accounted for in the F.D.A. reports, has at times fluctuated without any notice or explanation.

Furthermore, there seem to be discrepancies between the count of exemptions set forth in the first three F.D.A. reports and the number indicated by the announcements in the Federal Register.

In addition, we are troubled that in the second report the F.D.A. exempted 18 drugs under paragraph XIV despite the lack of hearing requests, even though it removed a drug from the exemption list in the third report because the manufacturer did not request a hearing. We would like to know whether exemptions may be given without hearing requests.

Our second major concern is the F.D.A.'s failure even to issue notices of hearing in the case of 188 of the 290 drugs still subject to action (excluding paragraph XIV exemptions). This is particularly troublesome for two reasons. First, in each category of drugs defined by effectiveness, the deadlines for issuing notices were the most proximate to the date of the court order. Second, one can expect the withdrawal procedures to drag on for months after notices are finally issued.

We would like the F.D.A. to explain why it has failed to issue these 188 notices of hearing timely. Apparently, the preparation of such notices need not involve substantial administrative resources. According to 21 C.F.R. § 314.200(a)(1) the F.D.A. need include in a notice of hearing merely a general statement of its reasons for proposing to withdraw the drug. Such a statement could be drawn, presumably, from the NAS-NRC study itself.

We have several other areas of concern. Regarding rulings on hearing requests, we would like clarified whether the F.D.A. has removed from the market all those drugs concerning which it has denied a hearing. We would also like the F.D.A. to justify its failure for all drugs. Given the court order and the history of delay and study and restudy, how does the F.D.A. defend the double review of hearing requests set forth in 21 C.F.R. § 314.200(f) and 21 C.F.R. § 430.20(b)(7)? We also wonder whether the F.D.A. has plans to hold more hearings in the future, and if it does, whether general compliance efforts will be slowed. Apparently only one adjudicative hearing has been held in the past.

In addition, please advise us whether the F.D.A. has removed from the market all of the drugs concerning which no request for a hearing was made within the time period for submitting a request. And we would like to know the number of cases, unnoted in the F.D.A. semi-annual reports, in which a notice of hearing has been issued, but a manufacturer still has time according to the regulations to submit a request for a hearing before the drug may be withdrawn. Will this number increase significantly the number of drugs on which rulings on hearing requests will have to be made?

The court, under paragraph XV of its order, permitted the exemption of drugs included in the F.D.A.'s over-the-counter study. We would like to know how many drugs the F.D.A. has exempted because they are similar or identical to drugs in the over-the-counter study?

The F.D.A. has repeatedly excused failures to meet the court ordered deadlines by stating that it has moved with the greatest possible speed given its limited resources. We wonder what percentage of the F.D.A.'s resources have in fact been committed to effectuating the 1962 amendments to the Act. Moreover, has the F.D.A. ever requested additional funding from Congress for the specific purpose of implementing the drug effectiveness requirements Congress intended to be implemented in 1964?

We hope to have an opportunity soon to discuss these and other questions with you. We would appreciate your calling us so that we might arrange to meet as soon as possible in July.

Sincerely,

MICHAEL C. HARPER.

2. DRAFT OF REPLY BY DONALD KENNEDY TO ABOVE LETTER, AUGUST 17, 1977

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., August 17, 1977.

MICHAEL C. HARPER, Esq.
Center for Law and Social Policy,
1751 N Street NW.,
Washington, D.C.

Dear MR. HARPER: I am responding to your letter of July 6, 1977, and to our discussion in my office on July 25, 1977, in which you expressed your concerns regarding our implementation of the 1962 efficacy amendments and the 1972 court order in the Veneman case.

I share your concern about the availability of drugs that have not been demonstrated to be effective, and the need to remove them from the market. Contrary to your assertions, however, it is my belief that FDA has substantially implemented the amendments and order. The efficacy provisions have been applied to all drug products approved by the agency subsequent to the 1962 amendments. Approximately 5,000 new drug applications have been received since 1962. In addition, decisions on more than 90% of the drugs approved prior to 1962 have already been made, and compliance activities have resulted in the removal of approximately 6800 products. The drugs remaining for administrative decision represent a small group of products for which considerable additional data were submitted to the agency by their manufacturers subsequent to the Panel Reports of the National Academy of Sciences/National Research Council. Although these drugs have presented some of the most difficult and time-consuming issues, we expect that many of them may very well be shown to be effective.

As you know, there are three areas remaining for completion in the Drug Efficacy Study Implementation (DESI): (1) drug products subject to Paragraph XIV of the court order, (2) drugs subject to requests for hearings; and (3) drugs with paragraphs which follow.

1. There are presently 303 drug products remaining subject to Paragraph XIV. In your letter, you expressed concern about the drugs now in Paragraph XIV. In our product "count" there may be a single drug entity of ingredient, but each supplier, dosage form, and dosage form strength is counted as a separate drug product. Thus, the figure "303" refers to individual products, not to drug entities or ingredients, and represents 8.7% of the products originally in the NAS/NRC Study. These comprise 19 classes or categories based on their indications and pharmacological effects in medical therapy. This figure fluctuates as products are added to or removed from the list of products which comprises Paragraph XIV. There is also an occasional variation resulting from a data base adjustment (e.g., to show that an additional strength tablet was included among the products reviewed). As listed in the Federal Register notices, the drugs do not necessarily reflect the product count of the data base. This may explain the fluctuations you observed in the semi-annual reports to Judge Bryant.

Our general plan for implementing Paragraph XIV is to publish for each class certain conditions for marketing that, if met, entitle the manufacturer to market the drug while studies are undertaken. Those conditions include time limits within which each manufacturer must submit protocols, commence studies, forward progress reports, and complete the studies. A firm that fails to meet the conditions in a timely manner, or to participate in a cooperative study that complies with the marketing conditions, is subject to action to remove his product from the market. At this time, final action has been completed on five categories of drug products in Paragraph XIV and partially completed on two categories. Conditions for marketing for two large groups (containing a total of 139 drug products out of the 303) have been published and studies are underway; for a third category, a document setting forth conditions for marketing has been prepared and publication is imminent. Two categories, containing 57 drug products, are scheduled for discussion by an Advisory Committee and by our Fixed Combination Committee.

in August. Thereafter, we plan to move on these quickly. In the remaining categories there are some studies underway.

The principal problem in implementing Paragraph XIV has been the lack of agreement on appropriate methodology to perform the studies; in addition, the studies available for these products did not meet our present criteria for being adequate and controlled as detailed in 21 CFR 314.111(a)(5). Considerable effort has been devoted to development of protocols for the performance of clinical trials (and, in appropriate cases, bioavailability studies) that will permit a definitive conclusion on the effectiveness of the products in a category. We believe that well-crafted protocols will, if adhered to, generate data that will preclude extensive further debate over the continued marketability of these products. To this end, we have involved our standing advisory committees in reviewing guidelines for protocols and have even contracted to have appropriate methodology developed. As guideline protocols are completed, conditions for marketing are published.

Perhaps an example will illustrate the problem more clearly. The coronary vasodilators (Category I of Paragraph XIV) are drugs used in the treatment of angina, a common medical condition that is often incapacitating without adequate treatment. The Agency contracted with experts at Purdue University to attempt to develop methodology. After an intensified and consistent effort which required two full years, a method is now available. This method has been written into the study guidelines for these products. Conditions for marketing for this category have been completed, and it is this category for which publication is imminent. The deadline for completion of bioavailability studies for these products is six months and for completion of clinical trials using this methodology is two additional years. (It should be noted that for the anabolic steroids used in the treatment of osteoporosis, Category X of Paragraph XIV, experts have indicated that the studies may need to go on for ten years before a final result of this treatment may be seen.)

The following factors reflect the considerations that went into the decision to place drug products under Paragraph XIV:

- (a) The seriousness of the disease or condition for which the drug products are indicated.
- (b) Absence of effective alternative drug therapy.
- (c) Greater risks or other serious disadvantages of alternative drug products available on the market not exhibited by the exempted drugs.
- (d) The distinct likelihood of proving effectiveness.
- (e) Lack of methodology to determine effectiveness (i.e., the inability of manufacturers to evaluate efficacy in a definitive way) and need for its development.
- (f) Only recently available adequate methodology for certain products and the need for definitive information about them.
- (g) Uniqueness of dosage form needed for alternative therapy.

These criteria were applied on a case-by-case basis. Paragraph XIV is not restrictive to drugs with published notices of opportunity for hearings or notices of hearing; it is based, pursuant to the court order, on justification of a medical need.

In addition to the above criteria, some drug products were included in Paragraph XIV because related drug products were being considered, pursuant to 21 CFR 330, by the Over-The-Counter (OTC) drug review panels. The factors considered were:

- 1. Their medical importance;
- 2. Volume of use-apparent need for such products in the market place and the potential for confusion if prescription products were removed from the market while OTC products containing the same ingredients remained available during the OTC review process; and
- 3. The likelihood that decisions in the OTC review would be applicable to these prescription drug products and the need for consistency in regulatory and scientific conclusions.

There are 66 DESI prescription drug products subject to Paragraph XIV because of the close relationship between their ingredients and uses and those of OTC product ingredients and uses. In these cases it was felt that the best and most current review of their use and efficacy could be obtained through the agency's OTC drug review process.

As your letter mentions, paragraph XV of the court order exempts DESI OTC drugs from its provisions. There were 512 OTC drug products in DESI. After the OTC Study was begun, almost all of these were exempted from implementation in DESI. The few reserved for DESI action (as listed in 21 CFR 330.12) consisted of products clearly not to be reviewed in the OTC study (e.g., insulin) and certain

products already the subject on hearing requests or final action to remove them from the market.

A lot of progress has already been made in an effort to reach valid scientific conclusions concerning the effectiveness of drugs subject to Paragraph XIV. When data from studies become available, they will be reviewed on a high priority basis, and our decisions will be published in the Federal Register. Appropriate labeling for those drugs that have demonstrated effectiveness will be required. For those not demonstrating effectiveness, regulatory action will be initiated to remove them and all related products from the market..

2. There are presently 200 drugs for which requests for a formal evidentiary public hearing are pending. The data submitted in support of such requests has generally been voluminous. Not all of these hearing requests will be granted. But before a decision can be made, the data must undergo medical and legal scrutiny.

As Mr. Merrill indicated during our meeting on July 25, a hearing requires nearly the full-time efforts of two lawyers and three scientists for six months. The denying of a hearings, where there is no factual issue because the studies fail to meet the statutory and regulatory standards, also takes considerable resources and time of both the legal and medical staffs. These denials, in order to withstand a court challenge, must be explained with sufficient specificity in order to meet the stringent judicial review standard that was established subsequent to the 1972 court order.

All DESI drugs for which hearings were denied have been removed from the market except those that are the subject of pending litigation, approximately 30 products, and 31 products in routine compliance action. Our policy is to require removal of drugs for which hearings are not requested as soon as a final order withdrawing approval is published in the Federal Register. We are essentially current in publishing such orders.

I am deeply concerned about the resources needed to complete this portion of the DESI program, and am presently exploring ways to determine how we can efficiently reduce the number of pending hearing requests consistent with our other legal obligations. Your suggestions on this matter are welcomed.

With respect to your question concerning our procedures for reviewing hearing requests, I refer you to the discussion of this matter at paragraph number 3 on page 9754 of the Federal Register of March 13, 1974 (copy attached). These procedures assure that an independent judgment is reached by an arbiter who is not involved in the initiation of the withdrawal proceedings, preclude bias, and guarantee fairness.

3. The final group of drugs consists of those products with interim classifications: 28 possibly effective products; 13 probably effective products; and 136 products with effective as well as less-than-effective indications. As you will recall, each initial announcement that classified a drug product or an indication as less-than-effective invited the manufacturers to submit data supporting the claims for the product. In some cases, volumes of material have been received for review. For this reason, the next regulatory step, publication of a notice of opportunity for a hearing that analyzes the submitted data if the data do not support effectiveness, has not occurred. I have directed that an intensive effort be made to complete these reviews and to publish determinations by the end of this summer. We are hopeful that virtually all conclusions will be published by October.

4. You have asked about our resource expenditures for DESI. Attached is a table indicating these expenditures for fiscal years 1969-1977.

Budget Requests for DESI increases are as follows:

Fiscal year 1971, 5 positions-----	\$80, 000
Fiscal year 1972, 40 positions-----	600, 000

In the fiscal year 1979 preliminary budget, 7 positions for DESI have been approved by the Department.

I believe that the above discussion and our discussion at our meeting of July 25, 1977, cover the concerns in your letter of July 6, 1977. I welcome the opportunity to explore these matters more fully at a subsequent meeting.

Although a considerable amount of the Agency's limited resources has been utilized to implement the DESI program, I have directed that an intensified effort be applied to the completion of this area of drug regulation. I am personally committed to the concept that all drug products on the market in this country be safe, effective, and properly labeled, as Congress has mandated.

Sincerely yours,

DONALD KENNEDY,
Commissioner of Food and Drugs.

DESI—HUMAN DRUGS—FDA RESOURCES (MAN-YEARS) FISCAL YEARS 1969-77

Fiscal years	DESI ¹	FDA ²	DESI/FDA (percent)	HD ³	DESI/HD (percent)
1969-----	10.2	4,069	0.25	1,727	0.59
1970-----	60.0	4,152	1.4	1,838	3.2
1971-----	68.6	4,360	1.5	1,841	3.7
1972-----	112.8	5,173	2.1	1,689	6.6
1973-----	124.2	5,904	2.1	1,751	7.1
1974-----	105.9	6,069	1.7	⁴ 1,530	6.9
1975-----	91.2	6,176	1.4	1,748	5.2
1976-----	109.0	6,303	1.7	1,823	5.9
Estimate 1977-----	105.8	7,299	1.4	2,022	5.2
Total-----	787.7	49,505	1.59	15,969	4.93

¹ Based on report prepared by Dr. Paul Bryan in July 1975. Annual man-year totals include Bureau and EDRO workforce but exclude other FDA personnel, e.g., General Counsel. Totals for fiscal year 1969, 1970, and 1971 exclude EDRO resources since no direct reporting against DESI was done at that time.

² FDA totals are taken from "actual" quotations in Justification of Appropriation Estimates (Congressional Budget) fiscal year 1971-78.

³ Based on Congressional Budget for human drugs program (HD) totals for fiscal years 1972-76 are actuals. Fiscal year 1977 is an estimate. Fiscal years 1969-71 are also estimates and do not account for lapses in hiring and unforeseen problems which cause diversion of field resources.

⁴ Fiscal year 1974 was the year of the mushroom crisis, thus human drugs field resources were diverted.

Note: Overall percentages exclusive of fiscal year 1969 are 5.45 percent and 1.71 percent respectively.

3. DONALD KENNEDY TO MICHAEL C. HARPER, AUGUST 30, 1977

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md. 20857, August 30, 1977.

MICHAEL C. HARPER, Esq.,
Center for Law and Social Policy,
1751 N Street, NW.,
Washington, D.C.

DEAR MR. HARPER: I am responding to your letter of July 6, 1977, and to our discussion in my office on July 25, 1977, in which you expressed your concerns regarding our implementation of the 1962 efficacy amendments and the 1972 court order in the *Veneman* case.

I share your concern about the availability of drugs that have not been demonstrated to be effective, and the need to remove them from the market. As we tried to explain in the meeting, however, we think FDA has substantially implemented the amendments and order. The efficacy provisions have been applied to all drug products approved by the Agency subsequent to the 1962 amendments. Approximately 5,000 new drug applications have been received since 1962. In addition, decisions on almost 90 percent of the drugs approved prior to 1962 have already been made, and compliance activities have resulted in the removal from the market of approximately 6800 products. The drugs remaining for administrative decision, other than those subject to further studies under Paragraph XIV of the court order, represent a small group of products for which considerable additional data were submitted to the Agency by their manufacturers subsequent to the Panel Reports of the National Academy of Sciences/National Research Council. These drugs have presented some of the most difficult and time-consuming problems, and we expect that many of them will ultimately be shown to be effective.

As you know, there are three areas remaining for completion in the Drug Efficacy Study Implementation (DESI): (1) drug products subject to Paragraph XIV of the court order; (2) drugs subject to requests for hearings; and (3) drugs with interim effectiveness classifications. They are discussed in that order in the following paragraphs:

1. There are presently 303 drug products subject to Paragraph XIV. In our product "count" for a single drug entity or ingredient, each supplier, dosage form, and dosage form strength is counted as a separate drug product. Thus, the figure "303" refers to individual products, not to drug entities or ingredients, and represents 8.7 percent of the products originally in the NAS/NRC study. These comprise 19 categories based on their indications and pharmacological effects in medi-

cal therapy. This figure fluctuates as specific products are added to or removed from the list of products covered under Paragraph XIV. There is also an occasional variation resulting from a data base adjustment (e.g., to show that an additional strength tablet was included among the products reviewed). Consequently, as listed in the Federal Register notices, the number of drug entities does not necessarily reflect the product count of the data base. This may explain the fluctuations you observed in the semi-annual reports to Judge Bryant.

Our general plan for implementing Paragraph XIV is to publish for each class certain conditions for marketing that, if met, entitle the manufacturer to market the drug while studies are undertaken. Those conditions include time limits within which each manufacturer must submit protocols, commence studies, forward progress reports, and complete the studies. A firm that fails to meet the conditions in a timely manner, or to participate in a cooperative study that complies with the marketing conditions, is subject to action to remove its product from the market. At this time, final action has been completed on five categories. Conditions for marketing for two large groups (containing a total of 139 drug products out of the 303) have been published and studies are underway; for a third category, a document setting forth marketing conditions has been prepared and publication is imminent. Two categories, containing 57 drug products, are scheduled for discussion by an advisory committee and by our Fixed Combination Committee in August. Thereafter, we plan to move on these quickly. In the remaining categories there are some studies underway.

The principal problem in implementing Paragraph XVI has been the lack of agreement on appropriate methodology to perform the studies; in addition, the studies available for these products did not meet our present criteria for being adequate and well controlled as detailed in 21 CFR 314.111(a)(5). Considerable effort has been devoted to development of protocols for the performance of clinical trials (and, in appropriate cases, bioavailability studies) that will permit a definitive conclusion on the effectiveness of the products in a category. We believe that well-crafted protocols will, if adhered to, generate clear results that will limit further debate over the continued marketability of these products. To this end, we have involved our standing advisory committees in reviewing guidelines for protocols and also have contracted to have appropriate methodology developed. As guideline protocols are completed for a drug class or category, conditions for marketing are published.

The following factors reflect the considerations that went into the decision to place drug products under Paragraph XIV:

- (a) The seriousness of the disease or condition for which the drug products are indicated.
- (b) Absence of effective alternative drug therapy.
- (c) Greater risks or other serious disadvantages of alternative drug products available on the market not exhibited by exempted drugs.
- (d) The distinct likelihood of proving effectiveness.
- (e) Lack of methodology to determine effectiveness (i.e., the inability of manufacturers to evaluate efficacy in a definitive way) and need for its development.
- (f) Only recently available adequate methodology for certain products and the need for definitive information about them.
- (g) Uniqueness of dosage form needed for alternative therapy.

These criteria were applied on a case-by-case basis. Paragraph XIV is not restrictive to drugs with published notices of opportunity for hearing or notices of hearing; it is based, pursuant to the court order, on justification of a medical need.

In addition to the above criteria, some drug products were included in Paragraph XIV because related drug products were being considered, pursuant to 21 CFR 330, by the Over-The-Counter (OTC) drug review panels. The factors considered were:

- (a) Their medical importance.
- (b) Volume of use—apparent need for such products in the marketplace and the potential for confusion if prescription products were removed from the market while OTC products containing the same ingredients remained available during the OTC review process.
- (c) The likelihood that decisions in the OTC review would be applicable to these prescription drug products and the need for consistency in regulatory and scientific conclusions.

There are 66 DESI prescription drug products subject to Paragraph XIV because of the close relationship between their ingredients and uses and those of OTC product ingredients and uses. In these cases it was felt that the best and

most current review of their use and efficacy could be obtained through the Agency's OTC drug review process.

As your letter mentions, paragraph XV of the court order exempts DESI OTC drugs from its provisions. There were 512 OTC drug products in DESI. After the OTC study was begun, almost all of these were exempted from implementation in DESI. The few reserved for DESI action (as listed in 21 CFR 330.12) consisted of products clearly not to be reviewed in the OTC study (e.g., insulin) and certain products already the subject of hearing requests or final action to remove them from the market.

A lot of progress already has been made in an effort to reach valid scientific conclusions concerning the effectiveness of drugs subject to Paragraph XIV. When data from studies become available, they will be reviewed on a high priority basis, and our decisions will be published in the Federal Register. Appropriate labeling for those drugs that have demonstrated effectiveness will be required. For those not demonstrating effectiveness, regulatory action will be initiated to remove them and all related products from the market.

2. There are presently 200 DESI and related drug products for which requests for a formal evidentiary public hearing are pending. The data submitted in support of such requests generally have been voluminous. Not all of these hearing requests will be granted. But before a decision can be made, the data must undergo medical and legal scrutiny.

As Mr. Merrill indicated during our meeting on July 25, a hearing requires nearly the full-time efforts of two lawyers and three scientific or professional staff members for six months. Denying a hearing, where there is no factual issue because the studies fail to meet the statutory and regulatory standards, also takes considerable resources and time of both the legal and medical staffs. These denials, in order to withstand a court challenge, must be explained with great specificity in order to meet the stringent judicial review standard that was established after the 1972 court order.

All DESI drugs for which hearings were denied have been removed from the market except those that are the subject of pending litigation, approximately 30 products, and 31 products in routine compliance action. Our policy is to require removal of drugs for which hearings are not requested as soon as a final order withdrawing approval is published in the Federal Register. We are essentially current in publishing such orders.

I am deeply concerned about the resources needed to complete this portion of the DESI program, and am presently exploring ways to determine how we can efficiently reduce the number of pending hearing requests consistent with our other legal obligations. Your suggestions on this matter are welcomed.

With respect to your question concerning our procedures for reviewing hearing requests, I refer you to the discussion of this matter at paragraph number 3 on page 9754 of the Federal Register on March 13, 1974 (copy enclosed). These procedures assure that an independent judgment is reached by an arbiter who is not involved in the initiation of the withdrawal proceedings, preclude bias, and guarantee fairness.

3. The final group of drugs consists of those products with interim classifications: 28 possibly effective products; 13 probably effective products; and 136 products with effective as well as less-than-effective indications. As you will recall, each initial announcement that classified a drug product or an indication as less-than-effective invited the manufacturers to submit data supporting the claims for the product. In some cases, volumes of material have been received for review. For this reason, the next regulatory step, publication of a notice of opportunity for a hearing that analyzes the submitted data if the data do not support effectiveness, has not occurred. I have directed that an intensive effort be made to complete these reviews and to publish determinations by the end of this summer. We are hopeful that virtually all conclusions will be published by October.

You have asked about our resource expenditures for DESI. Enclosed is a table indicating these expenditures for fiscal years 1969-1977. Budget Requests for DESI increases are as follows:

Fiscal year 1971, 5 positions	\$80, 000
Fiscal year 1972, 40 positions	600, 000

Seven new positions for DESI have been requested in the FY 1979 preliminary budget submitted to the Department.

I believe we have now covered all the specific concerns raised in your letter of July 6, 1977. I welcome the opportunity to explore these matters more fully at a subsequent meeting.

Sincerely yours,

DONALD KENNEDY,
Commissioner of Food and Drugs.

ATTACHMENT

[From the Federal Register, Vol. 39, No. 50, March 13, 1974]

RULES AND REGULATIONS

* * * * *

Experience with requests for hearing during the past few years has demonstrated a compelling need for the formats and analyses required in the new regulations. The Commissioner has no interest whatever in meaningless requirements. Some requests for hearings, however, have been so disorganized, incomplete, and confusing as to hinder the agency's effective and efficient implementation of the act. References have been made to material that is inaccessible; literature reprints in foreign languages have been submitted without translations; some supporting material has been included only in part; material on safety and effectiveness has been intermixed; and, in general, it has frequently been apparent that the purpose of the submission was simply to overwhelm the agency with as much paper as could be found relating to the subject, regardless of its quality or relevance. The Commissioner concludes that the overall poor quality of requests for hearing submitted to date clearly necessitates the adoption of standard procedural rules designed to reduce the material submitted to those tests that have clear relevance to the question whether a hearing is justified, and to require that the material be presented in a clear, concise, and meaningful way.

3. Several comments suggested that an administrative law judge should decide if there is an issue of fact justifying a hearing, rather than the Commissioner. The comments contended that it is prejudicial and unfair for the same person who issues a notice of opportunity for hearing to rule on whether a hearing is justified. At least one comment argued that constitutional requirements preclude this form of procedure.

The Commissioner notes that the same legal arguments were made in the pharmaceutical industry briefs before the Supreme Court in the *Hynson* case, and that the Supreme Court rejected them in holding that the present summary judgment procedures meets all statutory and constitutional requirements.

Nevertheless, the Commissioner recognizes that a substantial amount of concern with respect to use of summary judgment arises from the feeling, even if not justified, of prejudgment and unfairness. Accordingly, even though the legality of the present procedure has been upheld in the courts, the Commissioner concludes that some modification of this procedure is desirable in order to dispel the perception of prejudgment and unfairness that now exists.

The Commissioner concludes that, in the future, there will be a strict separation of functions between the Bureau of Drugs and the office of the Commissioner on these matters. The Bureau of Drugs will be delegated the authority to issue a notice of opportunity for hearing. If a hearing is requested, the Bureau of Drugs will analyze the submission and draft a proposed order ruling on the matter. That proposal will then be forwarded to the office of the Commissioner along with the request for hearing, for independent review and decision. No negotiations or ex parte contacts will be permitted. The Bureau of Drugs will not in any way participate in the review of the matter by the office of the Commissioner. The Commissioner will then publish a notice granting or denying a hearing.

This formal separation of functions, which exceeds statutory and constitutional requirements as interpreted by the Supreme Court in the *Hynson* decision, will guarantee that an independent judgment is reached by an arbiter who is not involved in the initiation of the proceeding, and thus will preclude bias and guarantee fairness. It should be noted that, under the Administrative procedure Act (5 U.S.C. 556(b)) all hearings may be conducted either by an administrative law judge or by the head of the agency. Thus, in this instance the office of the Commissioner will be serving the same function as an administrative law judge.

The office of the General Counsel will observe the same separation of functions in dealing with these matters. The attorneys who are designated to work with the Bureau of Drugs on these matters will be disqualified from participating in any way in work on them with the office of the Commissioner.

4. It was contended that there is no need for new regulations, and that the existing regulations are entirely adequate for implementation of the Drug Amendments of 1962.

The Commissioner concludes that the existing regulations are inadequate in several respects. They fail to require a standard format and analyses which will enable the Commissioner to evaluate the request for hearing expeditiously and accurately; they establish no policy or requirements with respect to the "grandfather" and other issues inherently raised in any request for hearing; and they are not as precise and explicit as they should be in numerous other areas. The purpose of regulations is to interpret and apply the law, and thus to clarify the law by apprising the public and the regulated industry of all applicable legal requirements in greater detail than is possible in a statute. The Commissioner concludes that the new regulations are both necessary and appropriate to achieve this purpose.

5. A number of comments argued that it is not legally permissible to deny a hearing simply because the hearing request does not contain the required analyses, or is not in the required formats, set out in the proposed regulations. Other comments recognized that standard analyses and formats could be required, but contended that a hearing should not be denied for minor or technical deficiencies and suggested that modification or resubmission should be allowed under these circumstances. One comment suggested that data inadvertently or carelessly omitted should not automatically be excluded if the manufacturer later discovers and seeks to submit such data.

It is a well-recognized principle, applied both by the courts and by administrative agencies, that requests for hearings or other applications and pleadings may be required to be in a standard format and to contain specified types of information. The failure to file the correct form in the correct court by a particular date has always constituted a waiver of legal rights. Section 701(a) of the act (21 U.S.C. 371(a)) clearly authorizes the Commissioner to promulgate comparable requirements for the Food and Drug Administration as long as they are reasonable. Accordingly, the suggestion that the Commissioner is without legal authority to require standardized formats or analyses for a request for hearing is rejected.

On the other hand, the Commissioner does not wish to impose undue hardship, and would not intend to reject a request for hearing solely because of minor technical deficiencies, as long as a good faith attempt to meet all the requirements of § 130.14 is apparent and any deficiencies noted are immediately corrected. In the event that, through inadvertence, critical data are excluded from a request for hearing, the Commissioner will entertain a request to receive the data upon a showing that the excluded information was overlooked in good faith. The regulations have therefore been modified to make this clear.

6. Some comments contended that the purpose of the formant was to permit the Commissioner to resolve factual disputes, and pointed out that a factual dispute must be resolved at a hearing.

The Commissioner fully recognizes that a factual dispute must be resolved at a hearing. The regulations have been modified to make this clear. The sole purpose of the required format and analyses is to permit the Commissioner to determine whether a factual dispute does exist, or whether there is no factual dispute that justifies a hearing.

7. One comment contended that the Commissioner may not properly require a point-by-point analysis of a drug study against the criteria in §§ 130.12(a)(5) or 3.86.

*

*

*

*

*

*

*

4. J. RICHARD CROUT, M.D., DIRECTOR OF BUREAU OF DRUGS, TO MICHAEL C. HARPER, ESQ., DECEMBER 7, 1977

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., December 7, 1977.

MICHAEL C. HARPER, Esq.,
Center for Law and Social Policy,
1721 N Street, NW.,
Washington, D.C.

DEAR MR. HARPER:

As was indicated to you in our meeting of November 18, 1977, when you were given our best estimates of completion of Agency evaluation and Federal Register publication of the DESI drug products and/or indications now considered to be less-than-effective, we are now presenting to you our best estimates of the completion of those drug products in Judge Bryant's Paragraph XIV that have yet to be resolved.

In making these estimates, we have carefully considered the time we believe will be required for each step of the process: publishing "Conditions for Marketing" for those categories still requiring this publication; submission of notices of intent to do the studies; submission of protocols for the studies; evaluations of the protocols and communicating these evaluations to the manufacturers; estimated duration of the studies; submission of study data and analysis; review of the data with recommendations and conclusions; preparation of the Federal Register documents; approval of the documents through the established approval chain; and Federal Register publication.

By utilizing all the estimates for each step in the process, we have the following estimated dates when efficacy conclusions for each category of drug products in Paragraph XIV should appear in the Federal Register.

Category I: Coronary vasodilators	May 1, 1981.
Category II: Peripheral vasodilators	Mar. 1, 1982.
Category III: Dermatologic antiinfectives	Jan. 1, 1979.
Category IV: Otic combinations	Jan. 1, 1982.
Category V: Numorphan suppositories	Dec. 1, 1978.
Category VII: Ophthalmic combinations	Apr. 1, 1979.
Category X: Anabolic steroids	Apr. 1, 1984.
Category XI: Parenteral multivitamins	Dec. 1, 1982.
Category XIII: Benzoquin	June 1, 1978.
Category XIV: Poorly absorbed sulfonamides	Sept. 16, 1978.
Category XV: Cough/cold preparations	May 1, 1979.
Category XVII: Isoproterenol S.A.	Dec. 1, 1978.
Category XVIII: Anticholinergics	Dec. 1, 1980.
Category XIX: Xanthine derivatives	June 16, 1978.
Category XX: Parnate	May 15, 1981.

You will recognize that those drug products for which substantial evidence of effectiveness will have been demonstrated should be published as effective on or before the estimated dates, and no further action of the Agency will be required except for compliance follow-up to assure that the manufacturers meet the labeling, manufacturing, and any other requirements for continued marketing. If scientifically valid studies are done, we believe this is likely to be the outcome for many if not most, of the drugs under Paragraph XIV. However, for those drug products not demonstrating substantial evidence of effectiveness, we estimate a Notice of Opportunity for Hearing will be published on or before the projected dates. These notices may result in Hearing Requests that will require resolution, and adverse conclusions at this point may still result in court action, which would delay a final, enforceable order.

We trust that this is the information which you have requested. Should you require further information, we will attempt to provide it at your request.

Sincerely yours,

J. RICHARD CROUT, M.D.,
Director, Bureau of Drugs.

PROGRESS REPORT—STATUS OF DESI PRESCRIPTION DRUG PRODUCTS—NOVEMBER 1978

[Last month's balance in parentheses; others are current month's balance]

Initial classification	Actions published during month of November 1978					Status of drug products at end of November 1977						Disposition at end of November 1978		W/D actions safety or labeling
	Total	Deferred under par. XIV	Interim action	Tentative final action	Final action taken	Products in initial classification	1st follow-up pending	Deferred under par. XIV	NOH pub., final action pending	Other action taken	Final action taken	Upgraded to effective	Downgraded to ineffective	
Ineffective-----	0	0	0	0	0	524	(0)/0	(41)/41	(43)/43	(1)/1	(439)/439	(9)/9	(430)/430	-----
Possibly-----	0	0	0	0	0	685	(4)/4	(205)/205	(89)/89	(4)/4	(383)/383	(77)/77	(306)/306	-----
Probably-----	0	0	0	0	0	1,201	(13)/13	(42)/42	10	(0)/0	(149)/149	(59)/59	(90)/90	-----
Effective/less-----	0	0	0	0	0	1,633	(55)/55	(0)/0	(49)/49	(3)/2	(1,526)/1,527	(1,524)/1,525	(2)/2	(5)/5
Effective-----						420	-----	-----	-----	-----	(420)/420	(420)/420	-----	(1)/1
Total-----						(3,476)/3,463	72	288	191	7	2,918	2,090	828	6

1 Plus transfers: 4 from possibly, 1 from ineffective, 8 from effective (214) w/less.

NOTES

Interim action: NOH—Notice of opportunity for hearing. HEG—Hearing granted. Upgrading to less than effective.
Final action taken: WDE—Withdraw of approval based on efficacy. NRE—Notice that a released drug is no longer eligible for release. REE—Reevaluation of drug's indications to effective.

Tentative final action: FOH/FWR*—Opportunity for hearing where NDA approval has already been withdrawn for failure to report. REE/EOH*—Reevaluations of drug's indications to effective with opportunity for hearing on ineffective indications.

Other action taken: Transferred out—(change in classification to other than effective). REE/EOH*—Reevaluation of drug's indications to effective with opportunity for hearing on ineffective indications. FOH/FWR*—Opportunity for hearing where NDA approval has already been withdrawn for failure to report. Court action.

*Becomes final action after 30 days if hearing not requested.

STATUS OF DISI Rx PRODUCTS HEARING REQUEST ACTIONS AT END OF NOVEMBER 1978

[All figures represent products unless otherwise indicated]

Initial classification	Industry requests			Actions on requests during month					Total actions on requests to date					
	During month	Total to date	Pending	In OC for independent review	Withdrawn by firm, F.O.			Denied	Granted	Denied	Withdrawn by firm F.O.		Hearings held	
					Pub.	Not required	NOH rescinded				Pub.	Not required		NOH rescinded
Ineffective-----	0	95	42	0	0	0	0	0	0	43	5	0	3	2
Possibly-----	0	76	50	0	0	0	0	0	0	7	10	5	4	0
Probably-----	0	9	8	0	0	0	0	0	0	0	0	0	1	0
Effective with less-----	0	49	47	0	0	0	0	0	0	0	0	2	0	0
No-NAS-review-----	0	2	2	0	0	0	0	0	0	0	0	0	0	0
Related drugs-----	1	115	92	1	0	0	0	19	0	0	0	4	0	0
Total-----	1	346	241	1	0	0	0	69	0	0	15	11	8	2

Notes: Not counted in industry requests are 11 ineffective products and 1 possibly effective product that were placed in par. XIV. Pending requests include 11 products having final actions set aside by court order. Results of hearings held: Approval withdrawn (2).

APPENDIX E—COURT ORDER

APHA v. Veneman, No. 1847-70 (D. D.C., Oct. 10, 1972)

FEDERAL SUPPLEMENT



Volume 349

*Cases Argued and Determined
in the*

UNITED STATES DISTRICT COURTS
UNITED STATES CUSTOMS COURT

and Rulings of the

JUDICIAL PANEL ON MULTIDISTRICT
LITIGATION

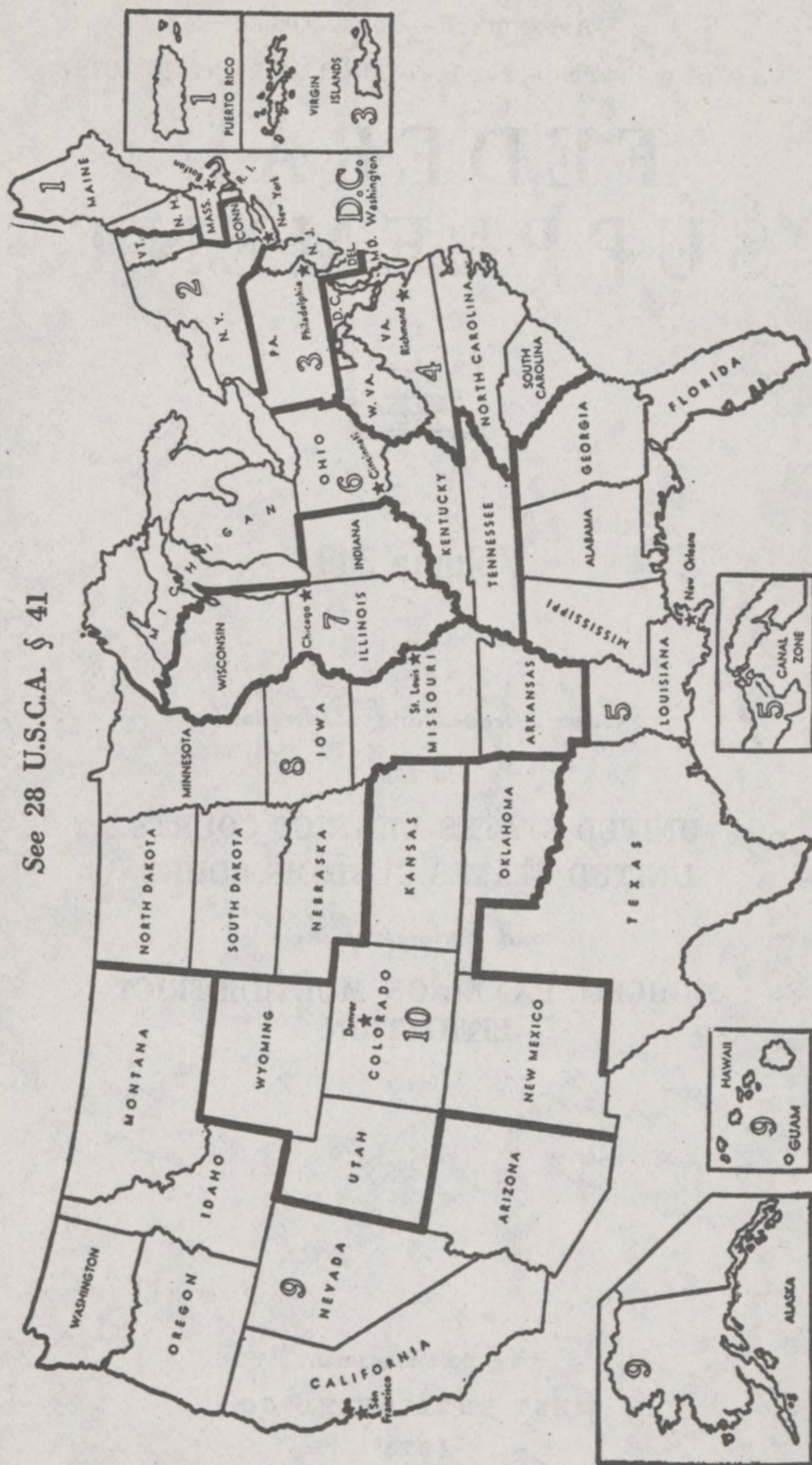
ST. PAUL, MINN.

WEST PUBLISHING CO.

1973

The Eleven Federal Judicial Circuits

See 28 U.S.C.A. § 41



AMERICAN PUBLIC HEALTH ASSOCIATION v. VENEMAN

1311

Cite as 319 F.Supp. 1311 (1972)

Counsel for all parties have submitted comprehensive and well prepared briefs, which have been very helpful to the court.

Pursuant to Rule 14(b) of the local rules of court, plaintiff will prepare and file a draft of judgment in accordance with this opinion and serve a copy upon each other party.

On Motions for New Trial or to Amend Judgment

Counsel for all of the named defendants have filed motions for a new trial or to amend the judgment. Prior to entry of its order of September 29, 1972, the court considered all of the statutes, treaties, executive orders, and cases cited in support of the motions and ruled against defendants' contentions.

Nothing has been presented to persuade the court to modify its conclusions. On the contrary, the court finds support in the per curiam opinion of the United States Supreme Court in *United States v. Jim*, and *Utah v. Jim*, — U.S. —, 93 S.Ct. 261, 34 L.Ed.2d 282, decided November 20, 1972. The Court held that a 1933 statute (47 Stat. 1418) conferring oil and gas royalties on Indians residing on the Aneth extension of the Navajo Reservation "did not create constitutionally protected property rights" in the beneficiaries of the Act and upheld a 1968 Act (82 Stat. 121) enlarging the class of beneficiaries to include the entire Navajo tribe residing in San Juan County, Utah.

Defendants Williamson and Bowen, noting the similarity between the 1933 statutory grant to the residents of the Aneth extension and the 1926 Act upon which the defendants here rely, urged this court to follow the opinion of the Utah District Court (unreported) holding that the 1933 Act vested property rights in the Aneth extension residents

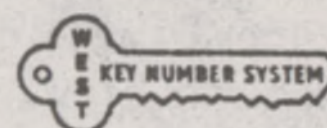
not assert that its permittees and licensees have a right to go on and strip mine, which would in essence destroy the surface estate of the defendants. The

and that the 1968 Act was unconstitutional.

The Supreme Court reversed. Following *Gritts v. Fisher*, 224 U.S. 640, 32 S.Ct. 580, 56 L.Ed. 928 (1912), the Court concluded:

"Congress has not deprived the Navajo of the benefits of mineral deposits on their tribal lands. It has merely chosen to re-allocate the * * * royalties * * * in a more efficient and equitable manner. This was well within the power of Congress to do. As no 'property,' in a Fifth Amendment sense, was conferred upon residents of the Aneth extension by the 1933 Act, no violation of the Fifth Amendment was effected by the 1968 legislation."

The motions for a new trial or to amend the judgment are denied.



AMERICAN PUBLIC HEALTH ASSOCIATION and National Council of Senior Citizens, Plaintiffs,

v.

John G. VENEMAN, Acting Secretary of the Department of Health, Education and Welfare, and Charles Edwards, Commissioner of the Food and Drug Administration, Defendants.

Civ. A. No. 1847-70.

United States District Court,
District of Columbia.

Aug. 23, 1972.

Proceeding on complaint, by public health association and senior citizens association against Acting Secretary of the Department of Health, Education and Welfare and against Commissioner

plaintiff recognizes that its licensees or permittees have no right to destroy the surface estate without compensating the individual defendants."

of the Food and Drug Administration, challenging Food and Drug Administration's administering of statutes requiring that drugs have effect they are represented to have under conditions of use prescribed, recommended or suggested in labeling. On plaintiffs' motion for summary judgment and defendants' motions to dismiss and for summary judgment, the District Court, Bryant, J., held that in view of two-year grace period until October 10, 1964 with respect to statutory requirement that drugs have effect they are represented to have under conditions of use prescribed, recommended or suggested in labeling and in view of congressional mandate that drugs in the market place be both safe and effective, reports reviewing efficacy of all drugs which had been given approval by the Food and Drug Administration from 1938 to 1962 should be immediately made public, and deadline should be set for the Food and Drug Administration to complete its evaluation of all drugs with regard to efficacy.

Plaintiffs' motion granted, and defendants' motion denied.

1. Administrative Law and Procedure

⌚701

Drugs and Narcotics ⌚10

Issues which were presented in complaint challenging Food and Drug Administration's administering of statutes, governing withdrawal of approval of antibiotic and nonantibiotic drugs upon finding of lack of substantial evidence that the drugs have effect they are represented to have under conditions of use prescribed, recommended or suggested in labeling, and which did not deal with agency discretion were subject to review under the Administrative Procedure Act. 5 U.S.C.A. §§ 701-706; Federal Food, Drug, and Cosmetic Act, §§ 505, 507, 21 U.S.C.A. §§ 355, 357.

2. Drugs and Narcotics ⌚10

Secretary of Health, Education and Welfare must, under statutes governing withdrawal of antibiotic and nonantibiotic drugs upon finding of lack of sub-

stantial evidence that the drugs have effect they are represented to have under conditions of use prescribed, recommended or suggested in labeling, begin procedures to withdraw a drug when he concludes that there is no substantial evidence or efficacy rather than thereafter granting manufacturers time to bolster record regarding the drug's effectiveness. Federal Food, Drug, and Cosmetic Act, §§ 505(d, e), 507(f, h), 21 U.S.C.A. §§ 355(d, e), 357(f, h).

3. Drugs and Narcotics ⌚10

In circumstance in which the Food and Drug Administration publishes in Federal Register the required notice to drug manufacturers of opportunity for hearing and proposed withdrawal of drugs from market and manufacturers then fail to avail themselves of opportunity for the hearing within required 30 days, withdrawal of drugs from market is required by statute governing withdrawal of drugs and is purely a ministerial duty, and failure to withdraw constitutes agency action unlawfully withheld. Federal Food, Drug, and Cosmetic Act, §§ 505(e), 507(f, h), 21 U.S.C.A. §§ 355(e), 357(f, h).

4. Drugs and Narcotics ⌚10

Hearing on withdrawal of a new drug application is to be scheduled as soon as practicable after request by drug manufacturers for such a hearing; and, while some agency discretion is conferred in scheduling the hearing, interminable delay is not contemplated. Federal Food, Drug, and Cosmetic Act, §§ 505(e), 507(f, h), 21 U.S.C.A. §§ 355(e), 357(f, h).

5. Drugs and Narcotics ⌚10

Record was inadequate to support finding that Food and Drug Administration abused its discretion by failing to exercise authority to immediately suspend drugs which present an imminent hazard to the public health. Federal Food, Drug, and Cosmetic Act, § 505(e), 21 U.S.C.A. § 355(e).

6. Drugs and Narcotics ⌚10

Invocation of emergency procedure to immediately suspend drugs which

AMERICAN PUBLIC HEALTH ASSOCIATION v. VENEMAN

1313

Cite as 349 F.Supp. 1311 (1972)

present an imminent hazard to the public health is matter which is peculiarly one of judgment. Federal Food, Drug, and Cosmetic Act, § 505(e), 21 U.S.C.A. § 355(e).

7. Drugs and Narcotics ⇐10

In view of two-year grace period until October 10, 1964 with respect to statutory requirement that drugs have effect they are represented to have under conditions of use prescribed, recommended or suggested in labeling and in view of congressional mandate that drugs in the market place be both safe and effective, reports reviewing efficacy of all drugs which had been given approval by the Food and Drug Administration from 1938 to 1962 should be immediately made public, and deadline should be set for the Food and Drug Administration to complete its evaluation of all drugs with regard to efficacy.

Bruce J. Lerris, Washington, D. C., for plaintiff.

Thomas A. Flannery, U. S. Atty., Joseph M. Hannon, Mary E. Folhard, Asst. U. S. Attys., Washington, D. C., for defendants.

MEMORANDUM

BRYANT, District Judge.

I

Before the court are the cross-motions of the parties for summary judgment. Because of the complex nature of this case, a detailed recitation of the facts is appropriate.

In 1962, the Congress amended the Food, Drug, and Cosmetic Act of 1938 to require that all drugs on the market be proven effective for their suggested use.¹ Under 21 U.S.C. § 355(e) (1970),

The Secretary shall, after due notice and opportunity for a hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary

finds . . . (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof. . . .

Section 355 relates solely to non-antibiotic drugs. Under § 357(h), antibiotic drugs may be ordered withdrawn when

(2) the Secretary finds, on the basis of new information with respect to such drug evaluated together with the information before him when the application under section 355 of this title became effective or was approved, that there is a lack of substantial evidence (as defined in section 355(d) of this title) that the drug has the effect it purports or is represented to have under such conditions of use.

The term "substantial evidence," as used in §§ 355(e) and 357(h) means

evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. 21 U.S.C. § 355(d) (1970).

Under the terms of P.L. 87-781, Section 107(c)(3)(B), the effectiveness requirement did not take effect until October 10, 1964, two years after enactment of the statute. The Food and Drug Administration in 1964 promulgated regulations to require the drug manufacturers to report whether approved drugs were still being marketed in conformity with the conditions for which they had

1. P.L. 87-781. The pertinent amendments are codified in 21 U.S.C. §§ 355, 357 (1970 ed.).

been approved and to submit scientific data in support of any claims in promotional material which departed from the approved labeling. The drug industry failed to comply, and litigation instituted in the District of Delaware by the Pharmaceutical Manufacturers Association challenging the legality of the regulation was still pending as of September 3, 1970.²

In 1966, Dr. James Goddard became Commissioner of the FDA and began to move ahead with efficacy studies of the various drugs. In July of 1966, a contract with the National Academy of Sciences-National Research Council was signed, whereby the NAS-NRC was to review the efficacy of all drugs which had been given FDA approval from 1938 to 1962. The FDA then published orders in the Federal Register requiring the drug manufacturers to submit certain information regarding each approved drug, including references to evaluations of the effectiveness of the drug. The purpose was to permit the manufacturers the "opportunity to identify the best available evidence which they believed supported the claims made for the drug."³ After several extensions, the manufacturers were required to submit their information by July 1, 1967.⁴ NAS-NRC began submitting its first reports on October 11, 1967, and submitted the last report on April 15, 1969; there were 2,824 reports submitted, covering approximately 3,700 drugs manufactured by 237 companies.

In January, 1968, the FDA began implementation of the NAS-NRC reports. The procedure adopted has been to evaluate each report and to release it to the public only after the FDA evaluation is completed. When the FDA completes its evaluation of an NAS-NRC report, an

announcement is made in the Federal Register that the FDA has concluded that the drugs involved are "effective," "probably effective," "possibly effective," or "lack substantial evidence of effectiveness"; the first three classifications are the same as those used in the NAS-NRC reports, but the last seems to be an FDA substitution for the NAS-NRC classification "ineffective."

After announcing the classification of a drug in the Federal Register, the FDA affords the drug manufacturer a period of time to provide additional data to the FDA in every case where the drug is classified as anything other than "effective." The manufacturer is given 12 months or 6 months where the drug is listed as probably or possibly effective, respectively,⁵ and 30 days where the drug is classified as lacking substantial evidence of effectiveness.⁶ During this time period, the manufacturer is permitted to continue marketing the drug. If, at the end of the interim period, no studies have been undertaken by the manufacturer, or if the studies do not provide substantial evidence of effectiveness, procedures are supposed to be instituted to withdraw approval of the drug pursuant to 21 U.S.C. § 355(e).⁷

When the Secretary finds that a drug lacks substantial evidence of efficacy, §§ 355(e) and 357(h) & (f) require that there be an opportunity for a hearing. 21 C.F.R. § 130.27 (1971) prescribes the procedure for withdrawal of non-antibiotic drugs. The Secretary is required to notify the holder of a new drug application of an opportunity for a hearing on the proposed withdrawal, and notice must be published in the Federal Register. The manufacturer has 30 days then to avail himself of the hearing

2. Affidavit of Charles C. Edwards, filed September 4, 1970, p. 3.

3. Affidavit of Charles C. Edwards, *supra*, Note 2, pp. 5-6.

4. It should be noted that this date is nearly three years after the effective date of §§ 355 and 357.

5. See Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study, 35 Fed.Reg. 11273 (1970).

6. See, e. g., 35 Fed.Reg. 12423 (1970).

7. See Conditions for Marketing New Drugs, *supra*, Note 5. It is unclear from the record whether this procedure has been applied to antibiotics.

(Cite as 310 F.Supp. 1311 (1972))

opportunity.⁸ If the manufacturer fails to avail himself of the opportunity for the hearing, the FDA may enter a final order withdrawing the drug.⁹ When a manufacturer desires to have a hearing, he must respond within the 30 days after notice is published, giving reasons, supported by an analysis of clinical and investigative data which he would present at the hearing in support of his opposition to withdrawal of the drug.¹⁰ The FDA may refuse a hearing and withdraw the drug where the data presented is insufficient on its face to support a claim of effectiveness.

Though the language of 21 C.F.R. § 130.14(b) (1971) is ambiguous, it appears that a hearing, when permitted, must commence as soon as practicable. After the hearing the examiner submits tentative findings of facts and an order which becomes final if no objection is made within 20 days thereafter. The Commissioner of the FDA then issues the final order. The procedure followed in the cases of antibiotic drugs is contained in 21 C.F.R. § 146.1 (1971) and is sufficiently similar as to not require separate discussion.

II

[1] As a preliminary matter, the question of jurisdiction is quickly resolved. The defendants contend that the matters in controversy are within the agency's discretion and are thus subject neither to mandamus nor judicial review. The court has considered both the allegations of the complaint and the merits and concludes, as will be shown later in this memorandum, that the issues presented do not deal with agency discretion and are subject to review under the Administrative Procedure Act.¹¹

III

The plaintiffs' complaint challenges in several respects the manner in which the

FDA is administering Sections 355 and 357.

A.

[2] First the plaintiffs assert that the FDA practice of granting manufacturers time to bolster the record regarding a drug's effectiveness, after the FDA has publicly concluded that a drug is less than effective, is a violation of the statutory mandate. The statute states unequivocally that

The Secretary *shall* . . . withdraw approval of any application with respect to any drug under this section if the Secretary finds . . . that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed . . . 21 U.S.C. § 355(c) [Emphasis added].

While § 355(c) pertains only to non-antibiotic drugs, 21 C.F.R. § 146.1(g) (1) (1971) declares that

No regulation providing for the certification of any batch [of antibiotic drugs] . . . and no existing regulation will be continued in effect unless it is established by substantial evidence that the drug will have such characteristics . . . to adequately insure safety and efficacy of use.

Thus it could not be clearer that the Secretary *must* begin the procedures to withdraw a drug when he concludes that there is no substantial evidence of efficacy. The defendants contend that the many announcements which have been published in the Federal Register regarding FDA conclusions about the efficacy of various drugs are not findings by the agency¹² and that the FDA is "not required by law to notice the cases [where a drug has been found less than effective] or press them to hearing immediately upon its announcement of the NAS-NRC findings and its concurrence.

8. 21 C.F.R. § 130.14(a) (1971).

9. 21 C.F.R. § 130.15 (1971).

10. 21 C.F.R. § 130.14 (1971).

11. 5 U.S.C. §§ 701-706 (1970).

12. Defendants' Reply Brief, p. 2.

It has discretion in the selection of cases to notice for hearing."¹³ This argument is unpersuasive in view of the clear language of the statute and regulations and the Congressional intent to rid the marketplace of ineffective drugs.¹⁴

B.

[3] The plaintiffs' second claim is that once the FDA commences the procedure outlined in the statute or regulation for withdrawing a drug, it fails to adhere to those procedures. Plaintiffs assert, and the defendants do not refute it, that for many drugs the FDA has published in the Federal Register the required notice of an opportunity for a hearing and that the manufacturers have failed to avail themselves of the opportunity for the hearing within the required 30 days; nevertheless the FDA has failed to withdraw these drugs from the market. In these circumstances, the withdrawal is both required by the statute and purely a ministerial duty, and failure to withdraw constitutes agency action unlawfully withheld.

[4] In addition, plaintiffs contend that where drug manufacturers have requested a hearing, such hearings have been a long time in coming. They cite as examples two drugs where no hearing had been scheduled at the time the plaintiffs filed their memorandum, even though the manufacturers had requested hearings one and a half years before. Indeed, this situation was commented upon unfavorably in *United States v.*

Pharmaceutical Corporation v. Secretary, HEW, No. 24,900, slip op. at 14 (D.C.Cir. August 14, 1972). As the court reads 21 C.F.R. § 130.14(b), a hearing on withdrawal of a new drug application is to be scheduled as soon as practicable, and while such a provision confers some agency discretion in scheduling the hearing, interminable delay obviously is not contemplated.

C.

[5, 6] Plaintiffs also claim that the FDA has failed to exercise its authority to immediately suspend drugs which present an imminent hazard to the public health.¹⁵ The invocation of this emergency procedure is a matter which is peculiarly one of judgment, and while the agency has been, perhaps, overcautious on occasion in view of the lengthy delays in removing drugs from the market, the record before the court is inadequate to support a finding of an abuse of discretion.

IV

When the final motion paper was filed in this case on December 1, 1970, less than half of the NAS-NRC reports had been evaluated and published.¹⁶ In his affidavit filed September 4, 1970, the defendant Commissioner of the FDA stated

In summary, it is expected that all the reports will be released and FDA

understand the solicitude of the FDA for the drug manufacturers in giving additional time to supplement the record when in all cases the manufacturers have been on notice regarding the statute's efficacy requirement for at least four or more years. The hearing procedure provides ample opportunity for drug manufacturers to produce their scientific evidence, when they have any, in opposition to withdrawal.

15. 21 U.S.C. § 355(e) (1970) and 21 C.F.R. § 146.1 (1971).

16. Defendants' Reply Brief, p. 6, indicates that 1188 out of 2771 NAS-NRC reports have been published.

13. Defendants' Memorandum in Support of Defendants' Motion to Dismiss and for Summary Judgment, p. 20.

14. The court feels compelled to state that even if the statute and regulation did not require immediate action by the FDA to withdraw an ineffective drug, the court would grant mandamus based upon not only the statute, but also the failure of the FDA to adhere to its regulation declaring that a drug would be withdrawn at the end of a 30 day, 60 month or 12 month period. 35 Fed.Reg. 11273 (1970). See pp. 30-32 of Plaintiffs' Memorandum in Support of Motion for Summary Judgment. Furthermore, the court cannot

AMERICAN PUBLIC HEALTH ASSOCIATION v. VENEMAN

1317

Cite as 349 F.Supp. 1311 (1972)

and Academy findings published prior to July 1, 1971.¹⁷

In response to the court's inquiry the defendants advised the court on February 2, 1972, that 814 reports still had not been evaluated by the FDA. Of these outstanding reports, 327 had been returned to NAS-NRC for further evaluation in early 1971 and were reported on by NAS-NRC in October, 1971; they are presently being reevaluated by the FDA. In addition, the FDA has advised that the 260 NAS-NRC reports on over-the-counter drugs will not be rated by the FDA (and hence will remain unpublished) because it has announced a new program with regard to over-the-counter drugs.¹⁸ The plaintiffs have protested that the proposed procedures are "enormously elaborate" and will create extensive delay in applying the efficacy requirement to over-the-counter drugs. The court shares this concern, since over-the-counter drugs are purchased without medical advice in most cases, and an NAS-NRC report on over-the-counter drugs indicates that only 25% of all such drugs are effective.¹⁹

Because the FDA has responsibility in matters which directly and literally affect the nation's health and welfare, it is one of the most important of all Federal regulatory agencies. Its enforcement stance must be well balanced, but nevertheless effective. A timid approach can vitiate whatever protection the Congress has created for the consumer. On the

other hand, an overly zealous approach can ruin a drug manufacturer by destroying public confidence in its products. Thus, it is understandable that the agency might have legitimate concern for drug manufacturers who must comply with new statutory requirements, and surely the question of time necessary to adduce new evidence of efficacy is an important consideration in creating an administrative scheme for implementation of the statute.

However, the FDA must remember that it does not stand alone in this regard. At the very outset the Congress also was sensitive to this problem, and allowed a two-year grace period before the 1962 amendments were to become effective. When, as is the case here, the Congress has shown an awareness of a problem and has acted accordingly, it seems inappropriate for an agency to adopt procedures which extend the grace period far beyond that envisioned by the statute, and which effectively stay implementation of the Congressional mandate that drugs in the marketplace be both safe and effective.²⁰

[7] Based upon the entire record in this case, the court concludes that there is no compelling reason why the remaining NAS-NRC reports should not be immediately released, that it would be an abuse of agency discretion to refuse to make such reports public, and that the court should set a deadline for the FDA to complete its evaluation of all drugs with regard to efficacy.

17. Affidavit of Charles C. Edwards, *supra*, Note 2, p. 12.

18. 37 Fed.Reg. 85 (1972).

19. *Id.* at 85. The type of intolerable procrastination in the FDA evaluation of NAS-NRC reports has been dramatically evidenced very recently. The FDA has just released for publication an NAS-NRC report on over-the-counter drugs, specifically cold remedies, that was submitted to the FDA three years ago. The report indicates that many of the nation's leading cold medications lack substantial evidence of effectiveness and are subject to withdrawal. *Washington Post*, July 8, 1972, p. 2.

20. The defendants cite *Pfizer, Inc. v. Richardson*, 434 F.2d 536 (CA2 1970) and *Pharmaceutical Manufacturers Assn. v. Richardson*, 318 F.Supp. 301 (D.Del. 1970) as "specifically approv[ing] the procedures adopted by the defendants for the implementation of the NAS-NRC Drug Efficacy Study," but their reliance on these cases is misplaced, since they deal with the validity of FDA regulations regarding the definition of "substantial evidence" and the right to a hearing prior to withdrawal of a drug. Neither case deals with the issues before this court.

Accordingly, the plaintiffs' motion for summary judgment is granted, and the defendants' motion to dismiss and for summary judgment is denied.

Counsel are directed to present an appropriate order.

APPENDIX F—PHYSICIAN INFORMATION

Physician information as provided in the 1978 Physicians' Desk Reference (PDR) for certain still-marketed "ineffective" fixed combination antibiotic drug products: Achrostatin V, Declostatin, Terrastatin, and Mysteclin-F, capsules and syrup.

ACHROSTATIN® V

(Tetracycline HCl and Nystatin)

A.H.F.S. 8:12.24

This product is listed in U.S.P., a Medicare designated compendium.

Each capsule contains:

Tetracycline HCl	250 mg.
Nystatin	250,000 units.

How supplied: CAPSULES: (hard shell, pink)—bottles of 16 and 100.

[Shown in Product Identification Section]

DECLOSTATIN®

(Demeclocycline Hydrochloride and Nystatin) for Oral Use

A.H.F.S. 8:12.24

The ingredients in these products are listed in one or more of Medicare designated compendia.

DESCRIPTION: TABLETS

Each tablet contains 300 mg. of DECLOMYCIN® *demeclocycline HCl* and 500,000 units of Nystatin.

CAPSULES

Each capsule contains 150 mg. of DECLOMYCIN *demeclocycline HCl* and 250,000 units of Nystatin.

DECLOMYCIN *demeclocycline hydrochloride* is an antibiotic isolated from a mutant strain of *Streptomyces aureofaciens*. Chemically it is the hydrochloride of 7-chloro-4-dimethylamino-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 6, 10, 12, 12a-pentahydroxy-1, 11-dioxo-2-naphthacene carboxamide.

Nystatin is an antibiotic with antifungal activity produced by a strain of *Streptomyces noursei*.

Actions: The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. Tetracyclines are active against a wide range of gram-negative and gram-positive organisms.

The drugs in the tetracycline class have closely similar antimicrobial spectra, and cross resistance among them is common. Micro-organisms may be considered susceptible if the M.I.C. (minimum inhibitory concentration) is not more than 4.0 mcg./ml. and intermediate if the M.I.C. is 4.0 to 12.5 mcg./ml.

Susceptibility plate testing: A tetracycline disc may be used to determine microbial susceptibility to drugs in the tetracycline class. If the Kirby-Bauer method of disc susceptibility testing is used, a 30 mcg. tetracycline disc should give a zone of at least 19 mm. when tested against a tetracycline-susceptible bacterial strain.

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile and excreted in the urine and feces at high concentrations and in a biologically active form. Nystatin is an antifungal agent against *Candida* (monilia) *albicans*. It is absorbed very sparingly following oral administration, with no detectable blood levels when given in recommended doses. Most of the unabsorbed nystatin is passed unchanged in the stool.

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications section as follows:

Ineffective as a fixed combination. DECLOMYCIN *demeclocycline hydrochloride* is indicated in infections caused by the following micro-organisms:

Rickettsiae: (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, tick fevers.)

Mycoplasma pneumoniae (PPLO, Eaton agent).

Agents of psittacosis and ornithosis.

Agents of lymphogranuloma venereum and granuloma inguinale.

The spirochetal agent of relapsing fever (*Borrelia recurrentis*).

The following gram-negative micro-organisms:

Haemophilus ducreyi (chancroid),

Pasteurella pestis and *Pasteurella tularensis*,

Bartonella bacilliformis,

Bacteroides species,

Vibrio comma and *Vibrio fetus*.

Brucella species (in conjunction with streptomycin).

Because many strains of the following groups of micro-organisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

Demeclocycline is indicated for treatment of infections caused by the following gram-negative micro-organisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Escherichia coli,

Enterobacter aerogenes (formerly *Aerobacter aerogenes*),

Shigella species,

Mima species and *Herellea* species.

Haemophilus influenzae (respiratory infections),

Klebsiella species (respiratory and urinary infections).

Demeclocycline is indicated for treatment of infections caused by the following gram-positive micro-organisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Streptococcus species:

Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be sensitive.

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

Diplococcus pneumoniae,

Staphylococcus aureus, skin and soft tissue infections. Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infection.

When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of infections due to:

Neisseria gonorrhoeae,

Treponema pallidum and *Treponema pertenue* (syphilis and yaws),

Listeria monocytogenes,

Clostridium species,

Bacillus anthracis,

Fusobacterium fusiforme (Vincent's infection),

Actinomyces species.

In acute intestinal amebiasis, the tetracyclines may be a useful adjunct to amebicides.

DECLOMYCIN *demeclocycline hydrochloride* is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis may be treated with oral tetracyclines or with a combination of oral and topical agents.

Nystatin, the antifungal antibiotic is combined for added protection against monilial superinfection thought to be associated with the use of broad-spectrum antibiotics.

Contraindications: This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines or nystatin.

Warnings: The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction

is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used in this age group unless other drugs are not likely to be effective or are contraindicated.

If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated and, if therapy is prolonged, serum level determinations of the drug may be advisable.

Phototoxic reactions can occur in individuals taking demeclocycline, and are characterized by severe burns of exposed surfaces resulting from direct exposure of patients to sunlight during therapy with moderate or large doses of demeclocycline. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur, and treatment should be discontinued at the first evidence of skin erythema.

The anti-anabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis.

Usage in pregnancy (See above "Warnings" about use during tooth development.)

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Usage in newborns, infants, and children (See above "Warnings" about use during tooth development.)

All tetracyclines form a stable calcium complex in any bone forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg./kg. every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

Note; The information on each product appearing here is based on labelling effective in August, 1977 and is either the entire official brochure or an accurate condensation therefrom. Official brochures are enclosed in product packages. Information concerning all Lederle products may be obtained from the Medical Department, Lederle Laboratories, Pearl River, New York, 10965.

Precautions: As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy should be instituted.

In venereal diseases when coexistent syphilis is suspected, darkfield examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

Because the tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed.

All infections due to Group A beta-hemolytic streptococci should be treated for at least 10 days.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving demeclocycline in conjunction with penicillin.

Interpretation of Bacteriologic Studies: Following a course of therapy, persistence for several days in both urine and blood of bacterio-suppressive levels of demeclocycline may interfere with culture studies. These levels should not be considered therapeutic.

ADVERSE REACTIONS

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. These reactions have been caused by both the oral and parenteral administration of tetracyclines.

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See "Warnings".)

Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See "Warnings".)

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid prupura, pericarditis and exacerbation of systemic lupus erythematosus.

Bulging fontanels have been reported in young infants following full therapeutic dosage. This sign disappeared rapidly when the drug was discontinued.

Blood: Hemolytic anemia, thrombocytopenia neutropenia and eosinophilia have been reported.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

Nystatin has been associated with nausea and vomiting, gastrointestinal distress and diarrhea (occasionally with large doses.)

DOSAGE AND ADMINISTRATION

Adults: Usual daily dose—Four divided doses of 150 mg. each or two divided doses of 300 mg. each, based on demeclocycline HCl content. Children: Usual daily dose, 3–6 mg. per pound body weight per day, depending upon the severity of the disease, divided into 2 or 4 doses, based on the demeclocycline HCl content.

Therapy should be continued for a least 24–48 hours after symptoms and fever have subsided. Concomitant therapy: Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given to patients taking oral tetracycline.

Foods and some dairy products also interfere with absorption. Oral forms of tetracycline should be given 1 hour before or 2 hours after meals. Pediatric oral dosage forms should not be given with milk formulas and should be given at least 1 hour prior to feeding.

In patients with renal impairment: (See "Warnings.") Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

In the treatment of streptococcal infections, a therapeutic dose of demeclocycline should be administered for at least 10 days.

Gonorrhea patients sensitive to penicillin may be treated with demeclocycline administered as an initial oral dose of 600 mg. followed by 300 mg. every 12 hours for 4 days to a total of 3 grams.

HOW SUPPLIED

Capsules

150 mg. demeclocycline HCl and 250,000 units of nystatin soft shell—coral, Bottles of 16 and 100.

Tablets

300 mg. demeclocycline HCl and 500,000 units of nystatin film coated—pink, Bottles of 12 and 48.

(Date of last revision: March 1977)

[Tablets and Capsules shown in Product Identification Section]

TERRASTATIN®

oxytetracycline-----	250 mg.
nystatin-----	250,000 units.

Glucosamine Hydrochloride

CAPSULES

Actions: The capsules contain oxytetracycline for broad-spectrum antibiotic therapy; nystatin, an antifungal antibiotic, as added protection against possible monilial superinfection.

Terramycin® (oxytetracycline) is a widely used antibiotic with clinically proved activity against gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain protozoa. Terramycin (oxytetracycline) is well tolerated and well absorbed after oral administration. It diffuses readily through the placenta and is present in the fetal circulation. It diffuses into the pleural fluid, and under some circumstances, into the cerebrospinal fluid. Oxytetracycline appears to be concentrated in the hepatic system and is excreted in

the bile. It is excreted in the urine and in the feces, in high concentrations, in a biologically active form.

Glucosamine hydrochloride (2-amino-D-glucose, a normal body constituent) permits maximum absorption and thus provides blood levels higher than those attainable with oxytetracycline alone.

Nystatin is an antibiotic with activity against a number of fungi, including *Candida albicans* (Monilia). It provides significant antifungal prophylaxis against overgrowth or superinfection by such fungi.

INDICATIONS

Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

"Lacking substantial evidence of effectiveness as a fixed combination":

Extensive clinical experience with oxytetracycline has firmly established its broad therapeutic range against both gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain parasites (amebae, pinworms). Nystatin, the first available antifungal antibiotic, has been used successfully as a prophylactic agent for the suppression of *Candida albicans*, and as a therapeutic agent in the management of active monilial infections. Indications include:

Pneumonia: Pneumococcal pneumonia, with and without bacteremia; pneumonia caused by streptococci, susceptible strains of staphylococci, *Hemophilus influenzae*, *Klebsiella pneumoniae*, enteric bacilli or mixed flora; Eaton Agent (PPLO).

Other infections of Respiratory Tract and Related Structures: Tonsillitis, pharyngitis, acute infectious croup, otitis media, mastoiditis, lung abscesses, sinusitis, bronchitis, bronchiolitis, laryngotracheitis, bronchiectasis, empyema, pulmonary infections associated with pancreatic insufficiency, whooping cough.

Genitourinary Infections: Pyelonephritis and other urinary tract infections caused by streptococci, susceptible staphylococci, *Escherichia coli*, *Aerobacter aerogenes*, or mixed organisms. Chancroid, granuloma inguinale, lymphogranuloma venereum, gonorrheal urethritis, nonspecific urethritis. If concomitant syphilis is suspected, a dark, field examination should be made of any lesion before treatment of gonorrheal urethritis, and seriological tests for syphilis should be made monthly for at least four months afterwards.

Ophthalmic Infections: Ophthalmia caused by gonococci, staphylococci, *H. influenzae*, or other susceptible bacteria; trachoma.

Surgical Infections: Prophylaxis and therapy of infections complicating wounds, burns, and surgery, including obstetric and gynecologic procedures. Suppression of susceptible colonic bacterial flora in preparation for surgery of large bowel; osteomyelitis.

In the treatment of staphylococcal infections, indicated surgical procedures should be carried out in all cases.

Soft Tissue Infections: Cellulitis, abscesses, furuncles, carbuncles, wound and burn infections, lymphadenitis.

Spirochetal Infections: Yaws, Vincent's infection, and syphilis.

Meningeal Infections: Initial doses of the antibiotic should be administered intravenously in treatment of meningitis caused by meningococci, *K. pneumoniae*, *H. influenzae*, or other susceptible organisms.

Use in Dentistry: Prophylactically and therapeutically against a wide range of infections caused by susceptible organisms.

Gastrointestinal Infections: Bacillary dysentery, intestinal amebiasis, pinworm infestations, and infections caused by species of *Salmonella*.

Rickettsial Infections: Typhus (epidemic, murine, scrub), Q fever, Rocky Mountain spotted fever, Rickettsialpox.

Miscellaneous: Other infections caused by pneumococci, streptococci, susceptible staphylococci, gonococci, meningococci, *E. coli*, *A. aerogenes*, *Bacteroides*, species of *Shigella*, *Salmonella*, *Pasteurella* (tularemia, plague), *H. influenzae*, Brucellosis, psittacosis, Listeriosis.

It is usually not possible to predict with certainty which patients may develop clinical moniliasis as a result of broad-spectrum antibiotic therapy. However, the added protection afforded by nystatin against monilial superinfection is especially important for patients who are most likely to be susceptible to the overgrowth of *Candida albicans*. Among such patients are debilitated or elderly patients; diabetics; infants, particularly prematures; patients receiving concomitant cortisone or related steroid therapy; those requiring high or prolonged antibiotic dosages;

patients who have developed a monilial complication on previous broad-spectrum therapy; and women, particularly during pregnancy.

Final classification of the less than effective indications require further investigation. New clinical studies to substantiate the efficacy of Terrastatin have been submitted to FDA and are now under review. Results of these studies will provide data for final classification of these indications.

Contraindications: This drug is contraindicated in individuals who have shown hypersensitivity to any of its components.

Warning: If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity. Under such conditions, lower than usual doses are indicated and if therapy is prolonged, tetracycline serum level determinations may be advisable.

Oxytetracycline may form a stable calcium complex in any bone forming tissue with no serious harmful effects reported thus far in humans. However, use of oxytetracycline during tooth development (last trimester of pregnancy, neonatal period and early childhood) may cause discoloration of the teeth (yellow-grey-brownish). This effect occurs mostly during long term use of the drug but it has also been observed in usual short treatment courses.

Certain hypersensitive individuals may develop a photodynamic reaction precipitated by exposure to direct sunlight during the use of this drug. This reaction is usually of the photoallergic type which may also be produced by other tetracycline derivatives. Individuals with a history of photosensitivity reactions should be instructed to avoid exposure to direct sunlight while under treatment with this or other tetracycline drugs, and treatment should be discontinued at first evidence of skin discomfort.

Note: Reactions of a photoallergic nature are exceedingly rare with Terramycin (oxytetracycline). Phototoxic reactions are not believed to occur with Terramycin (oxytetracycline).

Precautions: As with all antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate specific therapy should be instituted.

Increased intracranial pressure with bulging fontanelles has been observed occasionally in infants receiving therapeutic doses of oxytetracycline. Although the mechanism for this phenomenon is unknown, the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae.

Adverse Reactions: Glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis and dermatitis, as well as reactions of an allergic nature, may occur but are rare. If adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

Bulging fontanelles in children and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages. These conditions disappeared rapidly when the drug was discontinued.

Dosage: The dosage of Terramycin (oxytetracycline) required to produce optimum therapeutic response will vary from one patient to another depending upon the severity, response, and susceptibility of the infection. In the average adult the suggested minimum daily dose should be 1 g. Higher daily doses (2 to 4 g daily) may be required for severe infections or for those patients who do not respond rapidly to lower dosages. The total daily dose should be administered in four equal portions given at six-hour intervals.

Duration of therapy should be for at least 24 to 48 hours after symptoms and fever have subsided.

Certain diseases are treated in courses: 10 days for amebiasis; 7 days for pinworm infestation; two 500 mg doses at six-hour intervals for acute gonorrheal infections; 6 to 8 weeks or longer for bacterial endocarditis, depending on the bacteriologic and clinical response, with appropriate follow-up studies; three weeks (supplemented with intramuscular injections of streptomycin in a dosage of 1 g twice daily the first week, and 1 g daily the second and third weeks) in Brucellosis; ten days in the treatment of hemolytic streptococcal infections to reduce the possibility of development of rheumatic fever or glomerulonephritis.

The dosage in amebiasis, endocarditis and Brucellosis should provide 2 g of oxytetracycline daily for adults. A dosage of 10 mg per pound of body weight (25 mg/kg) daily should be effective in pinworm infestations and streptococcal infections.

The recommended dosage of Terrastatin as indicated above is the same as that of Terramycin® (oxytetracycline). Because of the diminished possibility of fungal overgrowth, gastrointestinal disturbances may be minimized.

Food and some dairy products also interfere with absorption. Oral forms of oxytetracycline should be given 1 hour before or 2 hours after meals.

Aluminum hydroxide gel given with antibiotics has been shown to decrease their absorption and is contraindicated.

Supply: Terrastatin Capsules are available as:

Opaque, pink and yellow hard gelatin capsules (imprinted with code number 088) which contain 250 mg of oxytetracycline, glucosamine hydrochloride, and 250,000 units of nystatin per capsule; bottles of 50.

(60-1060-00-3)

Literature available: Yes.

[Shown in Product Identification Section]

MYSTECLIN-F® CAPSULES

(Tetracycline-Amphotericin B Capsules)

MYSTECLIN-F SYRUP

(Tetracycline-Amphotericin B Syrup)

Recently, a panel of the National Academy of Sciences—National Research Council has stated that in its informed judgment Mysteclin-F is ineffective as fixed combination. Further, it stated, "The Panel is not aware of evidence of proved efficacy of this combination on the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished. It should be noted that the apparent reduction of organisms in the feces may be an artifact due to residual antibiotic activity and thus may not reflect the true state in the patient. It is preferable, in the Panel's opinion, to prescribe antifungal drugs when clinically indicated, rather than to use them indiscriminately as 'prophylaxis' against an uncommon clinical entity seen during therapy with tetracyclines and other antibiotics."

Mysteclin-F Capsules (Tetracycline-Amphotericin B Capsules) contain tetracycline equivalent to 250 mg. tetracycline hydrochloride with 50 mg. amphotericin B buffered with potassium metaphosphate.

Mysteclin-F '125' Capsules (Tetracycline-Amphotericin B Capsules) contain tetracycline equivalent to 125 mg. tetracycline hydrochloride with 25 mg. amphotericin B buffered with potassium metaphosphate.

Mysteclin-F Syrup (Tetracycline-Amphotericin B Syrup) is a fruit-flavored syrup containing, in each 5 ml. teaspoonful, tetracycline equivalent to 125 mg. tetracycline hydrochloride, buffered with potassium metaphosphate, and 25 mg. amphotericin B.

Action: These preparations have been designed to provide simultaneous antimicrobial therapy and anticandidal prophylaxis, a concept first developed by Squibb.

The preparations, which contain the broadspectrum antibiotic tetracycline, well known for its pronounced antimicrobial effect against a wide range of pathogenic organisms, produce exceptionally high initial tetracycline blood levels as well as excellent diffusion to tissues and body fluids.

Furthermore, these preparations also contain prophylactic amounts of the antifungal antibiotic, amphotericin B. This antibiotic, first isolated and described by the Squibb Institute for Medical Research, is substantially more active *in vitro* against *Candida* strains than nystatin and has been widely used by the intravenous route in the treatment of many deep-seated mycotic infections.

Given orally, amphotericin B is extremely well tolerated and is virtually non-toxic in prophylactic doses. Although poorly absorbed from the gut, amphotericin B has a high degree of activity against *Candida* species in the intestinal tract and prevents the overgrowth of these organisms commonly associated with broad-spectrum antibiotic therapy (amphotericin B has no antibacterial activity). By suppressing the overgrowth of *Candida* in the gastrointestinal tract, thereby minimizing a possible reservoir of this organism, Mysteclin-F (Tetracycline-Amphotericin B) provides added protection for the patient against troublesome, or even serious, candidal superinfections, e.g., intestinal (diarrheal), anogenital, vulvovaginal, mucocutaneous candidiasis.

Note: Microorganisms that have become insensitive to one tetracycline invariably exhibit cross-resistance to other tetracyclines. In addition, gram-negative bacilli made tetracycline resistant may also show cross-resistance to chloramphenicol.

Indications: Candidal overgrowth occurs in a large number of patients taking broad-spectrum antibiotics. Although it is impossible to predict exactly which patient will develop candidal complications and which will not, certain types of patients are known to be particularly susceptible to candidiasis. Among these are elderly or debilitated patients; patients on high or prolonged antibiotic dosage; diabetics; infants; patients on corticoid therapy; patients who have developed candidiasis on previous broad-spectrum therapy; women, particularly during pregnancy. Because the danger of candidal complications is greatest in these patients, they are potential candidates for therapy with Mysteclin-F.

Mysteclin-F (Tetracycline-Amphotericin B) Capsules and Syrup, are indicated for the many common infections, including those of the respiratory, gastrointestinal and genitourinary systems, which are amenable to tetracycline therapy. Infections caused by gram-positive and gram-negative bacteria, spirochetes, viruses of the lymphogranuloma-psittacosistrachoma group, rickettsiae, and *Endamoeba histolytica* can be expected to respond. Because of the wide range of antimicrobial activity, the preparations are particularly useful in the treatment of mixed infections due to susceptible organisms.

The Capsules and Syrup are also a useful part of the armamentarium in the management of chronic cases of acne vulgaris which, in the judgment of the clinician, require long-term treatment. The cystic and pustular forms of this condition respond most satisfactorily to tetracycline therapy; the papular form may also show improvement in some individuals. Because long-term maintenance therapy with tetracycline is involved, the presence of amphotericin B in the Capsules and Syrup is a particular advantage, helping to guard against the risk of candidal overgrowth.

Note: A number of strains of staphylococci and streptococci have shown resistance to tetracyclines. A few strains of pneumococci, *E. coli* and shigellae also have been reported as resistant. Indicated laboratory studies, including sensitivity tests, should be performed.

Contraindications: The products should not be used in persons with a history of hypersensitivity to any of their components.

Warning: If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity. Under such conditions, lower-than-usual doses are indicated and if therapy is prolonged, tetracycline serum level determinations may be advisable.

Certain hypersensitive individuals may develop a photodynamic reaction precipitated by exposure to direct sunlight during the use of this drug. This reaction is usually of the photoallergic type which may also be produced by other tetracycline derivatives. Individuals with a history of photosensitivity reactions should be instructed to avoid exposure to direct sunlight while under treatment with this or other tetracycline drugs and treatment should be discontinued at first evidence of skin discomfort.

Note: Photosensitization reactions have occurred most frequently with demethylchlortetracycline, less with chlortetracycline and very rarely with oxytetracycline and tetracycline.

Precautions: As with any antibiotic preparation, prolonged use may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. Should superinfection occur, the preparation should be discontinued and/or appropriate therapy instituted. **Note:** Superinfection of the bowel by staphylococci may be life threatening.

Tetracycline may form a stable calcium complex in any bone forming tissue with no serious harmful effects reported thus far in humans. However, use of tetracycline during tooth development (i.e., latter half of gestation, neonatal period and early childhood) may cause discoloration of the teeth (i.e., yellow-grey-brownish). This effect occurs mostly during long-term use of the drug but it has also been observed in usual short treatment courses.

During long-term therapy, periodic assessment of organ system function, including renal, hepatic and hematopoietic systems, should be made.

Increased intracranial pressure with bulging fontanels has been observed in infants taking therapeutic doses of tetracycline. Occurrence has been rare and all signs and symptoms have disappeared rapidly upon cessation of treatment.

Since sensitivity reactions are more likely to occur in persons with a history of allergy, asthma, hay fever, or urticaria, the preparation should be used with caution in such individuals. Cross-sensitization among the various tetracyclines is extremely common.

In the treatment of gonorrhea, patients with a suspected lesion of syphilis should have darkfield examinations before receiving tetracycline and monthly serologic tests for a minimum of three months.

The use of tetracycline in staphylococcal infections does not preclude the need for indicated surgical procedures.

Adverse Reactions: Oral administration of amphotericin B is usually well tolerated. The following adverse reactions have been reported with tetracycline preparations:

Gastrointestinal irritation (anorexia, epigastric distress, nausea, vomiting) as well as bulky loose stools, and diarrhea may occur. Glossitis, stomatitis, enterocolitis, proctitis, and pruritus ani may occur in some patients. Black hairy tongue, sore throat, dysphagia, and hoarseness have also been reported. However, tetracycline is generally well tolerated, undesirable gastrointestinal side effects occurring significantly less frequently than with the two analogues, oxytetracycline and chlortetracycline.

Tetracyclines may also cause maculopapular and erythematous skin rashes. A rare case of exfoliative dermatitis has been reported. Photosensitivity, manifested by an exaggerated sunburn reaction has been observed in some individuals (see *Warning*). Onycholysis and discoloration of the nails have been reported rarely.

Rise in BUN has been reported and is apparently dose related. Urinary loss of nitrogen has been observed in some patients receiving tetracyclines and may result in negative nitrogen balance. Increased excretion of sodium has also been reported. The development of peptic ulcers and bleeding has been observed in uremic patients receiving tetracyclines.

Hypersensitivity reactions may include urticaria, serum sickness-like reactions (fever, rash, arthralgia), angioneurotic edema, and anaphylactoid shock. If allergic reactions occur, or if an individual idiosyncrasy appears, tetracycline therapy should be discontinued.

Increased intracranial pressure with bulging fontanel has been reported in infants following full therapeutic doses of tetracycline. This symptom disappears rapidly when administration of tetracycline is discontinued (see *Precautions*).

The use of tetracycline during the mineralization phase of tooth development (latter half of gestation, neonatal period, and early childhood) may cause discoloration of the teeth (yellow-grey-brownish) which may sometimes be accompanied by enamel hypoplasia (see *Precautions*).

Anemia, thrombocytopenic purpura, neutropenia, and eosinophilia have been reported. Tetracyclines may delay blood coagulation. Hepatic cholestasis has been reported rarely, and is usually associated with high dosage levels of tetracycline.

Dosage and Administration: Dosage should be based on the tetracycline content. For the many common infections amenable to tetracycline therapy, adults should receive a minimum of 250 mg four times daily. Higher dosages, such as 500 mg four times daily, may be required for severe infections or for those infections which do not respond to the smaller dose. In general, the pediatric dosage should supply 10 to 20 mg. tetracycline per pound of body weight each day, in divided doses, depending on the type and severity of the infection.

Representative pediatric dosages of Mysteclin-F Syrup (Tetracycline-Amphotericin B Syrup) are as follows: 20 lb.: one-half teaspoonful q.i.d.; 40 lb.: 1 teaspoonful q.i.d.; 60 lb.: one and one-half teaspoonfuls q.i.d.; 80 lb.: 2 teaspoonfuls q.i.d.

Oral forms of tetracycline should be given 1 hour before or 2 hours following meals. Pediatric dosage forms (oral) should not be given with milk formulas or other calcium-containing foods and should be given at least 1 hour prior to feeding.

Treatment of most common infections should continue for 24 to 48 hours after symptoms and fever subside. However, if the preparations are used in the treatment of streptococcal infections due to susceptible organisms, therapy should be continued for a full ten days to guard against the risk of rheumatic fever or glomerulonephritis. Higher dosage and even more prolonged therapy is necessary for sub-acute bacterial endocarditis and may be required in certain staphylococcal infections.

In chronic cases of acne vulgaris which, in the judgment of the clinician, require long-term treatment, the recommended initial dosage of the Capsules and Syrup is 1 g. daily in divided doses. When improvement is noted, usually within one week, dosage should be gradually reduced to maintenance levels ranging from 125 to 500 mg. daily. In some patients it may be possible to maintain adequate remission of lesions with alternate-day or intermittent therapy. Tetracycline therapy of acne vulgaris should augment the other standard measures known to be of value.

How Supplied: *Mysteclin-F Capsules (Tetracycline-Amphotericin B Capsules), bottles of 16 and 100 Unimatic® Single Dose Packs of 100; *Mysteclin-F '125' Capsules, bottles of 100. Mysteclin-F Syrup (Tetracycline-Amphotericin B Syrup) (fruit-flavored), bottles of 60 ml. and 240 ml. (8 oz.).

* [Shown in Product Identification Section]

APPENDIX G—PHYSICIAN INFORMATION

Physician information as provided in the 1978 PDR for four approved fixed-combination drug products: one synthetic antibacterial combination product, Bactrim; and three antibiotic combination products, Rifamate, Rimactazid, and Polycillin-PRB.

BACTRIM™

(trimethoprim and sulfamethoxazole)

TABLETS, SUSPENSION, DS (DOUBLE STRENGTH) TABLETS

The following text is complete prescribing information based on official labeling in effect August 1, 1977.

Description: Bactrim is a synthetic antibacterial combination product, available in double strength, notched, capsule-shaped, white tablets, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole; in scored light-green tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole; and as a pink, fruit-licorice flavored oral suspension, each teaspoonful (5 ml) containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, compounded with 0.3% alcohol.

Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.3.

Sulfamethoxazole is *N*¹-(5-methyl-3-isoxazolyl) sulfanilamide. It is an almost white in color, odorless, tasteless compound with a molecular weight of 253.28.

Actions: Microbiology: Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with *para*-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, Bactrim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

In vitro studies have shown that bacterial resistance develops more slowly with Bactrim than with trimethoprim or sulfamethoxazole alone.

In vitro serial dilution tests have shown that the spectrum of antibacterial activity of Bactrim includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*. The following organisms are usually susceptible: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis* and indole positive proteus species.

[See table below].

Human Pharmacology: Bactrim is rapidly absorbed following oral administration. The blood levels of trimethoprim and sulfamethoxazole are similar to those achieved when each component is given alone. Peak blood levels for the individual components occur one to four hours after oral administration. The half-lives of sulfamethoxazole and trimethoprim, 10 and 16 hours respectively, are relatively the same regardless of whether these compounds are administered as individual components or as Bactrim. Detectable amounts of trimethoprim and sulfamethoxazole are present in the blood 24 hours after drug administration. Free sulfamethoxazole and trimethoprim blood levels are proportionately dose dependent. On repeated administration, the steady-state ratio of trimethoprim to sulfamethoxazole levels in the blood is about 1:20.

REPRESENTATIVE MINIMUM INHIBITORY CONCENTRATION VALUES FOR BACTRIM-SUSCEPTIBLE ORGANISMS

[MIC—mcg/ml]

Bacteria	Trimethoprim alone	Sulfamethoxazole alone	TMP/SMX (1:20)	
			TMP	SMX
<i>Escherichia coli</i>	0.05–1.5	1.0–245	0.05–0.5	0.95–9.5
<i>Proteus</i> spp. indole positive.....	.5–5.0	7.35–300	.05–1.5	.95–28.5
<i>Proteus mirabilis</i>	.5–1.5	7.35–30	.05–.15	.95–28.5
<i>Klebsiella-Enterobacter</i>	.15–5.0	2.45–245	.05–1.5	.95–28.5

Sulfamethoxazole exists in the blood as free, conjugated and protein-bound forms; trimethoprim is present as free, protein-bound and metabolized forms. The free forms are considered to be the therapeutically active forms. Approximately 44 percent of trimethoprim and 70 percent of sulfamethoxazole are protein-bound in the blood. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim to an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Excretion of Bactrim is chiefly by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. When administered together as in Bactrim, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

INDICATIONS AND USAGE

Urinary tract infections: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris* and *Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of these urinary tract infections.

***Pneumocystis carinii* pneumonitis:** Bactrim is also indicated in the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

The recommended quantitative disc susceptibility method (*Federal Register*, 37: 20527-20529, 1972; Bauer AW, Kirby WMM, Sherris JC, Truck M: Antibiotic Susceptibility Testing by a Standardized Single Disk Method, *Am J Clin Pathol*, 45: 493-496, 1966) may be used for estimating the susceptibility of bacteria to Bactrim. With this procedure, a report from the laboratory of "Susceptible to trimethoprim-sulfamethoxazole" indicates that the infection is likely to respond to therapy with Bactrim. If the infection is confined to the urine, a report of "Intermediate susceptibility to trimethoprim-sulfamethoxazole" also indicates that the infection is likely to respond. A report of "Resistant to trimethoprim-sulfamethoxazole" indicates that the infection is unlikely to respond to therapy with Bactrim.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period (see Reproduction Studies). Infants less than two months of age.

Warnings: Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but it has been reported to interfere with hematopoiesis in occasional patients. In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombopenia with purpura has been reported.

The presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. Complete blood counts should be done frequently in patients receiving Bactrim. If a significant reduction in the count of any formed blood element is noted, Bactrim should be discontinued.

Precautions: Bactrim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Adverse Reactions: For completeness, all major reactions to sulfonamides and trimethoprim are included below, even though they may not have been reported with Bactrim.

Blood dyscrasias: Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia.

Allergic reactions: Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis.

Gastrointestinal reactions: Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis.

C.N.S. reactions: Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness.

Miscellaneous reactions: Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarteritis nodosa and L. E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Goiter production, diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

Dosage and Administration: Not recommended for use in infants less than two months of age.

URINARY TRACT INFECTIONS

The usual adult dosage in the treatment of urinary tract infections:

Bactrim DS (double strength) tablets—one double strength tablet every 12 hours for 10 to 14 days.

Bactrim tablets—two tablets every 12 hours for 10 to 14 days.

Bactrim suspension—four teaspoonfuls (20 ml) every 12 hours for 10 to 14 days.

The recommended dose for children with urinary tract infections is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses for 10 days. In children weighing 80 lbs (36 kgs) or more, the dosage is one Bactrim DS (double strength) tablet every 12 hours for 10 days.

For patients with renal impairment:

Creatinine clearance (ml/min):

Above 30-----
15-30-----
Below 15-----

Recommended dosage regimen

Usual standard regimen.
 $\frac{1}{2}$ the usual regimen.
Use not recommended.

PNEUMOCYSTIS CARINII PNEUMONITIS

The recommended dosage for patients with *Pneumocystis carinii* pneumonitis is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 days. In children weighing 80 lbs (36 kgs), the dosage is 1 Bactrim DS (double strength) tablet every 6 hours for 14 days.

The following table is a guideline for the attainment of the correct dosage in children using Bactrim Tablets, Suspension or Bactrim DS Tablets.

Weight		Dose ¹	
Pounds	Kilograms	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	$\frac{1}{2}$ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	$1\frac{1}{2}$ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

¹ In urinary tract infections—every 12 hr; in *Pneumocystis carinii* pneumonitis—every 6 hr.

How Supplied: *Double Strength Tablets*, containing 160 mg trimethoprim and 800 mg sulfamethoxazole—bottles of 100; Tel E-Dose® packages of 100. Imprint on tablets: Bac-Trim-Ds Roche.

Tablets, containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10.

Oral Suspension, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole; fruit-licorice flavored—bottles of 16 oz (1 pint).

Reproduction studies: In rats, doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palates. The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed with 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. However, in one study, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In rabbits, trimethoprim administered by intubation from days 8 to 16 of pregnancy at dosages up to 500 mg/kg resulted in higher incidences of dead and resorbed fetuses, particularly at 500 mg/kg. However, there were no significant drug-related teratological effects.

[Shown in Product Identification Section]

RIFAMATE TM

rifampin-isoniazid

CAPSULES

Description: Rifamate is a combination capsule containing 300 mg. rifampin and 150 mg. isoniazid.

Rifampin is a semisynthetic antibiotic derivative of rifamycin B. Specifically, rifampin is the hydrazone, 3-(4-methylpiperazinyloxy) rifamycin SV.

Isoniazid is the hydrazide of isonicotinic acid. It exists as colorless or white crystals or as a white, crystalline powder that is water soluble, odorless, and slowly affected by exposure to air and light.

ACTIONS: RIFAMPIN

Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. This is the mechanism of action by which rifampin exerts its therapeutic effect. Rifampin cross resistance has only been shown with other rifamycins.

In a study of 14 normal human adult males, peak blood levels of rifampin occurred 1½ to 3 hours following oral administration of two Rifamate capsules. The peaks ranged from 6.9 to 14 mcg/ml with an average of 10 mcg/ml. In normal subjects the T ½ (biological half-life) of rifampin in blood is approximately 3 hours. Elimination occurs mainly through the bile and, to a much lesser extent, the urine.

ISONIAZID

Isoniazid acts against actively growing tubercle bacilli.

After oral administration isoniazid produces peak blood levels within 1 to 2 hours which decline to 50 percent or less within 6 hours. It diffuses readily into all body fluids (cerebrospinal, pleural, and ascitic fluids), tissues, organs, and excreta (saliva, sputum, and feces). The drug also passes through the placental barrier and into milk in concentrations comparable to those in the plasma. From 50 to 70 percent of a dose of isoniazid is excreted in the urine in 24 hours. Isoniazid is metabolized primarily by acetylation and dehydrazination. The rate of acetylation is genetically determined. Approximately 50 percent of Negroes and Caucasians are "slow inactivators"; the majority of Eskimos and Orientals are "rapid inactivators."

The rate of acetylation does not significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood levels of the drug, and thus an increase in toxic reactions.

Pyridoxine deficiency (B₆) is sometimes observed in adults with high doses of isoniazid and is considered probably due to its competition with pyridoxal phosphate for the enzyme apotryptophanase.

INDICATIONS: PULMONARY TUBERCULOSIS

In the initial treatment and re-treatment of all forms of pulmonary tuberculosis in which the tubercle bacilli are susceptible,

In the treatment of tuberculosis, small numbers of resistant cells, present within large populations of susceptible cells, can rapidly become the predominating type. Since rapid emergence of resistance can occur, culture and susceptibility tests should be performed in the event of persistent positive cultures.

This drug is *not* indicated for the treatment of meningococcal infections or asymptomatic carriers of *N. meningitidis* to eliminate meningococci from the nasopharynx.

Contraindications: A history of previous hypersensitivity reaction to any of the rifamycins or to isoniazid, including drug-induced hepatitis.

Warnings: Rifamate (rifampin-isoniazid) is a combination of two drugs, each of which has been associated with liver dysfunction. Liver function tests should be performed prior to therapy with Rifamate and periodically during treatment.

RIFAMPIN

Rifampin has been shown to produce liver dysfunction. There have been fatalities associated with jaundice in patients with liver disease or receiving rifampin concomitantly with other hepatotoxic agents. Since an increased risk may exist for individuals with liver disease, benefits must be weighed carefully against the risk of further liver damage.

ISONIAZID

Severe and sometimes fatal hepatitis associated with isoniazid therapy has been reported and may develop even after many months of therapy. Therefore, individuals on isoniazid therapy should be carefully monitored and interviewed at monthly intervals. They should be instructed to report immediately any of the prodromal symptoms of hepatitis such as fatigue, weakness, malaise, anorexia, nausea or vomiting. If these appear, the patient should be carefully evaluated. The drug should be discontinued promptly and appropriate therapy given if signs suggestive of hepatic damage are detected. Patients with tuberculosis should be given appropriate therapy with alternative drugs.

Isoniazid has been reported to induce pulmonary tumors in a number of strains of mice.

USAGE IN PREGNANCY—RIFAMPIN

Although rifampin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampin, alone or in combination with other anti-tuberculosis drugs, on the human fetus is not known. An increase in congenital malformations, primarily spina bifida and cleft palate, has been reported in the offspring of rodents given oral doses of 150-250 mg/kg/day of rifampin during pregnancy.

The possible teratogenic potential in women capable of bearing children should be carefully weighed against the benefits of therapy.

ISONIAZID

Although no harmful effects of isoniazid to the fetus have been observed in humans, isoniazid should be prescribed during pregnancy only when therapeutically necessary. The benefit of preventive therapy should be weighed against the risk to the fetus. Preventive treatment generally should be started after delivery because of increased risk of tuberculosis for mothers during the post-partum period.

It has been reported that isoniazid may exert an embryocidal effect when administered orally to rats and rabbits during pregnancy, but no isoniazid-related congenital anomalies have been found in reproduction studies in mammalian species (mice, rats and rabbits). Since isoniazid is known to cross the placental barrier and to pass into maternal breast milk, neonates and breast fed infants of isoniazid-treated mothers should be carefully observed for any evidence of adverse effects.

PRECAUTIONS: RIFAMPIN

Rifampin is not recommended for intermittent therapy; the patient should be cautioned against intentional or accidental interruption of the daily dosage regimen since rare renal hypersensitivity reactions have been reported when therapy was resumed in such cases.

Rifampin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. The cause of the phenomenon is unknown. In patients receiving anticoagulants and rifampin concurrently, it is recommended that the prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant.

Urine, feces, saliva, sputum, sweat and tears may be colored red-orange by rifampin and its metabolites. Individuals to be treated should be made aware of these possibilities in order to prevent undue anxiety.

It has been reported that the reliability of oral contraceptives may be affected in some patients being treated for tuberculosis with rifampin in combination with at least one other antituberculosis drug. In such cases, alternative contraceptive measures may need to be considered.

It has also been reported that rifampin given in combination with other antituberculosis drugs may affect the blood concentration of methadone, oral hypoglycemics, digitalis derivatives, dapsone and corticosteroids. In these cases, dosage adjustment of the interacting drugs is recommended.

Therapeutic levels of rifampin have been shown to inhibit standards assays for serum folate and vitamin B₁₂. Alternative methods must be considered when determining folate and vitamin B₁₂ concentrations in the presence of rifampin.

Since rifampin has been reported to cross the placental barrier and appear in cord blood and in maternal milk, neonates and newborns of rifampin-treated mothers should be carefully observed for any evidence of untoward effects.

ISONIAZID

All drugs should be stopped and an evaluation of the patient should be made at the first sign of a hypersensitivity reaction.

Use of isoniazid should be carefully monitored in the following:

(a) Patients who are receiving phenytoin (diphenylhydantoin) concurrently. Isoniazid may decrease the excretion of phenytoin or may enhance its effects. To avoid phenytoin intoxication, appropriate adjustment of the anticonvulsant dose should be made.

(b) Daily users of alcohol. Daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis.

(c) Patients with current chronic liver disease or severe renal dysfunction.

(d) Patients receiving concurrent medication on a long-term basis, because of possible drug interactions.

Periodic ophthalmoscopic examination during isoniazid therapy is recommended when visual symptoms occur.

ADVERSE REACTIONS: RIFAMPIN

Nervous system reactions: headache, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, visual disturbances, muscular weakness, pain in extremities and generalized numbness.

Gastrointestinal disturbances: in some patients heartburn, epigastric distress, anorexia, nausea, vomiting, gas, cramps, and diarrhea.

Hepatic reactions: transient abnormalities in liver function tests (e.g. elevations in serum bilirubin, BSP, alkaline phosphatase, serum transaminases) have been observed. Rarely, hepatitis or a shocklike syndrome with hepatic involvement and abnormal liver function tests.

Hematologic reactions: thrombocytopenia, transient leukopenia, hemolytic anemia, eosinophilia and decreased hemoglobin have been observed. Thrombocytopenia has occurred when rifampin and ethambutol were administered concomitantly according to an intermittent dose schedule twice weekly and in high doses.

Allergic and immunological reactions: occasionally pruritis, urticaria, rash, pemphigus, acneiform lesions, eosinophilia, sore mouth, sore tongue and exudative conjunctivitis. Rarely, hemolysis, hemoglobinuria, hematuria, renal insufficiency or acute renal failure have been reported which are generally considered to be hypersensitivity reactions. These have usually occurred during intermittent therapy or when treatment was resumed following intentional or accidental interruption of a daily dosage regimen and were reversible when rifampin was discontinued and appropriate therapy instituted.

Although rifampin has been reported to have an immunosuppressive effect in some animal experiments, available human data indicate that this has no clinical significance.

Metabolic reactions: elevations in BUN and serum uric acid have occurred.

Miscellaneous reactions: fever and menstrual disturbances have been noted.

ISONIAZID

Toxic effects are usually encountered only with higher doses of isoniazid and the incidence is reportedly higher in "slow inactivators."

Nervous system reactions: peripheral neuropathy occurs most often in the malnourished and is usually preceded by paresthesias in the feet and hands. Convulsions, toxic encephalopathy, optic neuritis and atrophy, and toxic psychosis have also been reported.

Gastrointestinal reactions: nausea, vomiting, epigastric distress.

Hepatic reactions: elevated serum transaminases (SGOT, SGPT), bilirubinemia, bilirubinuria, and occasionally severe and sometimes fatal hepatitis with and without jaundice.

Hematologic reactions: agranulocytosis, hemolytic sideroblastic or aplastic anemia, thrombocytopenia and eosinophilia.

Hypersensitivity reactions: fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy and vasculitis.

Metabolic and endocrine reactions: pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, and gynecomastia.

Miscellaneous reactions: rheumatic syndrome and systemic lupus erythematosus-like syndrome.

Dosage and Administration: In general, therapy should be continued until bacterial conversion and maximal improvement have occurred.

Adults: Two Rifamate (rifampin-isoniazid) capsules (600 mg rifampin, 300 mg isoniazid) once daily, administered one hour before or two hours after a meal.

Concomitant administration of pyridoxine (B⁶) is recommended in the malnourished, in those predisposed to neuropathy (e. g. diabetics) and in adolescents.

SUSCEPTIBILITY TESTING RIFAMPIN

Rifampin susceptibility powders are available for both direct and indirect methods of determining the susceptibility of strains of mycobacteria. The MIC's of susceptible clinical isolates when determined in 7H10 or other non-egg-containing media have ranged from 0.1 to 2 mcg/ml.

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with discs for testing susceptibility to rifampin. Interpretations correlate zone diameters from the disc test with MIC (minimal inhibitory concentration) values for rifampin.

OVERDOSAGE: RIFAMPIN, SIGNS AND SYMPTOMS

Nausea, vomiting, and increasing lethargy will probably occur within a short time after ingestion; actual unconsciousness may occur with severe hepatic involvement. Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears and feces is proportional to amount ingested.

Liver enlargement, possibly with tenderness, can develop within a few hours after severe overdosage and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. Other physical findings remain essentially normal.

Direct and total bilirubin levels may increase rapidly with severe overdosage; hepatic enzyme levels may be affected, especially with prior impairment of hepatic function. A direct effect upon hemopoietic system, electrolyte levels, or acid-base balance is likely.

ISONIAZID: SIGNS AND SYMPTOMS

Isoniazid overdosage produces signs and symptoms within 30 minutes to 3 hours. Nausea, vomiting, dizziness, slurring of speech, blurring of vision, visual hallucinations (including bright colors and strange designs), are among the early manifestations. With marked overdosage, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, are to be expected, along with severe, intractable seizures. Severe metabolic acidosis, acetonuria, and hyperglycemia are typical laboratory findings.

RIFAMATE (RIFAMPIN-ISONIAZID): TREATMENT

The airway should be secured and adequate respiratory exchange established. Only then should gastric emptying (lavage-aspiration) be attempted: this may be difficult because of seizures. Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis.

Activated charcoal slurry instilled into the stomach following evacuation of gastric contents can help absorb any remaining drug in the GI tract. Antiemetic medication may be required to control severe nausea and vomiting.

Blood samples should be obtained for immediate determination of gases, electrolytes, BUN, glucose, etc. Blood should be typed and cross-matched in preparation for possible hemodialysis.

Rapid control of metabolic acidosis is fundamental to management. Intravenous sodium bicarbonate should be given at once and repeated as needed, adjusting subsequent dosage on the basis of laboratory finding (i.e. serum sodium, pH, etc.) At the same time anticonvulsants should be given intravenously (i.e. barbiturates, diphenylhydantoin, diazepam) as required, and large doses of intravenous pyridoxine.

Forced osmotic diuresis may be started early and should be continued for some hours after clinical improvement to hasten renal clearance of drug and help prevent relapse. Fluid intake and output should be monitored.

Bile drainage may be indicated in presence of serious impairment of hepatic function lasting more than 24–48 hours. Under these circumstances, and for severe cases extracorporeal hemodialysis may be required; if this is not available, peritoneal dialysis can be used along with forced diuresis.

Along with measures based on initial and repeated determination of blood gases and other laboratory tests as needed, meticulous respiratory and other intensive care should be utilized to protect against hypoxia, hypotension, aspiration, pneumonitis, etc.

In patients with previously adequate hepatic function, reversal of liver enlargement and impaired hepatic excretory function probably will be noted within 72 hours, with rapid return toward normal thereafter.

Untreated or inadequately treated cases of gross isoniazid overdosage can terminate fatally, but good response has been reported in most patients brought under adequate treatment within the first few hours after drug ingestion.

Caution: Federal law prohibits dispensing without prescription.

How Supplied: Capsules (opaque red), containing 300 mg rifampin and 150 mg isoniazid; bottles of 60 (NDC 0183-0509-60).

[Shown in Product Identification Section]

RIMACTAZID®

Rifampin 300 mg, Isoniazid 150 mg

CAPSULES—INDICATIONS: PULMONARY TUBERCULOSIS

In the initial treatment and re-treatment of all forms of pulmonary tuberculosis in which the tubercle bacilli are susceptible.

In the treatment of tuberculosis, small numbers of resistant cells, present within large populations of susceptible cells, can rapidly become the predominating type. Since rapid emergence of resistance can occur, culture and susceptibility tests should be performed in the event of persistent positive cultures.

This drug is *not* indicated for the treatment of meningococcal infections or asymptomatic carriers of *N. meningitidis* to eliminate meningococci from the nasopharynx.

Contraindications: A history of previous hypersensitivity reaction to any of the rifamycins or to isoniazid, including drug-induced hepatitis.

Warnings: Rimactazid is a combination of two drugs, each of which has been associated with liver dysfunction. Liver function tests should be performed prior to Rimactazid therapy and periodically during treatment.

RIFAMPIN

Rifampin has been shown to produce liver dysfunction. There have been fatalities associated with jaundice in patients with liver disease or receiving rifampin concomitantly with other hepatotoxic agents. Since an increased risk may exist for individuals with liver disease, benefits must be weighted carefully against the risk of further liver damage.

ISONIAZID

Severe hepatitis associated with isoniazid therapy has been reported and may develop even after months of therapy.

Isoniazid has been reported to induce pulmonary tumors in a number of strains of mice.

USAGE OF PREGNANCY: RIFAMPIN

Although rifampin has been reported to cross the placental barrier in cord blood, the effect of rifampin, alone or in combination with other antituberculous drugs, on the human fetus is not known. An increase in congenital

malformations, primarily spina bifida and cleft palate, has been reported in the offspring of rodents given oral doses of 150–250 mg/kg/day of rifampin during pregnancy.

The possible teratogenic potential in women capable of bearing children should be carefully weighed against the benefits of therapy.

ISONIAZID

Although no isoniazid-related congenital anomalies have been found in reproduction studies in mammalian species (mice, rats and rabbits), it has been reported that in both rats and rabbits, isoniazid may exert an embryocidal effect when administered orally during pregnancy.

PRECAUTIONS: RIFAMPIN

Rifampin is not recommended for intermittent therapy; the patient should be cautioned against intentional or accidental interruption of the daily dosage regimen since rare renal hypersensitivity reactions have been reported when therapy was resumed in such cases.

Rifampin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. The cause of the phenomenon is unknown. In patients receiving anticoagulants and rifampin concurrently, it is recommended that the prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant.

Urine, feces, saliva, sputum, sweat and tears may be colored red-orange by rifampin and its metabolites. Individuals to be treated should be made aware of these possibilities in order to prevent undue anxiety.

It has been reported that the reliability of oral contraceptives may be affected in some patients being treated for tuberculosis with rifampin in combination with at least one other antituberculous drug. In such cases, alternative contraceptive measures may need to be considered.

Since rifampin has been reported to cross the placental barrier and appear in cord blood and in maternal milk, neonates and newborns of rifampin-treated mothers should be carefully observed for any evidence of untoward effects.

ISONIAZID

The use of isoniazid should be carefully monitored in patients with convulsive disorders, pre-existing hepatic disease and severe renal dysfunction.

Periodic ophthalmoscopic examination during isoniazid therapy is recommended when visual symptoms occur.

ADVERSE REACTIONS: RIFAMPIN

Nervous system, reactions: headache, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, visual disturbances, muscular weakness, pain in extremities and generalized numbness.

Gastrointestinal disturbances: in some patients heartburn, epigastric distress, anorexia, nausea, vomiting, gas, cramps, and diarrhea.

Hepatic reactions: transient abnormalities in liver function tests (e.g. elevations in serum bilirubin, BSP, alkaline phosphatase, serum transaminases) have been observed. Rarely, hepatitis or a shocklike syndrome with hepatic involvement and abnormal liver function tests.

Hematologic reactions: thrombocytopenia, transient leukopenia, hemolytic anemia, eosinophilia and decreased hemoglobin have been observed. Thrombocytopenia has occurred when rifampin and ethambutol were administered concomitantly according to an intermittent dose schedule twice weekly and in high doses.

Allergic and immunological reactions: occasionally pruritis, urticaria, rash, eosinophilia, sore mouth, and sore tongue. Rarely, hemolysis, hemoglobinuria, hematuria, renal insufficiency or acute renal failure have been reported which are generally considered to be hypersensitivity reactions. These have usually occurred during intermittent therapy or when treatment was resumed following intentional or accidental interruption of a daily dosage regimen and were reversible when rifampin was discontinued and appropriate therapy instituted.

Although rifampin has been reported to have an immunosuppressive effect in some animal experiments, available human data indicate that this has no clinical significance.

Metabolic reactions: elevations in BUN and serum uric acid have occurred.

Miscellaneous reactions: fever and menstrual disturbances have been noted.

ISONIAZID

Toxic effects are usually encountered only with higher doses of isoniazid and the incidence is reportedly higher in "slow inactivators."

Nervous system reactions: peripheral neuropathy occurs most often in the malnourished and is usually preceded by paresthesias in the feet and hands. Convulsions, toxic encephalopathy, optic neuritis and atrophy, and toxic psychosis have also been reported.

Gastrointestinal reactions: nausea, vomiting, epigastric distress.

Hepatic reactions: elevated serum transaminases (SGOT, SGPT), bilirubinemia, bilirubinuria, and occasionally severe and sometimes fatal hepatitis with and without jaundice.

Hematologic reactions: agranulocytosis, hemolytic or aplastic anemia, thrombocytopenia and eosinophilia.

Hypersensitivity reactions: fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy and vasculitis.

Metabolic and endocrine reactions: pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, and gynecomastia.

Miscellaneous reactions: rheumatic syndrome and systemic lupus erythematosus-like syndrome.

DOSAGE AND ADMINISTRATION

In general, therapy should be continued until bacterial conversion and maximal improvement have occurred.

Adults: Two Rimactazid capsules (600 mg rifampin, 300 mg isoniazid) once daily, administered one hour before or two hours after a meal.

Concomitant administration of pyridoxine (B⁶) is recommended in the malnourished, in those predisposed to neuropathy (*eg*, diabetics) and in adolescents.

SUSCEPTIBILITY TESTING—RIFAMPIN

Rifampin susceptibility powders are available for both direct and indirect methods of determining the susceptibility of strains of mycobacteria. The MIC's of susceptible clinical isolates when determined in 7H10 or other non-egg-containing media have ranged from 0.1 to 2 mcg/ml.

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with discs for testing susceptibility to rifampin. Interpretations correlate zone diameters from the disc test with MIC (minimal inhibitory concentration) values for rifampin.

OVERDOSAGE: RIFAMPIN—SIGNS AND SYMPTOMS

Nausea, vomiting, and increasing lethargy will probably occur within a short time after ingestion; actual unconsciousness may occur with severe hepatic involvement. Brownish-red or orange discoloration of urine, sweat, saliva, tears and feces is proportional to amount ingested.

Liver enlargement, possibly with tenderness, can develop within a few hours after severe overdosage and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. Other physical findings remain essentially normal.

Direct and total bilirubin levels may increase rapidly with severe overdosage; hepatic enzyme levels may be affected, especially with prior impairment of hepatic function. A direct effect upon hemopoietic system, electrolyte levels, or acid-base balance is unlikely.

ISONIAZID—SIGNS AND SYMPTOMS

Isoniazid overdosage produces signs and symptoms within 30 minutes to 3 hours. Nausea, vomiting, dizziness, slurring of speech, blurring of vision, visual hallucinations (including bright colors and strange designs), are among the early manifestations. With marked overdosage, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, are to be expected, along with severe, intractable seizures. Severe metabolic acidosis, acetonuria, and hyperglycemia are typical laboratory findings.

RIMACTAZID—TREATMENT

The airway should be secured and adequate respiratory exchange established. Only then should gastric emptying (lavage-aspiration) be attempted; this may be difficult because of seizures. Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis.

Activated charcoal slurry instilled into the stomach following evacuation of gastric contents can help absorb any remaining drug in GI tract. Antiemetic medication may be required to control severe nausea and vomiting. Blood samples should be obtained for immediate determination of gases, electrolytes, BUN, glucose, etc. Blood should be typed and cross-matched in preparation for possible hemodialysis.

Rapid control of metabolic acidosis is fundamental to management. Intravenous sodium bicarbonate should be given at once and repeated as needed, adjusting subsequent dosage on the basis of laboratory findings (*i.e.* serum sodium, pH, etc.). At the same time, anticonvulsants should be given intravenously (*i.e.* barbiturates, diphenylhydantoin, diazepam) as required, and large doses of intravenous pyridoxine.

Forced osmotic diuresis must be started early and should be continued for some hours after clinical improvement to hasten renal clearance of drug and help prevent relapse. Fluid intake and output should be monitored. Bile drainage may be indicated in presence of serious impairment of hepatic function lasting more than 24–48 hours. Under these circumstances, and for severe cases extracorporeal hemodialysis may be required; if this is not available, peritoneal dialysis can be used along with forced diuresis.

Along with measures based on initial and repeated determination of blood gases and other laboratory tests as needed, meticulous respiratory and other intensive care should be utilized to protect against hypoxia, hypotension, aspiration, pneumonia, etc.

In patients with previously adequate hepatic function, reversal of liver enlargement and impaired hepatic excretory function probably will be noted within 72 hours, with rapid return toward normal thereafter.

Untreated or inadequately treated cases of gross isoniazid overdose can terminate fatally, but good response has been reported in most patients brought under adequate treatment within the first few hours after drug ingestion.

How Supplied: Capsules (opaque green and orange), containing 300 mg rifampin and 150 mg isoniazid; bottles of 60.

C75-24 Rev. 5/75

[Shown in Product Identification Section]

POLYCILLIN-PRB®

(Ampicillin-probenecid)

FOR ORAL SUSPENSION—AMPICILLIN TRIHYDRATE EQUIVALENT TO 3.5 GRAMS AMPICILLIN WITH 1.0 GRAM PROBENECID

This is the full text of the latest Official Package Circular dated November 1973.

Description: Polycillin-PRB (ampicillin-probenecid) is a semisynthetic penicillin in combination with probenecid.

ACTIONS: PHARMACOLOGY

Ampicillin is stable in the presence of gastric acid and is well-absorbed from the gastrointestinal tract. It diffuses readily into most body tissues and fluids. However, penetration into the cerebrospinal fluid and brain occurs only when the meninges are inflamed. Ampicillin is excreted largely unchanged in the urine and its excretion can be delayed by concurrent administration of probenecid. The active form appears in the bile in higher concentrations than those found in serum. Ampicillin is the least serum-bound of all the penicillins, averaging about 20% compared to approximately 60 to 90% for other penicillins. Probenecid inhibits the renal tubular secretion of penicillins causing an increased serum level of the antibiotic.

MICROBIOLOGY

Neisseria gonorrhoeae has been shown in in vitro studies to be susceptible to ampicillin.

Indications: Ampicillin-probenecid is indicated for the treatment of uncomplicated infections (urethral, endocervical, or rectal) due to *N. gonorrhoeae* in males and females.

Susceptibility studies should be performed with recurrent infections or when resistant strains are encountered. Therapy may be instituted prior to obtaining results of susceptibility testing.

CONTRAINDICATIONS: AMPICILLIN

A history of previous hypersensitivity reactions to any of the penicillins is a contraindication.

Diluent	Concentrations	Stability periods (hours)
Room temperature (25° C.):		
Sterile water for injection.....	Up to 30 mg/ml.....	8
Isotonic sodium chloride.....	Up to 30 mg/ml.....	8
M/6 sodium lactate solution.....	Up to 30 mg/ml.....	8
5 percent dextrose in water.....	10 to 20 mg/ml.....	2
5 percent dextrose in water.....	Up to 2 mg/ml.....	4
5 percent dextrose in 0.45 percent NaCl.....	Up to 2 mg/ml.....	4
10 percent invert sugar in water.....	Up to 2 mg/ml.....	4
Lactated Ringer's solution.....	Up to 30 mg/ml.....	8
Refrigerated (4° C.):		
Sterile water for injection.....	30 mg/ml.....	48
Sterile water for injection.....	Up to 20 mg/ml.....	72
Isotonic sodium chloride.....	30 mg/ml.....	48
Isotonic sodium chloride.....	Up to 20 mg/ml.....	72
Lactated Ringer's solution.....	Up to 30 mg/ml 24 hr.....	
M/6 sodium lactate.....	Up to 30 mg/ml.....	8
5 percent dextrose in water.....	Up to 20 mg/ml.....	4
5 percent dextrose in 0.4 percent NaCl.....	Up to 10 mg/ml.....	4
10 percent invert sugar.....	Up to 20 mg/ml.....	3

PROBENECID

Polycillin-PRB should not be given to individuals with a known hypersensitivity to probenecid. It is not recommended for patients with known blood dyscrasias, uric acid kidney stones or during an acute attack of gout.

Warnings: Serious and occasionally fatal hypersensitivity reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the patient should be treated with the usual agents, e.g., pressor amines, antihistamines, and corticosteroids. Serious anaphylactoid reactions require emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in pregnancy: Safety for use in pregnancy has not been established.

Precautions: Cases of gonococcal infection with a suspected lesion of syphilis should have darkfield examinations ruling out syphilis before receiving ampicillin. Patients who do not have suspected lesions of syphilis and are treated with ampicillin should have a followup serologic test for syphilis each month for four months to detect syphilis that may have been masked by treatment for gonorrhea. Patients with gonorrhea who also have syphilis should be given additional appropriate parenteral penicillin treatment.

Adverse reactions: As with other penicillins, it may be expected that untoward reactions to ampicillin will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

Gastrointestinal—Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, and diarrhea. (These reactions are usually associated with oral dosage forms.)

Hypersensitivity reactions—Skin rashes and urticaria have been reported frequently. A few cases of exfoliative dermatitis and erythema multiforme have been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral form.

Serious acute hypersensitivity reactions may require the use of epinephrine, oxygen, and airway management, which may include endotracheal intubation, intravenous steroids, and repletion of plasma volume.

Liver—A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, but the significance of this finding is unknown.

Hemic and Lymphatic Systems—Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Dosage: Acute N. gonorrhoeae infections in adult males and females.

3.5 Grams ampicillin, with 1.0 Gram probenecid, administered simultaneously. One bottle contains enough of each drug for the required single dose.

It is desirable that follow-up cultures be obtained from the original site(s) of infection 7 to 14 days after therapy.

In women, it is also desirable to obtain culture test-of-cure from both the endocervical and anal canal.

Directions For Dispensing Oral Suspension: Prepare this formulation at the time of dispensing. For ease in preparation, add water to the bottle in two portions and shake well after each addition. Add the total amount of water as directed on the labeling of the package being dispensed. The reconstituted formulation is stable for 24 hours at room temperature.

Supply: Polycillin-PRB (Ampicillin-Probenecid) for Oral Suspension Ampicillin Trihydrate equivalent to 3.5 Grams ampicillin with 1.0 Gram probenecid, single-dose bottle.

NDC 0015-7607 [7607 DIRO-05]

APPENDIX H—FDA ANNOUNCEMENT

DRUG IMPLEMENTATION FOLLOWUP NOTICE

[From the Federal Register, August 9, 1973]

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

FOOD AND DRUG ADMINISTRATION

[DESI 8674]

CERTAIN OTIC PREPARATIONS CONTAINING ANTIBIOTICS

DRUGS FOR HUMAN USE; DRUG EFFICACY STUDY IMPLEMENTATION
FOLLOWUP NOTICE

In a notice (DESI 8674) published in the Federal Register of June 29, 1972 (37 FR 12855), the Commissioner of Food and Drugs announced his conclusions pursuant to evaluation of reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group on the following drugs (other drugs were also included in that notice, and other notices concerning them will be published in future issues of the FEDERAL REGISTER):

1. Cortomixin Sterile Ear Drops containing polymyxin B sulfate and hydrocortisone; Broemmel Pharmaceuticals, 1235 Sutter St., San Francisco, CA 94109 (NDA 60-719 (previously published as 60-179)).

2. Cortisporin Otic Drops containing polymyxin B sulfate, neomycin sulfate and hydrocortisone; Burroughs-Wellcome and Co., Inc., 3030 Cornwallis Rd., Research Triangle Park, NC 27709 (NDA 60-613).

3. Coly-mycin S Otic with Neomycin and Hydrocortisone containing colistin sulfate, neomycin sulfate, thonzonium bromide, and hydrocortisone acetate; Warner Chilcott Laboratories Division, Warner Lambert Pharmaceutical Co., 201 Tabor Rd., Morris Plains, NJ 07950 (NDA 50-356).

4. Cor-Otic P-N Ear drops containing neomycin sulfate, polymyxin B sulfate and hydrocortisone; Don Hall Laboratories, 1935 North Argyle, Portland, OR 97217 (NDA 90-263).

The notice stated that the drugs were regarded as lacking substantial evidence of effectiveness when labeled for treatment of otitis media and possibly effective for their other labeled indications.

Based upon a reevaluation of the preparations listed above, the Commissioner concludes that these drugs are effective for the indications set forth in the labeling guidelines below.

DESCRIPTION

(To be supplied by the manufacturer)

ACTIONS

(To be supplied by the manufacturer)

INDICATIONS

For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotic(s), and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotic(s).

CONTRAINDICATIONS

This product is contraindicated in those individuals who have shown hypersensitivity to any of its components, and in herpes, simplex, baccinia and varicella.

WARNINGS

As with other antibiotic preparations, prolonged treatment may result in overgrowth of nonsusceptible organisms and fungi.

If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

Patients who prefer to warm the medication before using should be cautioned against heating the solution above body temperature, in order to avoid loss of potency.

PRECAUTIONS

If sensitization or irritation occurs, medication should be discontinued promptly. (To be included for neomycin-containing preparations). This drug should be used with care in cases of perforated ear drum and in longstanding cases of chronic otitis media because of the possibility of ototoxicity caused by neomycin.

Treatment should not be continued for longer than ten days.

Allergic cross-reactions may occur which could prevent the use of any of all of the following antibiotics for the treatment of future infections: Kanamycin, paromomycin, streptomycin, and possibly gentamicin.

ADVERSE REACTIONS (FOR PREPARATIONS CONTAINING NEOMYCIN)

Neomycin is a not uncommon cutaneous sensitizer. There are articles in the current literature that indicate an increase in the prevalence of persons sensitive to neomycin.

DOSAGE AND ADMINISTRATION

The external auditory canal should be thoroughly cleansed and dried with a sterile cotton applicator.

For adults, 4 drops of the solution should be instilled into the affected ear 3 or 4 times daily. For infants and children, 3 drops are suggested because of the smaller capacity of the ear canal.

The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear.

If preferred, a cotton wick may be inserted into the canal and then the cotton may be saturated with the solution. This wick should be kept moist by adding further solution every four hours. The wick should be replaced at least once every 24 hours.

HOW SUPPLIED

(To be supplied by the manufacturer)

Batches of drugs for which certification is requested should provide for labeling information in accord with the guidelines developed on the basis of the reevaluation of the drugs and published in the notice.

Batches of such drugs with labeling bearing indications other than those published in this announcement are no longer acceptable for certification or release.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-51, as amended; 59 Stat. 463, as amended; 21 U.S.C. 352, 357) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: August 2, 1963.

SAM D. FINE,
Associate Commissioner for Compliance.

APPENDIX I—SELECTED TOPICAL INDEX OF 1970 HEARINGS

Volume 12 refers to present status of competition in the pharmaceutical industry: "Drug Combinations—Antibiotics."

Volume 3 refers to effect of promotion and advertising of over-the-counter drugs on competition, small business, and the health and welfare of the public: "Misuse of Antibiotics."

	Volume:	Page(s)
1. Fixed-dose combination drugs:		
a. Antibiotic combinations-----	12:	5054, 5055, 5056, 5078.
b. Antibiotics combined with other drugs---	12:	5141, 5142, 5019, 5020, 5056; 3: 1044-1045, 1094-1095.
c. Rationale for the development and use of fixed-combination antibiotics.	12:	5003-5004.
d. Justification for fixed-dose combinations---	12:	5014-5017.
Table from testimony of witness, Dr. Robert I. Wise.	12:	5077-5078.
The current status of fixed-dose combinations.	12:	5024-5025.
2. Drug advertising and physician information about drugs:		
a. The influence of advertising on the use of fixed-dose combination antibiotics.	12:	5009-5010, 5011, 5017, 5045, 5046-5047, 5110, 5111, 5112, 5113, 5271.
b. The AMA's role in the advertising of fixed-dose combination antibiotics.	12:	5011, 5010, 5011, 5038, 5039, 5251-5252.
c. Drug advertising and physician information.	12:	5000, 5010, 5017, 5045, 5046, 5072, 5111; 3: 1117-1119.
3. The Federal Government's actions:		
a. The drug efficacy study and DESI-----	12:	5013.
b. The FDA's response to the drug efficacy study.	12:	5167, 5173-5174, 5175.
c. FDA's progress in withdrawing drugs from the market.	3:	1045, 1052.
4. The current status of fixed-dose combination antibiotic drugs.	12:	5025, 5031-5032, 5183.
FDA brief <i>Achrocidin</i> case-----	3:	1046-1051.

