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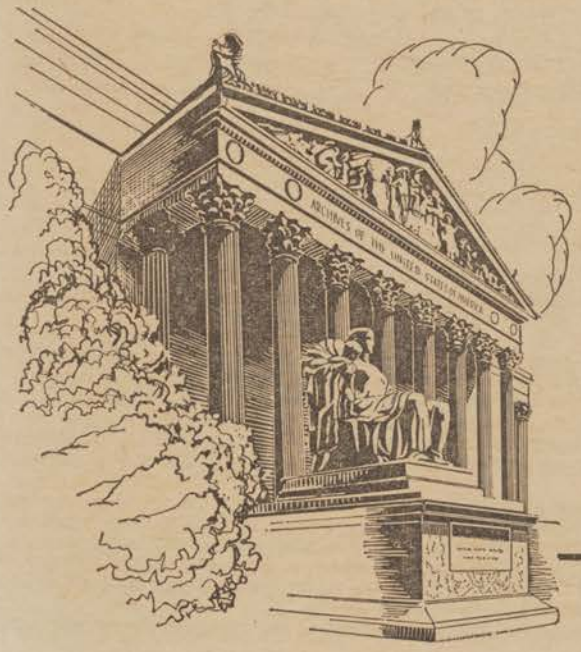
Pages 13871–13961

Part I

(Part II begins on page 13921)

Agencies in this issue—

Detailed list of Contents appears inside.



Volume 82

UNITED STATES STATUTES AT LARGE

[90th Cong., 2d Sess.]

Contains laws and concurrent resolutions enacted by the Congress during 1968, reorganization plans, and Presidential proclamations. Also included are: a subject index, tables of prior laws affected, a numerical listing of bills enacted into public and private law, and a guide to the legislative history of bills enacted into public law.

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Contents

(Continued on next page)

List of CFR Parts Affected

The following numerical guide is a list of the parts of each title of the Code of Federal Regulations affected by documents published in today's issue. A cumulative list of parts affected, covering the current month to date, appears at the end of each issue beginning with the second issue of the month.

A cumulative guide is published separately at the end of each month. The guide lists the parts and sections affected by documents published since January 1, 1970, and specifies how they are affected.

7 CFR

909 13875
932 13877
PROPOSED RULES:
906 13887

9 CFR

76 (2 documents) 13878

14 CFR

39 13879
PROPOSED RULES:
71 (3 documents) 13889, 13890

20 CFR

PROPOSED RULES:
405 13888

21 CFR

3 13880
141 13881
PROPOSED RULES:
3 13887
191 13887

24 CFR

1914 13882
1915 13883

29 CFR

520 13884

41 CFR

5A–7 13885

42 CFR

73 13922

43 CFR

PROPOSED RULES:
1850 13887

45 CFR

121 13885

47 CFR

PROPOSED RULES:
73 13890

49 CFR

PROPOSED RULES:
1048 13890

Rules and Regulations

Title 7—AGRICULTURE

Chapter IX—Consumer and Marketing Service (Marketing Agreements and Orders; Fruits, Vegetables, Nuts), Department of Agriculture

PART 909—GRAPEFRUIT GROWN IN ARIZONA; IN IMPERIAL COUNTY, CALIF.; AND IN THAT PART OF RIVERSIDE COUNTY, CALIF., SITUATED SOUTH AND EAST OF WHITE WATER, CALIF.

Order Amending the Order, As Amended, Regulating Handling

§ 909.0 Findings and determinations.

The findings and determinations hereinafter set forth are supplementary and in addition to the findings and determinations made in connection with the issuance of the order and of the previously issued amendment thereto; and all of said previous findings and determinations are hereby ratified and affirmed except insofar as such findings and determinations may be in conflict with the findings and determinations set forth herein.

(a) Findings upon the basis of the hearing record. Pursuant to the Agricultural Marketing Agreement Act of 1937, as amended (secs. 1–19, 48 Stat. 31, as amended; 7 U.S.C. 601–674), and the applicable rules of practice and procedure effective thereunder (7 CFR Part 900), a public hearing was held at Indio, Calif., on February 18, 1970, upon proposed amendments to the marketing agreement, as amended, and Order No. 909, as amended (7 CFR Part 909), regulating the handling of grapefruit grown in the State of Arizona, in Imperial County, Calif., and in that part of Riverside County, Calif., situated south and east of White Water, Calif. Upon the basis of the evidence introduced at such hearing and the record thereof, it is found that:

(1) The said order, as amended and as hereby further amended, and all of the terms and conditions thereof, will tend to effectuate the declared policy of the act;

(2) The said order, as amended and as hereby further amended, regulates the handling of grapefruit grown in the designated production area in the same manner as, and is applicable only to persons in the respective classes of commercial or industrial activity specified in, the marketing agreement and order upon which the hearing has been held;

(3) The said order, as amended and as hereby further amended, is limited in its application to the smallest regional production area that is practicable consistently with carrying out the declared policy of the act; and

(4) The said order, as amended and as hereby further amended, prescribes, so far as practicable, such different terms, applicable to different parts of the production area, as are necessary to give due recognition to differences in the production and marketing of the grapefruit covered thereunder.

(b) *Additional findings.* It is hereby found, on the basis hereinafter indicated, that good cause exists for making the provisions of this amendatory order effective not later than September 1, 1970, and that it would be contrary to the public interest to postpone such effective date until 30 days after publication (5 U.S.C. 553). The provisions of this amendment should become effective September 1, 1970, because the provisions of this order change the composition of the Administrative Committee, the term of office of members and alternate members, and enlarge the area of regulation. It is desirable for the industry to nominate individuals for appointment on the committee on the new basis and for the term of office specified in this amendment as soon as possible so that regulatory and other activity may be applicable at the beginning of the fiscal period and shipping season, and no useful purpose would be served by delaying the effective date beyond September 1, 1970. The provisions of this order are well known to producers and handlers. The hearing in connection therewith was held at Indio, Calif., on February 18, 1970, and the recommended decision and the final decision were published in the FEDERAL REGISTER on May 21, 1970 (35 F.R. 7806), and July 9, 1970 (35 F.R. 11027) respectively. Copies of the provisions of the amendatory order were made available to all known interested parties, and compliance with such provisions will not require advance preparation on the part of persons subject thereto which cannot be completed prior to the effective time specified.

(c) *Determinations.* It is hereby determined that handlers (excluding cooperative associations of producers who are not engaged in processing, distributing, or shipping grapefruit covered by this order) of more than 80 percent of the volume of the California-produced grapefruit covered by the said order, as amended, and as hereby further amended, refused or failed to sign the proposed amendment of the marketing agreement, as amended, regulating the handling of grapefruit grown in Arizona; in Imperial County, Calif.; and in that part of Riverside County, Calif., situated south and east of White Water, Calif.; and it is hereby further determined that:

(1) The refusal or failure of such handlers to sign the proposed amendment of the marketing agreement, as amended, tends to prevent the effectuation of the declared policy of the act;

(2) The issuance of this order, amending the aforesaid order, as amended, is the only practical means pursuant to the declared policy of the act of advancing the interests of the producers of grapefruit grown in the said production area;

(3) The issuance of this order, amending the aforesaid order, as amended, is favored or approved by at least three-fourths of the producers who participated in a referendum on the question of its approval and who, during the determined representative period (Aug. 1, 1968, through July 31, 1969), were engaged, within the State of California, in the production of grapefruit for market, and by at least two-thirds of the producers who participated in such referendum and who, during such determined representative period, were engaged, within the State of Arizona, in the production of grapefruit for market; all such producers having also produced for market at least two-thirds of the volume of grapefruit represented in such referendum; and

(4) On the effective date of this order amending the order, as amended, the provisions of the marketing agreement, as amended, as now effective, will no longer tend to effectuate the declared policy of the act because the said marketing agreement would be inconsistent with this order amending the order, as amended. Accordingly, the provisions of the current marketing agreement, as amended, are hereby terminated effective September 1, 1970.

It is, therefore, ordered, That, on and after the effective date hereof, all handling of grapefruit grown in the production area shall be in conformity to, and in compliance with, the terms and conditions of the said order, as amended and as hereby further amended as follows:

1. The provisions of § 909.4 *Grapefruit* are revised to read as follows:

§ 909.4 Grapefruit.

"Grapefruit" means all varieties of Citrus paradisi, MacFadyen, grown in the production area.

2. A new § 909.4a is added as follows:

§ 909.4a Production area.

"Production area" means the State of Arizona; Imperial County, California; and the described portions of the following counties of the State of California: that part of San Bernardino County situated east of a line drawn due north and south through Rice; that part of Riverside County situated east of a line drawn due north and south through the Post Office in White Water; and that part of San Diego County situated east of a line drawn due north and south through the Post Office in Julian.

3. The provisions of § 909.5 are revised to read as follows:

§ 909.5 Districts and subdistricts.

The production area shall be divided into districts and subdistricts as defined below:

(a) "Arizona District" means the total area defined within the following subdistricts:

(1) "Yuma Subdistrict" means that part of the State of Arizona situated within Yuma County and that part of Imperial County, Calif., situated east of a line drawn due north and south through the Post Office in Winterhaven, Calif.

(2) "Phoenix Subdistrict" means that part of the State of Arizona outside of Yuma County.

(b) "California District" means that part of the production area in California not included under Yuma Subdistrict.

4. The provisions of § 909.8 *Handle* are amended by adding thereto the following sentence:

§ 909.8 Handle.

* * * The term "handle" shall not include the transportation of grapefruit from the point of production to a packinghouse within the production area for preparation for market.

§ 909.9 [Amended]

5. The provisions of § 909.9 are amended by deleting "828.23" and inserting "43615" in lieu thereof.

6. The provisions of § 909.10 *Fiscal period* are amended to read as follows:

§ 909.10 Fiscal period.

"Fiscal period" means the period from August 1, 1969, through August 31, 1970, and after August 31, 1970, such term shall mean the period from September 1 of any year to August 31 of the following year.

7. The provisions of § 909.20 *Establishment and membership* are revised to read as follows:

§ 909.20 Establishment and membership.

(a) An Administrative Committee composed of 10 members is hereby established. For each member there shall be an alternate member and the provisions of this part applicable to qualification, number, affiliation, nomination, and selection of members shall also apply to the qualification, number, affiliation, nomination, and selection of alternate members: *Provided*, That the alternate member specified in § 909.20(c) need not be of the same group affiliation as the member. Each member and alternate member shall be a producer in the district or subdistrict being represented on the committee.

(b) The term of office of members and alternate members shall be one fiscal period: *Provided*, That an incumbent member or alternate member, as applicable, shall continue to serve as such until his successor is selected and has qualified.

(c) The California District shall be represented on the committee by five members. Two members shall be affiliated with a cooperative marketing organization, two members shall not be so affiliated, and one member shall be affiliated with the group whose producers, during the fiscal period preceding the one in which nominations for members and alternates are made, produced more than 50 percent of the total production of grapefruit produced by all producers in that district: *Provided*, That the alternate member for such member shall be a producer in the California District outside that portion of Riverside County which is situated east of a line drawn due north and south through the Post Office in White Water and west of a line drawn due north and south through Shavers Summit: *And provided further*, That such alternate member need not be of the same group affiliation as the member.

(d) The Arizona District shall be represented on the committee by five members determined as follows:

(1) Except as otherwise provided, each subdistrict shall be represented by two members who are producers in the subdistrict being represented: *Provided*, That the subdistrict whose producers, during the fiscal period preceding the one in which nominations for members and alternate members are made, produced more than 50 percent of the total production of grapefruit in the Arizona District shall be represented by three members: *And provided further*, That in the event the production in any such subdistrict during such fiscal period is less than for the preceding fiscal period by 25 percent or more, the average production during the three fiscal periods preceding the one in which such nominations are made shall be used.

(2) One member in each subdistrict shall be affiliated with a cooperative marketing organization and one member shall not be so affiliated. Whenever a subdistrict is represented by three members, the third member shall be alternated between such groups.

(e) Annually, prior to nomination meetings, apportionment of the committee shall be effected as specified in the provisions of this section.

8. The provisions of § 909.21 *Nomination* are revised to read as follows:

§ 909.21 Nomination.

(a) The Secretary shall cause to be held each year a meeting or meetings of producers in the California District and in the Yuma Subdistrict and the Phoenix Subdistrict for the purpose of making nominations for members and alternate members of the Administrative Committee.

(b) Not more than one nominee for member and not more than one nominee for alternate member from each district or subdistrict may be affiliated with the same packinghouse.

(c) Except as hereinafter provided, only producers affiliated with cooperative marketing organizations may elect nominees affiliated with such organizations; and only producers not affiliated with cooperative marketing organizations may elect nominees not so affiliated. In the event some of a producer's grapefruit is handled through a cooperative marketing organization and some is handled through an organization that is not a cooperative marketing organization, such producer shall be eligible to participate in only the category (i.e., as affiliated with or not affiliated with a cooperative marketing organization) by which the major volume of his fruit is handled. At least one nominee shall be elected for each member and alternate member position to be filled. If nominations are not made by a particular category of producers, as provided in this section, producers present at the nomination meeting may, regardless of the affiliation previously referred in this paragraph (c), elect nominees for all the positions to be filled and, in such event, any limitations as to such affiliation of the nominees shall not apply.

(d) In the event a producer produces grapefruit in more than one district or subdistrict, such producer may participate in the nomination meeting or meetings in only one district or subdistrict. Each producer shall be entitled to cast one vote for each of the nominees from the district or subdistrict; and each vote shall be cast on behalf of himself, his agents, partners, subsidiaries, affiliates, and representatives.

(e) Nominations shall be submitted to the Secretary on or before July 1 of each year.

9. The provisions of § 909.22 *Selection* are revised to read as follows:

§ 909.22 Selection.

From the nominations made pursuant to § 909.21, or from other qualified producers, the Secretary shall select the members and alternate members from each district. In the event nominations are not made in accordance with the provisions of § 909.21, the Secretary may select the members and alternate members without regard to their affiliation.

10. The provisions of § 909.25 *Alternate members* are revised to read as follows:

§ 909.25 Alternate members.

Except as hereinafter provided, an alternate member of the Administrative Committee shall act in the place and stead of the member for whom he is an alternate during such member's absence. In the event of the death, removal, resignation, or disqualification of a member, his alternate shall act for him until a successor is selected and has qualified. If both a member and his alternate are absent from an assembled committee meeting, the chairman, with the concurrence of the majority of members from the district affected who are present, shall designate an alternate member from the same district who is present at the meeting and is not acting as a member, to act in the place and stead of the absent member and alternate: *Provided*, That to the extent practicable the alternate member so designated shall be of the same affiliation as the absent member.

11. The provisions of § 909.29 *Compensation and expenses* are revised to read as follows:

§ 909.29 **Compensation and expenses.**

The members of the Administrative Committee, and alternates when acting as members, shall serve without compensation; but they may be reimbursed for reasonable expenses necessarily incurred by them in the performance of their duties and in the exercise of their powers under this subpart. An alternate member may be reimbursed for reasonable expenses necessarily incurred by him in attending committee meetings, notwithstanding that the committee member for whom he serves as alternate also attends such meeting, and for performing other committee business at the request of the committee.

12. The provisions of § 909.31 *Procedure* are amended by revising paragraphs (a) and (b) to read as follows:

§ 909.31 **Procedure.**

(a) Seven members of the Administrative Committee shall be necessary to constitute a quorum of the committee.

(b) For any decision of the Administrative Committee to be valid, at least seven members must cast a concurring vote. At all assembled meetings, each vote must be cast in person.

* * * * *

13. The provisions of § 909.40 *Expenses* are amended to read as follows:

§ 909.40 **Expenses.**

The Administrative Committee is authorized to incur such expenses, including inspection expenses, as the Secretary finds are reasonable and likely to be incurred to carry out the functions of the committee under this subpart during each fiscal period. The funds to cover such expenses shall be acquired by the levying of assessments upon handlers, as provided in § 909.41.

14. The provisions of § 909.41 *Assessments* are amended by revising the first sentence of paragraph (a), redesignating paragraph (c) as paragraph (d), and adding a new paragraph (c) to read as follows:

§ 909.41 **Assessments.**

(a) Each handler who first handles grapefruit shall, with respect to the grapefruit so handled by him, pay to the Administrative Committee, upon demand, his pro rata share of the expenses, including inspection expenses, which the Secretary finds are reasonable and likely to be incurred by the committee for its maintenance and functioning during each fiscal period. * * *

* * * * *

(c) Notwithstanding the requirement that credits and refunds shall be deferred as provided in § 909.42(b), the Administrative Committee may, with approval of the Secretary, credit each handler entitled to a refund with such refund against assessments currently owed by him.

* * * * *

15. The provisions of § 909.42 *Accounting* are amended by revising paragraph (b) to read as follows:

§ 909.42 **Accounting.**

* * * * *

(b) Notwithstanding the provisions of paragraph (a) of this section, the Administrative Committee may, with the approval of the Secretary, establish an operating reserve from funds remaining at the end of a fiscal period, which are in excess of expenses incurred during such period. Such operating reserve shall be accumulated over such period of time as the committee determines is fair and equitable to all handlers and shall not exceed an amount approximating the preceding year's budget exclusive of inspection expenses. The reserve shall be managed as a revolving fund, and the credits and refunds provided in paragraph (a) of this section deferred until such time as the reserve reaches the amount prescribed by the committee: *Provided,* That pursuant to § 909.41(c), funds in such reserve shall be available to be applied as credits against handlers' assessments.

16. The provisions of § 909.56 *Marketing zones* are amended to read as follows:

§ 909.56 **Marketing zones.**

(a) Zone 1: The States of California and Arizona.

(b) Zone 2: The State of Florida.

(c) Zone 3: The State of Texas.

(d) Zone 4: The States of Washington, Oregon, Montana, Idaho, Wyoming, Nevada, and Utah.

(e) Zone 5: The States not enumerated in Zones 1, 2, 3, 4, and 6.

(f) Zone 6: All export markets and States of Hawaii and Alaska.

§ 909.23 **[Amended]**

17. The provisions of § 909.23 are amended by deleting "§ 909.21(i)" and inserting "§ 909.21(e)" in lieu thereof.

(Secs. 1–19, 48 Stat. 31, as amended; 7 U.S.C. 601–674)

Dated, August 27, 1970, to become effective September 1, 1970.

RICHARD E. LYNG,
Assistant Secretary.

[F.R. Doc. 70–11562; Filed, Sept. 1, 1970; 8:47 a.m.]

PART 932—OLIVES GROWN IN CALIFORNIA

Subpart—Rules and Regulations

SIZES OF PROCESSED OLIVES

Notice is hereby given of the approval of amendment, as hereinafter set forth, of the rules and regulations (Subpart—Rules and Regulations; 7 CFR 932.108–932.161) currently effective pursuant to the applicable provisions of the marketing agreement, as amended, and Order No. 932, as amended (7 CFR Part 932), regulating the handling of olives grown in California. This is a regulatory program effective under the Agricultural Marketing Agreement Act of 1937, as amended (7 U.S.C. 601–674).

The amendment of said rules and regulations was unanimously recommended by the Olive Administrative Committee, established under said marketing agreement and order as the agency to administer the terms and provisions thereof.

The provisions of § 932.153 specify, in terms of minimum weights for individual olives, the minimum sizes of olives that may be used currently in the production of halved, sliced, chopped, and minced styles of canned ripe olives. This amendment extends, for one year, the effective period of the section and establishes larger minimum sizes for certain specified varieties used as aforesaid. Such changes reflect the committee's appraisal of the 1970–71 olive crop (including the anticipated larger sizes of certain varieties) and marketing conditions and are its recommendations for the minimum sizes of olives that will provide consumers with good quality fruit and maximize returns to growers pursuant to the declared policy of the act.

It is hereby found that amendment of said rules and regulations as hereinafter set forth is in accordance with the provisions of the marketing agreement and order, and will tend to effectuate the declared policy of the Agricultural Marketing Agreement Act of 1937, as amended.

The provisions of paragraphs (a) (2), (3), and (b) of § 932.153 are amended to read as follows:

§ 932.153 **Establishment of sizes of processed olives for use in the production of halved, sliced, chopped, or minced styles of canned ripe olives.**

(a) * * *

(2) Variety Group 1 olives of the Ascolano, Barouni, or St. Agostino varieties, of a size which individually weigh one one-hundred-and-fiftieth pound: *Provided,* That not to exceed 35 percent of the olives in any lot may be smaller than one one-hundred-and-fiftieth pound;

(3) Variety Group 2 olives, except the Obliza variety, of a size which individually weigh one one-hundred-and-fiftieth pound: *Provided,* That not to exceed 30 percent of the olives in any lot may be smaller than one one-hundred-and-fiftieth pound;

* * * * *

(b) The provisions of this section shall be applicable only during the crop year ending August 31, 1971.

It is hereby further found that it is impracticable, unnecessary, and contrary to the public interest to give preliminary notice, engage in public rule-making procedure, and postpone the effective date of this amendment until 30 days after publication in the FEDERAL REGISTER (5 U.S.C. 553), and good cause exists for making the provisions hereof effective at the time hereinafter set forth, in that (1) the time intervening between the date when the information upon which this amendment is based became available and the time such amendment must become effective in order to effectuate the declared policy of the act is insufficient; (2) the handling of the 1970 crop of olives is expected to begin about September 1, 1970—the beginning of the crop year—and the amendment of the rules and regulations should be in effect by that time

so as to apply to the handling of olives during the entire crop year to effectuate the declared policy of the act; (3) necessary supplemental data for consideration and inclusion in this amendment were not available until August 27, 1970; (4) unless extended by further amendment, the section hereby amended will, by its provisions, terminate on August 31, 1970, and the more restrictive requirements of the order provisions would then apply to the handling of the crop; (5) compliance with the amended rules and regulations will require of handlers no special preparation therefor which cannot be completed by the effective time hereof; (6) in order to facilitate the handling of the 1970 crop the industry should have knowledge of the revised requirements, contained in the amendment, as soon as possible; and (7) the amendment was unanimously recommended by members of the Olive Administrative Committee after an open meeting on August 6, 1970, at which all interested persons were afforded an opportunity to submit their views.

(Sec. 1–19, 48 Stat. 31, as amended; 7 U.S.C. 601–674)

Dated, August 28, 1970, to become effective August 31, 1970.

PAUL A. NICHOLSON,
Acting Director, Fruit and Vegetable Division, Consumer and Marketing Service.

[F.R. Doc. 70–11582; Filed, Sept. 1, 1970; 8:48 a.m.]

Title 9—ANIMALS AND ANIMAL PRODUCTS

Chapter I—Agricultural Research Service, Department of Agriculture

SUBCHAPTER C—INTERSTATE TRANSPORTATION OF ANIMALS AND POULTRY

[Docket No. 70–250]

PART 76—HOG CHOLERA AND OTHER COMMUNICABLE SWINE DISEASES

Areas Quarantined

Pursuant to provisions of the Act of May 29, 1884, as amended, the Act of February 2, 1903, as amended, the Act of March 3, 1905, as amended, the Act of September 6, 1961, and the Act of July 2, 1962 (21 U.S.C. 111–113, 114g, 115, 117, 120, 121, 123–126, 134b, 134f), Part 76, Title 9, Code of Federal Regulations, restricting the interstate movement of swine and certain products because of hog cholera and other communicable swine diseases, is hereby amended in the following respects:

In § 76.2, in subparagraph (e) (21) relating to the State of Alabama, subdivision (i) relating to Covington County is amended, and a new subdivision (iii) relating to Crenshaw, Coffee, and Covington Counties is added to read:

(e) * * *

(21) *Alabama.* (i) That portion of Covington County bounded by a line beginning at the junction of the Patsaliga Creek and the Covington-Crenshaw County line; thence, following the Covington-Crenshaw County line in an easterly direction to Big Creek; thence, following Big Creek in a southeasterly direction to the south bank of the Conecuh River; thence, following the south bank of the Conecuh River in a generally northeasterly direction to the Dozier to Rose Hill Road; thence, following the Dozier to Rose Hill Road in a generally southeasterly direction to the Rose Hill to Haygood Road; thence, following the Rose Hill to Haygood Road in a southwesterly direction to the Haygood to Heath Road; thence, following the Haygood to Heath Road in a southwesterly direction to the Heath to River Falls Road; thence, following the Heath to River Falls Road in a southwesterly direction to State Highways 12, 55; thence, following State Highways 12, 55 in a northwesterly direction to the west bank of the Conecuh River; thence, following the west bank of the Conecuh River in a generally northeasterly direction to Patsaliga Creek; thence, following Patsaliga Creek in a generally northeasterly direction to its junction with the Covington-Crenshaw County line.

* * * * *

(iii) The adjacent portions of Crenshaw, Coffee, and Covington Counties bounded by a line beginning at the junction of Lightwood Knot Creek and State Highway 141 in Crenshaw County; thence, following State Highway 141 in a southeasterly direction to U.S. Highway 84, also State Highway 12, in Coffee County; thence, following U.S. Highway 84, also State Highway 12, in a generally southwesterly direction to U.S. Highway 331, also State Highway 9, in Covington County; thence, following U.S. Highway 331, also State Highway 9, in a generally northwesterly direction to Lightwood Knot Creek; thence, following Lightwood Knot Creek in a southwesterly direction to Pale Creek; thence, following Pale Creek in a generally northerly direction to the Covington-Crenshaw County line; thence, following the Covington-Crenshaw County line in an easterly direction to U.S. Highway 331, also State Highway 9, in Crenshaw County; thence, following U.S. Highway 331, also State Highway 9, in a northerly and thence, northeasterly direction to Parker Creek; thence, following Parker Creek in a southeasterly direction to Lightwood Knot Creek; thence, following Lightwood Knot Creek in a northeasterly direction to its junction with State Highway 141 in Crenshaw County.

(Secs. 4–7, 23 Stat. 32, as amended, secs. 1, 2, 32 Stat. 791–792, as amended, secs. 1–4, 33 Stat. 1264, 1265, as amended, sec. 1, 75 Stat. 481, secs. 3 and 11, 76 Stat. 130, 132; 21 U.S.C. 111, 112, 113, 114g, 115, 117, 120, 121, 123–126, 134b, 134f; 29 F.R. 16210, as amended)

Effective date. The foregoing amendment shall become effective upon issuance.

The amendment quarantines portions of Crenshaw and Coffee Counties in Alabama because of the existence of hog cholera. This action is deemed necessary to prevent further spread of the disease. The restrictions pertaining to the interstate movement of swine and swine products from or through quarantined areas as contained in 9 CFR Part 76, as amended, will apply to the quarantined portions of such counties.

The amendment also excludes a portion of Covington County, Ala., from the areas quarantined because of hog cholera. Therefore, the restrictions pertaining to the interstate movement of swine and swine products from or through quarantined areas as contained in 9 CFR Part 76, as amended, will not apply to the excluded area, but will continue to apply to the quarantined areas described in § 76.2. Further, the restrictions pertaining to the interstate movement of swine and swine products from nonquarantined areas contained in said Part 76 will apply to the area excluded from quarantine.

Insofar as the amendment imposes certain further restrictions necessary to prevent the interstate spread of hog cholera, it must be made effective immediately to accomplish its purpose in the public interest. Insofar as it relieves restrictions, it should be made effective promptly in order to be of maximum benefit to affected persons.

Accordingly, under the administrative procedure provisions in 5 U.S.C. 553, it is found upon good cause that notice and other public procedure with respect to the amendment are impracticable, unnecessary, and contrary to the public interest, and good cause is found for making it effective less than 30 days after publication in the FEDERAL REGISTER.

Done at Washington, D.C., this 27th day of August 1970.

F. J. MULHERN,
Acting Administrator, Agricultural Research Service.

[F.R. Doc. 70–11581; Filed, Sept. 1, 1970; 8:48 a.m.]

[Docket No. 70–253]

PART 76—HOG CHOLERA AND OTHER COMMUNICABLE SWINE DISEASES

Areas Quarantined

Pursuant to provisions of the Act of May 29, 1884, as amended, the Act of February 2, 1903, as amended, the Act of March 3, 1905, as amended, the Act of September 6, 1961, and the Act of July 2, 1962 (21 U.S.C. 111–113, 114g, 115, 117, 120, 121, 123–126, 134b, 134f), Part 76, Title 9, Code of Federal Regulations, restricting the interstate movement of swine and certain products because of hog cholera and other communicable swine diseases, is hereby amended in the following respects:

In § 76.2, the introductory portion of paragraph (e) is amended by adding the name of the State of Missouri, and a new

subparagraph (e)(6) relating to the State of Missouri is added to read:

(e) * * *

(6) *Missouri.* That portion of Stoddard County bounded by a line beginning at the junction of the west bank of the Castor River and State Highway 25; thence, following State Highway 25 in a southwesterly direction to State Highway M; thence, following State Highway M in a generally northwesterly direction to State Highway PP; thence, following State Highway PP in a generally southwesterly direction to the division line between Range 9 East and Range 10 East; thence, following the division line between Range 9 East and Range 10 East in a southerly direction to State Highway J; thence, following State Highway J in a southerly direction to State Highway F; thence, following State Highway F in a generally southwesterly direction to the division line between Township 25 North and Township 26 North; thence, following the division line between Township 25 North and Township 26 North in an easterly direction to State Highway AD; thence, following State Highway AD in a southerly direction to U.S. Highway 60; thence, following U.S. Highway 60 in a northeasterly direction to State Highway N; thence, following State Highway N in a generally northerly direction to the west bank of the Castor River; thence, following the west bank of the Castor River in a generally northwesterly direction to its junction with State Highway 25.

(Secs. 4–7, 23 Stat. 32, as amended, secs. 1, 2, 32 Stat. 791–792, as amended, secs. 1–4, 33 Stat. 1264, 1265, as amended, sec. 1, 75 Stat. 481, secs. 3 and 11, 76 Stat. 130, 132; 21 U.S.C. 111, 112, 113, 114g, 115, 117, 120, 121, 123–126, 134b, 134f; 29 F.R. 16210, as amended)

Effective date. The foregoing amendment shall become effective upon issuance.

The amendment quarantines a portion of Stoddard County, Mo., because of the existence of hog cholera. This action is deemed necessary to prevent further spread of the disease. The restrictions pertaining to the interstate movement of swine and swine products from or through quarantined areas as contained in 9 CFR Part 76, as amended, will apply to the quarantined portion of such county.

The amendment imposes certain further restrictions necessary to prevent the interstate spread of hog cholera and must be made effective immediately to accomplish its purpose in the public interest. Accordingly, under the administrative procedure provisions in 5 U.S.C. 553, it is found upon good cause that notice and other public procedure with respect to the amendment are impracticable and contrary to the public interest, and good cause is found for making it effective less than 30 days after publication in the FEDERAL REGISTER.

Done at Washington, D.C., this 28th day of August 1970.

F. J. MULHERN,
Acting Administrator,
Agricultural Research Service.

[F.R. Doc. 70-11580; Filed, Sept. 1, 1970; 8:48 a.m.]

Title 14—AERONAUTICS AND SPACE

Chapter I—Federal Aviation Administration, Department of Transportation

[Docket No. 10276; Amdt. 39-1073]

PART 39—AIRWORTHINESS DIRECTIVES

British Aircraft Corp. Model BAC 1-11 200 and 400 Series Airplanes

A proposal to amend Part 39 of the Federal Aviation Regulations to include an airworthiness directive requiring inspections of the taper bolts securing the flap beam main attachment brackets for looseness or failure, replacement of bolts found to be loose or failed, and modification to introduce increased diameter bolts was published in the FEDERAL REGISTER, 35 F.R. 6967.

Interested persons have been afforded an opportunity to participate in the making of the amendment. One comment to the proposal suggested that the repetitive inspection intervals specified in paragraph (a) be relaxed to allow the inspections to be performed at the established inspection interval for the BAC 1-11 airplane, which happens to be at 560 landings, rather than the 500 landing interval specified in the proposal. The FAA agrees, and a new paragraph (i) provides for adjustment of the inspection intervals specified in paragraphs (a), (b), and (c) to permit compliance at an established inspection period of the operator.

Another comment proposed that a single failed bolt on any one bracket could be replaced by the new increased diameter bolt and that the bracket could then remain in service for so long as periodic inspections reveal no defects. However, it has been determined that the remaining bolts on a bracket having one failed bolt may have been overstressed, and it is therefore necessary to require replacement of all bolts within 300 landings from the discovery of the failed bolt.

In consideration of the foregoing, and pursuant to the authority delegated to me by the Administrator (14 CFR 11.89), § 39.13 of Part 39 of the Federal Aviation Regulations is amended by adding the following new airworthiness directive:

BRITISH AIRCRAFT CORP. Applies to Models BAC 1-11 200 and 400 series airplanes. Compliance is required as indicated.

To prevent failure of the flap beam bracket to wing attachments at flap beam 2 (200 and 400 series airplanes), and at flap beams 3 and 4 (200 series airplanes only), accomplish the following:

(a) For 200 and 400 series airplanes, within the next 300 landings after the effective date of this AD, unless already accomplished within the last 200 landings, and thereafter at intervals not to exceed 500 landings since the last inspection, inspect the six flap beam bracket attachment bolts through the wing lower skin at flap beam 2 for looseness or failure in accordance with British Aircraft Corp. Model BAC 1-11 Alert Service Bulletin No. 57-A-PM 4407, Issue 2, dated January 6, 1970, or later ARB-approved issue or an FAA-approved equivalent.

(b) For 200 series airplanes, within the next 300 landings after the effective date of this AD, unless already accomplished within the last 700 landings, and thereafter at intervals not to exceed 1,000 landings since the last inspection, inspect the four flap beam bracket attachment bolts through the wing lower skin at flap beam 3 for looseness or failure in accordance with British Aircraft Corp. Model BAC 1-11 Alert Service Bulletin No. 57-A-PM 4407, Issue 2, dated January 6, 1970, or later ARB-approved issue or an FAA-approved equivalent.

(c) For 200 series airplanes which have not had incorporated BAC Modification PM3216, within the next 300 landings after the effective date of this AD, unless already accomplished within the last 700 landings, and thereafter at intervals not to exceed 1,000 landings since the last inspection, inspect the four flap beam bracket attachment bolts through the wing lower skin at flap beam 4 for looseness or failure in accordance with British Aircraft Corp. Model BAC 1-11 Alert Service Bulletin No. 57-A-PM 4407, Issue 2, dated January 6, 1970, or later ARB-approved issue or an FAA-approved equivalent.

(d) If one bolt through the wing lower skin on any one bracket (there are two brackets per flap beam location) is found to be loose or failed during the inspections required by paragraphs (a), (b), and (c), before further flight comply with paragraph (i) and either—

(1) Replace the loose or failed bolt with a new bolt of the same part number or an equivalent new parallel shank bolt in accordance with British Aircraft Corp. Model BAC 1-11 Alert Service Bulletin No. 57-A-PM 4407, Issue 2, dated January 6, 1970, or later ARB-approved issue or an FAA-approved equivalent; or

(2) Comply with paragraph (h).

(e) If the loose or failed bolt through the wing lower skin is replaced in accordance with paragraph (d)(1), within the next 300 landings accomplish the modifications required by paragraph (h).

(f) If a single loose bolt through the wing lower skin on any one flap beam location is found during the inspection required by paragraphs (a), (b), and (c), comply with paragraph (i) before further flight, and

(1) Comply with paragraph (d); or

(2) Within the next 300 landings accomplish the modifications required by paragraph (h).

(g) If more than one loose or failed bolt through the wing lower skin is found on any one bracket during the inspections required by paragraphs (a), (b), and (c), before further flight comply with paragraphs (h) and (i).

(h) Replace all the flap beam bracket attachment bolts through the wing lower skin with new increased diameter bolts at the affected flap beam location in accordance with British Aircraft Corp. Model BAC 1-11 Service Bulletin No. 57-PM 4407, dated November 17, 1969, or later ARB-approved issue or an FAA-approved equivalent.

(i) As required in paragraphs (d), (f), or (g), accomplish the following at the affected flap beam location:

(1) Inspect the two lower horizontal attachment bolts which pass through the forward flange of the flap beam attachment bracket and the rear spar lower boom angle (one on each side) for looseness or failure in accordance with British Aircraft Corp. Model BAC 1-11 Alert Service Bulletin No. 57-A-PM 4407, Issue 2, dated January 6, 1970, or later ARB-approved issue or an FAA-approved equivalent.

(2) If one or more loose or failed horizontal bolts are found during the inspection required by this paragraph, inspect the wing structure in the area of the affected flap beam location for damage or fuel leaks.

(3) If any loose or failed horizontal bolts or any damage to the wing structure or fuel leaks are found during the inspection required by this paragraph, before further flight replace the loose or failed horizontal bolts, repair the damage to the wing structure and seal the fuel leaks in accordance with British Aircraft Corp. Model BAC 1-11 Alert Service Bulletin No. 57-A-PM 4407, Issue 2, dated January 6, 1970, or later ARB-approved issue or an FAA-approved equivalent.

(j) The repetitive inspections required by paragraphs (a), (b), and (c) may be discontinued at each flap beam location where the modifications of paragraph (h) have been incorporated.

(k) For the purpose of complying with this AD, subject to acceptance by the assigned FAA maintenance inspector the number of landings may be determined by dividing each airplane's hours' time in service by the operator's fleet average time from takeoff to landing for BAC 1-11 200 and 400 series airplanes.

(l) Upon request of the operator, an FAA maintenance inspector, subject to prior approval of the Chief, Aircraft Certification Staff, FAA Europe, Africa, and Middle East Region may adjust the repetitive inspection intervals specified in paragraphs (a), (b), and (c) of this AD to permit compliance at an established inspection period of the operator if the request contains substantiating data to justify the increase for that operator.

This amendment becomes effective October 2, 1970.

(Secs. 313(a), 601, and 603, Federal Aviation Act of 1958, 49 U.S.C. 1354(a), 1421, and 1423, sec. 6(c), Department of Transportation Act, 49 U.S.C. 1655(c))

Issued in Washington, D.C., on August 20, 1970.

EDWARD C. HODSON,
Acting Director,
Flight Standards Service.

[F.R. Doc. 70-11546; Filed, Sept. 1, 1970; 8:45 a.m.]

Title 21—FOOD AND DRUGS

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

SUBCHAPTER A—GENERAL

PART 3—STATEMENTS OF GENERAL POLICY OR INTERPRETATION

Labeling of Crabmeat; Revision

In the FEDERAL REGISTER of April 12, 1969 (34 F.R. 6441), a notice was published proposing a revision of the policy statement regarding the labeling of certain crabmeats (§ 3.34) to extend its provisions to crabmeat preserved by freezing or other methods, as well as that preserved by canning, and to crabmeat of the species in question when produced domestically, as well as that imported, and to include crabmeat from *Chionoecetes tanneri, C. bairdii,* and *C. angulatus* with that from *C. opilio* under the common name of "Snow crabmeat." The notice provided for the filing of comments within 30 days after its publication, and this was extended to June 11, 1969, by a notice published May 27, 1969 (34 F.R. 8205).

A substantial number of comments were received in response. Many respondents objected to the name "Snow crabmeat" for crabmeat from crabs of the *Chionoecetes* species in question on the grounds that low quality crabmeat produced from *C. opilio* in the Orient, or from crabs other than the *Chionoecetes* species, had created consumer resistance to, and consequently marketing difficulties for, crabmeat under the name "Snow crabmeat"; many of those opposing this name advocated "Queen crabmeat" instead. One comment advocated the name "Queen crabmeat," but that it be permitted to be used only on domestically produced crabmeat. None of those opposing the name "Snow crabmeat," or advocating the name "Queen crabmeat," denied that the name "Snow crabmeat" had been applied commonly to crabmeat from *C. opilio* for many years, or denied that "Queen crabmeat" was of recently coined origin.

Some respondents commented that "Snow crabmeat" was already established by usage as the common name for crabmeat from *C. opilio,* that "Queen crabmeat" was recently coined and thus could not be the common name and was likely to be misleading by causing confusion with a different and more expensive article, king crabmeat.

Most of the comments received agreed that crabmeat from the *Chionoecetes* species in question should have one common name. Some stated that a substantial period of time would be needed for those marketing crabmeat to secure appropriate labeling or make other changes necessary to conform to the name finally adopted for crabmeat from the *Chionoecetes* species in question.

A number of those responding requested a public hearing. No comments were received with respect to the labeling of crabmeat other than that produced from crabs of the *Chionoecetes* species in question.

Although there is no statutory provision for a formal hearing in this matter, the Commissioner of Food and Drugs concluded that an informal hearing should be held and by notice published April 1, 1970 (35 F.R. 5412), scheduled such hearing for April 24, 1970, on which date it was held. Fewer persons appeared at the hearing than had offered comments in response to the proposal of April 12, 1969.

Comments were offered at the hearing both opposing the name "Snow crabmeat" and advocating the name "Queen crabmeat," and advocating the name "Snow crabmeat" and opposing the name "Queen crabmeat," on substantially the same grounds as given in the comments made in response to the proposed revision of § 3.34. Comment was also offered that the name "Queen crabmeat" would not cause confusion with "King crabmeat," on the basis that the latter's higher price would alert consumers to the fact that "Queen crabmeat'" was a different article.

One firm submitted for the hearing a letter of objection to the name "Snow crabmeat" on grounds that it would conflict with, and infringe upon, the trademark "Snow's" owned by that firm. Comments were made by some that a reasonable period of time would be needed by those who market crabmeat to secure appropriate labeling or make other necessary changes to conform to the name finally adopted for crabmeat from the *Chionoecetes* species in question.

The Commissioner of Food and Drugs finds that:

1. No evidence has been received controverting that the name "Snow crabmeat" has been used commonly for many years to designate crabmeat from *Chionoecetes opilio,* or that the crabs *C. tanneri, C. barrdii,* and *C. angulatus,* and the crabmeat therefrom, are for practical purposes indistinguishable from *C. opilio.*

2. No evidence has been received controverting that "Queen crabmeat" is a recently coined name designed to lead consumers to believe that crabmeat under that name is a different article than that formerly purchased under the name "Snow crabmeat."

3. Comments have been received that the name "Snow crabmeat" will lead consumers to believe that crabmeat so designated is of inferior quality, but quality is a function of the article itself and its preparation, and not of the name by which it is designated.

4. There is no provision in the Federal Food, Drug, and Cosmetic Act by which a legally suitable food name can be confined to the domestically produced food and denied to the food if imported from other countries.

5. The common or usual name of a food does not cease to be such merely because another, similar term has been trademarked.

6. It is not possible for those who market crabmeat from the *Chionoecetes* species to have labels which comply with this statement without a reasonable period of time allowed for securing such labels. A period of 180 days after date of publication of this document in the FEDERAL REGISTER is reasonable.

Having considered the comments submitted in response to the proposal, the comments and information presented at the informal hearing, and other relevant material, the Commissioner concludes that the proposed revision should be adopted as set forth below. Therefore, pursuant to provisions of the act (secs. 403(b), (i)(1), 701(a), 52 Stat. 1047, 1048, 1055; 21 U.S.C. 343(b), (i)(1), 371(a)) and under authority delegated to the Commissioner (21 CFR 2.120), § 3.34 is revised to read as follows:

§ 3.34 Labeling of crabmeat.

(a) For many years canned crabmeat has been imported into the United States from Japan. Such imports have consisted primarily of a product designated as "King crabmeat." There have been limited importations of articles designated as "Korean crabmeat" and "Snow crabmeat." Two closely allied species of crab have been packed in Japan for export to the United States under the designation "King crabmeat." These species

are *Paralithodes camtschatica* (tarabagani) and *Paralithodes platypus* (aburagani). A third species of crab, *Paralithodes brevipes*, has been labeled either as "King crabmeat" or "Hanasaki crabmeat" when intended for export to the United States. The Food and Drug Administration considers the term "King crabmeat" as an acceptable common name for the product prepared from any one of the three species *P. camtschatica*, *P. platypus*, and *P. brevipes*. The Food and Drug Administration also considers the name "Hanasaki crabmeat" as an alternative common name for the product prepared from *P. brevipes*.

(b) Prior to World War II, there was a limited pack of crabmeat from the species *Erimacrus isenbeckii* at canneries located on the coast of Korea, but only a small quantity of this product was imported into the United States. To distinguish the product from the various species of *Paralithodes* and to connote its geographic origin, the article was designated by the name "Korean crab." In the past, there has been a certain amount of the species *Erimacrus isenbeckii* packed in Japan or on Japanese factory ships operating in the Bering Sea. This species of crab is generally known in Japan as "Kegani." This product, packed in Japan, when offered for entry into the United States has been designated by a variety of names including "Korean crabmeat," "Snow crabmeat," "Eliza crabmeat," "Kegani crabmeat," and "Zuwai crabmeat," with resulting confusion to importers and consumers. The term "Korean crab" is no longer applicable to the product as an indication of its geographic origin. The long absence of the product from the domestic market, until its subsequent reintroduction under a variety of names, has largely eliminated consumer recognition of the identity of the product under the name "Korean crabmeat." The Food and Drug Administration therefore considers the designation "Korean variety crabmeat" or, alternatively, "Kegani crabmeat" as suitable common names for the product packed from the species *Erimacrus isenbeckii*.

(c) There has also been a limited pack of *Chionoecetes opilio* (zuwai-gani) offered for entry into the United States from the Orient and from Canada, and a limited pack of this species produced in the United States. This product has for many years been designated by the name "Snow crabmeat." Three other *Chionoecetes* species, *C. tanneri*, *C. bairdii*, and *C. angulatus*, produce crabmeat similar to that of *C. opilio*, and the four *Chionoecetes* species at times may be taken and processed into crabmeat together. The Food and Drug Administration regards the designation "Snow crabmeat" as the common or usual name for crabmeat from any of these four species when distributed in the United States.

(d) Section 403(i)(1) of the Federal Food, Drug, and Cosmetic Act requires that the label of a food for which there is no definition and standard of identity shall bear the common or usual name of the food, if any there be. No definition and standard of identity has been established for crabmeat under the act. The Food and Drug Administration regards the label designations for crabmeat prepared from the various species of crab as stated in paragraphs (a), (b), and (c) of this section, whether canned, frozen, or otherwise, and whether imported into or produced in this country, as satisfactory compliance with section 403(i)(1) of the act. For convenient reference, the scientific name of the crabs in question and the acceptable common name of the crabmeat produced from each are listed below.

Scientific name of crab	*Common name of crabmeat*
Paralithodes camtschatica and *Paralithodes platypus*.	King crabmeat.
Paralithodes brevipes.	King crabmeat or Hanasaki crabmeat.
Erimacrus isenbeckii.	Korean variety crabmeat or Kegani crabmeat.
Chionoecetes opilio, *Chionoecetes tanneri*, *Chionoecetes bairdii*, and *Chionoecetes angulatus*.	Snow crabmeat.

(e) The Food and Drug Administration will not institute regulatory action against crabmeat produced from the species *Chionoecetes opilio*, *C. tanneri*, *C. bairdii*, and *C. angulatus* solely for failure to comply with the provisions of this § 3.34 only by reason of being designated as, or sold under the name of, "Queen crabmeat" instead of "Snow crabmeat" when the introduction into or delivery for introduction into interstate commerce, or the offering for importation, occurs less than 180 days following the date of publication of this section in the FEDERAL REGISTER.

(Secs. 403(b), (i)(1), 701(a), 52 Stat. 1047, 1048, 1055; 21 U.S.C. 343 (b), (i)(1), 371(a))

Dated: August 27, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70-11550; Filed, Sept. 1, 1970; 8:46 a.m.]

SUBCHAPTER C—DRUGS

PART 141—TESTS AND METHODS OF ASSAY OF ANTIBIOTIC AND ANTIBIOTIC-CONTAINING DRUGS

Test for Particulate Contamination in Ophthalmic Ointments

The following test for particulate contamination is added to the antibiotic drug regulations to formalize the already applied specification for certifiable antibiotic ophthalmic ointments. A limit of 50 particles exceeding 50 microns in any single dimension per 10 tubes of ointment is prescribed.

Accordingly, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357) and under authority delegated to the Commissioner (21 CFR 2.120), Part 141 is amended by adding a new section, as follows:

§ 141.508 Test for particulate contamination in ophthalmic ointments.

(a) *Procedure.* Extrude the contents of each of 10 tubes as completely as practicable into separate, clear, glass Petri dishes (60 millimeters in diameter), cover the dishes, and heat to 80° C. to 85° C. for at least 2 hours or until the ointment has melted completely and evenly in the dishes. A higher temperature of 100° C.±2° C. may be used if necessary to allow adequate settling of particles. Allow the ointment to cool to room temperature without agitation. Invert each Petri dish on the stage of a suitable microscope adjusted to furnish 30 times (30X) magnification and equipped with an eye-piece micrometer disc which has been calibrated at the magnification being used. In addition to the usual source of light, direct an illuminator from above the ointment at a 45° angle. Examine the entire bottom of the Petri dish for particles, recording the total number exceeding 50 microns in any single dimension.

(b) *Evaluation.* The batch is acceptable if (1) a total of not more than 50 such particles is found in 10 tubes; and (2) not more than one tube is found to contain more than eight such particles. If the batch fails the above test, repeat the test on 20 additional tubes of ointment. The total number of particles exceeding 50 microns in any single dimension from the 30 tubes tested shall not exceed 150, with not more than three tubes containing more than eight such particles.

Notice and public procedure and delayed effective date are not prerequisites to promulgation of this regulation because the specifications set forth have been applied and adopted by manufacturers of the subject products since 1965.

Effective date. This order shall be effective upon publication in the FEDERAL REGISTER.

(Sec. 507, 59 Stat. 463, as amended; 21 U.S.C. 357)

Dated: August 21, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70-11543; Filed, Sept. 1, 1970; 8:45 a.m.]

Title 24—HOUSING AND HOUSING CREDIT

Chapter VII—Federal Insurance Administration, Department of Housing and Urban Development

SUBCHAPTER B—NATIONAL FLOOD INSURANCE PROGRAM

PART 1914—AREAS ELIGIBLE FOR THE SALE OF INSURANCE

List of Designated Areas

Section 1914.4 is amended by adding in alphabetical sequence a new entry to the table, which entry reads as follows:

§ 1914.4 List of designated areas.

* * * * * * *

State	County	Location	Map No.	State map repository	Local map repository	Effective date of authorization of sale of flood insurance for area
* * *	* * *	* * *	* * *	* * *	* * *	* * *
California	Del Norte	Lower Klammath River Watershed, Zone 4.	E 06 015 0000 01	Department of Water Resources, Box 338, Sacramento, Calif. 95802. California Insurance Department, 107 South Broadway, Los Angeles, Calif. 90012, and 1407 Market St., San Francisco, Calif. 94103.	Del Norte County Flood Control District, Courthouse, Crescent City, Calif. 95531.	Sept. 4, 1970.
Do	Los Angeles	Arcadia	E 06 037 0120 01 through E 06 037 0120 04	do	Office of the City Clerk, City Hall, Post Office Box 60, Arcadia, Calif. 91006.	Do.
Do	Monterey	King City	E 06 053 1760 01 E 06 053 1760 02	do	City Hall, City of King, 212 South Vanderhurst, King City, Calif. 93930.	Do.
Louisiana	Cameron (Parish)		E 22 023 0000 01	Louisiana Department of Public Works, Baton Rouge, La. 70804. Commissioner of Insurance, State of Louisiana, Box 44214, Capitol Station, Baton Rouge, La. 70804.	Office of the Parish Treasurer, Police Jury Annex, Cameron, La. 70631.	Do.
Minnesota	Wilkin	Breckenridge	E 27 167 0790 01	Department of Conservation, Division of Soils, Waters, and Minerals, Room 345, Centennial Bldg., St. Paul, Minn. 55101. Commissioner of Insurance, State Office Bldg., R 210, St. Paul, Minn. 55101.	Office of the City Clerk, City of Breckenridge, City Hall, Breckenridge, Minn. 56520.	Do.
New Jersey	Passaic	Pompton Lakes	I 34 031 2670 02	Department of Environmental Protection, Division of Water Policy and Supply, Post Office Box 1390, Trenton, N.J. 08625. Department of Banking and Insurance, State House Annex, Trenton, N.J. 08625.	Municipal Bldg., Borough of Pompton Lakes, 25 Lenox Ave., Pompton Lakes, N.J. 08260.	Do.
South Carolina	Charleston	Isle of Palms	E 45 019 1225 01 E 45 019 1225 02	South Carolina Water Resources Planning and Coordinating Committee, 1411 Barnwell St., Columbia, S.C. 29201. South Carolina Insurance Department, Federal Land Bank Bldg., 1401 Hampton St., Columbia, S.C. 29201.	City Hall, City of Isle of Palms, 1301 Palm Blvd., Isle of Palms, S.C. 29451.	Do.
Texas	Dallas	Unincorporated areas.	E 48 113 0000 01	Texas Water Development Board, 301 West Second St., Austin, Tex. 78711. State Board of Insurance, 11th and San Jacinto, Austin, Tex. 78701.	County Department of Public Works, 412 Records Bldg., Dallas, Tex. 75202.	Do.
Do	Karnes	Kenedy	E 48 255 3630 01	do	City Hall, 222 Tilden St., Kenedy, Tex. 78119.	Do.

(National Flood Insurance Act of 1968 (title XIII of the Housing and Urban Development Act of 1968), effective Jan. 28, 1969 (33 F.R. 17804, Nov. 28, 1968), as amended (secs. 408–410, Public Law 91–152, Dec. 24, 1969), 42 U.S.C. 4001–4127; Secretary's delegation of authority to Federal Insurance Administrator, 34 F.R. 2680, Feb. 27, 1969; and designation of Acting Federal Insurance Administrator effective July 22, 1970, 35 F.R. 12360, Aug. 1, 1970)

Issued: September 1, 1970.

RICHARD W. KRIMM,
Acting Federal Insurance Administrator.

[F.R. Doc. 70-11529; Filed, Sept. 1, 1970; 8:45 a.m.]

PART 1915—IDENTIFICATION OF FLOOD-PRONE AREAS

List of Flood Hazard Areas

Section 1915.3 is amended by adding in alphabetical sequence a new entry to the table, which entry reads as follows:

§ 1915.3 **List of flood hazard areas.**

* * * * * * *

State	County	Location	Map No.	State map repository	Local map repository	Effective date of identification of areas which have special flood hazards
* * *	* * *	* * *	* * *	* * *	* * *	* * *
California	Del Norte	Lower Klamath River Watershed, Zone 4.	H 06 015 0000 01	Department of Water Resources, Box 338, Sacramento, Calif. 95802. California Insurance Department, 107 South Broadway, Los Angeles, Calif. 90012, and 1407 Market St., San Francisco, Calif. 94103.	Del Norte County Flood Control District, Courthouse, Crescent City, Calif. 95531.	Sept. 1, 1970.
Do	Los Angeles	Arcadia	T 06 037 0120 01 through T 06 037 0120 04	do	Office of the City Clerk, City Hall, Post Office Box 60, Arcadia, Calif. 91006.	Do.
Do	Monterey	King City	T 06 053 1760 01 T 06 053 1760 02	do	City Hall, City of King, 212 South Vanderhurst, King City, Calif. 93930.	Do.
Louisiana	Cameron (Parish)		H 22 023 0000 01	Louisiana Department of Public Works, Baton Rouge, La. 70804. Commissioner of Insurance, State of Louisiana, Box 44214, Capitol Station, Baton Rouge, La. 70804.	Office of the Parish Treasurer, Police Jury Annex, Cameron, La. 70631.	June 19, 1970.
Minnesota	Wilkin	Breckenridge	H 27 167 0790 01	Department of Conservation, Division of Soils, Waters, and Minerals, Room 345, Centennial Bldg., St. Paul, Minn. 55101. Commissioner of Insurance, State Office Building, R 210, St. Paul, Minn. 55101.	Office of the City Clerk, City of Breckenridge, City Hall, Breckenridge, Minn. 56520.	Sept. 1, 1970.
New Jersey	Ocean	Stafford Township.	H 34 029 3270 01 H 34 029 3270 02	Department of Environmental Protection, Division of Water Policy and Supply, Post Office Box 1390, Trenton, N.J. 08625. Department of Banking and Insurance, State House Annex, Trenton, N.J. 08625.	Office of the Township Clerk, 775 East Bay Ave., Manahawkin, N.J. 08050.	Do.
Do	Passaic	Pompton Lakes	H 34 031 2670 02	do	Municipal Bldg, Borough of Pompton Lakes, 25 Lenox Ave., Pompton Lakes, N.J. 08260.	Do.
Do	Union	Cranford	H 34 039 0705 01	do	Office of the Township Engineer, Cranford Municipal Bldg., 8 Springfield Ave., Cranford, N.J. 07016.	June 16, 1970.
South Carolina	Charleston	Isle of Palms	T 45 019 1225 01 T 45 919 1225 02	South Carolina Water Resources Planning and Coordinating Committee, 1411 Barnwell St., Columbia, S.C. 29201. South Carolina Insurance Department, Federal Land Bank Bldg., 1401 Hampton St., Columbia, S.C. 29201.	City Hall, City of Isle of Palms, 1301 Palm Blvd., Isle of Palms, S.C. 29451.	Sept. 1, 1970.
Texas	Dallas	Unincorporated areas.	T 48 113 0000 01	Texas Water Development Board, 301 West Second St., Austin, Tex. 78711. State Board of Insurance, 11th and San Jacinto, Austin, Tex. 78701.	County Department of Public Works, 412 Records Bldg., Dallas, Tex. 75202.	Do.
Do	Jefferson	Beaumont	H 48 245 0490 01 through H 48 245 0490 04	do	City Hall, 700 Pearl St., Beaumont, Tex. 77704.	June 16, 1970.
Do	Karnes	Kenedy	T 48 255 3630 01	do	City Hall, 222 Tilden St., Kenedy, Tex. 78119.	Sept. 1, 1970.
Virginia	Wise	Saint Paul	H 51 195 2160 01	Division of Water Resources, Seventh Floor, 911 East Broad St., Richmond, Va. 23219. Virginia Insurance Department, 700 Blanton Bldg., Richmond, Va. 23209.	Clerk's Office, Town Hall, St. Paul, Va. 24283.	June 16, 1970.

(National Flood Insurance Act of 1968 (title XIII of the Housing and Urban Development Act of 1968), effective Jan. 28, 1969 (33 F.R. 17804, Nov. 28, 1968), as amended (secs. 408–410, Public Law 91–152, Dec. 24, 1969), 42 U.S.C. 4001–4127; Secretary's delegation of authority to Federal Insurance Administrator, 34 F.R. 2680, Feb. 27, 1969; and designation of Acting Federal Insurance Administrator effective July 22, 1970, 35 F.R. 12360, Aug. 1, 1970)

Issued: September 1, 1970.

RICHARD W. KRIMM,
Acting Federal Insurance Administrator.

[F.R. Doc. 70–11530; Filed, Sept. 1, 1970; 8:45 a.m.]

Title 29—LABOR

Chapter V—Wage and Hour Division

PART 520—EMPLOYMENT OF STUDENT-LEARNERS

Temporary Certification by School Officials

On June 30, 1970, there was published in the FEDERAL REGISTER a proposal to amend Part 520 of Title 29 of the Code of Federal Regulations to provide a simplified method of certification for the employment of student-learners at subminimum wages below those otherwise required under section 6 of the Fair Labor Standards Act, under which simplified method the temporary authority provided by the certification by the appropriate school official under conditions set forth in the regulations would become the permanent special student-learner certificate unless the Administrator or his authorized representative denies the application or expressly extends the period of review. After consideration of all written matter presented in response to the proposal, the proposed changes are adopted, together with a clarification that the temporary authority may be superseded by a certificate with modified terms and conditions issued by the Administrator or his authorized representative, and certain editorial changes, updating references to the Wage and Hour Division, etc.

These amendments shall become effective immediately.

1. § 520.3 is amended to read as follows:

§ 520.3 Application for a special student-learner certificate.

(a) Whenever the employment of a student-learner at wages lower than the minimum wage applicable under section 6 of the Fair Labor Standards Act of 1938, as amended, is believed necessary to prevent curtailment of opportunities for employment, an application for a special certificate authorizing the employment of such student-learner at subminimum wages shall be filed in duplicate by the employer with the authorized representative of the Administrator at the appropriate Regional or Caribbean Office of the Wage and Hour Division, U.S. Department of Labor.

(b) Application must be made on the official form furnished by the Division and must be signed by the employer, the appropriate school official and the student-learner. The application must contain all information required by such form, including among other things, a statement clearly outlining the vocational training program and showing, particularly, the processes in which the student-learner will be engaged when in training on the job; a statement clearly outlining the school instruction directly related to the job; the total number of workers employed in the establishment; the number and hourly wage rate of experienced workers employed in the occupation in which the student-learner is to be trained; the hourly wage rate or progressive wage schedule which the employer proposes to pay the student-learner; data regarding the age of the student-learner; the period of employment training at subminimum wages; the number of hours of employment training a week; the number of hours of school instruction a week; and a certification by the appropriate school official that the student named therein will be receiving instruction in an accredited school, college or university and will be employed pursuant to a bona fide vocational training program, as defined in § 520.2(b).

(c) The certification by the appropriate school official must satisfy the following conditions:

(1) The application must be properly executed in conformance with § 520.3.

(2) The employment training must conform with the provisions of §§ 520.5 (a), (c), (d), and (g) and paragraphs (a) and (c) of § 520.6.

(3) The occupation must not be one for which a student-learner application was previously submitted by the employer and a special certificate was denied by the Administrator or his authorized representative.

2. § 520.4 is amended to read as follows:

§ 520.4 Procedure for action upon application.

(a) The certification by the appropriate school official on an application for a special student-learner certificate authorizing the employment of a student-learner at subminimum wages (see § 520.3(b)) shall constitute a temporary authorization for the employment of a student-learner at wages lower than the minimum wage applicable under section 6 of the act, effective from the date such application is forwarded to the Division in conformance with § 520.3 and, at the end of 30 days, shall become the permanent special student-learner certificate unless, after review, the Administrator or his authorized representative denies the application, issues a certificate with modified terms and conditions, or expressly extends the period of review.

(b) Upon receipt of an application for the employment of a student-learner, the Administrator or his authorized representative shall review the application for compliance with this part. If an application is to be denied, notification of denial should be made to the appropriate school official, the employer, and the student within the 30 days following the date such application was forwarded to the Division, unless additional time for review is considered necessary or appropriate, and in which case the appropriate school official, the employer, and the student shall be so notified. To the extent feasible, the Administrator or his authorized representative shall provide an opportunity to other interested persons to present data and views on the application before denying a special student-learner certificate.

(c) Whenever a notification of denial is mailed to the employer, such denial shall be without prejudice to any subsequent application, except under the circumstances referred to in § 520.3(c)(3). Two copies of the notification of denial shall be mailed to the appropriate school official, one of which shall be retained for his records and the other shall be presented to the student-learner.

3. In § 520.5 the heading is amended to read as follows:

§ 520.5 Conditions necessary for favorable review.

* * * * *

4. In § 520.6, paragraph (a) and subparagraph (c)(2) are deleted, and, as amended, § 520.6 reads as follows:

§ 520.6 Terms and conditions of employment under special student-learner certificates.

(a) The special minimum wage rate shall be not less than 75 percent of the applicable minimum under section 6 of the act.

(b) No special student-learner certificate may be issued retroactively.

(c) (1) The number of hours of employment training each week at subminimum wages pursuant to a certificate, when added to the hours of school instruction, shall not exceed 40 hours, except that authorization may be granted by the Administrator or his authorized representative for a greater number of hours if found to be justified by extraordinary circumstances.

(2) When school is not in session on any school day, the student-learner may work a number of hours in addition to the weekly hours of employment training authorized by the certificate: *Provided, however,* That the total hours worked shall not exceed 8 hours on any such day. A notation shall be made in the employer's records to the effect that school not being in session was the reason additional hours were worked on such day.

(3) During the school term, when school is not in session for the entire week, the student-learner may work at his employment training a number of hours in the week in addition to those authorized by the certificate: *Provided, however,* That the total hours shall not exceed 40 hours in any such week. A notation shall be made in the employer's records to the effect that school not being in session was the reason additional hours were worked in such week.

(d) A special student-learner certificate shall not constitute authorization to pay a subminimum wage rate to a student-learner in any week in which he is employed for a number of hours in addition to the number authorized in the certificate, except as provided in paragraphs (c), (1), (2), and (3) of this section.

5. In § 520.7 paragraphs (b) and (c) are amended to read as follows:

§ 520.7 Employment records to be kept.

* * * * *

(b) The employer's copy of the application, filed in accordance with § 520.4 (a) and any certificate issued by the Administrator or his authorized representative must be available at all times for inspection for a period of 3 years

from the last date of employment of the student-learner.

(c) Notations should be made in the employer's records when additional hours are worked by reason of school not being in session as provided in §§ 520.6(c)(2) and (3).

6. § 520.8 is amended to read as follows:

§ 520.8 Duration of certificates.

A special student-learner certificate shall be effective for a period not to exceed the length of 1 school year unless a longer period is found to be justified by extraordinary circumstances. No certificate shall authorize employment training beyond the date of graduation.

7. § 520.9 is amended to read as follows:

§ 520.9 Compliance with established standards.

No provision of the regulations contained in this part, or of any certificate or temporary authority thereunder, shall excuse noncompliance with higher standards applicable to student-learners which may be established under any other Federal law, or any State law, municipal ordinance or trade union agreement.

(Sec. 14, 52 Stat. 1068, as amended; 29 U.S.C. 214)

Signed at Washington, D.C., this 24th day of August 1970.

ROBERT D. MORAN,
Administrator,
Wage and Hour Division.

[F.R. Doc. 70-11578; Filed, Sept. 1, 1970; 8:48 a.m.]

Title 41—PUBLIC CONTRACTS AND PROPERTY MANAGEMENT

Chapter 5A—Federal Supply Service, General Services Administration

PART 5A-7—CONTRACT CLAUSES

Subpart 5A-7.1—Fixed-Price Supply Contracts

VARIATION IN QUANTITY CLAUSE

Paragraphs (b), (c), and (d) of § 5A-7.101-4 are revised to read as follows:

§ 5A-7.101-4 Variation in quantity.

* * * * *

(b) The Variation in Quantity clause set forth in paragraph (a) of this section is included in GSA Form 1424, GSA Supplemental Provisions, solely for the purpose of administrative convenience in avoiding the need to amend contracts or purchase orders when an overshipment or an under-shipment within prescribed limits is determined to be acceptable. This standard clause is in no way intended to establish a general policy with respect to the extent to which FSS or the agencies it serves will accept variations in quantity. If experience indicates that a different variation percentage should be used in a particular procurement or class of procurements, due to the particular industry practices involved, the contracting officer may determine that a variation percentage, other than the 3 percent normally called for in the Variation in Quantity clause, shall be used. In this regard, based on Central Office studies, it has been determined that (1) a 5 percent variation shall be specified when procuring printing stationery paper, (2) a 10 percent variation shall be specified when procuring aluminum foil items, and (3) a 10 percent variation shall be specified when purchasing special paint when the purchase is for 500 gallons or less, particularly if it is of an unusual type or color or a specialty item (e.g., gray or olive drab baking enamel for metal equipment).

(c) When other than a 3 percent variation is to be specified, the following clause shall be used:

VARIATION IN QUANTITY

(*Enter Item Description*)

Article 4, Variation in Quantity, of GSA Form 1424, GSA Supplemental Provisions, is hereby deleted in its entirety and the following substituted: A variation in quantity when caused by the conditions specified in Article 4 of Standard Form 32 will be accepted, provided that such variation is not in excess of _____ percent[1] of the quantity ordered.

(d) When no variation in quantity is to be permitted, the following clause shall be used:

VARIATION IN QUANTITY

Article 4, Variation in Quantity, of GSA Form 1424, GSA Supplemental Provisions, is hereby deleted and no variation in quantity shall be permitted in deliveries under this contract.

(Sec. 205(c), 63 Stat. 390; 40 U.S.C. 486(c); 41 CFR 5-1.101(c))

Effective date. This amendment is effective 30 days following the date of publication in the FEDERAL REGISTER.

Dated: August 24, 1970.

H. A. ABERSFELLER,
Commissioner, Federal Supply Service.

[F.R. Doc. 70-11541; Filed, Sept. 1, 1970; 8:45 a.m.]

Title 45—PUBLIC WELFARE

Chapter I—Office of Education, Department of Health, Education, and Welfare

PART 121—GRANTS TO STATES FOR THE EDUCATION OF HANDICAPPED CHILDREN

Miscellaneous Amendments

In fiscal year 1971 the State-administered program currently being conducted under Title VI, Part A, of the Elementary and Secondary Education Act of 1965 will be continued in essential respects under Part B of the recently amended Education of the Handicapped Act (Title VI of Public Law 91-230). The regulations in this Part 121 that were developed for administration of the program under title VI, Part A, of the Elementary and Secondary Education Act of 1965 will continue to govern the program to be carried out under the new Part B of the Education of the Handicapped Act, except that for the purpose of this new program, the following amendments will be applicable:

1. The Table of Contents is amended by adding the following to Subpart B thereof:

Sec.
121.12 Coordination by special education personnel.
121.13 Publication and opportunity for comment.

2. The phrase "Title VI," wherever it occurs in Part 121, is amended to read "Part B."

3. Section 121.1(b) is amended to read as follows:

§ 121.1 Definitions.

* * * * *

(b) "Act" means the Education of the Handicapped Act (Title VI of Public Law 91-230).

* * * * *

4. Section 121.4(a) is amended to read as follows:

§ 121.4 Needs of handicapped children.

(a) Each State plan shall set forth such policies and procedures as will provide satisfactory assurance that funds paid to the State under this part will be expended either directly or through individual, or combinations of, local educational agencies, solely to initiate, expand, or improve programs and projects, including preschool programs and projects, (1) which are designed to meet the special educational and related needs of handicapped children throughout the State, and (2) which are of sufficient size, scope, and quality (taking into consideration the special educational needs of such children) as to give reasonable promise of substantial progress toward meeting those needs.

(20 U.S.C. 874)

§ 121.6 [Amended]

5. Section 121.6(a) is revoked and § 121.6(b) is renumbered § 121.6.

5. A new section, § 121.12, is added to Subpart B of Part 121 as follows:

§ 121.12 Coordination by special education personnel.

The State plan shall contain a statement of policies and procedures designed to insure that all education programs for the handicapped in the State will be properly coordinated by the persons in charge of special education programs for handicapped children in the State educational agency.

(Sec. 613(a)(11) of Public Law 91-230)

6. A new section, § 121.13, is added to Subpart B of Part 121 as follows:

[1] Enter appropriate percentage.

§ 121.13 Publication and opportunity for comment.

(a) Each State plan, prior to its submission by the State educational agency to the Commissioner, shall be made public as a separate document by the State educational agency, and a reasonable opportunity shall be given by that agency for comment thereon by interested persons.

(b) Each State plan as finally approved by the Commissioner shall also be made public by the State educational agency.

(c) Each State plan, upon submission to the Commissioner by the State educational agency, shall be accompanied by a statement describing the method by which, and the extend to which, the plan has been and, when approved, will be made public.

(d) "Interested persons," for purposes of paragraph (a) of this section, includes not only public officials, public employees, or other persons involved in the education of handicapped children, but also persons who are themselves handicapped or the parents of handicapped children.

(Sec. 613(c)(1) of Public Law 91-230)

§ 121.21 [Amended]

7. Section 121.21 is amended by changing "$75,000" to "$100,000," by changing "$25,000" to "$35,000," and by changing "603" to "612."

Effective date. The amendments hereby made to Part 121 will not become effective before 30 days after publication in the FEDERAL REGISTER.

Dated: July 20, 1970.

T. H. BELL,
Acting U.S. Commissioner of Education.

Approved: August 27, 1970.

JOHN G. VENEMAN,
Acting Secretary of Health, Education, and Welfare.

[F.R. Doc. 70-11556; Filed, Sept. 1, 1970; 8:46 a.m.]

Proposed Rule Making

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[43 CFR Part 1850]

CONTEST AND PROTEST PROCEEDINGS

Notice of Proposed Rule Making

Notice is hereby given that it is proposed to amend Subpart 1852 as set forth below. These amendments would relieve the United States of certain procedural requirements in Government contest proceedings. The proposed revisions would eliminate the requirement for furnishing the age of each heir of deceased entrymen in the complaint, clarify the effect of an answer by a contestee before dismissal, and provide specifically in Government contests for summary dismissal of contest complaints only as to any contestees not served.

It is the policy of this Department, whenever practicable, to afford the public an opportunity to participate in the rule making process. Accordingly, interested parties may submit written comments, suggestions, or objections to the proposed rules to the Bureau of Land Management (210), Washington, D.C. 20240, within 30 days of the date of publication of this notice in the FEDERAL REGISTER.

1. In paragraph (a)(1) of § 1852.1–4, delete the words "including the age of each heir of any deceased entryman," so § 1852.1–4(a)(1) will read as follows:

§ 1852.1–4 Complaints.

* * * * *

(a) * * *

(1) The name and address of each party interested.

* * * * *

2. In paragraph (a) of § 1852.1–5, add the words "as to such answering contestee" to the last sentence so that sentence will read as follows:

§ 1852.1–5 Service.

* * * * *

(a) *Summary dismissal; waiver of defect in service.* If a complaint when filed does not meet all the requirements of § 1852.1–4 (a) and (c), or if the complaint is not served upon each contestee as required by this section, the complaint will be summarily dismissed by the manager and no answer need be filed. However, where prior to the summary dismissal of a complaint a contestee answers without questioning the service or proof of service of the complaint, any defect in service will be deemed waived as to such answering contestee.

* * * * *

3. In § 1852.2–2, renumber the present paragraphs (b) through (i) to read (c) through (j) respectively, and add a new paragraph (b) to read as follows:

§ 1852.2–2 Proceedings in Government contests.

* * * * *

(b) A Government contest complaint will not be insufficient and subject to dismissal for failure to name all parties interested, or for failure to serve every party who has been named.

* * * * *

FRED J. RUSSELL,
Acting Secretary of the Interior.

AUGUST 26, 1970.

[F.R. Doc. 70–11545; Filed, Sept. 1, 1970; 8:45 a.m.]

DEPARTMENT OF AGRICULTURE

Consumer and Marketing Service

[7 CFR Part 906]

ORANGES AND GRAPEFRUIT GROWN IN LOWER RIO GRANDE VALLEY IN TEXAS

Notice of Proposed Rule Making With Respect to Expenses and Fixing of Rate of Assessment for the 1970–71 Fiscal Period

Consideration is being given to the following proposals submitted by the Texas Valley Citrus Committee, established pursuant to the marketing agreement, as amended, and Order No. 906, as amended (7 CFR Part 906), regulating the handling of oranges and grapefruit grown in Lower Rio Grande Valley in Texas, effective under the Agricultural Marketing Agreement Act of 1937, as amended (7 U.S.C. 601–674), as the agency to administer the terms and provisions thereof:

(1) That expenses that are reasonable and likely to be incurred by the Texas Valley Citrus Committee, during the period August 1, 1970, through July 31, 1971, will amount to $660,000.

(2) That there be fixed at $0.045 per seven-tenths bushel carton or equivalent quantity of oranges and grapefruit, the rate of assessment payable by each handler in accordance with § 906.34 of the aforesaid marketing agreement and order.

All persons who desire to submit written data, views, or arguments in connection with aforesaid proposals shall file the same, in quadruplicate, with the Hearing Clerk, United States Department of Agriculture, Room 112A, Administration Building, Washington, D.C. 20250, not later than the 10th day after the publication of this notice in the FEDERAL REGISTER. All written submissions made pursuant to this notice will be made available for public inspection at the office of the Hearing Clerk during regular business hours (7 CFR 1.27(b)).

Dated: August 27, 1970.

PAUL A. NICHOLSON,
Acting Director, Fruit and Vegetable Division, Consumer and Marketing Service.

[F.R. Doc. 70–11563; Filed, Sept. 1, 1970; 8:47 a.m.]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 3]

LABELING OF MOUTHWASH, MOUTH FRESHENER, AND GARGLE PREPARATIONS

Extension of Time for Filing Comments on Proposed Statement of Policy

The notice published in the FEDERAL REGISTER of August 4, 1970 (35 F.R. 12411), proposing a statement of policy on labeling of mouthwashes, mouth fresheners, gargles, and similar preparations, provided for the filing of comments within 30 days after said date.

The Commissioner of Food and Drugs has received a request to extend such time and, good reason therefor appearing, the time for filing comments on the subject proposal is hereby extended to November 2, 1970.

This action is taken pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502(a), (f), 505, 701 (a), 52 Stat. 1050, 1051, 1052, as amended, 1055; 21 U.S.C. 352(a), (f), 355, 371(a)) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: August 27, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70–11558; Filed, Sept. 1, 1970; 8:46 a.m.]

[21 CFR Part 191]

CHARCOAL BRIQUETTES AND OTHER FORMS OF CHARCOAL

Proposed Declaration as Hazardous Substances That Require Special Labeling

Carbon monoxide, a toxic gas, is colorless, odorless, and tasteless and gives no warning when being inhaled. Charcoal not only generates carbon monoxide

when burned, but also consumes available oxygen when burned in enclosed or confined areas.

Through investigations by the Food and Drug Administration, from review of death certificates, and from other available information, the Commissioner of Food and Drugs has learned that at least 31 fatalities have occurred in the United States in recent years (including at least 18 in the last 3½ years) because individuals have used charcoal for cooking or heating purposes indoors or in tents, trailers, automobiles, boats, and similar areas. The Commissioner finds that charcoal briquettes and other forms of charcoal when burned (1) create an atmosphere that is toxic by inhalation and (2) have the capacity to produce personal injury and death to man through reasonably foreseeable handling or use. The Commissioner also finds that individuals would be unlikely to burn charcoal in confined spaces if they knew that it could cause death. Accordingly, the Commissioner concludes that charcoal briquettes and other forms of charcoal should be declared to be hazardous substances and required to bear a conspicuous statement warning of this hazard as proposed below.

Therefore, pursuant to provisions of the Federal Hazardous Substances Act (sec. 3 (a), (b), 74 Stat. 374–75, as amended; 15 U.S.C. 1262) and the Federal Food, Drug, and Cosmetic Act (sec. 701, 52 Stat. 1055, as amended; 21 U.S.C. 371) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Part 191 be amended by adding a new § 191.5 and by adding to § 191.7(b) a new subparagraph (6), as follows:

§ 191.5 Products declared to be hazardous substances under section 3(a) of the act.

(a) The Commissioner finds that the following articles are hazardous substances within the meaning of the act because they are capable of causing substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use:

(1) Charcoal briquettes and other forms of charcoal.

§ 191.7 Products requiring special labeling under section 3(b) of the act.

* * * * *

(b) * * *

(6) Charcoal briquettes and other forms of charcoal.

(i) Because inhalation of the carbon monoxide produced by burning charcoal indoors or in confined areas may cause serious brain damage or death, containers of such products shall bear the following statement:

> WARNING: May Cause Death If Used Indoors or in Confined Areas Due to Formation of Carbon Monoxide.

(ii) For bags of charcoal the statement specified in subdivision (i) of this subparagraph shall appear within a heavy borderline in sharply contrasting colors on both front and back panels of the bag at least 2 inches from the top seam, and above any other printed or graphic matter, in type size as follows: Bags containing up to 5 pounds of charcoal—one-eighth inch in height; bags containing 5 to 10 pounds of charcoal—three-sixteenth inch in height; bags containing more than 10 pounds of charcoal—one-fourth inch in height.

(iii) For containers other than bags the statement specified in subdivision (i) of this subparagraph shall be in conformance with § 191.101 and shall be printed within a borderline.

Interested persons may, within 30 days after publication hereof in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6–62, 5600 Fishers Lane, Rockville, Md. 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof.

Dated: August 25, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70-11551; Filed, Sept. 1, 1970; 8:46 a.m.]

Social Security Administration

[20 CFR Part 405]

FEDERAL HEALTH INSURANCE FOR THE AGED

Fire and Safety Requirements for Extended Care Facilities and for Hospitals Not Accredited by Joint Commission on Accreditation of Hospitals or American Osteopathic Association

Notice is hereby given, pursuant to the Administrative Procedure Act (5 U.S.C. 552 et seq.) that the regulations set forth in tentative form are proposed by the Commissioner of Social Security, with the approval of the Secretary of Health, Education, and Welfare. The proposed regulations would provide that in order for extended care facilities and hospitals not accredited by the Joint Commission on Accreditation of Hospitals or the American Osteopathic Association to qualify for participation under the Medicare program, (1) the standards in the National Fire Protection Association's Life Safety Code shall be complied with; (2) carpeting, carpet assemblies, and other floor coverings installed in inpatient care areas shall have a flame spread rating of not more than 75, when tested in accordance with the "Steiner Tunnel Test" prescribed by the American Society for Testing and Materials (ASTM–E84–68—Surface Burning Characteristics of Building Materials), or a flame propagation index of less than 4.0 when tested in accordance with the "Underwriters' Laboratories Chamber Test" (UL 992—Chamber Test Method for the Flame Propagation Classification of Flooring and Floor Covering Materials), or in other than inpatient areas a flame spread rating that meets the standards under the Flammable Fabrics Act (DOC FF 1–70 and DOC FF 2–70), provided that these areas are separated from inpatient care areas; and (3) specific safety precautions shall be taken in the handling and storage of oxygen. The proposed regulations also make changes of an editorial nature.

Prior to the final adoption of the proposed regulations, consideration will be given to any data, comments, or arguments pertaining thereto which are submitted in writing in duplicate to the Commissioner of Social Security, Department of Health, Education, and Welfare Building, Fourth and Independence Avenue SW., Washington, D.C. 20201, within a period of 30 days from the date of publication of this notice in the FEDERAL REGISTER.

The proposed regulations are to be issued under the authority contained in sections 1102, 1842, 1862, 1870, 1871, 49 Stat. 647, as amended, 79 Stat. 309, 79 Stat. 325, 79 Stat. 331, 81 Stat. 846–847; 42 U.S.C. 1302, 1395 et seq.

Dated: August 12, 1970.

ROBERT M. BALL,
Commissioner of Social Security.

Approved: August 26, 1970.

JOHN G. VENEMAN,
Acting Secretary of Health, Education, and Welfare.

Regulations No. 5 of the Social Security Administration (20 CFR 405), are further amended as follows:

1. Paragraph (b) of § 405.1022 is amended by revising the material preceding subparagraph (1) and subparagraph (1) and adding new subparagraphs (4) and (5) to such paragraph to read as follows:

§ 405.1022 Condition of participation—physical environment.

* * * * *

(b) *Standard; fire control.* The hospital conforms to the current standards of the National Fire Protection Association's Life Safety Code, as amended from time to time. The hospital provides fire protection by the elimination of fire hazards; the installation of necessary safeguards such as extinguishers, sprinkling devices, and fire barriers to insure rapid and effective fire control; and the adoption of written fire control plans rehearsed four times a year by key personnel on each shift. The factors explaining the standard are as follows:

(1) The hospital has:

(i) Written evidence of regular inspection and approval by State or local fire control agencies;

(ii) Equipment as close to fireproof as possible;

(iii) A sufficient number of fire extinguishers properly situated, checked annually for type, replacement, and renewal dates, and maintained in workable condition;

(iv) If flammable anesthetics are used in the operating and delivery rooms, these rooms have conductive floors with the required equipment and underground electrical circuits;

(v) Proper routine storage and prompt disposal of trash;

(vi) "No Smoking" signs prominently displayed, where appropriate, with rules governing the ban on smoking in designated areas of the hospital which are enforced and required to be obeyed by all personnel; and

(vii) Fire regulations prominently posted and all fire codes rigidly observed and carried out.

* * * * *

(4) Flame spread rating of carpet, carpet assemblies, and other floor coverings installed in inpatient care areas is not more than 75, when tested in accordance with the "Steiner Tunnel Test" prescribed by the American Society for Testing and Materials (ASTM–E84–68—Surface Burning Characteristics of Building Materials) or a flame propagation index of less than 4.0 when tested in accordance with the "Underwriters' Laboratories Chamber Test" (UL 992—Chamber Test Method for the Flame Propagation Classification of Flooring and Floor Covering Materials).

(5) Flame spread rating of carpet and carpet assemblies and other floor coverings installed in other than inpatient areas meets the standards promulgated under the Flammable Fabrics Act (DOC FF 1–70 and DOC FF 2–70), provided that these areas are separated from inpatient care areas by fire resistive construction or suitable smokestop partitions that are approved by State or local fire authorities. Floor coverings in areas which are not so separated from inpatient areas shall meet the ASTM–E84–68 or UL 992 requirements contained in subparagraph (4) of this paragraph.

* * * * *

2. In § 405.1134 the material preceding paragraph (a) and paragraph (a) are revised to read as follows:

§ 405.1134 Condition of participation—physical environment.

The extended care facility is constructed, equipped, and maintained to insure the safety of patients and provides a functional, sanitary, and comfortable environment.

(a) *Standard; safety of patients.* The extended care facility is constructed, equipped, and maintained to insure the safety of patients. It is structurally sound and conforms to the current standards of the National Fire Protection Association's Life Safety Code as amended from time to time and it satisfies the following conditions:

(1) The facility complies with all applicable State and local codes governing construction.

(2) Fire resistance and flame spread ratings of construction, materials, and finishes comply with current State and local fire protection codes and ordinances.

(3) Flame spread rating of carpet, carpet assemblies, and other floor coverings installed in inpatient care areas is not more than 75, when tested in accordance with the "Steiner Tunnel Test" prescribed by the American Society for Testing and Materials (ASTM–E84–68—Surface Burning Characteristics of Building Materials), or a flame propagation index of less than 4.0 when tested in accordance with the "Underwriters' Laboratories Chamber Test" (UL 992—Chamber Test Method for the Flame Propagation Classification of Flooring and Floor Covering Materials).

(4) Flame spread rating of carpet and carpet assemblies and other floor coverings installed in other than inpatient areas meets the standards promulgated under the Flammable Fabrics Act (DOC FF 1–70 and DOC FF 2–70), provided that these areas are separated from inpatient care areas by fire resistive construction or suitable smokestop partitions that are approved by State or local fire authorities. Floor coverings in areas which are not so separated from inpatient areas shall meet the ASTM–E84–68 or UL 992 requirements contained in subparagraph (3) of this paragraph.

(5) Fire and smoke alarm systems providing complete coverage of the building are installed and inspected regularly. Fire extinguishers are conveniently located on each floor. Fire regulations are prominently posted and carefully observed.

(6) Corridors are equipped with firmly secured handrails on each side.

(7) Unless the facility is of 2-hour fire resistive construction, blind and nonambulatory or physically handicapped persons are not housed above the street level floor.

(8) Reports of periodic inspections of the structure by the fire control authority having jurisdiction in the area are on file in the facility.

(9) The building is maintained in good repair and kept free of hazards such as those created by any damaged or defective parts of the building.

(10) No occupancies or activities undesirable to the health and safety of patients are located in the building or buildings of the extended care facility.

(11) Safety precautions in the handling and storage of oxygen shall include:

(i) Shockproof and sparkproof equipment;

(ii) Posted safety regulations; and

(iii) All other applicable safety provisions required by the current National Fire Code (NFPA No. 56).

* * * * *

[F.R. Doc. 70–11555; Filed, Sept. 1, 1970; 8:46 a.m.]

DEPARTMENT OF TRANSPORTATION

Federal Aviation Administration

[14 CFR Part 71]

[Airspace Docket No. 70–EA–64]

TRANSITION AREA

Proposed Designation

The Federal Aviation Administration is considering amending § 71.181 of Part 71 of the Federal Aviation Regulations so as to designate a Barnesville, Ohio, transition area.

The VOR instrument approach procedure for Bradfield Airport, Barnesville, Ohio, requires designation of a 700-foot transition area to provide airspace protection for aircraft executing the instrument approach procedure.

Interested persons may submit such written data or views as they may desire. Communications should be submitted in triplicate to the Director, Eastern Region, Attention: Chief, Air Traffic Division, Department of Transportation, Federal Aviation Administration, Federal Building, John F. Kennedy International Airport, Jamaica, N.Y. 11430. All communications received within 30 days after publication in the FEDERAL REGISTER will be considered before action is taken on the proposed amendment. No hearing is contemplated at this time, but arrangements may be made for informal conferences with Federal Aviation Administration officials by contacting the Chief, Airspace and Standards Branch, Eastern Region. Any data or views presented during such conferences must also be submitted in writing in accordance with this notice in order to become part of the record for consideration. The proposal contained in this notice may be changed in the light of comments received.

The official docket will be available for examination by interested persons at the Office of Regional Counsel, Federal Aviation Administration, Federal Building, John F. Kennedy International Airport, Jamaica, N.Y.

The Federal Aviation Administration, having completed a review of the airspace requirements for the terminal area of Barnesville, Ohio, proposes the air space action hereinafter set forth:

1. Amend § 71.181 of Part 71 of the Federal Aviation Regulations so as to designate a Barnesville, Ohio, transition area described as follows:

BARNESVILLE, OHIO

That airspace extending upward from 700 feet above the surface within a 7-mile radius of the center, 40°00'10" N., 81°11'30" W., of the Bradfield Airport, Barnesville, Ohio.

This amendment is proposed under section 307(a) of the Federal Aviation Act of 1958 (72 Stat. 749; 49 U.S.C. 1348) and section 6(c) of the Department of Transportation Act (49 U.S.C. 1655(c)).

Issued in Jamaica, N.Y., on August 19, 1970.

WAYNE HENDERSHOT,
Acting Director, Eastern Region.

[F.R. Doc. 70–11547; Filed, Sept. 1, 1970; 8:46 a.m.]

[14 CFR Part 71]

[Airspace Docket No. 70–EA–66]

TRANSITION AREA

Proposed Designation

The Federal Aviation Administration is considering amending § 71.181 of Part 71 of the Federal Aviation Regulations so as to designate a Connellsville, Pa., transition area.

The NDB (ADF) RWY 5 instrument approach procedure established for Connellsville Airport, Connellsville, Pa., requires designation of a 700-foot transition area to provide controlled airspace protection for aircraft executing the instrument approach procedure.

Interested persons may submit such written data or views as they may desire. Communications should be submitted in triplicate to the Director, Eastern Region, Attention: Chief, Air Traffic Division, Department of Transportation, Federal Aviation Administration, Federal Building, John F. Kennedy International Airport, Jamaica, N.Y. 11430. All communications received within 30 days after publication in the FEDERAL REGISTER will be considered before action is taken on the proposed amendment. No hearing is contemplated at this time, but arrangements may be made for informal conferences with Federal Aviation Administration officials by contacting the Chief, Airspace and Standards Branch, Eastern Region. Any data or views presented during such conferences must also be submitted in writing in accordance with this notice in order to become part of the record for consideration. The proposal contained in this notice may be changed in the light of comments received.

The official docket will be available for examination by interested persons at the Office of Regional Counsel, Federal Aviation Administration, Federal Building, John F. Kennedy International Airport, Jamaica, N.Y.

The Federal Aviation Administration, having completed a review of the airspace requirements for the terminal area of Connellsville, Pa., proposes the airspace action hereinafter set forth:

1. Amend § 71.181 of Part 71 of the Federal Aviation Regulations so as to designate a Connellsville, Pa., transition area described as follows:

CONNELLSVILLE, PA.

That airspace extending upward from 700 feet above the surface within a 5.5-mile radius of the center 39°57'35" N., 79°39'25" W. of Connellsville Airport and within 9.5 miles northwest and 4.5 miles southeast of the 230° bearing from the Connellsville, Pa. RBN 39°57'37" N., 79°39'16" W., extending from the RBN to 19.5 miles southwest of the RBN, excluding the portion that coincides with the Morgantown, W. Va. transition area.

This amendment is proposed under section 307(a) of the Federal Aviation Act of 1958 (72 Stat. 749; 49 U.S.C. 1348) and section 6(c) of the Department of Transportation Act (49 U.S.C. 1655(c)).

Issued in Jamaica, N.Y., on August 19, 1970.

WAYNE HENDERSHOT,
Acting Director, Eastern Region.

[F.R. Doc. 70-11548; Filed, Sept. 1, 1970; 8:46 a.m.]

[14 CFR Part 71]

[Airspace Docket No. 70-EA-68]

TRANSITION AREA

Proposed Designation

The Federal Aviation Administration is considering amending § 71.181 of Part 71 of the Federal Aviation Regulations so as to designate a Titusville, Pa., transition area.

The new VOR-1 instrument approach procedure developed for Titusville Airport, Titusville, Pa., requires designation of a 700-foot floor transition area to provide controlled airspace protection for aircraft executing the instrument approach procedure.

Interested persons may submit such written data or views as they may desire. Communications should be submitted in triplicate to the Director, Eastern Region, Attention: Chief, Air Traffic Division, Department of Transportation, Federal Aviation Administration, Federal Building, John F. Kennedy International Airport, Jamaica, N.Y. 11430. All communications received within 30 days after publication in the FEDERAL REGISTER will be considered before action is taken on the proposed amendment. No hearing is contemplated at this time, but arrangements may be made for informal conferences with Federal Aviation Administration officials by contacting the Chief, Airspace and Standards Branch, Eastern Region. Any data or views presented during such conferences must also be submitted in writing in accordance with this notice in order to become part of the record for consideration. The proposal contained in this notice may be changed in the light of comments received.

The official docket will be available for examination by interested persons at the Office of Regional Counsel, Federal Aviation Administration, Federal Building, John F. Kennedy International Airport, Jamaica, N.Y.

The Federal Aviation Administration, having completed a review of the airspace requirements for the terminal area of Titusville, Pa., proposes the airspace action hereinafter set forth:

1. Amend § 71.181 of Part 71 of the Federal Aviation Regulations so as to designate a Titusville, Pa., transition area described as follows:

TITUSVILLE, PA.

That airspace extending upward from 700 feet above the surface with a 7-mile radius of the center 41°36'45" N., 79°44'45" W. of Titusville Airport, excluding the portion that coincides with the Franklin, Pa., transition area.

This amendment is proposed under section 307(a) of the Federal Aviation Act of 1958 (72 Stat. 749; 49 U.S.C. 1348) and section 6(c) of the Department of Transportation Act (49 U.S.C. 1655(c)).

Issued in Jamaica, N.Y., on August 19, 1970.

WAYNE HENDERSHOT,
Acting Director, Eastern Region.

[F.R. Doc. 70-11549; Filed, Sept. 1, 1970; 8:46 a.m.]

FEDERAL COMMUNICATIONS COMMISSION

[47 CFR Part 73]

[Docket No. 18882]

TELEVISION BROADCAST STATIONS

Order Further Extending Time for Filing Comments and Reply Comments

1. This proceeding was begun by notice of proposed rule making (FCC 70-638) adopted June 17, 1970, released June 19, 1970, and published in the FEDERAL REGISTER on June 25, 1970 (35 F.R. 10375). The dates for filing comments and reply comments are presently August 10 and August 20, 1970, respectively.

2. On August 20, 1970, Vue-Metrics, Inc. (Vue-Metrics), filed a request to extend the time for filing comments to September 18, 1970, and reply comments to September 28, 1970. Vue-Metrics states that the additional time is necessary in order for it to furnish the New Jersey Public Broadcasting Authority with additional information requested in their recent meeting on its alternative plan for the assignment of a TV channel other than Channel 23 to Camden, N.J., and for the Authority to take a position on the proposal. Counsel for the New Jersey Public Broadcasting Authority states that it has no objection to a grant of this petition.

3. We are of the view that the additional time requested is warranted and would serve the public interest. *Accordingly, it is ordered,* That the time for filing comments and reply comments in Docket No. 18882 is extended to and including September 18, 1970, and September 28, 1970, respectively.

4. This action is taken pursuant to authority found in sections 4(i), 5(d)(1), and 303(r) of the Communications Act of 1934, as amended, and § 0.281(d)(8) of the Commission's rules.

Adopted: August 24, 1970.

Released: August 25, 1970.

[SEAL] GEORGE S. SMITH,
Chief, Broadcast Bureau.

[F.R. Doc. 70-11577; Filed, Sept. 1, 1970; 8:48 a.m.]

INTERSTATE COMMERCE COMMISSION

[49 CFR Part 1048]

[Ex Parte No. MC-7]

WASHINGTON, D.C., COMMERCIAL ZONE

Proposed Redefinition

AUGUST 28, 1970.

Petitioner: Prince George's County, Md. Petitioner's representative: Francis J. Aluisi, Chairman, Prince George's County Commissioners, Courthouse, Upper Marlboro, Md. 20870.

By petition filed August 13, 1970, petitioner requests the Commission to institute a proceeding for the purpose of specifically defining the limits of the zone adjacent to and commercially a part of Washington, D.C., which are now prescribed in Washington, D.C., Commercial Zone, 111 M.C.C. 400 (49 CFR 1048.4) so as to include therein all of Prince George's County, Md. As pertinent herein, the present zone limits are as follows: Beginning at Colesville, Md., thence southeasterly along Beltsville Road to its junction with Powder Mill Road (Maryland Highway 212), thence easterly over Powder Mill Road to its junction with Montgomery Road, thence northeasterly along Montgomery Road, approximately 0.2 mile, to its junction with an unnumbered highway extending northeasterly to the north of Ammendale Normal Institute, thence along such unnumbered highway for a distance of about 2.2 miles to its junction somewhat north of Virginia Manor, Md., with an unnumbered highway extending easterly through Muirkirk, Md., thence along such unnumbered highway through Muirkirk to its junction, approximately 1.8 miles east of the Baltimore and Ohio Railroad, with an unnumbered highway, thence southwesterly along such unnumbered highway for a distance of about 0.5 mile to its junction with an unnumbered highway, thence southeasterly along such unnumbered highway through Springfield and Hillmeade, Md., to its junction with Defense Highway (U.S. Highway 50), thence southwesterly along Defense Highway approximately 0.8 mile to its junction with Enterprise Road (Maryland Highway 556), thence southerly over Enterprise Road to its junction with Central Avenue (Maryland Highway 214), thence westerly over Central Avenue about 0.5 mile to its crossing of Western Branch, thence southerly down the course of Western Branch to Maryland Highway 202, thence westerly approximately 0.3 mile along Maryland Highway 202 to its junction with White House Road, thence southwesterly along White House Road to its junction with Maryland Highway 221, thence southeasterly along Maryland Highway 221 to its junction with Maryland Highway 4, thence westerly along Maryland Highway 4 to the boundary of Andrews Air Force Base, thence south and west along said boundary to Brandywine Road (Maryland Highway 5), thence northwesterly along Maryland Highway 5 to its junction with Maryland Highway 337, thence southwesterly along Maryland Highway 337 to its junction with Maryland Highway 224, thence southerly along Maryland Highway 224 to a point opposite the mouth of Broad Creek, thence due west across the Potomac River to the west bank thereof.

Specifically, the instant petition requests redefinition of the Washington, D.C., commercial zone to include all of the area which is presently within the zone, and, in addition, an area extending from the present zone limits as follows: Beginning at the Montgomery County and Prince Georges County line, at its intersection with Beltsville Road, a point within the present zone, thence northeasterly, easterly, southeasterly, southerly, and westerly along the Prince Georges County line to its interesection with the Potomac River, thence northerly along the Potomac River to its intersection with the present zone limits near Broad Creek, and thence along the present zone limits to the point of beginning.

No oral hearing is contemplated at this time, but anyone wishing to make representations in favor of, or against, the above-proposed redefinition of the limits of the Washington, D.C., commercial zone, may do so by the submission of written data, views, or arguments. An original and seven copies of such data, views, or arguments shall be filed with the Commission on or before October 30, 1970. Each such statement shall include a statement of position with respect to the proposed revision, and a copy thereof should be served upon petitioner's representative.

Notice to the general public of the matter herein under consideration will be given by depositing a copy of this notice in the Office of the Secretary of the Commission for public inspection and by filing a copy thereof with the Director, Office of the Federal Register.

By the Commission.

[SEAL] JOSEPH M. HARRINGTON,
Acting Secretary.

[F.R. Doc. 70-11588; Filed, Sept. 1, 1970; 8:49 a.m.]

Notices

DEPARTMENT OF THE TREASURY

Internal Revenue Service

WILLIAM VALSON FASSLER

Notice of Granting of Relief

Notice is hereby given that William Valson Fassler, Jefferson, Ark. 72079, has applied for relief from disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms incurred by reason of his conviction on April 17, 1935, in the U.S. District Court, Little Rock, Ark., of a crime punishable by imprisonment for a term exceeding 1 year. Unless relief is granted, it will be unlawful for Mr. Fassler because of such conviction, to ship, transport or receive in interstate or foreign commerce any firearm or ammunition, and he would be ineligible for a license under chapter 44, title 18, United States Code as a firearms or ammunition importer, manufacturer, dealer or collector. In addition, under title VII of the Omnibus Crime Control and Safe Streets Act of 1968, as amended (82 Stat. 236; 18 U.S.C., Appendix), because of such conviction, it would be unlawful for Mr. Fassler to receive, possess, or transport in commerce or affecting commerce, any firearm.

Notice is hereby given that I have considered Mr. Fassler's application and:

(1) I have found that the conviction was made upon a charge which did not involve the use of a firearm or other weapon or a violation of chapter 44, title 18, United States Code, or of the National Firearms Act; and

(2) It has been established to my satisfaction that the circumstances regarding the conviction and the applicant's record and reputation are such that the applicant will not be likely to act in a manner dangerous to public safety, and that the granting of the relief would not be contrary to the public interest.

Therefore, pursuant to the authority vested in the Secretary of the Treasury by section 925(c), title 18, United States Code and delegated to me by 26 CFR 178.144: *It is ordered*, That William Valson Fassler be, and he hereby is, granted relief from any and all disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms and incurred by reason of the conviction hereinabove described.

Signed at Washington, D.C., this 26th day of August 1970.

[SEAL] RANDOLPH W. THROWER,
Commissioner of Internal Revenue.

[F.R. Doc. 70-11589; Filed, Sept. 1, 1970; 8:49 a.m.]

ROBERT GLYDE FLIPPEN

Notice of Granting of Relief

Notice is hereby given that Robert Glyde Flippen, Palmer Springs, Va., has applied for relief from disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms incurred by reason of his convictions on October 22, 1932, March 26, 1935, and June 7, 1935, in the U.S. District Court for the Eastern District of North Carolina of crimes punishable by imprisonment for a term exceeding 1 year. Unless relief is granted, it will be unlawful for Robert G. Flippen because of such convictions, to ship, transport or receive in interstate or foreign commerce any firearm or ammunition, and he would be ineligible for a license under chapter 44, title 18, United States Code as a firearms or ammunition importer, manufacturer, dealer or collector. In addition, under title VII of the Omnibus Crime Control and Safe Streets Act of 1968, as amended (82 Stat. 236; 18 U.S.C., Appendix), because of such convictions, it would be unlawful for Robert G. Flippen to receive, possess, or transport in commerce or affecting commerce, any firearm.

Notice is hereby given that I have considered Robert G. Flippen's application and:

(1) I have found that the convictions were upon charges which did not involve the use of a firearm or other weapon or a violation of chapter 44, title 18, United States Code, or of the National Firearms Act; and

(2) It has been established to my satisfaction that the circumstances regarding the convictions and the applicant's record and reputation are such that the applicant will not be likely to act in a manner dangerous to public safety, and that the granting of the relief would not be contrary to the public interest.

Therefore, pursuant to the authority vested in the Secretary of the Treasury by section 925(c), title 18, United States Code and delegated to me by 26 CFR 178.144: *It is ordered*, That Robert G. Flippen be, and he hereby is, granted relief from any and all disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms and incurred by reason of the convictions hereinabove described.

Signed at Washington, D.C., this 26th day of August 1970.

[SEAL] RANDOLPH W. THROWER,
Commissioner of Internal Revenue.

[F.R. Doc. 70-11590; Filed, Sept. 1, 1970; 8:49 a.m.]

LeROY MELVIN JOHNSON

Notice of Granting of Relief

Notice is hereby given that LeRoy Melvin Johnson, 10663 Washington Boulevard NE., Blaine, Minn. 55433, has applied for relief from disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms incurred by reason of his conviction on or about March 30, 1961, in the District Court, Fourth Judicial District, Hennepin, Minn., of a crime punishable by imprisonment for a term exceeding 1 year. Unless relief is granted it will be unlawful for LeRoy Melvin Johnson because of such conviction, to ship, transport or receive in interstate or foreign commerce any firearm or ammunition, and he would be ineligible for a license under chapter 44, title 18, United States Code as a firearms or ammunition importer, manufacturer, dealer or collector. In addition, under title VII of the Omnibus Crime Control and Safe Streets Act of 1968, as amended (82 Stat. 236; 18 U.S.C., Appendix), because of such conviction, it would be unlawful for Mr. Johnson to receive, possess, or transport in commerce or affecting commerce, any firearm.

Notice is hereby given that I have considered LeRoy Melvin Johnson's application and:

(1) I have found that the conviction was made upon a charge which did not involve the use of a firearm or other weapon or a violation of chapter 44, title 18, United States Code, or of the National Firearms Act; and

(2) It has been established to my satisfaction that the circumstances regarding the conviction and the applicant's record and reputation are such that the applicant will not be likely to act in a manner dangerous to public safety, and that the granting of the relief would not be contrary to the public interest.

Therefore, pursuant to the authority vested in the Secretary of the Treasury by section 925(c), title 18, United States Code and delegated to me by 26 CFR 178.144: *It is ordered*, That LeRoy Melvin Johnson be, and he hereby is, granted relief from any and all disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms and incurred by reason of the conviction hereinabove described.

Signed at Washington, D.C., this 26th day of August 1970.

[SEAL] RANDOLPH W. THROWER,
Commissioner of Internal Revenue.

[F.R. Doc. 70-11591; Filed, Sept. 1, 1970; 8:49 a.m.]

SERGIO MAGI

Notice of Granting of Relief

Notice is hereby given that Sergio Magi, 1836 West Eighth Street, Brooklyn, N.Y. 11223, has applied for relief from disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms incurred by reason of his conviction on August 30, 1944, in the U.S. District Court for the Eastern District of New York, of a crime punishable by imprisonment for a term exceeding 1 year. Unless relief is granted, it will be unlawful for Sergio Magi because of such conviction, to ship, transport or receive in interstate or foreign commerce any firearm or ammunition, and he would be ineligible for a license under chapter 44, title 18, United States Code as a firearms or ammunition importer, manufacturer, dealer or collector. In addition, under title VII of the Omnibus Crime Control and Safe Streets Act of 1968, as amended (82 Stat. 236; 18 U.S.C., Appendix), because of such conviction, it would be unlawful for Mr. Magi to receive, possess, or transport in commerce or affecting commerce, any firearm.

Notice is hereby given that I have considered Sergio Magi's application and:

(1) I have found that the conviction was made upon a charge which did not involve the use of a firearm or other weapon or a violation of chapter 44, title 18, United States Code, or of the National Firearms Act; and

(2) It has been established to my satisfaction that the circumstances regarding the conviction and the applicant's record and reputation are such that the applicant will not be likely to act in a manner dangerous to public safety, and that the granting of the relief would not be contrary to the public interest.

Therefore, pursuant to the authority vested in the Secretary of the Treasury by section 925(c), title 18, United States Code and delegated to me by 26 CFR 178.144: *It is ordered,* That Sergio Magi be, and he hereby is, granted relief from any and all disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms and incurred by reason of the conviction hereinabove described.

Signed at Washington, D.C., this 20th day of August 1970.

[SEAL] RANDOLPH W. THROWER,
Commissioner of Internal Revenue.

[F.R. Doc. 70-11592; Filed, Sept. 1, 1970; 8:49 a.m.]

HARRY MANOOGIAN

Notice of Granting of Relief

Notice is hereby given that Harry Manoogian, 6763 Edinborough Drive, Birmingham, Mich. 48010, has applied for relief from disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms incurred by reason of his conviction on March 3, 1954, in the Recorder's Court of the City of Detroit, Mich., of a crime punishable by imprisonment for a term exceeding 1 year. Unless relief is granted, it will be unlawful for Harry Manoogian because of such conviction, to ship, transport or receive in interstate or foreign commerce any firearm or ammunition, and he would be ineligible for a license under chapter 44, title 18, United States Code as a firearms or ammunition importer, manufacturer, dealer or collector. In addition, under title VII of the Omnibus Crime Control and Safe Streets Act of 1968, as amended (82 Stat. 236; 18 U.S.C., Appendix), because of such conviction, it would be unlawful for Mr. Manoogian to receive, possess, or transport in commerce or affecting commerce, any firearm.

Notice is hereby given that I have considered Harry Manoogian's application and:

(1) I have found that the conviction was made upon a charge which did not involve the use of a firearm or other weapon or a violation of chapter 44, title 18, United States Code, or of the National Firearms Act; and

(2) It has been established to my satisfaction that the circumstances regarding the conviction and the applicant's record and reputation are such that the applicant will not be likely to act in a manner dangerous to public safety, and that the granting of the relief would not be contrary to the public interest.

Therefore, pursuant to the authority vested in the Secretary of the Treasury by section 925(c), title 18, United States Code and delegated to me by 26 CFR 178.144: *It is ordered,* That Harry Manoogian be, and he hereby is, granted relief from any and all disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms and incurred by reason of the conviction hereinabove described.

Signed at Washington, D.C., this 19th day of August 1970.

[SEAL] RANDOLPH W. THROWER,
Commissioner of Internal Revenue.

[F.R. Doc. 70-11593; Filed, Sept. 1, 1970; 8:49 a.m.]

HENRY McELROY

Notice of Granting of Relief

Notice is hereby given that Henry McElroy, 8517 Asbury Park, Detroit, Mich. 48228, has applied for relief from disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms incurred by reason of his conviction on May 13, 1946, in the Recorder's Court, Detroit, Mich., of a crime punishable by imprisonment for a term exceeding 1 year. Unless relief is granted, it will be unlawful for Mr. McElroy because of such conviction, to ship, transport or receive in interstate or foreign commerce any firearm or ammunition, and he would be ineligible for a license under chapter 44, title 18, United States Code as a firearms or ammunition importer, manufacturer, dealer or collector. In addition, under title VII of the Omnibus Crime Control and Safe Streets Act of 1968, as amended (82 Stat. 236; 18 U.S.C., Appendix), because of such conviction, it would be unlawful for Mr. McElroy to receive, possess, or transport in commerce or affecting commerce, any firearm.

Notice is hereby given that I have considered Henry McElroy's application and:

(1) I have found that the conviction was made upon a charge which did not involve the use of a firearm or other weapon or a violation of chapter 44, title 18, United States Code, or of the National Firearms Act; and

(2) It has been established to my satisfaction that the circumstances regarding the conviction and the applicant's record and reputation are such that the applicant will not be likely to act in a manner dangerous to public safety, and that the granting of the relief would not be contrary to the public interest.

Therefore, pursuant to the authority vested in the Secretary of the Treasury by section 925(c), title 18, United States Code and delegated to me by 26 CFR 178.144: *It is ordered,* That Henry McElroy be, and he hereby is, granted relief from any and all disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms and incurred by reason of the conviction hereinabove described.

Signed at Washington, D.C., this 19th day of August 1970.

[SEAL] RANDOLPH W. THROWER,
Commissioner of Internal Revenue.

[F.R. Doc. 70-11594; Filed, Sept. 1, 1970; 8:49 a.m.]

JOHN ROBERT NELSON

Notice of Granting of Relief

Notice is hereby given that Mr. John Robert Nelson, 1839 Buchanan SW., Grand Rapids, Mich. 49507, has applied for relief from disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms incurred by reason of his conviction on November 22, 1949, in the Circuit Court for the county of Kent, State of Mich., of a crime punishable by imprisonment for a term exceeding 1 year. Unless relief is granted, it will be unlawful for Mr. Nelson because of such conviction, to ship, transport or receive in interstate or foreign commerce any firearm or ammunition, and he would be ineligible for a license under chapter 44, title 18, United States Code as a firearms or ammunition importer, manufacturer, dealer or collector. In addition, under title VII of the Omnibus Crime Control and Safe Streets Act of 1968, as amended (82 Stat. 236; 18 U.S.C., Appendix), because of such conviction, it would be unlawful for Mr. Nelson to receive, possess, or transport in commerce or affecting commerce, any firearm.

Notice is hereby given that I have considered Mr. John Robert Nelson's application and:

(1) I have found that the conviction was made upon a charge which did not involve the use of a firearm or other weapon or a violation of chapter 44, title 18, United States Code, or of the National Firearms Act; and

(2) It has been established to my satisfaction that the circumstances regarding the conviction and the applicant's record and reputation are such that the applicant will not be likely to act in a manner dangerous to public safety, and that the granting of the relief would not be contrary to the public interest.

Therefore, pursuant to the authority vested in the Secretary of the Treasury by section 925(c), title 18, United States Code and delegated to me by 26 CFR 178.144; *It is ordered*, That Mr. John Robert Nelson be, and he hereby is, granted relief from any and all disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms and incurred by reason of the conviction hereinabove described.

Signed at Washington, D.C., this 19th day of August 1970.

[SEAL] RANDOLPH W. THROWER,
Commissioner of Internal Revenue.

[F.R. Doc. 70-11595; Filed, Sept. 1, 1970; 8:49 a.m.]

JOSEPH MANUEL VIEIRA

Notice of Granting of Relief

Notice is hereby given that Joseph Manuel Vieira, Box 28, Dairy, Oreg. 97625, has applied for relief from disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms incurred by reason of his conviction on or about January 5, 1968, in the Klamath County Circuit Court, Klamath Falls, Oreg., of a crime punishable by imprisonment for a term exceeding 1 year. Unless relief is granted, it will be unlawful for Mr. Vieira, because of such conviction, to ship, transport or receive in interstate or foreign commerce any firearm or ammunition, and he would be ineligible for a license under chapter 44, title 18, United State Code as a firearms or ammunition importer, manufacturer, dealer or collector. In addition, under title VII of the Omnibus Crime Control and Safe Streets Act of 1968, as amended (82 Stat. 236; 18 U.S.C., Appendix), because of such conviction, it would be unlawful for Mr. Vieira to receive, possess, or transport in commerce or affecting commerce, any firearm.

Notice is hereby given that I have considered Joseph Manuel Vieira's application and:

(1) I have found that the conviction was made upon a charge which did not involve the use of a firearm or other weapon or a violation of chapter 44, title 18, United States Code, or of the National Firearms Act; and

(2) It has been established to my satisfaction that the circumstances regarding the conviction and the applicant's record and reputation are such that the applicant will not be likely to act in a manner dangerous to public safety, and that the granting of the relief would not be contrary to the public interest.

Therefore, pursuant to the authority vested in the Secretary of the Treasury by section 925(c), title 18, United States Code and delegated to me by 26 CFR 178.144: *It is ordered*, That Mr. Vieira be, and he hereby is, granted relief from any and all disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms and incurred by reason of the conviction hereinabove described.

Signed at Washington, D.C., this 26th day of August 1970.

[SEAL] RANDOLPH W. THROWER,
Commissioner of Internal Revenue.

[F.R Doc. 70-11597; Filed, Sept. 1, 1970; 8:50 a.m.]

MARVIN GLEN WERTJES

Notice of Granting of Relief

Notice is hereby given that Marvin Glen Wertjes, 913 Bluff Street, Cedar Falls, Iowa 50613, has applied for relief from disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms incurred by reason of his conviction on November 30, 1962, in the District Court, Waterloo, Iowa, of a crime punishable by imprisonment for a term exceeding 1 year. Unless relief is granted, it will be unlawful for Marvin Glen Wertjes, because of such conviction, to ship, transport or receive in interstate or foreign commerce any firearm or ammunition, and he would be ineligible for a license under chapter 44, title 18, United States Code as a firearms or ammunition importer, manufacturer, dealer or collector. In addition, under Title VII of the Omnibus Crime Control and Safe Streets Act of 1968, as amended (82 Stat. 236; 18 U.S.C., Appendix), because of such conviction, it would be unlawful for Marvin Glen Wertjes to receive, possess, or transport in commerce or affecting commerce, any firearm.

Notice is hereby given that I have considered Marvin Glen Wertjes' application and:

(1) I have found that the conviction was made upon a charge which did not involve the use of a firearm or other weapon or a violation of chapter 44, title 18, United States Code, or of the National Firearms Act; and

(2) It has been established to my satisfaction that the circumstances regarding the conviction and the applicant's record and reputation are such that the applicant will not be likely to act in a manner dangerous to public safety, and that the granting of the relief would not be contrary to the public interest.

Therefore, pursuant to the authority vested in the Secretary of the Treasury by section 925(c), title 18, United States Code and delegated to me by 26 CFR 178.144: *It is ordered*, That Marvin Glen Wertjes be, and he hereby is, granted relief from any and all disabilities imposed by Federal laws with respect to the acquisition, receipt, transfer, shipment, or possession of firearms and incurred by reason of the conviction hereinabove described.

Signed at Washington, D.C., this 24th day of August 1970.

[SEAL] RANDOLPH W. THROWER,
Commissioner of Internal Revenue.

[F.R. Doc. 70-11596; Filed, Sept. 1, 1970; 8:50 a.m.]

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

DISTRICT MANAGERS, NEVADA

Delegation of Authority

AUGUST 25, 1970.

1. Designating Acting Area Managers and Acting Chiefs, Divisions of Resource Management, Operations, and Administration in the Nevada District Offices. The authorities delegated to the Area Managers, Chiefs, Divisions of Resource Management, Operations, and Administration in the District Offices may in the absence of the designated Area Manager, Chiefs, Divisions of Resource Management, Operations, or Administration be performed by an Acting Area Manager or Acting Chiefs, Divisions of Resource Management, Operations, or Administration. Such "acting" officials shall be designated by written orders of the District Manager.

2. Each designated employee who serves in such capacity shall, when serving, sign documents and other papers as "Acting (name of position)." Each such acting official shall maintain a document to be kept in the district office showing the date and hour of commencement and termination of each period of such service as "Acting (name of position)."

NOLAN F. KEIL,
State Director.

[F.R. Doc. 70-11544; Filed, Sept. 1, 1970; 8:45 a.m.]

[Wyoming-25470]

WYOMING

Order Providing for Opening of Public Lands

AUGUST 26, 1970.

1. In exchanges of lands made under the provisions of section 8 of the Act of June 28, 1934 (48 Stat. 1269) as amended (43 U.S.C. 315g), the following described lands have been reconveyed to the United States:

SIXTH PRINCIPAL MERIDIAN, WYOMING

GROUP 1

T. 35 N., R. 80 W.,
Sec. 32, NE¼SE¼.

T. 34 N., R. 109 W.,
Sec. 15, SE¼SE¼;
Sec. 16, E½ and NE¼NW¼;
Sec. 21, NE¼;
Sec. 22, N½NE¼, SW¼NE¼, and E½NW¼.
T. 35 N., R. 109 W.,
Sec. 33, E½SE¼.

Those portions of the W½SW¼ sec. 9, W½NW¼, SE¼NW¼, and E½SW¼ sec. 16, T. 34 N., R. 109 W., described as follows: From the west one-fourth section corner of Sec. 9, proceed S. 89°45′ E. along the latitudinal centerline of said sec. 9, a distance of 772 feet to the point of beginning; thence S. 6°30′ E., a distance of 3,918 feet; thence S. 19°00′ E., a distance of 1,484 feet; thence S. 8°47′ E., a distance of 2,660 feet, more or less, to a point on the south boundary of sec. 16; thence S. 89°50′ E., along the south boundary of said sec. 16, a distance of 545 feet, more or less, to the south one-fourth section corner of sec. 16; thence N. 0°03′ W., a distance of 3,960 feet, more or less, to the point for the center-north one-sixteenth section corner of sec. 16; thence N. 89°48′ W., a distance of 1,322 feet, more or less, to the point for the northwest one-sixteenth section corner of sec. 16; thence N. 0°03′ W., a distance of 3,960 feet, more or less, to the point for the center-west one-sixteenth section corner of sec. 9; thence N. 89°45′ W., along the latitudinal centerline of sec. 9, a distance of 549 feet, more or less, to the point of beginning.

GROUP II

T. 33 N., R. 110 W.,
Sec. 15, S½SE¼;
Sec. 22, NW¼NE¼.
T. 30 N., R. 111 W.,
Sec. 36.
T. 33 N., R. 111 W.,
Sec. 16.
T. 33 N., R. 112 W.,
Sec. 1, S½SW¼;
Sec. 2, SE¼SE¼;
Sec. 11, NE¼, SE¼NW¼, and SW¼;
Sec. 12, N½NW¼;
Sec. 14, NW¼NW¼;
Sec. 15, NE¼NE¼.

GROUP III

T. 28 N., R. 111 W.,
Sec. 36.
T. 27 N., R. 112 W.,
Sec. 36, N½ and SW¼.

The areas described aggregate 4,207.10 acres.

2. The lands are located in Natrona and Sublette Counties. The topography ranges from nearly level to rough and the lands have value for watershed, grazing, wildlife, and recreation.

3. The mineral rights in the lands were not exchanged. Therefore, the mineral status of the lands is not affected by this order.

4. Subject to valid existing rights, the provisions of existing withdrawals, and the requirements of applicable law, the lands will at 10 a.m. on September 28, 1970, be open to application, petition, and selection under the public land laws with the exception that all the lands in Group II are subject to multiple use classification W–19140, and all the lands in Group III are subject to multiple-use classification W–12668, and are not open to application under the agricultural land laws (43 U.S.C. Part 7 and 9; 25 U.S.C. 334), or to public sale under section 2455 of the Revised Statutes (43 U.S.C. 1171). The SW¼SE¼ sec. 15, T. 33 N., R. 110 W., is further segregated from appropriation under the general mining laws. All valid applications received at or prior to 10 a.m. on September 28, 1970 shall be considered as simultaneously filed at that time. Those received thereafter shall be considered in the order of filing.

5. Inquiries concerning the lands should be addressed to the Bureau of Land Management, Post Office Box 1828, Cheyenne, Wyo. 82001.

ROBERT E. WILBER,
Acting State Director.

[F.R. Doc. 70–11571; Filed, Sept. 1, 1970; 8:48 a.m.]

DEPARTMENT OF AGRICULTURE

Consumer and Marketing Service

POULTRY AND POULTRY PRODUCTS

Notice of Intended Designation of States

Notice of intended designation of Arkansas, Colorado, Georgia, Idaho, Maine, Michigan, Minnesota, Montana, New Jersey, North Dakota, Oregon, South Dakota, Utah, and West Virginia under the Poultry Products Inspection Act.

Subsection 5(c) of the Poultry Products Inspection Act (21 U.S.C. 454(c)) requires the Secretary of Agriculture to designate promptly after August 18, 1970, any State[1] as one in which the requirements of sections 1–4, 6–10, and 12–22 of said Act shall apply to intrastate operations and transactions, and to persons engaged therein, with respect to poultry, poultry products, and other articles subject to the Act, if he determines after consultation with the Governor of the State, or his representative, that the State involved has not developed and activated requirements, at least equal to those under sections 1–4, 6–10, and 12–22, with respect to establishments within the State (except those that would be exempted from Federal inspection under paragraph 5(c)(2) of the Act), at which poultry are slaughtered or poultry products are processed for use as human food, solely for distribution within such State, and the products of such establishments. However, if the Secretary has reason to believe that the State will activate the necessary requirements within an additional year, he may allow the State the additional year in which to activate such requirements.

The Secretary has determined after consultation with the Governors of the States of Arkansas, Colorado, Georgia, Idaho, Maine, Michigan, Minnesota, Montana, New Jersey, North Dakota, Oregon, South Dakota, Utah, and West Virginia that each of such States has not developed and activated the prescribed requirements, and the Secretary does not have reason to believe that any of these States will activate such requirements if the State is allowed an additional year in accordance with the Act. Therefore, notice is hereby given that the Secretary of Agriculture will designate said States under paragraph 5(c) of the Act as soon as necessary arrangements can be made for determining which establishments in these States are eligible for Federal inspection, for providing inspection at the eligible establishments, and for otherwise enforcing the applicable provisions of the Federal Act with respect to intrastate activities in these States when the designation is made and becomes effective. As soon as these arrangements are completed, notice of the designation will be published in the FEDERAL REGISTER. Upon the expiration of 30 days after such publication, the provisions of sections 1–4, 6–10, and 12–22 of the Act shall apply to intrastate operations and transactions and persons engaged therein in said States to the same extent and in the same manner as if such operations and transactions were conducted in or for "commerce" within the meaning of the Act, and any establishment in any of said States which conducts any slaughtering of poultry or processing of poultry products as described above must have Federal Inspection or cease its operations, unless it qualifies for an exemption under paragraph 5(c)(2) or section 15 of the Act.

Therefore, the operator of each such establishment in any of said States who desires to continue such operations after designation of the State becomes effective should immediately communicate with the appropriate Regional Director, as listed below.

Dr. E. M. Christopherson, Director Western Region, Room 822, Appraisers Building, 630 Sansome Street, San Francisco, Calif. 94111.
Dr. Willis H. Irvin, Director Southwestern Region, Room 376, Merchandise Mart Building, 500 South Ervay Street, Dallas, Tex. 75201.
Dr. C. C. Hamilton, Acting Director Northern Region, Room 638, Federal Building and U.S. Courthouse, 316 Robert Street, St. Paul, Minn. 55101.
Dr. L. J. Rafoth, Director North Central Region, Room 514, 226 West Jackson Boulevard, Chicago, Ill. 60606.
Dr. M. J. Hatter, Director Southeastern Region, Room 206, 1795 Peachtree Road NE., Atlanta, Ga. 30309.
Dr. G. Harner, Director Mid-Atlantic Region, Post Office Box 25231, Raleigh, N.C. 27611.
Dr. C. F. Diehl, Director Northeastern Region, Seventh Floor, 1421 Cherry Street, Philadelphia, Pa. 19102.

Done at Washington, D.C., on August 26, 1970.

RICHARD E. LYNG,
Assistant Secretary.

[F.R. Doc. 70–11564; Filed, Sept. 1, 1970; 8:47 a.m.]

[1] As used in section 5(c) of the Act, the term "State" includes the Commonwealth of Puerto Rico and any organized territory of the United States.

DEPARTMENT OF COMMERCE

Bureau of International Commerce

[Case No. 404]

ME-RA-OY MUUNTAJATEHDAS AND JOUKO SATUKANGAS

Order Setting Aside Default and Modifying Denial Order

In the matter of Me-Ra-Oy Muuntajatehdas and Jouko Satukangas, Lonnjotinkatu 32 D, Helsinki 18, Finland, Case No. 404, respondents.

An order denying export privileges dated May 1, 1970, effective May 8, 1970, was issued in the above matter (35 F.R. 7265). Said order was issued after respondents were held in default for failure to answer the charging letter that was served on them. Pursuant to § 388.4(b), the respondents have now applied to set aside the default. They have shown good cause and have submitted evidentiary data in support of the application. The matter was referred to the Compliance Commissioner and he has submitted a recommendation as to the disposition of the application.

I confirm the findings of fact in the order of May 1, 1970. I also find that there were mitigating circumstances in respondents' favor not previously presented. On the basis of such mitigating circumstances, I conclude that it is appropriate to modify the order of May 1, 1970 by restoring respondents' export privileges and placing them on probation until May 8, 1973.

Accordingly, it is hereby ordered that the respondents' export privileges be and hereby are restored conditionally, and the said respondents are placed on probation until May 8, 1973. The conditions of probation are that the said respondents: (1) Shall fully comply with all of the requirements of the Export Administration Act of 1969, and all regulations, licenses, and orders issued thereunder; and (2) shall on request of the Office of Export Control, or a representative of the U.S. Government acting on its behalf, promptly disclose fully the details of their participation in any and all transactions involving U.S.-origin commodities or technical data, including information as to the disposition or intended disposition of such commodities or technical data, and on such request shall also furnish all records and documents relating to such matters.

Upon a finding by the Director, Office of Export Control, or such other official as may be exercising the duties now exercised by him, that said respondents have failed to comply with any of the conditions of probation, said official, with or without prior notice to said respondents, by supplemental order, may revoke the probation of said respondents and deny to him all export privileges for such period as said official may deem appropriate. Such order shall not preclude the Bureau of International Commerce from taking further action for any violation as may be warranted.

This order shall become effective forthwith.

Dated: August 27, 1970.

RAUER H. MEYER,
Director, Office of Export Control.

[F.R. Doc. 70-11565; Filed, Sept. 1, 1970; 8:47 a.m.]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[DESI 9386]

BUSULFAN

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drug:

Myleran Tablets containing busulfan, marketed by Burroughs Wellcome & Co., Inc., Scarsdale Road, Tuckahoe, N.Y. 10707 (NDA 9-386).

The drug is regarded as a new drug (21 U.S.C. 321(p)). Supplemental new-drug applications are required to revise the labeling in and to update previously approved applications providing for such drug. A new-drug application is required from any person marketing such drug without approval.

The Food and Drug Administration is prepared to approve new-drug applications and supplements to previously approved new-drug applications under conditions described in this announcement.

A. *Effectiveness classification.* The Food and Drug Administration has considered the Academy report, as well as other available evidence, and concludes that busulfan is effective in the palliative treatment of chronic myelocytic leukemia.

B. *Form of drug.* Busulfan preparations are in tablet form suitable for oral administration.

C. *Labeling conditions.* 1. The label bears the statement "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for the safe and effective use of the drug and is in accord with the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970. The "Indications" section is as follows:

INDICATIONS

Busulfan is indicated in the palliative treatment of chronic myelocytic leukemia.

D. *Marketing status.* Marketing of the drug may continue under the conditions described in paragraphs E and F of this announcement.

E. *Previously approved applications.* 1. Each holder of a "deemed approved" new-drug application (i.e., an application which became effective on the basis of safety prior to Oct. 10, 1962) for such drug is requested to seek approval of the claims of effectiveness and bring the application into conformance by submitting supplements containing:

a. Revised labeling as needed to conform to the labeling conditions described herein for the drug and complete current container labeling unless recently submitted.

b. Updating information as needed to make the application current in regard to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of the new-drug application form FD-356H to the extent described for abbreviated new-drug applications, § 130.4(f), FEDERAL REGISTER, April 24, 1970 (35 F.R. 6574). (One supplement may contain all the information described in this paragraph.)

2. Such supplements should be submitted within the following time periods after the date of publication of this notice in the FEDERAL REGISTER:

a. 60 days for revised labeling—the supplement should be submitted under the provisions of § 130.9 (d) and (e) of the new drug regulations (21 CFR 130.9) which permit certain changes to be put into effect at the earliest possible time.

b. 60 days for updating information.

3. Marketing of the drug may continue until the supplemental applications submitted in accord with the preceding subparagraphs 1 and 2 are acted upon, provided that within 60 days after the date of this publication, the labeling of the preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described in this announcement.

F. *New applications.* 1. Any other person who distributes or intends to distribute such drug which is intended for the conditions of use for which it has been shown to be effective, as described under A above, should submit an abbreviated new-drug application meeting the conditions specified in § 130.4(f) (1) and (2), published in the FEDERAL REGISTER April 24, 1970 (35 F.R. 6574). Such applications should include proposed labeling which is in accord with the labeling conditions described herein.

2. Distribution of any such preparation currently on the market without an approved new-drug application may be continued provided that:

a. Within 60 days from the date of publication of this announcement in the FEDERAL REGISTER, the labeling of such preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described herein.

b. The manufacturer, packer, or distributor of such drug submits, within 60 days from the date of this publication, a new-drug application to the Food and Drug Administration.

c. The applicant submits within a reasonable time additional information that may be required for the approval of the application as specified in a written communication from the Food and Drug Administration.

d. The application has not been ruled incomplete or unapprovable.

G. *Unapproved use or form of drug.* 1. If the article is labeled or advertised for use in any condition other than those provided for in this announcement, it may be regarded as an unapproved new drug subject to regulatory proceedings until such recommended use is approved

in a new-drug application or is otherwise in accord with this announcement.

2. If the article is proposed for marketing in another form or for a use other than the use provided for in this announcement, appropirate additional information as described in § 130.4 or 130.9 of the regulations (21 CFR 130.4, 130.9) may be required, including results of animal and clinical tests intended to show whether the drug is safe and effective.

A copy of the NAS–NRC report has been furnished to the firm referred to above. Any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with the reference number DESI 9386 and be directed to the attention of the appropriate office listed below and addressed (unless otherwise specified) to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Supplements (identify with NDA number): Office of Marketed Drugs (BD–200), Bureau of Drugs.

Original abbreviated new-drug applications (identify as such): Office of Marketed Drugs (BD–200), Bureau of Drugs.

All other communications regarding this announcement:

Special Assistant for Drug Efficacy Study Implementation (BD–201), Bureau of Drugs.

Requests for NAS–NRC report: Press Relations Office (CE–200), Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: August 20, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70–11542; Filed, Sept. 1, 1970; 8:45 a.m.]

[DESI 2855]

CERTAIN MOUTHWASH AND GARGLE PREPARATIONS

Drugs for Human Use; Drug Efficacy Study Implementation; Extension of Time for Filing Data

The notice published in the FEDERAL REGISTER of August 4, 1970 (35 F.R. 12423), concerning the intention of the Commissioner of Food and Drugs to withdraw approval of listed new-drug applications for specified mouthwash and gargle preparations, provided for the submission of pertinent data on the Commissioner's proposal within 30 days of said publication date.

The Commissioner has received a request to extend such time and; good reason therefor appearing, the time for submitting such data is hereby extended to November 2, 1970.

This action is taken pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 353, 355) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: August 27, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70–11552; Filed, Sept. 1, 1970; 8:46 a.m.]

[DESI 7322]

TETRACYCLINE; OXYTETRACYCLINE; CHLORTETRACYCLINE; DEMETHYLCHLORTETRACYCLINE; AND ROLITETRACYCLINE FOR SYSTEMIC USE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluation reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following antiinfective drugs for oral and parenteral use:

I. Tetracycline for oral administration; marketed as:

1.a. Tetrex Pediatric Drops (NDA 60–049),

b. Tetrex Syrup (NDA 60–049),

c. Bristacycline Capsules (NDA 60–211),

d. Tetracycline Phosphate Complex Capsules (NDA 50–212),

e. Tetrex Capsules (NDA 50–212), and

f. Polycycline for Suspension (NDA 60–032); Bristol Laboratories, Post Office Box 657, Syracuse, N.Y. 13201.

2.a. Tetramed Capsules (NDA 60–103),

b. Tetramed Syrup (NDA 60–117),

c. Tetracycline Hydrochloride Tablets (NDA 60–118),

d. Tetracycline Hydrochloride Capsules (NDA 60–103), and

e. Tetracycline Capsules (NDA 60–103); Continental Vitamin Corp., 150 South Dean Street, Englewood, N.J. 07631.

3. Tetracycline Hydrochloride Capsules; Davis-Edwards Pharmacal Corp., 432 Austin Place, Bronx, N.Y. 10455 (NDA 60–351).

4.a. Tetracycline Hydrochloride Tablets (NDA 90–048),

b. Tetracycline Syrup (NDA 60–275), and

c. Tetracycline Hydrochloride Capsules (NDA 60–059); Ketchum Laboratories, Inc., 800 Hinsdale Road, Brooklyn, N.Y. 11207.

5.a. Achromycin V Pediatric Drops (NDA 50–263),

b. Achromycin for Oral Suspension (NDA 50–269),

c. Achromycin Syrup (NDA 50–263),

d. Achromycin Capsules (NDA 50–278),

e. Achromycin Soluble Tablets (NDA 50–264),

f. Achromycin (Film Coated) Tablets (NDA 50–264),

g. Achromycin V Syrup (NDA 50–263),

h. Achromycin Pediatric Drops (NDA 50–263),

i. Achromycin V Capsules (NDA 60–432),

j. Achromycin V Capsules with Sodium Metaphosphate (NDA 50–278), and

k. Achromycin Spersoids Dispersible Powder (NDA 50–271); Lederle Laboratories Division, American Cyanamid Co., Pearl River, N.Y. 10965.

6.a. Tetracyn (Film Coated) Tablets (NDA 60–077),

b. Tetracycline Hydrochloride Capsules (NDA 60–082),

c. Tetracyn Capsules (NDA 60–082),

d. Tetracyn Syrup (NDA 60–095),

e. Tetracycline Syrup (NDA 60–095), and

f. Tetracyn Pediatric Drops (NDA 60–095); Chas. Pfizer and Co., Inc., 235 East 42d Street, New York, N.Y. 10017.

7.a. Tetracycline Hydrochloride Tablets (NDA 60–422),

b. Premocycline Syrup (NDA 60–423), and

c. Premocycline Aqueous Pediatric Drops (NDA 60–423); Premo Pharmaceutical Laboratories, Inc., 111 Leuning Street, South Hackensack, N.J. 07606.

8.a. Tetrachel Pediatric Drops and Tetracycline Pediatric Drops (NDA 60–342),

b. Tetrachel Syrup and Tetracycline Syrup (NDA 60–342),

c. Tetrachel Capsules and Tetracycline Hydrochloride Capsules (NDA 60–343), and

d. Tetrachel (Film Coated) Tablets (NDA 60–344); Rachelle Laboratories, Inc., 700 Henry Ford Avenue, Long Beach, Calif. 90810.

9.a. Tetracycline Hydrochloride Capsules (NDA 90–290), and

b. Tetrcycline Syrup (NDA 60–291); Rondex Laboratories, Inc., 68 69th Street, Guttenberg, N.J. 07093.

10.a. Tetracycline Hydrochloride Film-coated Tablets (NDA 60–048),

b. Tetracycline Hydrochloride Tablets (NDA 60–048),

c. Tetracycline Hydrochloride Capsules (NDA 60–057), and

d. Sumycin Syrup; E. R. Squibb & Capsules (NDA 90–481); Societa Prodotti Antibiotici, Milan, Via Biella 8, Italy.

11.a. Steclin Capsules,

b. Sumycin Capsules,

c. Sumycin Aqueous Drops, and

d. Sumycin Syrup; E. R. Squibb and Sons, Inc., Georges Road, New Brunswick, N.J. 08903 (NDA 60–429).

12. a. Panmycin Capsules (NDA 60–347),

b. Panmycin KM Syrup (NDA 60–278),

c. Panmycin Syrup (NDA 60–278),

d. Panmycin Phosphate Capsules (NDA 60–428), and

e. Panmycin Aqua Drops (NDA 60–278); The Upjohn Co., 7171 Portage Road, Kalamazoo, Mich. 49002

II. Tetracycline for intramuscular use, marketed as:

1. a. Tetrex Powder for Intramuscular Injection (NDA 50–215),

b. Polycycline Powder for Intramuscular Injection (NDA 60–044); Bristol Laboratories.

2. Achromycin Powder for Intramuscular Injection (NDA 50–276); Lederle Laboratories.

3. Tetracyn Powder for Intramuscular Injection (NDA 60–285) Chas. Pfizer & Co.

4. Tetrachel Powder for Intramuscular Injection (NDA 60–346) Rachelle Laboratories.

5. a. Steclin Powder for Intramuscular Injection, and

b. Sumycin Powder for Intramuscular Injection; E. R. Squibb & Sons, Inc. (NDA 60–396).

6. Panmycin Powder for Aqueous Injection (NDA 60–333); The Upjohn Co.

III. Tetracycline for intravenous use, marketed as:

1. Bristacycline Sterile Powder for Injection (NDA 60–024) Bristol Laboratories.

2. Achromycin Powder for Intravenous Injection (NDA 50–273) Lederle Laboratories.

3. Tetracyn Powder for Intravenous Injection (NDA 60–096) Chas. Pfizer & Co.

4. Tetrachel Powder for Intravenous Injection (NDA 60–345), Rachelle Laboratories.

5. Steclin Powder for Intravenous Injection (NDA 60–396), E. R. Squibb & Sons, Inc.

6. Panmycin Powder for Intravenous Injection (NDA 60–279), The Upjohn Co.

IV. Oxytetracycline for Oral Administration, marketed as:

1. a. Terramycin Capsules (NDA 7–322),

b. Terramycin Soluble Tablets (NDA 7–966),

c. Terramycin Syrup (NDA 12–050 and 10–501),

d. Terramycin Pediatric Drops (NDA 12–074), and

e. Oxytetracycline Powder for Oral Suspension (NDA 8–257); Chas. Pfizer & Co.

2. Oxytetracycline Tablets (NDA 60–190), Zenith Laboratories, Inc., 150 South Dean Street, Englewood, N.J.

V. Oxytetracycline for intravenous administration, marketed as:

1. Terramycin Powder for Intravenous Injection; Chas. Pfizer & Co. (NDA 7–651).

VI. Oxytetracycline for intramuscular administration marketed as:

1. Terramycin Intramuscular Solution; Chas. Pfizer & Co. (NDA 11–375).

VII. Chlortetracycline for oral administration, marketed as:

1. a. Aureomycin Capsules (NDA 50–251),

b. Aureomycin Soluble Tablets (NDA 50–250),

c. Aureomycin Oral Drops (NDA 50–249),

d. Aureomycin Syrup (NDA 50–249), and

e. Aureomycin Spersoids Dispersible Powder (NDA 50–253); Lederle Laboratories.

2. Chlortetracycline Hydrochloride Capsules (NDA 60–104); Zenith Laboratories, Inc.

VIII. Chlortetracycline for intravenous administration, marketed as:

1. Aureomycin Powder for Intravenous Injection; Lederle Laboratories (NDA 50–245).

IX. Demethylchlortetracycline for oral administration, marketed as:

1. a. Declomycin Capsules (NDA 50–262),

b. Declomycin (Film Coated) (NDA 50–261),

c. Declomycin Pediatric Drops (NDA 50–257),

d. Declomycin Syrup (NDA 50–257), and

e. Declomycin Powder for Oral Suspension (NDA 50–255); Lederle Laboratories.

X. Rolitetracycline for intravenous and intramuscular administration, marketed as:

1. a. Syntetrin Powder for Intravenous Injection (NDA 50–132), and

b. Syntetrin Powder for Intramuscular Injection (NDA 50–139); Bristol Laboratories.

Preparations containing tetracycline, oxytetracycline, chlortetracycline, demethylchlortetracycline, and rolitetracycline are subject to the antibiotic certification procedures pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act. Requests for certification of such drugs for oral and parenteral administration should provide for labeling information in accord with labeling guidelines developed on the basis of this reevaluation of the drugs and published in this announcement. These labeling guidelines are in accord with the concept of expressing indications for antibiotic drugs in terms of the etiologic agent rather than the anatomic site of disease or common name of disease or in terms of disease conditions grouped in broad, vaguely worded, nonspecific language. This has resulted in classifying some indications as effective when stated in terms of the bacterial organism causing an infection; indications stated otherwise are in general regarded as lacking substantial evidence of effectiveness.

The above-named firms and any other holders of applications approved for drugs of the kinds described above are requested to submit, within 60 days following publication of this announcement in the FEDERAL REGISTER, supplements to their antibiotic applications to provide for revised labeling. Reasonable quantities of products affected by this announcement may be certified in the interim period prior to approval and use of such labeling.

Batches of drugs which bear labeling with claims evaluated as possibly effective (see "Effectiveness Classification" paragraphs below) and are otherwise in accord with the labeling conditions herein will be accepted for release or certification by the Food and Drug Administration for a period of 6 months from the publication date of this announcement to allow any applicant to obtain and submit data to provide substantial evidence of effectiveness of the drug for use in such conditions.

Any person who would be adversely affected by deletion of the claims for which the drugs lack substantial evidence of effectiveness, as described in this announcement, may, within 30 days following the publication date of this announcement, submit comments or pertinent data bearing on the effectiveness of the drug for such use.

I. TETRACYCLINE FOR ORAL ADMINISTRATION

A. *Effectiveness classification.* The Food and Drug Administration has considered the reports of the Academy, as well as other available evidence, and concludes that tetracycline for oral administration:

1. Is effective for the indications in the labeling guidelines which follow.

2. Is possibly effective against *C. diphtheriae*, as adjunctive therapy with antitoxin and routine established therapy.

3. a. Lacks substantial evidence of effectiveness for its labeled indications: Pertussis; acute bacterial cholecystitis; and for deliveries in unsterile fields.

b. Further, in accordance with the concept of expressing indications for antibiotic drugs in terms of the bacterial organism causing the infection, indications in the labeling of oral tetracycline products, where they connote either the site of disease or common name of disease, or disease conditions grouped in broad, vaguely worded language, are regarded as lacking substantial evidence of effectiveness. These include the following: bacterial meningitis caused by meningococcus, *H. influenzae*, and other susceptible organisms; pneumococcal pneumonia; eye infections; pharyngitis; septic sore throat; tonsillitis (or follicular tonsillitis); otitis media; otitis externa; sinusitis; mastoiditis; a number of upper respiratory tract infections; bronchopulmonary infections; bronchopneumonia; bronchitis or acute broncitis; pneumonia (with and without bacteremia); other types of bacterial pneumonia; acute pyelonephritis; chronic pyelonephritis; pyelitis, cystitis; urethritis; genitourinary tract infections; prostatitis; cellulitis; furunculosis; skin infections caused by susceptible bacteria; serious soft tissue infections; abscesses; epidermal abscesses; scarlet fever; bacillary dysentery, pustular dermatoses; nongonococcal or nonspecific urethritis; gastroenteritis; bacterial diarrhea; gastrointestinal infections; preoperative and postoperative preparations of the gastrointestinal tract; preoperative and postoperative prophylaxis for suppressing intestinal bacteria in surgery of the large intestine; preoperative and postoperative prophylaxis where surgery must be performed in the presence of infections or potential infection; osteomyelitis; meningitis; purulent meningitis; bacterial infections located elsewhere in the nervous system; puerperal infections; salpingo-oophoritis; pelvic inflammatory disease; infections resulting from incomplete abortion; peritonitis; infected wounds and incisions; surgical and dental preoperative and postoperative prophylaxis of infection in contaminated fields; septicemia; subacute bacterial endocarditis due to susceptible organisms; subacute bacterial endocarditis produced by both gram-negative and gram-positive bacteria sensitive to tetracycline; pancreatic fibrosis and infections associated with

pancreatic fibrosis; mixed bacterial infections; agammaglobulinemia of hypogammaglobulinemia and recurring infections (in conjunction with gamma globulin); impetigo; laryngotracheitis; tracheobronchitis; infections of other sites; and diseases caused by tetracycline-sensitive organisms.

B. *Labeling conditions.* Those parts of the labeling indicated below should be substantially as follows (optional additional information applicable to the drug may be proposed under other appropriate paragraph headings and should follow the information given below):

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

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 grampositive organisms.

The drugs in the tetracycline class have closely similar antimicrobial spectra, and cross-resistance among them appears complete. Micro-organisms may be considered highly sensitive if the M.I.C. (minimum inhibitory concentration) is 0.5 mcg./ml. or less, moderately sensitive if the M.I.C. is 0.5 to 2 mcg./ml. and slightly sensitive if the M.I.C. is 2 to 5 mcg./ml.

Sensitivity plate testing: If the Kirby-Bauer method of disc sensitivity is used, a 30 mcg. tetracycline disc should give a zone of over 18 mm. when tested against a tetracycline-sensitive bacterial strain.

Tetracyclines are readily absorbed and are bound to palsma 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.

INDICATIONS

Many Strains of Bacteria Have Been Shown To Be Resistant to the Tetracyclines. These Include Streptococci, Staphylococci, Pneumococci, Gonococci, and Many Other Gram-Negative Organisms. Therefore, Culture and Sensitivity Testing Are Advised To Determine the Susceptibility of the Infecting Organisms to Tetracyclines.

Tetracycline 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 (*B. recurrentis*),

The following gram-negative organisms:

H. ducreyi (*chancroid*),

Past. pestis and *tularensis*,

Bartonella bacilliformia,

Bacteroides,

Vibrio comma and *V. fetus*.

Brucella organisms (in conjunction with streptomycin).

The following gram-negative organisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

E. coli,

A. aerogenes,

Shigella,

Mima, Herellea,

H. influenzae (respiratory infections),

Klebsiella infections, respiratory and urinary,

The following gram-positive organisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Anaerobic streptococcus,

Streptococcus pyogenes (For upper respiratory infections due to group A beta-hemolytic streptococcus, penicillin is the drug of choice).

D. pneumoniae,

Staphylococcus aureus,

When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of infections due to:

N. gonorrhoeae and meningitidis,

T. pallidum and *pertenue* (syphilis and yaws),

Listeria monocytogenes,

Clostridia.

B. anthracis,

Fusobacterium (Vincent's infection),

Actinomyces.

In acute intestinal amebiasis, the tetracyclines may be a useful adjunct to amebicides.

In severe acne the tetracyclines may be useful adjunctive therapy.

Tetracyclines are 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.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

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 doses are indicated and, if therapy is prolonged, serum level determinations of the drug may be advisable.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultra-violet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

As with other tetracyclines this drug forms 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.

The antianabolic action of the tetracycline 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.

PRECAUTIONS

As with other antibiotics, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, 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 to decrease the likelihood of rheumatic fever or acute glomerulonephritis.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

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 purpura, pericarditis and exacerbation of systemic lupus erythematosis.

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.

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.

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.

DOSAGE AND ADMINISTRATION

Adults: Usual daily dose, 1–2 Gm. divided in four equal doses, depending on the severity of the infection.

Children: Usual daily dose, 10–20 mg. (25–50 mg./kg.) per pound of body weight divided in four equal doses.

Therapy should be continued for at least 24–48 hours after symptoms and fever have subsided.

For treatment of brucellosis, 500 mg. tetracycline four times daily for 3 weeks should be accompanied by streptomycin, 1 gram intramuscularly twice daily the first week and once daily the second week.

For treatment of syphilis, a total of 30–40 grams in equally divided doses over a period of 10–15 days should be given. Close followup, including laboratory tests, is recommended.

II. TETRACYCLINE FOR INTRAMUSCULAR ADMINISTRATION

A. *Effectiveness classification.* The Food and Drug Administration has considered the reports of the Academy, as well as other available evidence, and concludes that tetracycline for intramuscular administration:

1. Is effective for the indications in the labeling guidelines which follow.

2. Is possibly effective against *C. diphtheriae,* as adjunctive therapy with antitoxin and routine established therapy.

3.a. Lacks substantial evidence of effectiveness for its claimed indications: pertussis and acute bacterial cholecystitis.

b. Further, in accordance with the concept of expressing indications for antibiotic drugs in terms of the bacterial organism causing the infection, indications in the labeling of intramuscular tetracycline preparations, where they connote either site of disease or common name of disease, or disease conditions grouped in broad, vaguely worded language, are regarded as lacking substantial evidence of effectiveness. These include the following: bacterial meningitis caused by meningococcus, *H. influenzae,* and other susceptible organisms; respiratory tract infections caused by pneumococci, staphylococci, streptococci, *K. pneumoniae, H. influenzae, H. pertussis, Pasteurella tularensis,* and mycoplasmae (PPLO); peritonitis caused by *E. coli,* enterococci, and staphylococci; pneumococcal pneumonia; pneumococcal lobar pneumonia; acute and chronic urinary tract infections caused by susceptible staphylococci, streptococci, *A. aerogenes, E. coli* and mixed infections; streptococcal infections; scarlet fever; staphylococcal infections; impetigo; laryngotracheitis; tracheobronchitis; pneumonia (with and without bacteremia); acute bronchitis; septic sore throat; pharyngitis; sinusitis; prostatitis; pyelonephritis; pyelitis; cystitis; cellulitis; furunculosis; acne; surgical and dental preoperative and postoperative prophylaxis of infection in contaminated fields; agammaglobulinemia or hypogammaglobulinemia and recurring infections (in conjunction with gamma globulin); bacterial diarrhea; gastroenteritis; preoperative and postoperative prophylaxis where surgery must be performed in the presence of infection or potential infection; bronchopneumonia; other types of bacterial pneumonia; tonsillitis; a number of upper respiratory tract infections; otitis media; mastoiditis; bacterial infections located elsewhere in the nervous system; peritonitis; infected wounds and incisions; soft-tissue infection; skin infections caused by susceptible bacteria; osteomyelitis; puerperal infections; salpingo-oophoritis; pelvic inflammatory disease; infections resulting from incomplete abortions; eye infections; gastrointestinal infections; septicemia (pneumococcal and staphylococcal); subacute bacterial endocarditis due to susceptible organisms; skin infections, including carbuncles, furunculosis, pustular eruptions, cellulitis, and acne (caused by staphylococci and streptococci); subacute bacterial endocarditis caused by some gram-negative organisms; preoperative and postoperative prophylaxis for suppressing intestinal bacteria in surgery of the large intestine; urethritis; bronchopulmonary infections; otitis externa; chronic pyelonephritis; genitourinary tract infections; purulent meningitis; abscesses; infections asociated with pancreatic fibrosis; mixed bacterial infections; acute pyelonephritis; bacillary dysentery; pustular dermatoses; and diseases caused by tetracycline-sensitive organisms.

B. *Labeling conditions.* Those parts of the labeling indicated below should be substantially as follows (optional additional information applicable to the drug may be proposed under other appropriate paragraph headings and should follow the information given below):

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

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 appears complete. Micro-organisms may be considered highly sensitive if the M.I.C. (minimum inhibitory concentration) is 0.5 mcg./ml. or less, moderately sensitive if the M.I.C. is 0.5 to 2.0 mcg./ml. and slightly sensitive if the M.I.C. is 2 to 5 mcg./ml.

Sensitivity plate testing: If the Kirby-Bauer method of disc sensitivity is used, a 30 mcg. tertacycline disc should give a zone of over 18 mm. when tested against a tetracycline-sensitive bacterial strain. The tetracyclines 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.

INDICATIONS

Many Strains of Bacteria Have Been Shown To Be Resistant to the Tetracyclines. These Include Streptococci, Staphylococci, Pneumococci, Gonococci, and Many Other Gram-Negative Organisms. Therefore, Culture and Sensitivity Testing Are Advised To Determine the Susceptibility of the Infecting Organisms to Tetracylines.

Tetracycline is indicated in infections caused by the following microorganisms:

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 (*B. recurrentis*).

The following gram-negative organisms:

H. ducreyi (chancroid),

Past. pestis and *tularensis,*

Bartonella bacilliformis,

Bacteroides,

Vibrio comma and *V. fetus,*

Brucella organisms (in conjunction with streptomycin).

The following gram-negative organisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

E. coli,

A. aerogenes,

Shigella,

Mima, Herellea,

H. influenzae (respiratory infections),

Klebsiella infections, respiratory and urinary.

The following gram-positive organisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Anaerobic streptococcis,

Streptococcus pyogenes (For upper respiratory infections due to group A beta-hemolytic streptococcus, penicillin is the drug of choice),

D. pneumoniae,

Staphylococcus aureus.

When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of infections due to:

N. gonorrheoae and *meningitidis,*

T. pallidum and *pertenue* (syphilis and yaws),

Listeria monocytogenes,

Clostridia,

B. anthracis,

Fusobacterium (Vincent's infection),

Actinomyces.

In acute intestinal amebiasis, the tetracyclines may be a useful adjunct to amebicides.

Tetracyclines are 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.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

The Use of Tetracyclines 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 Hypolasia Has Also Been Reported. *Tetracyclines, 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 doses are indicated and, if therepy is prolonged, serum level deteminations of the drug may be advisable. This hazard is of particular importance in the parenteral administration of tetracyclines to pregnant or postpartum patients with pyelonephritis. When used under these circumstances, the blood level should not exceed 15 micrograms/ml. and liver function tests should be made at frequent intervals. Other potentially hepatotoxic drugs should not be prescribed concomitantly.

(In the presence of renal dysfunction, particularly in pregnancy, intravenous tetracycline therapy in daily doses exceeding 2 grams has been associated with deaths due to liver failure.)

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultra-violet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be

discontinued at the first evidence of skin erythema.

As with other tetracyclines, this drug forms 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 q 6 hours. This reaction was shown to be reversible when the drug was discontinued. 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 this drug may lead to azotemia, hyperphosphatemia, and acidosis.

PRECAUTIONS

As with all antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

When used in the tratment of gonorrhea, a darkfield examination should be made of any lesion suggestive of syphilis before treatment is started, and serologic tests for syphilis should be made monthly for at least 4 months afterwards.

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 to prevent the occurrence of rheumatic fever or acute glomerulonephritis.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

ADVERSE REACTIONS

Local irritation may be present after intramuscular injection. The injection should be deep, with care taken not to injure the sciatic nerve nor inject intravascularly. The parenteral form should be replaced by oral tetracycline therapy as soon as feasible.

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 purpura, pericarditis, and exacerbation of systemic lupus erythematosis.

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.

DOSAGE AND ADMINISTRATION

Intramuscular administration. Adults: The usual daily dose is 250 mg. administered once every 24 hours or 300 mg. given in divided doses at 8- to 12-hour intervals.

Children: 15-25 mg./kg. body weight up to a maximum of 250 mg. per single daily injection. Dosage may be divided and given at 8- to 12-hour intervals.

Intramuscular therapy should be reserved for situations in which oral therapy is not feasible or for initiating therapy when assurance of sustained therapeutic levels is required.

The intramuscular administration of tetracycline produces lower blood levels than oral administration in the recommended dosages. Patients placed on intramuscular tetracyclines should be changed to the oral dosage form as soon as possible. If rapid, high blood levels are needed, tetracyclines should be administered intravenously.

III. TETRACYCLINE FOR INTRAVENOUS ADMINISTRATION

A. *Effectiveness classification.* The Food and Drug Administration has considered the reports of the Academy, as well as other available evidence, and concludes that tetracycline for intravenous administration:

1. Is effective for the indications in the labeling guidelines which follow.

2. Is possibly effective against *C. diphtheriae,* as adjunctive therapy with antitoxin and routine established therapy.

3.a. Lacks substantial evidence of effectiveness for its claimed indications: pertussis; and acute bacterial cholecystitis.

b. Further, in accordance with the concept of expressing indications for antibiotic drugs in terms of the bacterial organism causing the infection, indications in the labeling of intravenous tetracycline preparations, where they connote either the site of disease or common name of disease, or disease conditions grouped in broad, vaguely worded language are regarded as lacking substantial evidence of effectiveness. These include the following: Pneumococcal pneumonia; pneumococcal lobar pneumonia; bacterial meningitis caused by meningococcus, *H. influenzae,* and other susceptible organisms; respiratory tract infections caused by pneumococci, staphylococci, streptococci, *K. pneumoniae; H. influenzae, H. pertussis, Pasteurella tularensis* and mycoplasma (PPLO); urinary tract infections caused by *E. coli, A. aerogenes,* staphylococci, streptococci, gonococci, and mixed infections; peritonitis caused by *E. coli,* enterococci, and staphylococci; streptococcal infections; scarlet fever; staphylococcal infections; impetigo; laryngotracheitis; tracheobronchitis; pneumonia (with and without bacteremia); acute bronchitis; septic sore throat; pharyngitis; sinusitis; prostatitis; pyelonephritis; pyelitis; cystitis; cellulitis; furunculosis; acne; surgical and dental preoperative and postoperative prophylaxis of infection in contaminated fields; agammaglobulinemia or hypogammaglobulinemia and recurring infections (in conjunction with gamma globulin); bacterial diarrhea; gastroenteritis; preoperative and postoperative prophylaxis where surgery must be performed in the presence of infection of potential infection; bronchopneumonia; other types of bacterial pneumonia; tonsillitis; a number of upper respiratory tract infections; otitis media; mastoiditis; bacterial infections located elsewhere in the nervous system; peritonitis; infected wounds and incisions; soft-tissue infection; skin infections caused by susceptible bacteria; osteomyelitis; puerperal infections; salpingo-oophoritis; pelvic inflammatory disease; infections resulting from incomplete abortions; eye infections; gastrointestinal infections; septicemia (pneumococcal and staphylococcal); subacute bacterial endocarditis due to susceptible organisms; skin infections, including carbuncles, furunculosis, pustular eruptions, cellulitis, and acne (caused by staphylococci and streptococci); subacute bacterial endocarditis caused by some gram-negative organisms; preoperative and postoperative prophylaxis for suppressing intestinal bacteria in surgery of the large intestine; urethritis; bronchopulmonary infections; otitis externa; chronic pyelonephritis; genitourinary tract infections; purulent meningitis; abscesses; infections associated with pancreatic fibrosis; mixed bacterial infections; pustular dermatoses; bacillary dysentery; acute pyelonephritis.

B. *Labeling conditions.* Those parts of the labeling indicated below should be substantially as follows (optional additional information applicable to the drug may be proposed under other appropriate paragraph headings and should follow the information given below):

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

ACTIONS

The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. Tetracyclines are effective 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 appears complete. Micro-organisms may be considered highly sensitive if the M.I.C. (minimum inhibitory concentration) is 0.5 mcg./ml. or less, moderately sensitive if the M.I.C. is 0.5 to 2.0 mcg./ml. and slightly sensitive if the M.I.C. is 2 to 5 mcg./ml.

Sensitivity plate testing: If the Kirby-Bauer method of disc sensitivity is used, a 30 mcg. tetracycline disc should give a zone of over 18 mm. when tested against a tetracycline-sensitive bacterial strain. The tetracyclines 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.

INDICATIONS

Many Strains of Bacteria Have Been Shown To Be Resistant to the Tetracyclines. These Include Streptococci, Staphylococci, Pneumococci, Gonococci, and Many Other Gram-Negative Organisms. Therefore, Culture and Sensitivity Testing Are Advised To Determine the Susceptibility of the Infecting Organisms to Tetracyclines.

Tetracycline 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 (*B. recurrentis*).
The following gram-negative organisms:
H. ducreyi (chancroid),
Past. pestis and *tularensis*,
Bartonella bacilliformia,
Bacteroides,
Vibrio comma and *V. fetus*,
Brucella organisms (in conjunctive with streptomycin).
The following gram-negative organisms, when bacteriologic testing indicates high sensitivity to the drug:
E. coli,
A. aerogenes,
Shigella,
Mina, Herellea,
H. influenzae (respiratory infections),
Klebsiella infections, respiratory and urinary.
The following gram-positive organisms when bacteriologic testing indicates high sensitivity to the drug:
Anaerobic streptococcus,
Streptococcus pyogenes (For upper respiratory infections due to group A beta-hemolytic streptococcus, penicillin is the drug of choice),
D. pneumoniae,
Staphylococcus aureus.
When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of infections due to:
N gonorrhoeae,
T. pallidum and *pertenue* (syphilis and yaws),
Listeria monocytogenes,
C. diphtheriae, as adjunctive therapy with antitoxin,
Clostridia,
B. anthracis,
Fusobacterium (Vincent's infection),
Actinomyces.
In acute intestinal amebiasis, the tetracyclines may be a useful adjunct to amebicides.
Tetracyclines are indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immofluorescence.
In deep-seated infections, such as osteomyelitis due to staphylococcus, bactericidal antibiotics are preferable to tetracycline.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

In the Presence of Renal Dysfunction, Particularly in Pregnancy, Intravenous Tetracycline Therapy in Daily Doses Exceeding 2 Grams Has Been Associated With Deaths Through Liver Failure.
When the need for intensive treatment outweighs its potential dangers (mostly during pregnancy or in individuals with known or suspected renal or liver impairment), it is advisable to perform renal and liver function tests before and during therapy. Also, tetracycline serum concentrations should be followed.
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, serum level determinations of the drug may be advisable. This hazard is of particular importance in the parenteral administration of tetracyclines to pregnant or postpartum patients with pyelonephritis. When used under these circumstances, the blood level should not exceed 15 micrograms/ml. and liver function tests should be made at frequent intervals. Other potentially hepatotoxic drugs should not be prescribed concomitantly. The Use of Tetracyclines 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 Hypoplasis Has Also Been Reported. *Tetracyclines, Therefore, Should Not Be Used in This Age Group Unless Other Drugs Are Not Likely To Be Effective or Are Contraindicated.*
Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.
As with other tetracyclines this drug forms 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./q. 6 hours. This reaction was shown to be reversible when the drug was discontinued.
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 this drug may lead to azotemia, hyperphosphatemia, and acidosis.

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 therapy instituted.
When used in the treatment of gonorrhea, a darkfield examination should be made of any lesion suggestive of syphilis before treatment is started, and serologic tests for syphilis should be made monthly for at least 4 months afterwards.
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 to prevent the occurrence of rheumatic fever or acute glomerulonephritis.
Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

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".)
Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, and exacerbation of systemic lupus erythematosis.
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.

DOSAGE AND ADMINISTRATION

NOTE: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not adequate or tolerated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.
Adults: The usual adult dose is 250 to 500 mg. every 12 hours, and should not exceed 500 mg. every 6 hours. The drug may be dissolved and then diluted in 100–1,000 cc. of Dextrose 5 percent in water, Isotonic Sodium Chloride Solution or Ringer's solution, but not in other solutions containing calcium (a precipitate may form).
Children: The usual dose is 12 mg./kg. day, divided into 2 doses, but from 10 to 20 mg./kg./day may be given, depending on the severity of the infection.

IV. OXYTETRACYCLINE FOR ORAL ADMINISTRATION

A. *Effectiveness classification.* The Food and Drug Administration has considered the reports of the Academy, as well as other available evidence, and concludes that oxytetracycline for oral administration:

1. Is effective for the indications in the labeling guidelines which follow.

2. Is possibly effective in *C. diphtheriae*, as adjunctive therapy with antitoxin; and tuberculosis, as an accessory drug, particularly when resistance or poor toleration to specific antituberculosis drugs has developed.

3. a. Lacks substantial evidence of effectiveness for its claimed indications: laryngotracheitis; acute infectious croup; whooping cough (*H. pertussis*); prophylaxis against, and therapy of, infections complicating wounds, burns, and surgical procedures; infections caused by species of salmonella, including typhoid fever; tracheobronchitis; an antibacterial cover in virus infections of the respiratory tract, including influenza and primary atypical pneumonia; enterocolitis; acute cholecystitis or acute diverticulitis when due to susceptible organisms; paronychia; leptospirosis; and other infections caused by pneumococci, streptococci, susceptible staphylococci, gonococci, meningococci, *E. coli*, *A. aerogenes*, bacterioides, species of Shigella, and Salmonella.

b. Further, in accordance with the concept of expressing indications for antibiotic drugs in terms of the bacterial organism causing the infection, indications in the labeling of oral oxytetracycline preparations, where they connote either site of disease or common name of disease, or disease conditions grouped in broad, vaguely worded language, are regarded as lacking substantial evidence of effectiveness. These include the following: Pneumonia caused by susceptible

strains of staphylococci, streptococci, *Hemophilus influenzae, Klebsiella pneumonia* (Friedlander's pneumonia), mixed flora, or enteric bacilli; tonsillitis; pharyngitis; otitis media; mastoiditis (with and without appropriate surgical procedures); lung abscesses; sinusitis; bronchitis (or acute bronchitis); bronchiolitis; empyema; pulmonary infections associated with pancreatic insufficiency; pyelonephritis and other urinary tract infections caused by streptococci, susceptible staphylococci, *E. coli, Aerobacter aerogenes*, or mixed organisms; prophylaxis against, and treatment of, infections complicating obstetric and gynecologic procedures; reduction or suppression of susceptible colonic bacterial flora in preparation for surgery of the large bowel; osteomyelitis; cellulitis; abscesses; furuncles; carbuncles; lymphadenitis; prophylaxis and treatment of oral and dental infections caused by susceptible organisms; prophylaxis against infections complicating wounds, burns, and surgical procedures; mixed bacterial pneumonias (sensitive *Staph. aureus, N. catarrhalis, Strep. hemolyticus, Strep. viridans, D. pneumoniae*, and *H. influenzae*); ophthalmic infections; wound infections; streptococcal infections, with and without bacteremia (including acute follicular tonsillitis, septic sore throat, pharyngitis, urinary tract infections and meningitis); many staphylococcal infections, with and without bacteremia (including furunculosis, cellulitis, septicemia, abscesses, impetigo, chronic purulent otitis media, sinusitis, infections, and urinary tract infections); acute gonococcal infections (when penicillin is contraindicated); *H. influenzae;* subacute bacterial endocarditis resistant to penicillin; bronchopneumonia; upper respiratory infections such as laryngotracheitis; pharyngitis, laryngotracheobronchitis, tonsillitis, and acute infectious croup; infections associated with acute pancreatitis; infectious arthritis caused by susceptible organisms; folliculitis; erysipelas; impetigo, ecthyma; pyoderma; infected dermatitis and dermatoses; lyphangitis; cystis; pyelitis; pyelonephritis; ureteritis; prostatitis; orchitis; epididymitis; seminal vesiculitis and other genitourinary infections caused by susceptible organisms; mastitis; post partum infections; infected abortion; cervicitis; adnexitis; parametritis; endometritis; pelvic peritonitis; vaginitis; bartholinitis; perineal infections; acute and chronic blepharitis; conjunctivitis; blepharoconjunctivitis; corneal ulcer; superficial and interstitial keratis; keratoconjunctivitis; infected acne rosacea keratitis; sclerokeratitis; scleritis; episcleritis; infected herpes zoster ophthalmicus; dacryocystitis; ophthalmia neonatorum; other susceptible ophthalmic infections; prophylaxis before ophthalmic surgical procedures; infections of the external ear canal; septicemia; bacteremia; as an antibacterial cover in susceptible individuals during bacteremic states associated with bacterial endocarditis, rheumatic fever, nephrosis, or cystic fibrosis of the pancreas; scarlet fever, pneumococcal pneumonia (with and without bacteremia); bronchiectasis (or chronic bronchiectasis); nonspecific urethritis; gonorrheal urethritis; opthalmia caused by gonococci, staphylococci, *H. influenzae*, or other susceptible organisms; meningeal infections caused by meningococci; *K. pneumoniae, H. influenzae*, and other susceptible organisms; pinworm; urinary tract infections due to oxytetracycline sensitive organisms including *E. coli, A. aerogenes*, and sensitive *Staph. aureus;* acute infections due to *E. coli* and *A. aerogenes* including septicemia, cellulitis, diffuse bronchopneumonia, post partum endometritis, and urinary tract infections; intestinal ambiasis; listeriosis; and peritonitis.

B. *Labeling conditions.* Those parts of the labeling indicated below should be substantially as follows (optional additional information applicable to the drug may be proposed under other appropriate paragraph headings and should follow the information given below):

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

ACTIONS

The oxytetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. Oxytetracyclines 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 appears complete. Micro-organisms may be considered highly sensitive if the M.I.C. (minimum inhibitory concentration) is 0.5 mcg./ml. or less, moderately sensitive if the M.I.C. is 0.5 to 2.0 mcg./ml. and slightly sensitive if the M.I.C. is 2 to 5 mcg./ml.

Sensitivity plate testing: A tetracycline disc may be used to determine microbial sensitivity to any drugs in the tetracycline class. If the Kirby-Bauer method of disc sensitivity is used a 30 mcg. tetracycline disc should give a zone of over 18 mm. when tested against a oxytetracycline-sensitive bacterial strain.

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. 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.

INDICATIONS

Many strains of bacteria have been shown to be resistant to the oxytetracyclines. These include streptococci, staphylococci, pneumococci, gonococci and many other gram-negative organisms. Therefore, culture and sensitivity testing are advised to determine the susceptibility of the infecting organisms to oxytetracyclines.

(The remainder of the "indications" section should be the same as oral tetracycline labeling.)

CONTRAINDICATIONS

(This should be identical to oral tetracycline labeling.)

WARNINGS

(This should be identical to oral tetracycline labeling.)

PRECAUTIONS

(This should be identical to oral tetracycline labeling.)

ADVERSE REACTIONS

(This should be identical to oral tetracycline labeling.)

DOSAGE AND ADMINISTRATION

(This should be identical to oral tetracycline labeling.)

V. OXYTETRACYCLINE FOR INTRAVENOUS ADMINISTRATION

A. *Effectiveness classification.* The Food and Drug Administration has considered the reports of the Academy, as well as other available evidence and concludes that oxytetracycline for intravenous administration:

1. Is effective for the indications in the labeling guidelines which follow.

2. Is possibly effective against *C. diphtheriae* as adjunctive therapy with antitoxin.

3. In accordance with the concept of expressing indications for antibiotic drugs in terms of the bacterial organism causing the infection, indications in the labeling of oxytetracycline preparations for intravenous administration, where they connote either the site of disease or common name of disease, or disease conditions grouped in broad, vaguely worded language, are regarded as lacking substantial evidence of effectiveness. These include the following: Peritonitis; streptococcal infections due to most strains of hemolytic and nonhemolytic streptococci, including the enterococci (*Strep. fecalis*); staphylococcal infections, with and without bacteremia (including staphylococcal sepsis and subacute bacterial endocarditis); acute infections due to *E. coli, A. areogenes, K. pneumoniae* and other oxytetracycline-susceptible organisms; surgical infections; cellulitis; abscesses; wound infections; other soft tissue infections; lymphangitis due to *Staphylococcus aureus, Streptococcus hemolyticus*, or other oxytetracycline-susceptible organisms; reduction of fecal flora preoperative and postoperatively; and pneumococcal infections, with and without bacteremia; pneumococcal pneumonia; peritonitis, and meningitis.

B. *Labeling conditions.* Those parts of the labeling indicated below should be substantially as follows (optional additional information applicable to the drug may be proposed under other appropriate paragraph headings and should follow the information given below):

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

ACTIONS

Oxytetracycline, like the other tetracyclines, is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Tetracyclines are active against a wide range of gram-negative and gram-positive organisms. When bacteriologic studies and sensitivity testing indicate that the infecting organisms

are susceptible to the action of tetracyclines, they are usually effective. All the drugs in the tetracycline class have closely similar antimicrobial spectra, and cross-resistance among them appears complete. Micro-organisms may be considered highly sensitive if the M.I.C. (minimum inhibitory concentration) is 0.5 mcg./ml. or less, moderately sensitive if the M.I.C. is 0.5 to 2.0 mcg./ml. and slightly sensitive if the M.I.C. is 2 to 5 mcg./ml.

Sensitivity plate testing: If the Kirby-Bauer method of disc sensitivity is used, a 30 mcg. oxytetracycline (or tetracycline) disc should give a zone of over 18 mm. when tested against an oxytetracycline-sensitive bacterial strain.

Tetracycline drugs 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.

INDICATIONS

(This should be identical to intravenous tetracycline labeling.)

CONTRAINDICATIONS

(This should be identical to intravenous tetracycline labeling.)

WARNINGS

(This should be identical to intravenous tetracycline labeling.)

PRECAUTIONS

(This should be identical to intravenous tetracycline labeling.)

ADVERSE REACTIONS

(This should be identical to intravenous tetracycline labeling.)

DOSAGE AND ADMINISTRATION

NOTE: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not adequate or tolerated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

Adults: If in powder form, dissolve oxytetracycline powder in 10 cc. water for Injection U.S.P. or 5 percent Dextrose Injection U.S.P. Then redilute, to make at least 100 cc. Dextrose 5 percent in water, Isotonic Sodium Chloride Solution or Ringer's solution may be used. The usual adult dose is 250 to 500 mg. every 12 hours and should not exceed 500 mg. every 6 hours.

Children: The usual dose is 12 mg./kg./day, divided into two doses, but from 10 to 20 mg./kg./day may be given, depending on the severity of the infection.

VI. OXYTETRACYCLINE FOR INTRAMUSCULAR ADMINISTRATION

A. *Effectiveness classification.* The Food and Drug Administration has considered the reports of the Academy, as well as other available evidence, and concludes that oxytetracycline for intramuscular administration:

1. Is effective for the indications in the labeling guidelines which follow.

2. Is possibly effective against *C. diphtheriae*, as adjunctive therapy with antitoxin.

3. a. Lacks substantial evidence of effectiveness for its claimed indications: Laryngotracheobronchitis; whooping cough; enterocolitis; salmonellosis; acute cholecystitis or acute diverticulitis when due to susceptible organisms; and leptospirosis.

b. Further, in accordance with the concept of expressing indications for antibiotic drugs in terms of the bacterial organism causing the infection, indications in the labeling of oxytetracycline for intramuscular administration, where they connote either site of disease or common name of disease, or disease conditions grouped in broad, vaguely worded language, are regarded as lacking substantial evidence of effectiveness. These include the following: pharyngitis; tonsillitis; scarlet fever; bronchiolitis; pneumonia caused by susceptible strains of staphylococci; pneumonia caused by *Klebsiella pneumoniae;* otitis media; mastoiditis (with appropriate surgical procedure); sinusitis; conjunctivitis; superficial keratitis; acute trachoma; cholera; infections associated with acute pancreatitis; nonobstructive urinary tract infections caused by susceptible organisms (streptococci, some strains of staphylococci, coli-aerogenes bacilli, and mixed infections); pyelonephritis; ureteritis; cystitis; prostatitis; orchitis; epididymitis; seminal vesiculitis; furuncles; carbuncles; acne vulgaris (pustular phase); impetigo; ecthyma; erysipelas; infected dermatitis and dermatoses; bacteremia associated with skin infections; cervicitis; parametritis; endometritis; salpingitis; pelvic peritonitis; bartholinitis; perineal infections; puerperal sepsis; infected traumatic and surgical wounds; cellulitis; abscesses, osteomyelitis; infections arthritis caused by susceptible organisms; prophylaxis and treatment of bacteremia and bacterial endocarditis, depending on the susceptibility of the causitive organisms (gram-positive cocci, coli-aerogenes bacilli, and bacteroides are principal pathogens); pneumococcal pneumonia (with and without bacteremia); bacillary dysentery; chancroid; *Lymphogranuloma venereum;* gonorrheal urethritis; bronchiectasis; nonspecific urethritis; pneumonia caused by streptococci; and peritonitis.

B. *Labeling conditions.* Those parts of the labeling indicated below should be substantially as follows (optional additional information applicable to the drug may be proposed under other appropriate paragraph headings and should follow the information given below):

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

ACTIONS

Oxytetracycline, like the other tetracyclines, is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Tetracyclines are active against a wide range of gram-negative and gram-positive organisms. When bacteriologic studies and sensitivity testing indicate that the infecting organisms are susceptible to the action of tetracyclines, they are usually effective. All the drugs in the tetracycline class have closely similar antimicrobial spectra, and cross-resistance among them appears complete. Micro-organisms may be considered highly sensitive if the M.I.C. (minimum inhibitory concentration) is 0.5 mcg./ml. or less, moderately sensitive if the M.I.C. is 0.5 to 2.0 mcg./ml. and slightly sensitive if the M.I.C. is 2 to 5 mcg./ml.

Sensitivity plate testing: If the Kirby-Bauer method of disc sensitivity is used, a 30 mcg. oxytetracycline (or tetracycline) disc should give a zone of over 18 mm. when tested against an oxytetracycline-sensitive bacterial strain.

Tetracycline drugs 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.

INDICATIONS

(This should be identical to intramuscular tetracycline labeling.)

CONTRAINDICATIONS

(This should be identical to intramuscular tetracycline labeling.)

WARNINGS

(This should be identical to intramuscular tetracycline labeling.)

PRECAUTIONS

(This should be identical to intramuscular tetracycline labeling.)

ADVERSE REACTIONS

(This should be identical to intramuscular tetracycline labeling.)

DOSAGE AND ADMINISTRATION

Adults: The usual daily dose is 250 mg. administered once every 24 hours or 300 mg. given in divided doses at 8- to 12-hour intervals.

Children: 15–25 mg./kg. body weight up to a maximum of 250 mg. per single daily injection. Dosage may be divided and given at 8- to 12-hour intervals.

Intramuscular therapy should be reserved for situations in which oral therapy is not feasible or for initiating therapy when assurance of sustained therapeutic levels is required.

The intramuscular administration of oxytetracycline produces lower blood levels than oral administration in the recommended dosages. Patients placed on intramuscular oxytetracycline should be changed to the oral dosage form as soon as possible. If rapid, high blood levels are needed, oxytetracycline should be administered intravenously.

VII. CHLORTETRACYCLINE FOR ORAL ADMINISTRATION

A. *Effectiveness classification.* The Food and Drug Administration has considered the reports of the Academy, as well as other available evidence, and concludes that chlortetracycline for oral administration:

1. Is effective for the indications in the labeling guidelines which follow.

2. a. Lacks substantial evidence of effectiveness for its claimed indications: Acute laryngotracheobronchitis and laryngotracheitis; acute infectious croup (nondiphtheritic); acute extraintestinal amebic infections; amebic hepatitis and amebic abscess with surgery; subacute bacterial endocarditis produced by certain gram-negative or gram-positive bacteria susceptible to the action of chlortetracycline; and whooping cough.

b. Further, in accordance with the concept of expressing indications for antibiotic drugs in terms of the bacterial organism causing the infection, indications in the labeling of chlortetracycline for

oral administration, where they connote either site of disease or common name of disease, or disease conditions grouped in broad, vaguely worded language, are regarded as lacking substantial evidence of effectiveness. These include the following: treatment of bacillary infections produced by *E. coli*, including urinary tract infections; pneumococcal infections; *Clostridium perfringens* infections; secondary bacterial complications associated with primary atypical pneumonia psittacosis; beta-hemolytic streptococcal infections; bacillary infections produced by *A. aerogenes*, or *K. pneumoniae;* bacillary dysentery; uninary tract infections produced by *E. coli, A. aerogenes*, staphylococci, or streptococci; acute bronchitis; acute bronchiolitis; otitis media; mastoiditis; peritonitis; meningitis; abscesses, with surgical therapy; acute intestinal infections; miningococcal infections; spirochetal infections; infections caused by susceptible staphylococci; infections caused by susceptible streptococci; meningitis caused by *H. influenzae;* suppression of bacterial growth in the stool as preoperative and postoperative prophylactic measure in surgery of the large intestine; prophylaxis in puerperal sepsis; prevent development of rheumatic fever or glomerulonephritis in streptococcal infections; bronchopulmonary infections; pneumonia; subacute bacterial endocarditis; genitourinary infection; mixed bacterial infection; surgical preoperative and postoperative prophylaxis; puerperal sepsis; and dental preoperative and postoperative prophylaxis.

B. *Labeling conditions.* Those parts of the labeling indicated below should be substantially as follows (optional additional information applicable to the drug may be proposed under other appropriate paragraph headings and should follow the information given below):

DESCRIPTION

(This should be identical to oral tetracycline labeling.)

ACTION

(This should be identical to oral tetracycline labeling.)

INDICATIONS

(This should be identical to oral tetracycline labeling.)

CONTRAINDICATIONS

(This should be identical to oral tetracycline labeling.)

WARNINGS

(This should be identical to oral tetracycline labeling.)

PRECAUTIONS

(This should be identical to oral tetracycline labeling.)

ADVERSE REACTIONS

(This should be identical to oral tetracycline labeling.)

DOSAGE AND ADMINISTRATION

(This should be identical to oral tetracycline labeling.)

VIII. CHLORTETRACYCLINE FOR INTRAVENOUS ADMINISTRATION

A. *Effectiveness classification.* The Food and Drug Administration has considered the reports of the Academy, as well as other available evidence, and concludes that chlortetracycline for intravenous administration:

1. Is effective for the indications in the labeling guidelines which follow:

2. a. Lacks substantial evidence of effectiveness for its claimed indications: Nondiphtheritic croup; amebic hepatitis; and laryngotracheitis.

b. Further, in accordance with the concept of expressing indications for antibiotic drugs in terms of the bacterial organism causing the infection, indications in the labeling of chlortetracycline for intravenous administration, where they connote either site of disease or common name of disease, or disease conditions grouped in broad, vaguely worded language, are regarded as lacking substantial evidence of effectiveness. These include the following: abscesses; bronchiolitis; bronchitis; bronchopulmonary infections; bacillary dysentery; subacute bacterial endocarditis; genitourinary infection; mastoiditis; meningitis; mixed bacterial infection; otitis media; peritonitis; pneumonia; puerperal sepsis; surgical pre- and postoperative prophylaxis; dental pre- and postoperative prophylaxis; and secondary bacterial complications associated with primary atypical pneumonia psittacosis.

B. *Labeling conditions.* Those parts of the labeling indicated below should be substantially as follows (optional additional information applicable to the drug may be proposed under other appropriate paragraph headings and should follow the information given below):

DESCRIPTION

(This should be identical to intravenous tetracycline labeling.)

ACTIONS

(This should be identical to intravenous tetracycline labeling.)

INDICATIONS

(This should be identical to intravenous tetracycline labeling.)

CONTRAINDICATIONS

(This should be identical to intravenous tetracycline labeling.)

WARNINGS

(This should be identical to intravenous tetracycline labeling.)

PRECAUTIONS

(This should be identical to intravenous tetracycline labeling.)

ADVERSE REACTIONS

(This should be identical to intravenous tetracycline labeling.)

DOSAGE AND ADMINISTRATION

(This should be identical to intravenous tetracycline labeling.)

IX. DEMETHYLCHLORTETRACYCLINE FOR ORAL ADMINISTRATION

A. *Effectiveness classification.* The Food and Drug Administration has considered the reports of the Academy, as well as other available evidence, and concludes that demethylchlortetracycline for oral administration:

1. Is effective for the indications in the labeling guidelines which follow.

2. a. Lacks substantial evidence of effectiveness for its claimed indication: Activity against some strains of Psuedomonas and Proteus heretofore unresponsive to tetracycline therapy as shown by both in vivo and in vitro studies.

b. Further, in accordance with the concept of expressing indications for antibiotic drugs in terms of bacterial organism causing the infection, indications in the labeling of demethylchlortetracycline for oral administration, where they connote either site of disease or common name of disease, or disease conditions grouped in broad, vaguely worded language, are regarded as lacking substantial evidence of effectiveness. These include the following: abscesses caused by organisms sensitive to tetracycline; acne; bronchiectasis; bronchiolitis; bronchitis; bronchopulmonary infections; cellulitis; cystitis; erysipelas; furunculosis; genitourinary tract infections; laryngotracheitis; mixed bacterial infection; otitis externa; otitis media; pharyngitis; pneumonia; preoperative and postoperative prophylaxis of infection; primary atypical pneumonia; pustular folliculitis; pyelonephritis; pyoderma; sinusitis; streptococcal sore throat; tonsillitis; dental preoperative and postoperative prophylaxis; endometritis; and non-specific urethritis.

B. *Labeling conditions.* In the labeling guidelines which follow, the name "demethylchlortetracycline", official in the N.F. XII, has been used. However, the U.S. Adopted Name "demeclocycline" will become official when the N.F. XIII becomes official on September 1, 1970. To avoid confusion that could result from use of the new name, the labeling should initially identify the drug as democlocycline (formely demethylchlortetracycline).

Those parts of the labeling indicated below should be substantially as follows (optional additional information applicable to the drug may be proposed under other appropriate paragraph headings and should follow the information given below):

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

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 appears complete. Micro-organisms may be considered highly sensitive if the M.I.C. (minimum inhibitory concentration) is 0.5 mcg./ml. or less, moderately sensitive if the M.I.C. is 0.5 to 2.0 mcg./ml. and slightly sensitive if the M.I.C. is 2 to 5 mcg./ml.

Sensitivity plate testing: A tetracycline disc may be used to determine microbial sensitivity to any drugs in the tetracycline class. If the Kirby-Bauer method of disc sensitivity

is used, a 30 mcg. tetracycline disc should give a zone of over 18 mm. when tested against a demethylchlortetracycline-sensitive 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 in high concentrations and in a biologically active form.

INDICATIONS

(This should be identical to the oral tetracycline labeling, except that the following should be omitted: "In severe acne the tetracyclines may be useful adjunctive therapy".)

CONTRAINDICATIONS

(This should be identical to oral tetracycline labeling.)

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 doses are indicated and, if therapy is prolonged, serum level determinations of the drug may be advisable.

Phototoxic reactions can occur in individuals taking demethylchlortetracycline, 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 demethylchlortetracycline. 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.

As with other tetracyclines demethylchlortetracycline forms 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.

The anti-anabolic action of the tetracycline 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 demethylchlortetracycline lead to azotemia, hyperphosphatemia, and acidosis.

PRECAUTIONS

As with other antibiotics, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, 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 to decrease the likelihood of rheumatic fever or acute glomerulonephritis.

Interpretation of Bacteriologic Studies: Following a course of therapy, persistence for several days in both urine and blood of bacterio-suppressive levels of demethylchlortetracycline may interfere with culture studies. These levels should not be considered therapeutic.

ADVERSE REACTIONS

(This should be identical to oral tetracycline labeling.)

DOSAGE AND ADMINISTRATION

Adults: Usual daily dose—Four divided doses of 150 mg. each or two divided doses of 300 mg. each.

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.

Therapy should be continued beyond the time when characteristic symptoms or fever have subsided.

X. ROLITETRACYCLINE FOR INTRAVENOUS AND INTRAMUSCULAR ADMINISTRATION

A. *Effectiveness classification.* The Food and Drug Administration has considered the reports of the Academy, as well as other available evidence, and concludes that rolitetracycline for intravenous and intramuscular administration:

1. Is effective for the indications in the labeling guidelines which follow.

2. a. Lacks substantial evidence of effectiveness for its claimed indications: whooping cough; and gastroenteritis.

b. Further, in accordance with the concept of expressing indications for antibiotic drugs in terms of the bacterial organism causing the infection, indications in the labeling of rolitetracycline for intravenous and intramuscular administration, where they connote either site of disease or common name of disease, or disease conditions grouped in broad, vaguely worded language, are regarded as lacking substantial evidence of effectiveness. These include the following: pneumonia; acute bronchitis; pharyngitis; sinusitis; septic sore throat; pyelonephritis; pyelitis; cystitis; prostatitis; urethritis, bacillary dysentery; bacterial diarrhea; cellulitis; furunculosis; pustular dermatoses; and acne.

B. *Labeling conditions.* Those parts of the labeling indicated below should be substantially as follows (optional additional information applicable to the drug may be proposed under other appropriate paragraph headings and should follow the information given below):

DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

ACTIONS

Rolitetracycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Rolitetracycline is effective 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 appears complete. Micro-organisms may be considered highly sensitive if the M.I.C. (minimum inhibitory concentration) is 0.5 mcg./ml. or less, moderately sensitive if the M.I.C. is 0.5 to 2.0 mcg./ml. and slightly sensitive if the M.I.C. is 2 to 5 mcg./ml.

Sensitivity plate testing: A tetracycline disc may be used to determine microbial sensitivity to any drugs in the tetracycline class. If the Kirby-Bauer method of disc sensitivity is used, a 30 mcg. tetracycline disc should give a zone of over 18 mm. when tested against a rolitetracycline-sensitivity bacterial strain.

The tetracyclines 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.

INDICATIONS

Many Strains of Bacteria Have Been Shown To Be Resistant to the Tetracyclines. These Include Streptococci, Staphylococci, Pneumococci, Gonococci and Many Other Gram-negative Organisms. Therefore, Culture and Sensitivity Testing are Advised to Determine the Susceptibility of the Infecting Organisms to Rolitetracycline.

Rolitetracycline is indicated in infections caused by the following organisms:

(Remainder of Indications section is identical to that for I.M. and I.V. tetracyline.)

CONTRAINDICATIONS

(This should be identical to labeling for I.M. or I.V. tetracycline.)

WARNINGS

(This should be identical to labeling for I.M. or I.V. tetracycline.)

PRECAUTIONS

(This should be identical to labeling for I.M. or I.V. tetracycline.)

ADVERSE REACTIONS

(This should be identical to labeling for I.M. or I.V. tetracycline.)

DOSAGE AND ADMINISTRATION

For Intramuscular Rolitetracycline.

NOTE: Intramuscular therapy should be reserved for situations in which oral therapy is not feasible, or to initiate therapy.

Adult: The usual dose is 150 mg. every 8 or 12 hours. Doses up to 350 mg. every 12 hours may be used in severe infections or to initiate therapy.

Children: 15–25 mg./kg. body weight daily in one or two divided doses depending on the severity of the infection.

For Intravenous Rolitetracycline.

NOTE: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not adequate or tolerated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

Usual dose: 350 mg. to 700 mg. every 12 hours by intravenous infusion. Dissolve the reconstituted drug in 300 cc.–500 cc. of Dextrose 5 percent in water or Isotonic Sodium Chloride solution.

INSTRUCTIONS FOR USE

(Manufacturer to supply)

Representatives of the Administration are willing to meet with any interested person who desires to have a conference concerning proposed changes in the labeling set forth in this announcement. Requests for such meetings should be made to the Division of Anti-Infective Drugs (BD–140), at the address given

below, within 30 days after the publication of this notice in the FEDERAL REGISTER.

A copy of the NAS–NRC report has been furnished to each firm referred to above. Any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with the reference number DESI 7322 and be directed to the attention of the following appropriate office and addressed (unless otherwise specified) to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Supplements (Identify with NDA number): Division of Anti-Infective Drugs (BD–140), Office of New Drugs, Bureau of Drugs.

All other communications regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (BD–201), Bureau of Drugs.

Requests for NAS–NRC Report: Press Relations Staff, Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204.

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 12, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70–11553; Filed, Sept. 1, 1970; 8:46 a.m.]

Social Security Administration

HUNGARY

Notice of Finding Regarding Foreign Social Insurance or Pension System

Section 202(t)(1) of the Social Security Act (42 U.S.C. 402(t)(1)) prohibits payment of monthly benefits to aliens, subject to the exceptions described in sections 202(t)(2) through 202(t)(5) of the Social Security Act (42 U.S.C. 402(t)(2) through 402(t)(5)), for any month after they have been outside the United States for 6 consecutive calendar months.

Section 202(t)(2) of the Social Security Act (42 U.S.C. 402(t)(2)) provides that section 202(t)(1) shall not apply to any individual who is a citizen of a foreign country which the Secretary of Health, Education, and Welfare, finds has in effect a social insurance or pension system which is of general application in such country and under which (A) periodic benefits, or the actuarial equivalent thereof, are paid on account of old age, retirement, or death, and (B) individuals who are citizens of the United States but not citizens of such foreign country and who qualify for such benefits are permitted to receive such benefits or the actuarial equivalent thereof while outside such foreign country without regard to the duration of the absence.

Pursuant to authority vested in the Commissioner of Social Security by the Secretary of Health, Education, and Welfare, and redelegated to him, the Director of the Bureau of Retirement and Survivors Insurance has approved a finding that Hungary has a social insurance system of general application in effect which pays periodic benefits on account of old age, retirement, or death, but that under its social insurance system citizens of the United States, not citizens of Hungary, who leave Hungary, are not permitted to receive such benefits or their actuarial equivalent at the full rate without qualification or restriction while outside that country.

Accordingly, it is hereby determined and found that Hungary has in effect a social insurance system which is of general application in that country and which meets the requirements of section 202(t)(2)(A) of the Social Security Act (42 U.S.C. 402(t)(2)(A)), but not the requirements of section 202(t)(2)(B) of the Act (42 U.S.C. 402(t)(2)(B)).

Subparagraphs (A) and (B) of section 202(t)(4) of the Social Security Act (42 U.S.C. 402(t)(4) (A) and (B)) provide that section 202(t)(1) shall not be applicable to benefits payable on the earnings record of an individual who has 40 quarters of coverage under social security or who has resided in the United States for a period or periods aggregating 10 years or more. However, effective July 1, 1968, the provisions of subparagraphs (A) and (B) of section 202(t)(4) shall not apply to an individual who is a citizen of a foreign country that has in effect a social insurance or pension system which is of general application in such country and which satisfies the provisions of subparagraph (A) of section 202(t)(2) but not the provisions of subparagraph (B) of section 202(t)(2).

By virtue of the finding herein, the provisions of subparagraphs (A) and (B) of section 202(t)(4) do not apply to citizens of Hungary beginning July 1, 1968.

This augments the finding with respect to Hungary published in the FEDERAL REGISTER of December 24, 1958 (23 F.R. 10187).

Dated: August 25, 1970.

HUGH F. MCKENNA,
Director, Bureau of Retirement and Survivors Insurance.

[F.R. Doc. 70–11567; Filed, Sept. 1, 1970; 8:47 a.m.]

DEPARTMENT OF TRANSPORTATION

Coast Guard

[CGFR 70–51A]

NEW YORK HARBOR, WATERS SURROUNDING ELLIS ISLAND

Cancellation of Declaration of Security Zone

By virtue of the authority vested in the Commandant, U.S. Coast Guard, by Executive Order 10173, as amended (33 CFR Part 6), sec. 6(b)(1), 80 Stat. 937 (49 U.S.C. 1655(b)(1)), 49 CFR 1.46(b) and the redelegation of authority concerning security zones to Chief, Office of Operations, U.S. Coast Guard, as contained in 33 CFR 1.05–1(c)(3) (35 F.R. 8279), I hereby affirm for publication in the FEDERAL REGISTER the order of B. F. Engel, Rear Admiral, U.S. Coast Guard, Commander, Third Coast Guard District, who has exercised authority as District Commander, such order reading as follows:

NEW YORK HARBOR, WATERS SURROUNDING ELLIS ISLAND

CANCELLATION OF DECLARATION OF SECURITY ZONE

(Published in FEDERAL REGISTER March 27, 1970 (35 F.R. 5192))

The order of the Commander, Third Coast Guard District of Monday, March 16, 1970 establishing a security zone surrounding Ellis Island in Upper New York Bay, New York Harbor, is canceled as of 1210 p.m., e.s.t., July 23, 1970.

Dated: August 28, 1970.

R. E. HAMMOND,
Rear Admiral, U.S. Coast Guard, Chief, Office of Operations.

[F.R. Doc. 70–11579; Filed, Sept. 1, 1970; 8:48 a.m.]

ATOMIC ENERGY COMMISSION

[Docket No. 50–366]

GEORGIA POWER CO.

Notice of Receipt of Application for Construction Permit and Facility License

Georgia Power Co., 270 Peachtree Street NW., Atlanta, Ga. 30303, pursuant to section 104(b) of the Atomic Energy Act of 1954, as amended, has filed an application, dated July 24, 1970, for authorization to construct and operate a boiling water nuclear power reactor at the Edwin I. Hatch site on the south side of the Altamaha River in northwestern Appling County, about 11 miles north of Baxley, Ga.

The proposed reactor, designated by the applicant as the Edwin I. Hatch Nuclear Plant, Unit 2, is designed for initial operation at approximately 2,436 megawatts thermal with a gross electrical output of approximately 817 megawatts.

A copy of the application is available for public inspection at the Commission's Public Document Room, 1717 H Street NW., Washington, D.C.

Dated at Bethesda, Md., this 26th day of August 1970.

For the Atomic Energy Commission.

PETER A. MORRIS,
Director, Division of Reactor Licensing.

[F.R. Doc. 70–11568; Filed, Sept. 1, 1970; 8:47 a.m.]

CIVIL AERONAUTICS BOARD

[Docket No. 22496]

ALITALIA-LINEE AEREE ITALIANE-S.P.A.

Notice of Prehearing Conference

Notice is hereby given that a prehearing conference on the above-entitled application is assigned to be held on September 8, 1970, at 10 a.m., e.d.s.t., in Room 805, Universal Building, 1825 Connecticut Avenue NW., Washington, D.C., before Associate Chief Examiner Ralph L. Wiser.

Dated at Washington, D.C., August 27, 1970.

[SEAL] THOMAS L. WRENN,
Chief Examiner.

[F.R. Doc. 70-11572; Filed, Sept. 1, 1970; 8:48 a.m.]

[Docket No. 21866-7]

DOMESTIC PASSENGER FARE INVESTIGATION PHASE 7—FARE LEVEL

Notice of Hearing

Notice is hereby given, pursuant to the provisions of the Federal Aviation Act of 1958, as amended, that a hearing in the above-entitled proceeding will be held on September 29, 1970, at 10 a.m., e.d.s.t., in Room 726, Universal Building, 1825 Connecticut Avenue NW., Washington, D.C., before the undersigned Examiner.

For information concerning the issues involved and other details in this proceeding, interested persons are referred to the prehearing conference report, served April 15, 1970, the supplemental prehearing conference report, served May 4, 1970, and other documents which are in the docket of this proceeding on file in the Docket Section of the Civil Aeronautics Board.

Dated at Washington, D.C., August 28, 1970.

[SEAL] THOMAS P. SHEEHAN,
Hearing Examiner.

[F.R. Doc. 70-11573; Filed, Sept. 1, 1970; 8:48]

[Docket No. 22462; Order 70-8-108]

GOLDEN EAGLE AVIATION, INC.

Order To Show Cause

Issued under delegated authority August 26, 1970.

The Postmaster General filed a notice of intent August 10, 1970, pursuant to 14 CFR Part 298, petitioning the Board to establish for the above captioned air taxi operator, a final service mail rate of 51.79 cents per great circle aircraft mile for the transportation of mail by aircraft between Rolla, Mo., and Harrison, Ark., via Columbia, Sedalia, and Kansas City, Mo., Little Rock and Batesville, Ark.

No protest or objection was filed against the proposed services during the time for filing such objections. The Postmaster General states that the Department and the carrier agree that the above rate is a fair and reasonable rate of compensation for the proposed services. The Postmaster General believes these services will meet postal needs in the market. He states the air taxi plans to initiate mail service with Beechcraft D-18 aircraft.

It is in the public interest to fix, determine, and establish the fair and reasonable rate of compensation to be paid by the Postmaster General for the proposed transportation of mail by aircraft, the facilities used and useful therefor, and the services connected therewith, between the aforesaid points. Upon consideration of the notice of intent and other matters officially noticed, it is proposed to issue an order[1] to include the following findings and conclusions:

The fair and reasonable final service mail rate to be paid to Golden Eagle Aviation, Inc., in its entirety by the Postmaster General pursuant to section 406 of the Act for the transportation of mail by aircraft, the facilities used and useful therefor, and the services connected therewith, shall be 51.79 cents per great circle aircraft mile between Rolla, Mo., and Harrison, Ark., via Columbia, Sedalia, and Kansas City, Mo., Little Rock and Batesville, Ark., based on five round trips per week.

Accordingly, pursuant to the Federal Aviation Act of 1958, and particularly sections 204(a) and 406 thereof, and regulations promulgated in 14 CFR Part 302, 14 CFR Part 298, and 14 CFR 385.16(f),

It is ordered, That:

1. Golden Eagle Aviation, Inc., the Postmaster General, Braniff Airways, Inc., Delta Air Lines, Inc., Frontier Airlines, Inc., Ozark Air Lines, Inc., and all other interested persons are directed to show cause why the Board should not adopt the foregoing proposed findings and conclusions and fix, determine, and publish the final rate specified above for the transportation of mail by aircraft, the facilities used and useful therefor, and the services connected therewith as specified above as the fair and reasonable rate of compensation to be paid to Golden Eagle Aviation, Inc.;

2. Further procedures herein shall be in accordance with 14 CFR Part 302, and notice of any objection to the rate or to the other findings and conclusions proposed herein, shall be filed within 10 days, and if notice is filed, written answer and supporting documents shall be filed within 30 days after service of this order;

3. If notice of objection is not filed within 10 days after service of this order, or if notice is filed and answer is not filed within 30 days after service of this order, all persons shall be deemed to have waived the right to a hearing and all other procedural steps short of a final decision by the Board, and the Board may enter an order incorporating the findings and conclusions proposed herein and fix and determine the final rate specified herein;

4. If answer is filed presenting issues for hearing, the issues involved in determining the fair and reasonable final rate shall be limited to those specifically raised by the answer, except insofar as other issues are raised in accordance with Rule 307 of the rules of practice (14 CFR 302.307); and

5. This order shall be served upon Golden Eagle Aviation, Inc., the Postmaster General, Braniff Airways, Inc., Delta Air Lines, Inc., Frontier Airlines, Inc., and Ozark Air Lines, Inc.

This order will be published in the FEDERAL REGISTER.

[SEAL] HARRY J. ZINK,
Secretary.

[F.R. Doc. 70-11575; Filed, Sept. 1, 1970; 8:48 a.m.]

[1] This order to show cause is not a final action and is not regarded as subject to the review provisions of 14 CFR Part 385. These provisions will be applicable to final action taken by the staff under authority delegated in § 385.16(g).

[Docket No. 21770; Order 70-8-111]

INTERNATIONAL AIR TRANSPORT ASSOCIATION

Order Regarding Fares

Adopted by the Civil Aeronautics Board at its office in Washington, D.C., on the 27th day of August 1970.

Agreements have been filed with the Board, pursuant to section 412(a) of the Federal Aviation Act of 1958 (the Act) and Part 261 of the Board's economic regulations, between various air carriers, foreign air carriers, and other carriers, embodied in the resolutions of Joint Conferences 1-2 and 1-2-3 of the International Air Transport Association (IATA), and adopted by mail vote. The agreements, which are intended to be effective from September 1, 1970, through March 31, 1971, have been assigned the above-designated CAB agreement numbers.

Insofar as air transportation as defined by the Act is concerned, the agreements propose an across-the-board increase of $5 one way and $10 round trip in North Atlantic fares.[1] Based on New York-London, this would increase first-class fares by a little more than 1 percent, economy peak fares by 2 percent, and economy nonpeak fares by 2.4 percent. In terms of percentage, the greatest increase would apply to promotional or discounted fares. Increases for this category of fares would range from approximately 3 to 6 percent.

In support of the Agreement, Pan American World Airways, Inc. (Pan Am), and Trans World Airlines, Inc. (TWA), advert to a sharp decline in economy-class yield, and stress the current unsatisfactory results for North Atlantic operations as well as the unfavorable outlook they foresee for the future in the face of rising costs. In the latter respect, Pan American cites a contractual increase in 1970 of 17 percent for pilots, and from 4 to 9 percent in wages for other

[1] Exceptions include certain fares for military travel.

groups of employees. The pilots' contracts and others will be subject to review in 1971.

The Board has decided not to approve these increases proposed by the carriers on the eve of the IATA fare conference scheduled to begin in less than 2 weeks. That conference will afford an opportunity for careful review of economic trends and future prospects and for a general reassessment of the North Atlantic fare structure in the light of all relevant considerations. There has been no showing of a financial emergency which would warrant approval of these increases pending the results of that conference. The period of earnings upon which the carriers rely to support the increase is too brief to allow any conclusive determination as to their need, particularly when it coincides with the introduction of an entirely new type of aircraft. It should be noted that the Board authorized a significant increase in the normal fares a little more than a year ago when the IATA carriers eliminated the 5-percent round-trip discount. Finally, there is every indication that traffic on the North Atlantic this summer is showing exceptionally strong growth which augurs well for a more favorable result over a longer term.

The Board, acting pursuant to sections 102, 204(a), and 412 of the Act, finds that Agreements CAB 21856 and 21857 which incorporate the following resolutions are adverse to the public interest insofar as they apply in air transportation:

IATA Resolutions

JT12(Mail 749)002q. JT12(Mail 748)002p.
JT123(Mail 651)002q. JT123(Mail 650)002p.

Accordingly, it is ordered, That:

Agreements CAB 21856 and 21857 are disapproved insofar as air transportation is concerned, and otherwise approved.

This order will be published in the FEDERAL REGISTER.

By the Civil Aeronautics Board.[2]

[SEAL] HARRY J. ZINK,
Secretary.

[F.R. Doc. 70-11576; Filed, Sept. 1, 1970; 8:48 a.m.]

[Docket No. 22491]

WAGNER AVIATION LTD.

Notice of Hearing

Application for a foreign air carrier permit, issued pursuant to section 402 of the Federal Aviation Act of 1958, as amended, to perform a Class 3, Unit Toll, irregular air service between Kingston, Ontario, Canada, and Syracuse, N.Y., U.S.A.

Notice is hereby given, pursuant to the provisions of the Federal Aviation Act of 1958, as amended, that hearing on the above-entitled application is assigned to be held on September 11, 1970, at 10 a.m., e.d.s.t., in Room 805, Universal Building, 1825 Connecticut Avenue NW., Washington, D.C., before Examiner Joseph L. Fitzmaurice.

Dated at Washington, D.C., August 28, 1970.

[SEAL] THOMAS L. WRENN,
Chief Examiner.

[F.R. Doc. 70-11574; Filed, Sept. 1, 1970; 8:48 a.m.]

[2] Gillilland, Vice chairman, and Adams dissenting statement filed as part of the original document.

FEDERAL MARITIME COMMISSION

AMERICAN WEST AFRICAN FREIGHT CONFERENCE

Notice of Agreement Filed

Notice is hereby given that the following agreement has been filed with the Commission for approval pursuant to section 15 of the Shipping Act, 1916, as amended (39 Stat. 733, 75 Stat. 763, 46 U.S.C. 814).

Interested parties may inspect and obtain a copy of the agreement at the Washington office of the Federal Maritime Commission, 1405 I Street NW., Room 1202; or may inspect the agreement at the field offices located at New York, N.Y., New Orleans, La., and San Francisco, Calif. Comments on such agreements, including requests for hearing, may be submitted to the Secretary, Federal Maritime Commission, Washington, D.C. 20573, within 20 days after publication of this notice in the FEDERAL REGISTER. Any person desiring a hearing on the proposed agreement shall provide a clear and concise statement of the matters upon which they desire to adduce evidence. An allegation of discrimination or unfairness shall be accompanied by a statement describing the discrimination or unfairness with particularity. If a violation of the Act or detriment to the commerce of the United States is alleged, the statement shall set forth with particularity the acts and circumstances said to constitute such violation or detriment to commerce.

A copy of any such statement should also be forwarded to the party filing the agreement (as indicated hereinafter) and the statement should indicate that this has been done.

Notice of agreement filed by:

John K. Cunningham, Chairman, American West African Freight Conference, 67 Broad Street, New York, N.Y. 10004.

Agreement No. 7680-27, among the member lines of the American West African Freight Conference, will modify the basic agreement by changing the voting requirements of Article 10(b) (from a unanimous vote to a three-fourths vote of all of the active members) for the taking of all action under the basic agreement except action for the increasing or decreasing of rates or the adoption, rescission, amendment, and/or modification of any and all tariff rules and regulations of the conference tariffs. Consistent with the above, (1) Article 11(b) is modified to provide that for those actions defined in Article 10(b), three-fourths of the active membership shall constitute a quorum, and (2) Article 11(c) is modified to provide that when voting by telephone poll and/or circular letter, action relative to matters other than the increase or decrease of freight rates may be taken by an instrument in writing signed by three-fourths vote of all of the active members.

Dated: August 28, 1970.

By order of the Federal Maritime Commission.

JOSEPH C. POLKING,
Assistant to the Secretary.

[F.R. Doc. 70-11560; Filed, Sept. 1, 1970; 8:47 a.m.]

COMPAGNIE GENERALE TRANSATLANTIQUE AND ARMEMENT DEPPE S.A.

Notice of Agreement Filed

Notice is hereby given that the following agreement has been filed with the Commission for approval pursuant to section 15 of the Shipping Act, 1916, as amended (39 Stat. 733, 75 Stat. 763, 46 U.S.C. 814).

Interested parties may inspect and obtain a copy of the agreement at the Washington office of the Federal Maritime Commission, 1405 I Street NW., Room 1202; or may inspect the agreement at the field offices located at New York, N.Y., New Orleans, La., and San Francisco, Calif. Comments on such agreements, including requests for hearing, may be submitted to the Secretary, Federal Maritime Commission, Washington, D.C. 20573, within 20 days after publication of this notice in the FEDERAL REGISTER. Any person desiring a hearing on the proposed agreement shall provide a clear and concise statement of the matters upon which they desire to adduce evidence. An allegation of discrimination or unfairness shall be accompanied by a statement describing the discrimination or unfairness with particularity. If a violation of the Act or detriment to the commerce of the United States is alleged, the statement shall set forth with particularity the acts and circumstances said to constitute such violation or detriment to commerce.

A copy of any such statement should also be forwarded to the party filing the agreement (as indicated hereinafter) and the statement should indicate that this has been done.

Notice of agreement filed by:

Edwin Longcope, Esq., Hill, Betts & Nash, 26 Broadway, New York, N.Y. 10004.

Agreement No. 9891 is a sailing and rate agreement between French Line (Compagnie Generale Transatlantique) and Deppe Line (Armement Deppe S.A.) covering the trade between United States Gulf ports and ports in the Bordeaux/Hamburg range.

Dated: August 28, 1970.

By order of the Federal Maritime Commission.

JOSEPH C. POLKING,
Assistant to the Secretary.

[F.R. Doc. 70-11561; Filed, Sept. 1, 1970; 8:47 a.m.]

SOUTH ATLANTIC STEAMSHIP CONFERENCE

Notice of Agreement Filed

Notice is hereby given that the following agreement has been filed with the Commission for approval pursuant to section 15 of the Shipping Act, 1916, as amended (39 Stat. 733, 75 Stat. 763, 46 U.S.C. 814).

Interested parties may inspect and obtain a copy of the agreement at the Washington office of the Federal Maritime Commission, 1405 I Street NW., Room 1202; or may inspect the agreement at the field offices located at New York, N.Y., New Orleans, La., and San Francisco, Calif. Comments on such agreements, including requests for hearing, may be submitted to the Secretary, Federal Maritime Commission, Washington, D.C. 20573, within 20 days after publication of this notice in the FEDERAL REGISTER. Any person desiring a hearing on the proposed agreement shall provide a clear and concise statement of the matters upon which they desire to adduce evidence. An allegation of discrimination or unfairness shall be accompanied by a statement describing the discrimination or unfairness with particularity. If a violation of the Act or detriment to the commerce of the United States is alleged, the statement shall set forth with particularity the acts and circumstances said to constitute such violation or detriment to commerce.

A copy of any such statement should also be forwarded to the party filing the agreement (as indicated hereinafter) and the statement should indicate that this has been done.

Notice of agreement filed by:

Mr. E. J. Middleton, Chairman, South Atlantic Steamship Conference, Post Office Box 96, Savannah Bank and Trust Building, Savannah, Ga. 31402.

Agreement No. 8310-7, between the member lines of the South Atlantic Steamship Conference, modifies Article 1 of the basic agreement to provide that the parties reserve the right to each of them to alter for itself any rate, charge, classification, rule and/or regulation adopted by the parties and recorded in the Conference tariff or tariffs upon first giving the other parties and the Conference Chairman at least 48 hours advance notice in writing. All such alterations adopted by any of the individual parties will be recorded in the tariff or tariffs of the Conference.

Dated: August 27, 1970.

By order of the Federal Maritime Commission.

JOSEPH C. POLKING,
Assistant to the Secretary.

[F.R. Doc. 70-11559; Filed, Sept. 1, 1970; 8:47 a.m.]

FEDERAL RESERVE SYSTEM

BROWARD BANCSHARES, INC.

Notice of Application for Approval of Acquisition of Shares of Bank

Notice is hereby given that application has been made, pursuant to section 3(a)(3) of the Bank Holding Company Act of 1956 (12 U.S.C. 1842(a)(3)), by Broward Bancshares, Inc., which is a bank holding company located in Fort Lauderdale, Fla., for prior approval by the Board of Governors of the acquisition by Applicant of 80 percent or more of the voting shares of Lauderdale Lakes National Bank, Lauderdale Lakes, Fla., a proposed new bank.

Section 3(c) of the Act provides that the Board shall not approve:

(1) any acquisition or merger or consolidation under section 3 which would result in a monopoly, or which would be in furtherance of any combination or conspiracy to monopolize or to attempt to monopolize the business of banking in any part of the United States, or

(2) any other proposed acquisition or merger or consolidation under section 3 whose effect in any section of the country may be substantially to lessen competition, or to tend to create a monopoly, or which in any other manner would be in restraint of trade, unless the Board finds that the anticompetitive effects of the proposed transaction are clearly outweighed in the public interest by the probable effect of the transaction in meeting the convenience and needs of the community to be served.

Section 3(c) further provides that, in every case, the Board shall take into consideration the financial and managerial resources and future prospects of the company or companies and the banks concerned, and the convenience and needs of the community to be served.

Not later than thirty (30) days after the publication of this notice in the FEDERAL REGISTER, comments and views regarding the proposed acquisition may be filed with the Board. Communications should be addressed to the Secretary, Board of Governors of the Federal Reserve System, Washington, D.C. 20551. The application may be inspected at the office of the Board of Governors or the Federal Reserve Bank of Atlanta.

By order of the Board of Governors, August 26, 1970.

[SEAL] ELIZABETH L. CARMICHAEL,
Assistant Secretary.

[F.R. Doc. 70-11569; Filed, Sept. 1, 1970; 8:47 a.m.]

FEDERAL POWER COMMISSION

[Docket No. CP71-36]

ARKANSAS LOUISIANA GAS CO.

Notice of Application

AUGUST 24, 1970.

Take notice that on August 18, 1970, Arkansas Louisiana Gas Co. (Applicant), Post Office Box 1734, Shreveport, La. 71102, filed an application pursuant to section 7(b) of the Natural Gas Act for an order granting permission and approval for the abandonment of an obsolete compressor station, known as Mills Station, all as more fully set forth in the application which is on file with the Commission and open to public inspection.

Applicant states that the equipment contained in Mills Station, located in Caddo Parish, La., was manufactured and installed in its present location in 1912, and that it is now obsolete and has not been operated since July 30, 1969, although it has been maintained in operating condition for stand-by service.

Any person desiring to be heard or to make any protest with reference to said application should on or before September 15, 1970, file with the Federal Power Commission, Washington, D.C. 20426, a petition to intervene or a protest in accordance with the requirements of the Commission's rules of practice and procedure (18 CFR 1.8 or 1.10) and the regulations under the Natural Gas Act (18 CFR 157.10). All protests filed with the Commission will be considered by it in determining the appropriate action to be taken but will not serve to make the protestants parties to the proceeding. Any person wishing to become a party to a proceeding or to participate as a party in any hearing therein must file a petition to intervene in accordance with the Commission's rules.

Take further notice that, pursuant to the authority contained in and subject to the jurisdiction conferred upon the Federal Power Commission by sections 7 and 15 of the Natural Gas Act and the Commission's rules of practice and procedure, a hearing will be held without further notice before the Commission on this application if no petition to intervene is filed within the time required herein, if the Commission on its own review of the matter finds that permission and approval for the proposed abandonment is required by the public convenience and necessity. If a petition for leave to intervene is timely filed, or if the Commission on its own motion believes that a formal hearing is required, further notice of such hearing will be duly given.

Under the procedure herein provided for, unless otherwise advised, it will be unnecessary for Applicant to appear or be represented at the hearing.

GORDON M. GRANT,
Secretary.

[F.R. Doc. 70-11539; Filed, Sept. 1, 1970; 8:45 a.m.]

[Docket Nos. CS71-6, etc.]

JOHN L. CRAWFORD ET AL.

Notice of Applications for "Small Producer" Certificates [1]

AUGUST 24, 1970.

Take notice that each of the applicants listed herein has filed an application pursuant to section 7(c) of the

[1] This notice does not provide for consolidation for hearing of the several matters covered herein.

Natural Gas Act and § 157.40 of the Regulations thereunder for a "small producer" certificate of public convenience and necessity authorizing the sale for resale and delivery of natural gas in interstate commerce from areas for which just and reasonable rates have been established, all as more fully set forth in the applications which are on file with the Commission and open to public inspection.

Any person desiring to be heard or to make any protest with reference to said applications should on or before September 18, 1970, file with the Federal Power Commission, Washington, D.C. 20426, petitions to intervene or protests in accordance with the requirements of the Commission's rules of practice and procedure (18 CFR 1.8 or 1.10). All protests filed with the Commission will be considered by it in determining the appropriate action to be taken but will not serve to make the protestants parties to the proceeding. Persons wishing to become parties to a proceeding or to participate as a party in any hearing therein must file petitions to intervene in accordance with the Commission's rules.

Take further notice that, pursuant to the authority contained in and subject to the jurisdiction conferred upon the Federal Power Commission by sections 7 and 15 of the Natural Gas Act and the Commission's rules of practice and procedure, a hearing will be held without further notice before the Commission on all applications in which no petition to intervene is filed within the time required herein if the Commission on its own review of the matter believes that a grant of the certificates is required by the public convenience and necessity. Where a petition for leave to intervene is timely filed, or where the Commission on its own motion believes that a formal hearing is required, further notice of such hearing will be duly given.

Under the procedure herein provided for, unless otherwise advised, it will be unnecessary for Applicants to appear or be represented at the hearing.

GORDON M. GRANT,
Secretary.

Docket No.	Date filed	Name of applicant
CS71-6	7-21-70	John L. Crawford et al., 625 Southern National Bank Bldg., Houston, Tex. 77002.
CS71-7	7-30-70	Burk Gas Corp. 800 Oil and Gas Bldg., Wichita Falls, Tex. 76301.
CS71-8	8-13-70	Ginther, Warren & Co., 2438 Bank of the Southwest Bldg., Houston, Tex. 77002.
CS71-9	8-14-70	The Fundamental Oil Corp., 1900 One Main Pl., Dallas, Tex. 75250.

[F.R. Doc. 70-11540; Filed, Sept. 1, 1970; 8:45 a.m.]

INTERSTATE COMMERCE COMMISSION

[Ex Parte MC-82]

MOTOR CARRIER REVENUE PROCEEDINGS

Proposed New Procedures

Pursuant to the authority vested in the Interstate Commerce Commission by 49 U.S.C. 316, at a General Session held at its office in Washington, D.C., the Commission, on August 27, 1970, determined to publish for public comment new procedures governing the data and information to be submitted in motor common carrier revenue proceedings. The proposed procedures are intended to clarify and to make more specific, and they will supersede, those set forth in the statement of policy and the form of order immediately following that statement, published in 32 F.R. 7002-7004. The proposed procedures are consistent with the Commission's recent decision in Docket No. 34013, Rules To Govern the Assembling and Presenting of Cost Evidence, 337 I.C.C. 298, served July 30, 1970. They are not intended to limit the type of evidence which motor carrier respondents might wish to introduce, but are designed to reduce the time required for ultimate disposition, achieve greater uniformity in data submitted, avoid the service of detailed orders in individual proceedings, and provide adequate notice to the carriers and to the public of the evidence required.

Within 30 days from the publication of this notice in the FEDERAL REGISTER, any interested party may file with the Secretary of the Commission comments regarding the proposed procedures. A signed original and 15 copies should be submitted. After comments have been considered, the Commission will determine whether to require compliance with these procedures, or with some variation thereof.

The procedures themselves, together with an explanation where appropriate, are set forth below:

1. *Application.* Upon the filing of agency tariff schedules containing proposed general increases in rates or charges, where such proposal would result in an increase of $1 million or more in annual operating revenues (or in other revenue proceedings as the Commission may direct), (1) motor common carriers of general commodities on whose behalf such schedules are filed, where the number of carriers participating in the agency's tariffs exceeds 200, shall, concurrently with the filing of the tariff schedules, file and serve, as provided hereinafter, verified statements presenting and comprising the entire evidential case which is relied upon to support the proposed increase, and (2) motor common carriers represented by other agencies shall be required to comply with these procedures in the event an investigation is instituted, such evidence to be submitted at the time specified by the Commission in its orders instituting the investigation and setting the matter for hearing. Those carriers which will be required to submit their evidence when they file their schedules are hereby notified that special permission to file those schedules may be conditioned upon the publication of an effective date at least 45 days later than the date of filing, to enable proper evaluation of the evidence presented.

2. *Traffic study.* A traffic study shall be submitted which covers the most current 12-month period available, and is based upon the actual operations conducted during identical periods of time for each carrier included in the traffic study. The traffic study shall be shown to be representative of the traffic covered by the rate proposal. For sampling purposes, the frame shall be based on the issue traffic handled by all carriers subject to the requirements for allocation of expenses between line haul and pickup and delivery as provided in 49 CFR Part 1207, Instructions 27 and 9002, that participate in the tariffs in issue, plus any other carrier whose revenues from the issue traffic amount to 50 percent or more of its system revenues. The respondents shall show the representatives of traffic studies that rely on probability sampling techniques including the statistical adequacy of study design and the reliability of results for the intended purposes according to accepted standards of scientific sampling principles and practices. This requires explanation and evaluation of the sample as it relates both to the traffic of individual carriers and to the total traffic at issue, including sample design, procedures, management, and measures of the precision of inferences and estimates based thereon.

Such a traffic study is needed: (a) To develop present and projected revenues applicable to the issue traffic; (b) to determine the consist of the issue traffic, i.e., by weight brackets, mileage blocks, and other characteristics; and (c) to ascertain the number of traffic service units (e.g., hundredweight-miles hundredweight given pickup and delivery service, etc.) used in moving the issue traffic so that the service unit costs may be applied to these traffic service units for the purpose of costing out the issue traffic, and ultimately, to make a comparison of these costs with the present and projected revenues applicable thereto. This issue traffic is represented by the entire through movement from origin to ultimate destination. The last three sentences relate to the determination of a frame for sampling purposes, plus the requirement that information be submitted to test the representativeness of the sampling techniques and procedures used.

3. *Cost study.* A cost study shall be submitted. Highway Form B may be used for this purpose. Service unit costs shall be developed for carriers subject to the requirements for allocation of expenses between line haul and pickup and delivery as provided in 49 CFR Part 1207, Instructions 27 and 9002. The cost study carriers shall be selected from the Instruction 27 traffic study carriers listed in descending order beginning with the carrier deriving the greatest percentage of its total system revenue from the tariffs at issue. Proponents shall include in their selection of cost study carriers all those Instruction

27 carriers whose total amount of revenue derived under the bureau's tariffs at issue collectively is 75 percent or more of the total revenue derived by all carriers participating in those tariffs. If the revenue of these Instruction 27 carriers is less than 75 percent of the total, then all of the Instruction 27 carriers shall be used. The expenses and statistics by services for each cost study carrier obtained from Highway Form B shall be multiplied by the percent that each cost study carrier's issue traffic revenues bears to its system revenues. The total thus obtained shall be summarized and the total expenses by services divided by the applicable service units. The weighted composite service unit costs thus obtained for all cost study carriers shall be applied to the composite traffic service units for all traffic study carriers. When a portion of a through movement under the issue tariff is handled by a nontraffic study carrier then the unit costs for the territory within which the movement occurs, taken from the latest territorial cost study, as updated, published by the Commission's cost finding section, shall be applied to said traffic service units. Operating ratios shall be determined for shipments in the individual weight brackets included within the rate proposal, based on composite service unit costs developed for: (a) The annual reporting period preceding the filing date of the tariffs in issue, and (b) the projected annual reporting period concurrent with the filing date of said tariffs. Operating ratios shall also be shown by size of shipment for all other traffic not affected by the rate proposal for the period indicated in (a) above for the same weight brackets as shown for the issue traffic plus all other nonissue traffic combined.

The objective is to identify and select the cost study carriers (Instruction 27 carriers), to develop the composite service unit costs, and to apply those unit costs to the issue traffic by size of shipments, to obtain operating ratios by size of shipments for specified periods. It should be noted here that this paragraph applies to costing out of the entire traffic study, i.e., the entire through movement of the issue traffic from origin to destination. On the other hand, the appendix which is discussed later relative to revenue need, requires systemwide operating ratios, and the expenses and revenues allocated to the issue traffic, and other data, for traffic study carriers only. Also this paragraph requires the cost study carriers to be selected in descending order beginning with the Instruction 27 carrier deriving the greatest percentage of its total system revenues from the traffic at issue, which, it is believed, will provide a more representative selection of carriers for cost study purposes. Thus, a cost study carrier's expenses and statistics will be reflected in the composite service unit costs only to the extent of its participation in the issue traffic. To avoid misunderstanding, the following table illustrates how the proposed procedure should be used in selecting the cost study carriers. First, array all Class I and Class II carriers in descending order by the percent that each carrier's revenues from the issue traffic is to that carrier's system total revenues (column 5). Carriers obtaining less than 1 percent of their system revenue from the issue traffic may be grouped together under "all other carriers." The dollars of issue traffic revenues for the Instruction 27 carriers (column 4) are then added down until 75 percent of the issue traffic revenues for all participating carriers is reached. In the table, this percentage is obtained after line 21. Thus, the cost study carriers would include all Instruction 27 carriers above line 22.

ILLUSTRATION OF SELECTION OF COST STUDY CARRIERS

Line No.	Class I or Class II carrier name [1]	Instruction 27 or Non-instruction 27	Carrier system revenues	Issue traffic revenues	Percent issue traffic revenues to system revenues
	(1)	(2)	(3)	(4)	(5)
			(000)	(000)	
1		27	$10,000	$9,900	99.0
2		27	15,000	14,500	96.7
3		27	2,000	1,900	95.0
4		27	6,000	5,280	88.0
5		27	16,000	13,760	86.0
6		Non	1,000	850	85.0
7		Non	8,000	6,800	85.0
8		27	40,000	33,720	84.3
9		27	150,000	126,150	84.1
10		Non	2,500	2,020	80.8
11		27	7,500	6,045	80.6
12		Non	3,000	2,385	79.5
13		27	560	395	70.5
14		Non	750	525	70.0
15		27	20,000	13,600	68.0
16		27	13,000	8,580	66.0
17		27	2,000	1,300	65.0
18		Non	5,050	3,182	63.0
19		27	16,000	9,600	60.0
20		27	30,000	16,500	55.0
21		27	35,000	14,000	40.0
22		27	2,000	500	25.0
23		27	560,000	45,000	8.0
24		27	70,000	5,600	8.0
25		27	80,000	4,800	6.0
26	All other carriers			18,108	
27	Total all participating carriers			365,000	
28	Total Instruction 27 carriers above 75 percent			275,230	[2] 75.4

[1] List each Class I or Class II carrier obtaining 1 percent or more of its system revenue from the issue traffic. Carriers obtaining less than 1 percent of their system revenue from the issue traffic may be grouped together under "all other carriers."

[2] The subtotal in last line of column 4 ($275,230) represents the total of the issue traffic revenues over 75 percent of the revenues from the traffic at issue by all participating carriers ($365,000). Thus all Instruction 27 carriers above this line would be Cost and Traffic Study carriers; and the Non-instruction 27 carriers above line 22 plus all carriers below line 21, except those grouped in line 26, would be traffic study carriers.

Paragraph 3 also specifically identified how the composite service unit costs shall be applied to the traffic in issue. It also requires operating ratios to be shown by size of shipments for all other traffic not affected by the rate proposal for the most current 12-month period available preceding the filing date of the tariff in issue. When a nontraffic study carrier is involved in a through movement of issue traffic (e.g., when there is a prior, subsequent, or bridge movement by a traffic study carrier) the traffic service units of this carrier will be costed out by applying the latest applicable territorial costs, as updated, published by the Commission's cost finding section. As a result, a comparison may be made as to the relative profitability of the issue vs. nonissue traffic.

4. *Revenue need.* The proponent carriers shall submit evidence of the sum of money, in addition to operating expenses, needed to attract debt and equity capital which they require to insure financial stability and the capacity to render service. This evidence shall include (1) for each individual Class I and Class II traffic study carrier (without limiting the evidence that may be presented), the data required by Parts I and II of the appendix, and (2) for all such study carriers aggregated (again without limitation as to the evidence that may be presented), the data required by Parts I, II, and III of the appendix.

The purpose of this paragraph is to develop the sum of money, in addition to operating expenses, needed by the carriers to attract debt and equity capital to insure financial stability and capacity to render service. As set forth in the appendix, specific data regarding revenue need are required to be submitted.

In the appendix, Method A utilizes the ton and ton-mile method of allocating the constant costs and sum of money to the issue traffic (line 16). Also in the appendix, Method B utilizes the dollar (expense) method of allocating the constant cost and sum of money to the issue traffic (line 16). In the matter of allocating constant cost, the appendix, Methods A and B represent two methods of allocating constant costs. It is recognized that other methods might be shown to be justified by the nature of a particular proposal. In this connection, attention is called to the following ultimate finding of our recent decision in Docket No. 34013, Rules to Govern the Assembling and Presenting of Cost Evidence, supra:

(4) The allocation of constant costs to particular services, for ratemaking purposes, should result in the assignment of an equitable portion of such expenses to the particular services, and no single method can be considered as universally applicable to all transportation services.

The appendix requires in Parts I and II the following information for each Class I and Class II traffic study carrier included in the frame for sampling purposes on an actual (columns 3 and 4) and projected (column 5) year basis:

(1) System operating revenues and expenses.

(2) System "sum of money," above operating expenses, devoted to transportation service (line 14).

(3) Financial ratios on a system basis, viz.

(a) Rate of return on investment in operating property plus working capital (line 24).

(b) Rate of return on shareholders' equity less intangibles (line 25).

(c) Operating ratio (line 26).

(d) Turnover ratio (line 27).

Data in Parts I and II of the appendix for each individual traffic study carrier will be

summarized, and, in addition, Part III will show the operating expenses and operating revenues on the traffic at issue for all the Class I and Class II traffic study carriers combined. Line 30 will represent the total dollars that those carriers allegedly need to earn in the projected year. Line 31 of the appendix is a comparison of allegedly needed dollars with the revenues that the carriers project they will in fact obtain, and it should show whether an increase in rates is warranted.

Two items considered in computing the system and issue traffic sum of money, are income taxes (line 9) and rate of return on shareholders' equity less intangibles (line 25). Line 9, columns 3 and 4, will show the actual income taxes paid from the annual report. However, in column 5, the projected year income taxes will be based on the estimated taxable income reduced by the taxes applicable to "other income," such as capital gains transactions. In other words, the statutory tax rate of 48 percent (plus the surcharge tax, if any) should not be used. This represents a departure from previous computations of before-tax income. With respect to line 25, columns 3 and 4 will show the actual rate based on net income (line 10) divided by shareholders' equity less intangibles (line 8). However, in column 5, the amount of net income to be shown will be based on a percent which is to be supported by evidence that it is a just and reasonable rate of return on equity.

5. *Affiliate data.* All traffic study carriers included in the frame shall submit detailed data regarding carrier-affiliate financial and operating relationships and transactions, including any and all individuals, partnerships, and corporations affiliated with respondents, when such transactions aggregate $5,000 or more for any one affiliate during a given year. The sum of the affiliate profits for each traffic study carrier for the years indicated in the appendix shall be shown on line 12 therein. Also, for the years shown in the appendix, the following information shall be provided:

a. If the affiliate derives revenue from the sale or lease of property or from services through transactions with persons other than respondent, indicate the percentage of the revenue of such business to the total revenue of the affiliate for the years indicated.

b. A statement listing the amount of wages, salaries, bonuses, and other compensation paid by the affiliate to any individual who is also a respondent or an officer, director, or substantial stockholder of a respondent; or the wife or close relative of a respondent or officer, director, or substantial stockholder of a respondent.

c. The term "affiliate" as used herein means:

1. Any individual who is also a respondent; an officer, director, or substantial stockholder of a respondent; or the wife or close relative either of a respondent, or of an officer, director, or substantial stockholder of a respondent.

2. Any partnership in which one of the partners is a respondent; an officer, director, or substantial stockholder of a respondent; or the wife or close relative either of a respondent; or of an officer, director, or substantial stockholder of a respondent.

3. Any corporation whose stock is wholly or partly owned by a respondent; by an officer, director, or substantial stockholder of a respondent; or by the wife or close relative either of a respondent or of an officer, director, or substantial stockholder of a respondent.

4. Any corporation which exercises control over the operations or finances of respondent.

Certain detailed information previously required by orders entered in individual revenue proceedings has been eliminated because it has been found that such information is unnecessary to resolve the issues arising in these revenue proceedings. That required above conforms to the revised reporting requirements adopted in No. 35129, Annual Reports of Class I and Class II Motor Carriers of Property.

6. The Commission will take official notice of all of the proponent carriers' annual and quarterly reports on file with the Commission.

7. The detailed information called for herein shall be in writing and shall be verified by a person or persons having knowledge thereof. The original and 16 copies of each verified statement for the use of the Commission shall be filed with the Secretary, Interstate Commerce Commission, Washington, D.C. 20423. One copy of each statement shall be sent by first-class mail to each of the Regional Offices of the Commission in the area affected by the proposed increase, where it will be open to public inspection. A copy of each statement shall be mailed by first-class mail to each party of record in the last formal proceeding concerning a general rate increase in the affected area or territory, and that fact shall be evidenced by a certificate of service filed with the schedules or petitions. Information with respect to carrier affiliates may be served on the parties in summary form, if so desired. Where service is made by mail, the statements shall be mailed in time to be received on the date the original is filed with the Commission. A copy of each statement shall be furnished to any interested person on request.

8. All underlying data used in preparation of the material outlined above shall be made available in the office of the party serving such verified matter during usual office hours for inspection by any party of record desiring to do so, and shall be made available to the Commission upon request therefor. The underlying data shall be made available also at the hearing, but only if and to the extent specifically requested in writing and required by any party for the purpose of cross-examination.

By the Commission.

[SEAL] JOSEPH M. HARRINGTON,
Acting Secretary.

Cost Allocation See Part I, line 16 ☐ Method A, ☐ Method B Check one; provide both

Traffic Study Carrier.....

APPENDIX—REVENUE NEED, FINANCIAL RATIOS AND ALLOCATION TO TRAFFIC IN ISSUE

Line No.	Item	Source for columns 3 and 4 [1]	Second preceding calendar year (actual)	First preceding calendar year (actual)	Projected or constructed year [2]
	(1)	(2)	(3)	(4)	(5)
	Part I. Revenue Need:				
1	Operating revenues	Annual Report Schedule 2998, line 3.	$	$	$
2	Operating expenses	Annual Report Schedule 2998, line 10.	$	$	$
3	Lease of distinct operating unit (net)	Annual Report Schedule 2998, net of lines 12 and 13.	$	$	$
4	Miscellaneous deductions less other income.	Annual Report Schedule 2998 (line 27 minus line 20).	$	$	$
5	Interest included in miscellaneous deductions.	Annual Report Schedule 2998, line 23.	$	$	$
6	Shareholders' equity [3]	Annual Report Schedule 101, line 56.	$	$	$
7	Intangibles [3]	Annual Report Schedule 100, line 32.	$	$	$
8	Shareholders' equity less intangibles	Line 6 minus line 7.	$	$	$
9	Income taxes on ordinary income [4]	Annual Report Schedule 2998, line 29.	$	$	$
10	Net income or loss [5]	Annual Report Schedule 2998, line 35.	$	$	$
11	Sum of money above operating expenses	Sum of lines 4, 9, and 10	$	$	$
12	Affiliate profits [6]	From affiliate analysis	XXX	$	$
13	Sum of money less affiliate profits	Line 11 minus line 12	$	$	$
14	Sum of money devoted to transportation.	(Line 13×line 21)+line 3	$	$	$
15	System revenue need items and projected revenue need.	Line 2+line 14	$	$	$
16	Constant costs and sum of money allocated to issue traffic.	See Method A ☐ and Method B ☐, check one; provide both.	$	$	$
	Part II. Financial Ratios:				
17	Current assets [3]	Annual Report Schedule 100, line 18.	$	$	$
18	Current liabilities [3]	Annual Report Schedule 101, line 14.	$	$	$
19	Carrier operating property (owned plus leased to others). [3]	Annual Report Schedule 100, line 21+line 23.	$	$	$
20	Net tangible property [3]	Annual Report Schedule 100, line 26.	$	$	$
21	Percent property devoted to transportation.	Line 19÷line 20	%	%	%

See footnotes at end of table.

APPENDIX—REVENUE NEED, FINANCIAL RATIOS AND ALLOCATION TO TRAFFIC IN ISSUE—Continued

Line No.	Item	Source for columns 3 and 4 [1]	Second preceding calendar year (actual)	First preceding calendar year (actual)	Projected or constructed year [2]
	(1)	(2)	(3)	(4)	(5)
22	Net carrier operating income	Annual Report Schedule 2998, line 14.	$	$	$
23	Investment in operating property plus working capital.		$	$	$
24	Rate of return on investment	Line 22[7] ÷ line 23	%	%	%
25	Rate of return on shareholders' equity less intangibles.	Line 10 ÷ line 8	%	%	%
26	Operating ratio	Line 2 ÷ line 1	%	%	%
27	Turnover ratio	Line 1 ÷ line 23	$	$	$
	Part III. Data fort raffic at issue of traffic study carriers combined:				
28	Variable expenses from traffic at issue (90 percent) variable excluding return on investment).[8]	From traffic study	XXX	$	$
29	Operating revenues from traffic at issue [8]	From traffic study	XXX	$	$
30	Variable expenses plus constant costs and sum of money allocated to issue traffic.	Line 28 plus summation of line 16.	XXX	$	$
31	Revenue to cost comparison	Line 29 ÷ line 30	XXX	%	%

[1] Annual Report sources apply to Class I motor carriers. For Class II carriers use the comparable source.
[2] Data in this column must be appropriately explained and supported. Each of the projected dollar figures called for in column 5 shall be accompanied by an explanation of the bases or methods of projection, including explicit identification of all projected or assumed changes in wage rates and price levels of other expenses and property items and in productivity as compared with the preceding (actual) year results.
[3] In lines 6, 7, 17, 18, 19, and 20 show average of beginning and end of year figures.
[4] In column 5 show income taxes based on estimated taxable income reduced by the taxes applicable to other income such as, for example, capital gains transactions.
[5] In column 5 compute amount by multiplying line 8 by a percent which is to be supported by evidence that it is a just and reasonable rate of return on equity.
[6] Based upon an analysis of affiliate transactions, calculate the ratio which the charges made by affiliates to their carrier parent bear to the affiliates' total revenues. Apply this ratio to the net income after taxes of the affiliate and show this sum of resulting dollar amounts for all affiliates obtained in the manner on line 12.
[7] Multiply the ratio on line 21 by the difference between lines 17 and 18. Add that resulting amount to line 19.
[8] Show only expenses and revenues allocated to that portion of the issue traffic actually handled by Class I and Class II traffic study carriers included in the frame for sampling purposes based on an expansion of the sample period to a full year.

METHOD A—CONSTANT COSTS AND SUM OF MONEY ALLOCATED TO ISSUE TRAFFIC BASED ON TON AND TON-MILE METHOD (SEE NOTE A)

Line No.	Item	Source for columns 3 and 4	Second preceding calendar year (actual)	First preceding calendar year (actual)	Projected or constructed year
	(1)	(2)	(3)	(4)	(5)
(a)	System constant costs excluding unrelated	(See Note B)	$	$	$
(b)	Not related to distance	(See Note B)	$	$	$
(c)	Related to distance	(See Note B)	$	$	$
(d)	Percent not related to distance	Line (b) ÷ line (a)	%	%	%
(e)	Percent related to distance	Line (c) ÷ line (a)	%	%	%
(f)	System sum of money	Line 14, Part I	$	$	$
(g)	Not related to distance	Line (f) × line (d)	$	$	$
(h)	Related to distance	Line (f) × line (e)	$	$	$
(i)	Total system constant costs plus sum of money.	Line (a) + line (f)	$	$	$
(j)	Not related to distance	Line (b) + line (g)	$	$	$
(k)	Related to distance	Line (c) + line (h)	$	$	$
(l)	System tons carried	Annual Report Schedule 9003, Line 31 (b) + (c).	$	$	$
(m)	System ton-miles	Annual Report Schedule 9003, Line 32 (b) + (c).	$	$	$
(n)	Issue traffic tons carried	From traffic study	$	$	$

See footnotes at end of table.

METHOD A—CONSTANT COSTS AND SUM OF MONEY ALLOCATED TO ISSUE TRAFFIC BASED ON TON AND TON-MILE METHOD (SEE NOTE A)—Continued

Line No.	Item	Source for columns 3 and 4 [1]	Second preceding calendar year (actual)	First preceding calendar year (actual)	Projected or constructed year [2]
	(1)	(2)	(3)	(4)	(5)
(o)	Issue traffic ton-miles	From traffic study	$	$	$
(p)	Percent of issue traffic tons to system tons	Line (n) ÷ line (l)	%	%	%
(q)	Percent of issue traffic ton-miles to system ton-miles.	Line (o) ÷ line (m)	%	%	%
	Conrtant costs and sum of money allocated to issue traffic:				
(r)	Not related to distance	Line (p) × line (j)	$	$	$
(s)	Related to distance	Line (q) × line (k)	$	$	$
(t)	Total (enter amount on line 16, Part I)	Line (r) + line (s)	$	$	$

NOTE A: This procedure allocates constant costs and the sum of money based on the ton and ton-mile method and should be submitted for the information of the Commission. How much of the constant and sum of money costs may or should be recovered by any specific segment of traffic rests on (1) considerations including value of service, demand, and ability to pay, and (2) considerations which involve matters relating to regulatory policy.

NOTE B: When a Class I or Class II traffic study carrier (as defined for revenue need purposes) is an Instruction 27 carrier, separate the amount of constant costs, excluding unrelated, by using Statement No. 6-68, Highway Form B, Schedule A, line 111. Assign the dollars in columns 6, 7, 8, and 9 times 10 percent to line (b), and the dollars in columns 4 and 5 times 10 percent to line (c). When a Class I or Class II traffic study carrier is not an Instruction 27 carrier then use the composite percentage relationships developed for all Instruction 27 carriers (for revenue need purposes) in the following manner:

For Line (a)—
Divide Highway Form B, line 109, column 3 minus column 11 by line 109, column 3 and multiply the resulting percentage by line 2 in Part I. This result is them multiplied by 10 percent to provide the constant costs excluding unrelated.

For Lines (b) and (c)—
Add Highway Form B, line 111, columns 4 and 5 and divide by line 111, column 3. The resulting percentage is then multiplied by line (a) to obtain those system constant costs, excluding unrelated which are related to distance. This figure should be inserted on line (b). To obtain those system constant costs not related to distance subtract line (c) from line (a).

METHOD B—CONSTANT COSTS AND SUM OF MONEY ALLOCATED TO ISSUE TRAFFIC BASED ON DOLLAR (EXPENSE) METHOD (NOTE A)

Line No.	Item	Source for columns 3 and 4	Second preceding calendar year (Actual)	First preceding calendar year (Actual)	Projected or constructed Year
	(1)	(2)	(3)	(4)	(5)
(a)	System constant costs (excluding unrelated).	Note B	$	$	$
(b)	System sum of money	Part I, line 14	$	$	$
(c)	Total system constant costs plus sum of money.	Line (a) plus Line (b)	$	$	$
(d)	Variable expenses from traffic at issue	From traffic study	$	$	$
(e)	System variable expenses (excluding unrelated).	Note C	$	$	$
(f)	Percent relationship	Line (d) + line (e)	$	$	$
(g)	Constant costs and sum of money allocated to issue traffic (enter amount on line 16 Part I)	Line (c) times line (f)	$	$	$

NOTE A: This procedure allocates constant costs and the sum of money based on the dollar (expense) method and should be submitted for the information of the Commission. How much of the constant and sum of money costs may or should be recovered by any specific segment of traffic rests on (1) considerations including value of service, demand, and ability to pay, and (2) considerations which involve matters relating to regulatory policy.

NOTE B: When a Class I or Class II traffic study carrier (as defined for revenue need purposes) is an Instruction 27 carrier, determine the amount of constant costs, excluding unrelated, by using Statement No. 6-68, Highway Form B, Schedule A, line 111, column (3) multiplied by 10 percent; insert this amount on line (a). When a Class I or Class II traffic study carrier is not an Instruction 27 carrier then use the composite percentage relationship developed for all Instruction 27 carriers (for revenue need purposes) in the following manner for line (a): Divide Highway Form B, line 109, column 3 minus column 11 by line 109, column 3 and multiply the resulting percentage by line 2 in Part I. This result is then multiplied by 10 percent to provide the constant costs excluding unrelated.

NOTE C: When a Class I or Class II traffic study carrier (as defined for revenue need purposes) is an Instruction 27 carrier determine the amount of constant costs, excluding unrelated, by using Statement 6-68, Highway Form B, Schedule A, line 111 column 3 multiplied by 90 percent to obtain the variable portion. When a Class I or Class II traffic study carrier is not an Instruction 27 carrier then use the composite percentage relationship developed for all Instruction 27 carriers (for revenue need purposes) in the following manner: Divide Highway Form B, Line 109, column 3, minus column 11 by line 109, column 3, and multiply the resulting percentage by line 2 in Part I. This result is then multiplied by 90 percent.

[F.R. Doc. 70-11525; Filed, Sept. 1, 1970; 8:45 a.m.]

FOURTH SECTION APPLICATIONS FOR RELIEF

AUGUST 28, 1970.

Protests to the granting of an application must be prepared in accordance with § 1100.40 of the general rules of practice (49 CFR 1100.40) and filed within 15 days from the date of publication of this notice in the FEDERAL REGISTER.

LONG-AND-SHORT HAUL

FSA No. 42041—*Soda ash from Solvay and Syracuse, N.Y.* Filed by Traffic Executive Association-Eastern Railroads, agent (E.R. No. 2985), for interested rail carriers. Rates on soda ash, in bulk, in covered hopper cars, in carloads, as described in the application, from Solvay and Syracuse, N.Y., to West Carteret-Woodbridge, N.J.

Grounds for relief—Market competition.

Tariff—Supplement 93 to Erie Lackawana Railway Co. tariff ICC 24660 (DL&W Series).

FSA No. 42042—*Iron or steel pipe and related articles from Boston, Mass.* Filed by Southwestern Freight Bureau, agent (No. B-181), for interested rail carriers. Rates on iron or steel pipe and related articles, in carloads, as described in the application, from Boston, Mass., to points in southwestern territory.

Grounds for relief—Market competition and rate relationship.

Tariff—Supplement 162 to Southwestern Freight Bureau, agent, tariff ICC 4620.

By the Commission.

[SEAL] JOSEPH M. HARRINGTON,
Acting Secretary.

[F.R. Doc. 70-11587; Filed, Sept. 1, 1970; 8:49 a.m.]

[Notice 81]

MOTOR CARRIER APPLICATIONS AND CERTAIN OTHER PROCEEDINGS

AUGUST 28, 1970.

The following publications are governed by the new Special Rule 1.247 of the Commission's rules of practice, published in the FEDERAL REGISTER, issue of December 3, 1963, which became effective January 1, 1964.

The publications hereinafter set forth reflect the scope of the applications as filed by applicant, and may include descriptions, restrictions, or limitations which are not in a form acceptable to the Commission. Authority which ultimately may be granted as a result of the applications here noticed will not necessarily reflect the phraseology set forth in the application as filed, but also will eliminate any restrictions which are not acceptable to the Commission.

MOTOR CARRIERS OF PROPERTY

No. MC 109478 (Sub-No. 114) (Republication), filed September 18, 1969, published in the FEDERAL REGISTER issue of November 20, 1969, and republished this issue. Applicant: WORSTER MOTOR LINES, INC., Gay Road, North East, Pa. 16428. Applicant's representative: William W. Knox, 23 West 10th Street, Erie, Pa. 16501. A recommended report and order of the Hearing Examiner which was served July 16, 1970, and which became effective by operation of law on August 17, 1970, with a service date of August 25, 1970, finds; upon consideration of all evidence of record, that the present and future public convenience and necessity require operation by applicant, in interstate or foreign commerce as a common carrier by motor vehicle, over irregular routes, of (1) fruit juices and fruit juice products, from Brocton and Westfield, N.Y., and North East, Pa., to points in Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania, Delaware, Maryland, West Virginia, the District of Columbia, Indiana, Illinois, Ohio, and the Lower Peninsula of Michigan (except that no service may be performed under this authority from North East, Pa., to points in Pennsylvania), (2) vinegar, from Lindonville, North Rose, and Lyons, N.Y., to Champaign, Ill., and points in Pennsylvania, Ohio, Massachusetts, Connecticut, and Rhode Island, (3) wine and grape juice from Westfield, N.Y., to points in Pennsylvania, Massachusetts, Rhode Island, New York (except New York City), Connecticut, New Jersey, Delaware, Maryland, the District of Columbia, Indiana, Illinois, Ohio, and the Lower Peninsula of Michigan, and (4) wine, from Brocton, N.Y., to points in Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania, Delaware, Maryland, West Virginia, the District of Columbia, Indiana, Illinois, Ohio, and the Lower Peninsula of Michigan; subject to the restriction that any duplication between the authority granted herein and any other authority held by applicant shall be considered as resulting in a single operating right, not severable by sale or otherwise. Because it is possible that other parties who have relied upon the notice of the application as published, may have an interest in and would be prejudiced by the lack of proper notice of the authority described in the findings in this order, a notice of the authority actually granted will be published in the FEDERAL REGISTER and issuance of a certificate in this proceeding will be withheld for a period of 30 days from the date of such publication, during which period any proper party in interest may file a petition for leave to reopen the proceeding or for other appropriate relief setting forth in detail the precise manner in which it has been so prejudiced.

No. MC 119767 (Sub-No. 231) (Republication), filed December 4, 1969, published in the FEDERAL REGISTER issue of January 22, 1970, and republished this issue. Applicant: BEAVER TRANSPORT CO., a corporation, 100 South Calumet Street, Burlington, Wis. 53105. Applicant's representative: A. Bryant Torhorst (same address as applicant). The modified procedure has been followed in this proceeding and an order of the Commission, Operating Rights Board, dated July 31, 1970, and served August 20, 1970, finds; that the present and future public convenience and necessity require operation by applicant, in interstate or foreign commerce, as a common carrier by motor vehicle, over irregular routes, (1) of prepared food and beverages, from Munster, Ind., to Cincinnati, Ohio, and (2) (a) of charcoal, charcoal briquettes, wood chips, lighter fluid and fireplace logs and (b) accessories used in outdoor cooking, in mixed loads with the commodities authorized in (2) (a) above, from Waupaca, Wis., to points in Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota, Missouri, Nebraska, and Ohio, and to Kansas City, Kans. Because it is possible that other parties who have relied upon the notice of the application as previously published may have an interest in and would be prejudiced by the lack of proper notice of the authority described in the findings in this order, a notice of the authority actually granted will be published in the FEDERAL REGISTER and issuance of a certificate in this proceeding will be withheld for a period of 30 days from the date of such publication, during which period any proper party in interest may file an appropriate petition to reopen or for other appropriate relief setting forth in detail the precise manner in which it has been so prejudiced.

No. MC 124705 (Sub-No. 3) (Republication), filed August 19, 1968, published in the FEDERAL REGISTER issue of September 6, 1968, and November 7, 1968, and republished this issue. Applicant: SWAN MESSENGER SERVICE, INC., Post Office Box 3, East Brunswick, N.J. 08816. Applicant's representative: William J. Augello, Jr., 36 West 44th Street, New York, N.Y. 10036. A Report and Order of the Commission, Division 1, Acting as an Appellate Division, decided August 5, 1970, and served August 21, 1970, on reconsideration, finds; that the present and future public convenience and necessity require operation by applicant, as a common carrier by motor vehicle, over irregular routes of general commodities (except classes A and B explosives, household goods as defined by the Commission, commodities in bulk, commodities requiring special equipment, cash letters, articles of unusual value, radiopharmaceuticals and medical isotopes, and exposed and processed film and prints) between points in Middlesex County, N.J., on the one hand, and, on other, Baltimore, Md., restricted against the transportation (1) of any packages weighing more than 250

pounds each, and (2) of shipments weighing in the aggregate more than 5,000 pounds from one consignor to consignee on any 1 day; that applicant is fit, willing, and able properly to perform such service and to conform to the requirements of the Interstate Commerce Act and our rules and regulations thereunder; that a certificate authorizing such operation should be granted, subject to the condition that to the extent the authority granted herein duplicates any authority now held by applicant, it shall not be construed as conferring more than a single operating right. Because it is possible that other persons, who have relied upon the notice of the application as published, may have an interest in and would be prejudiced by a lack of proper notice of the authority described in the findings herein, a notice of the authority actually granted will be published in the FEDERAL REGISTER and issuance of a certificate in this proceeding will be withheld for a period of 30 days from the date of such publication, during which period any proper party in interest may file a petition to reopen the proceeding or for other appropriate relief setting forth in detail the precise manner in which it has been so prejudiced.

No. MC 133189 (Republication), filed September 25, 1968, published in the FEDERAL REGISTER issue of October 17, 1968, and republished this issue. Applicant: VANT TRANSFER, INC., 5075 Mulcare Drive, Minneapolis, Minn. 55421. Applicant's representative: William S. Rosen, 630 Osborne Building, St. Paul, Minn. 55102. A Report and Order of the Commission, Division 1, Acting as an Appellate Division, decided August 7, 1970, and served August 20, 1970, finds; that the present and future public convenience and necessity require operation by applicant, in interstate or foreign commerce, as a common carrier by motor vehicle, over irregular routes, of iron and steel articles, from the plantsites of North Star Steel Co., at Newport, Minn., to points in Colorado, Idaho, Illinois, Montana, Nebraska, North Dakota, South Dakota, Washington, Wisconsin, Wyoming, and Utah; that applicant is fit, willing, and able properly to perform such service and to conform to the requirements of the Interstate Commerce Act and to the Commission's rules and regulations thereunder. Because it is possible that other parties, who have relied upon the notice of the application as published, may have an interest in and would be prejudiced by the lack of proper notice of the authority described in the findings in this report, a notice of the authority actually granted will be published in the FEDERAL REGISTER and issuance of a certificate in this proceeding will be withheld for a period of 30 days from the date of such publication, during which period any proper party in interest may file an appropriate petition to reopen or for other appropriate relief setting forth in detail the precise manner in which it has been so prejudiced.

No. MC 134203 (Sub-No. 2) (Republication), filed December 22, 1969, published in the FEDERAL REGISTER issue of January 29, 1970, and republished this issue. Applicant: CHEMICAL STORAGE AND TRANSPORT CORPORATION, Post Office Box 419, 5100 Virginia Beach Boulevard, Norfolk, Va. 23501. Applicant's representative: Robert V. Peabody (same address as above). By application filed and published as indicated above, applicant seeks a permit as *contract carrier* by motor vehicle. The modified procedure has been followed in this proceeding and a Report and Order of the Commission, Review Board Number 1, decided August 15, 1970, and served August 24, 1970, finds; that viewing the substance of the application, the proposed service is actually that of a *common carrier* by motor vehicle; and that the present and future public convenience and necessity require operation by applicant, in interstate or foreign commerce, as a common carrier by motor vehicle, over irregular routes, of molten sulphur, in bulk, in tank vehicles, from Norfolk, Va., to Tunis, N.C.; that applicant is fit, willing, and able properly to perform such service and to conform to the requirements of the Interstate Commerce Act and the Commission's rules and regulations thereunder. Because it is possible that other parties, who have relied upon the notice of the application as published may have an interest in and would be prejudiced by the lack of proper notice of the authority described in this order, a notice of the authority actually granted will be published in the FEDERAL REGISTER and issuance of a certificate in this proceeding will be withheld for a period of 30 days from the date of such publication during which period any proper party in interest may file a petition to reopen or for other appropriate relief setting forth in detail the precise manner in which it has been so prejudiced.

NOTICE OF FILING OF PETITIONS

No. MC 30209 (Sub-Nos. 6, 9, and 18), (Notice of Filing of Petition for Modification and Amendment of Permits for Addition of Shipper and Change of Warehouse Location), filed August 7, 1970. Petitioner: JOHN O'SHEA, INC., Ridgefield Park, N.J. Petitioner's representative: Bert Collins, 140 Cedar Street, New York, N.Y. 10006. Petitioner holds permit in No. MC 30209 Sub No. 6 to operate as a motor contract carrier, transporting: Such merchandise as is dealt in by wholesale and retail grocery businesses, between Carlstadt, N.J., on the one hand, and, on the other, points in Orange, Rockland, Westchester, Nassau, and Suffolk Counties, N.Y., and points in Northampton, Lehigh, and Berks Counties, Pa., under a continuing contract, or contracts, with S and W Fine Foods, Inc., Carlstadt, N.J. It holds authority in No. MC 30209 Sub No. 9 to transport: Such merchandise as is dealt in by wholesale, retail, and chain grocery and food business houses, from the warehouse site of S and W Fine Foods, Inc., in Carlstadt, N.J., to Albany, N.Y., and points in Sullivan, Ulster, Dutchess, and Putnam Counties, N.Y.; and Returned shipments of the above-described commodities, from Albany, N.Y., and points in Sullivan, Ulster, Dutchess, and Putnam Counties, N.Y., to the warehouse site of S and W Fine Foods, Inc., in Carlstadt, N.J., under continuing contract, or contracts, with S and W Fine Foods, Inc., of Carlstadt, N.J. It holds authority in No. MC 30209 Sub No. 18 to transport: Such merchandise as is dealt in by wholesale, retail, and chain grocery and food business houses (except commodities in bulk in tank vehicles), between Newark, N.J., on the one hand, and, on the other, points in Orange, Rockland, Westchester, Nassau, Suffolk, Sullivan, Ulster, Dutchess, and Putnam Counties, N.Y.; and Northampton, Lehigh, Berks, Bucks, Montgomery, and Philadelphia Counties, Pa., under contract, or contracts with White Rose Foods Corp., of East Elizabeth, N.J. By the instant petition, petitioner requests that permits MC 30209 Subs 6 and 9 be modified by deleting Carlstadt, N.J., as an origin point and substituting the origin of Jersey City, N.J., and adding to MC 30209 Sub 18 the name of S and W Fine Foods, Inc., as an additional contracting shipper in connection therewith. Any interested person desiring to participate may file an original and six copies of his written representations, views, or argument in support of, or against the petition within 30 days from the date of publication in the FEDERAL REGISTER.

No. MC 45021 (Sub-No. 5) (Notice of Filing of Petition for Modification and Amendment of Permit for Addition of Shipper), filed August 13, 1970. Petitioner: SPEEDY TRUCKING CO., INC., Totowa, N.J. Petitioner's representative: Bert Collins, 140 Cedar Street, New York, N.Y. 10006. Petitioner holds a permit in No. MC 45021 (Sub-No. 5) authorizing the transportation as a motor contract carrier, over irregular routes, of: Such merchandise as is dealt in by wholesale and retail grocery houses (except in bulk), between points in Totowa Borough (Passaic County), N.J., on the one hand, and, on the other, points in Connecticut, Delaware, Massachusetts, New York, Pennsylvania, and Rhode Island. Restriction: The operations authorized herein are limited to a transportation service to be performed under a continuing contract, or contracts, with Filigree Foods, Inc., of Totowa, N.J. by the instant petition, petitioner seeks to add J. Ossola Co., Inc., as an additional shipper. Any interested person desiring to participate may file an original and six copies of his written representations, views, or argument in support of or against the addition of such shipper within 30 days from the date of publication in the FEDERAL REGISTER.

No. MC 125918 (Sub-Nos. 1, 4, and 6) (Notice of Filing of Petition to Add Name of Shipper), filed August 7, 1970. Petitioner: JOHN A. DIMEGLIO, Ancora, N.J. Petitioner's representative: George A. Olsen, 69 Tonnele Avenue, Jersey City, N.J. 07306. Petitioner holds authority in No. MC 125918 Sub 1, as follows: *Brick*, over irregular routes, from Winslow, N.J., to points in Chester, Montgomery, Bucks, Delaware, Lancaster, Berks, Philadelphia, and Lehigh Counties, Pa., and Delaware, with no

transportation for compensation on return except as otherwise authorized. From Washington, D.C., and Charleston, Martinsburg, and North Mountain, W. Va., to points in Chester, Montgomery, Bucks, Delaware, Lancaster, Berks, Philadelphia, and Lehigh Counties, Pa., Mercer, Middlesex, Monmouth, Ocean, Burlington, Camden, Gloucester, Salem, Atlantic, Cumberland, and Cape May Counties, N.J., and Delaware, with no transportation for compensation on return except as otherwise authorized. From Harrisburg, Middletown, Ephrata, Wyomissing, Shoemakersville, York, Watsontown, and Mifflinville, Pa., and points in the Beaver Falls, Pa., commercial zone as defined by the Commission (except Fallston, Pa.) to points in Mercer, Middlesex, Monmouth, Ocean, Burlington, Camden, Gloucester, Salem, Atlantic, Cumberland, and Cape May Counties, N.J., and Delaware, with no transportation for compensation on return except as otherwise authorized. Restriction: The operations authorized herein are limited to a transportation service to be performed under a continuing contract, or contracts, with the Diener Brick Co., of Collingswood, N.J. In No. MC 125918 Sub 4, as follows: *Brick, tile and clay products*, over irregular routes, from Ancora, N.J., to points in New Jersey, with no transportation for compensation on return except as otherwise authorized. Restriction: The service authorized herein is subject to the following conditions: The authority granted herein shall be restricted to shipments having a prior movement by rail from origins beyond New Jersey. The operations authorized herein are limited to a transportation service to be performed, under a continuing contract or contracts, with the following shipper: Diener Brick Co., of Collingswood, N.J., Glenwood Refractories Co., of Brooklyn, N.Y. In No. MC 102918 Sub 6 as follows: Brick and tile (except refractories), from Hazelton and Fallston, Pa., to points in Delaware and points in Mercer, Middlesex, Monmouth, Ocean, Burlington, Camden, Gloucester, Salem, Atlantic, Cumberland, and Cape May Counties, N.J., with no transportation for compensation on return except as otherwise authorized. From points in Virginia, North Carolina, and South Carolina, to points in Delaware, points in Mercer, Middlesex, Monmouth, Ocean, Burlington, Camden, Gloucester, Salem, Atlantic, Cumberland, and Cape May Counties, N.J., and those in Chester, Montgomery, Bucks, Delaware, Lancaster, Berks, Philadelphia, and Lehigh Counties, Pa., with no transportation for compensation on return except as otherwise authorized. Restriction: The operations authorized herein are limited to a transportation service to be performed, under a continuing contract, or contracts, with Diener Brick Co., of Collingswood, N.J. By the instant petition, petitioner seeks to add the name of Glen-Gery Corp., Reading, Pa., as an additional shipper. Any interested person desiring to participate may file an original and six copies of his written representations, views or argument in support of or against the petition within 30 days from the date of publication in the FEDERAL REGISTER.

TRANSFER APPLICATIONS UNDER SECTION 212(b) WHICH HAVE BEEN DESIGNATED FOR ORAL HEARING

No. MC–FC–71552 (Corection), published FEDERAL REGISTER, issue of August 5, 1970, and republished as corrected this issue. Authority sought by transferee, La Venture Bros. Transfer, a corporation, doing business as La Venture Bros. Van Lines, 3808 East Slauson Avenue, Maywood, Calif. 90270, to transfer to transferee a portion of the operating authority of transferor, Cartwright Van Lines, Inc., 4411 East 119th Street, Grandview, Mo. 64030. Transferee's and transferor's representatives: John S. Byrnes, Jr., Suite 219, Alhambra Professional Building, 317 West Main Street, Alhambra, Calif. 91801, for transferee, and Wentworth E. Griffin, Suite 812, Midland Building, 1221 Baltimore Avenue, Kansas City, Mo. 64105, for transferor. NOTE: The purpose of this partial publication is to show Wentworth E. Griffin as attorney for transferor, in lieu of Warren N. Grossman incorrectly shown as party in this transaction. The remainder of the notice remains as previously published.

APPLICATIONS FOR CERTIFICATES OR PERMITS WHICH ARE TO BE PROCESSED CONCURRENTLY WITH APPLICATIONS UNDER SECTION 5 GOVERNED BY SPECIAL RULE 240 TO THE EXTENT APPLICABLE.

No. MC 50307 (Sub-No. 54), filed July 23, 1970. Applicant: INTERSTATE DRESS CARRIERS, INC., 247 West 35th Street, New York, N.Y. 10001. Applicant's representative: Herbert Burstein, 30 Church Street, New York, N.Y. 10007. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Wearing apparel, materials, supplies, and equipment* used in the manufacture thereof. NOTE: The instant application seeks solely to remove New York, N.Y., as a gateway so that applicant may be able to operate directly from points which it is authorized to serve under its certificate No. MC 50307 and sub numbers thereunder, and the points in New Jersey presently held in No. MC 32631 and subs thereunder. Applicant states that the authority in said MC 32631 and subs thereunder generally authorizes service between points in the New York, N.Y., commercial zone and various counties in New Jersey, which authority applicant is seeking to acquire by an application filed under section 5 of the Interstate Commerce Act. The instant application is a matter directly related to No. MC–F–10904, published in the FEDERAL REGISTER issue of August 5, 1970. If a hearing is deemed necessary, applicant requests it be held at New York, N.Y.

No. MC 72140 (Sub-No. 57), filed August 11, 1970. Applicant: SHIPPERS DISPATCH, INC., 1216 West Sample Street, South Bend, Ind. 46624. Applicant's representative: Ferdinand Born, 601 Chamber of Commerce Building, Indianapolis, Ind. 46204. Authority sought to operate as a *common carrier*, by motor vehicle, over regular and irregular routes, transporting: Regular route: *General commodities* (except classes A and B explosives), between Decatur and Quincy, Ill, from Decatur over U.S. Highway 36 to junction Illinois Highway 125, thence over Illinois Highway 125 to junction U.S. Highway 67, thence over U.S. Highway 67 to junction U.S. Highway 24, thence over U.S. Highway 24 to Quincy, and return over the same route, serving all intermediate points, and the off-route points of Petersburg and Meredosia, Ill. Irregular routes: *General commodities*, serving Jerseyville, Ill., and points in Illinois within a 50-mile radius thereof. NOTE: This application is directly related to MC–F–10923, published in the FEDERAL REGISTER issue of August 19, 1970. Applicant states it could tack at East St. Louis, Springfield, Decatur, and Peoria, Ill. If a hearing is deemed necessary, applicant requests it be held at Chicago, Ill., or St. Louis, Mo.

No. MC 134029 (Sub-No. 1), filed January 22, 1970. Applicant: SIGEL HEAVY HAULING COMPANY, a corporation, Rural Delivery No. 5, Post Office Box 146, Cadiz, Ohio 43807. Applicant's representative: Paul F. Beery, 88 East Broad Street, Columbus, Ohio 43215. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Commodities* which because of size or weight require the use of special equipment, between points in Wood, Pleasants, Wirt, and Jackson Counties, W. Va., on the one hand, and, on the other, points in West Virginia, (2) *contractor's equipment, steel, lumber, plaster, plaster materials, brick, timbers*, (including posts and cross ties used for piling), *concrete and metal pipe, cement, heavy machinery and fabricated houses*, between points in Jackson, Putnam, Lincoln, Boone, Kanawha, Roane, Clay, Nicholas, Fayette, and Raleigh Counties, W. Va., and (3) *road building materials, contractor's equipment, and construction machinery* (except commodities in bulk), between points in Pleasants, Wood, Wirt, Calhoun, Gilmer, Braxton, Randolph, Pocahontas, Webster, Mason, Putnam, Kanawha, Roane, Clay, Nicholas, Greenbrier, Monroe, Summers, Fayette, Raleigh, Boone, Lincoln, Wayne, Cabell, Mingo, Logan, Wyoming, McDowell, and Mercer Counties, W. Va. NOTE: This application is directly related to MC–FC–71939, published in the FEDERAL REGISTER issue of February 3, 1970. The purpose of this application is to convert the certificate of registration of Badgett Trucking Co., MC 112798 Sub 6 to a Certificate of Public Convenience and Necessity. Applicant states that, if this application is approved, it will tack (1), (2), and (3) above and will further tack this authority so as to permit operations between points in West Virginia, on the one hand, and, on the other, points in Allegheny, Washington, and Fayette Counties, Pa. If a hearing is deemed necessary, applicant requests it be held at Columbus, Ohio.

APPLICATIONS UNDER SECTIONS 5 AND 210a(b)

The following applications are governed by the Interstate Commerce Commission's special rules governing notice of filing of applications by motor carriers of property or passengers under sections 5(a) and 210a(b) of the Interstate Commerce Act and certain other proceedings with respect thereto. (49 CFR 1.240).

MOTOR CARRIERS OF PROPERTY

No. MC-F-10901. (Correction) (NORTH PENN TRANSFER, INC.—Purchase (portion)—EASTON MOTOR FREIGHT, INC.), published in July 29, 1970 issue of the FEDERAL REGISTER on page 12170. This notice is to show that the regular route authority to be acquired by NORTH PENN TRANSFER, INC., is solely *between Phillipsburg, N.J., and Easton, Pa., serving off-route points in Lehigh and Northampton Counties, Pa., subject to certain restrictions.*

No. MC-F-10929. Authority sought for purchase by BANKERS DISPATCH CORPORATION, 4970 South Archer Avenue, Chicago, Ill., 60632, of the operating rights of B. D. C. LTD., 20 Sheffield St., Toronto, Ontario, Canada, and for acquisition by BANKERS UTILITIES CORP., also of Chicago, Ill., of control of such rights through the purchase. Applicants' attorneys: Arnold L. Burke, 69 West Washington Street, Chicago, Ill. 60602, and Warren W. Wallin, 330 South Jefferson, Chicago, Ill. 60606. Operating rights sought to be transferred: *Such commercial papers, documents, written instruments, and business records* (except currency and negotiable securities) as are used in the conduct and operation of banks and banking institutions, as a *common carrier* over irregular routes, between Buffalo, N.Y., on the one hand, and, on the other, those ports of entry on the United States-Canada boundary line at Fort Erie and Niagara Falls, N.Y.; *such commerial papers, documents, and written instruments* (except currency, and negotiable securities) as are used in the conduct and operation of banks and banking institutions, and *audit media and other business records,* between Seattle, Wash., on the one hand, and, on the other, the port of entry on the United States-Canada boundary line located at Blaine, Wash.; and in pending Docket No. MC-129416 Sub 7, covering the transportation of (1) processed and unprocessed film, prints, slides, audio and video tapes, and materials and supplies used in connection with commercial and television motion pictures; (2) audit media and other business records; and (3) graphic arts material, between Bellingham, Wash., on the one hand, and, on the other the port of entry on the international boundary line between the United States and Canada at Blaine, Wash. Vendee is authorized to operate as a *common carrier* in Nebraska, Kansas, Missouri, Illinois, Indiana, Michigan, Wisconsin, Iowa, Tennessee, Ohio, Utah, Colorado, California, Washington, Montana, Wyoming, Nevada, and Oregon, and as a *contract carrier* in Missouri, Illinois, Tennessee, Indiana, Michigan, Ohio, Kansas, Nebraska, Iowa, Utah, Idaho, and Colorado. Application has not been filed for temporary authority under section 210a(b).

No. MC-F-10932. Authority sought for control and merger by BOWLING GREEN EXPRESS, INC., Post Office Box 1111, Plum Springs Road, Bowling Green, Ky. 42101, of the operating rights and property of MORGANTOWN TRUCKING CO., INCORPORATED, 122 Tredco Drive, Nashville, Tenn. 37219, and for acquisition by DAMON MAJORS, Caneyville, Ky., of control of such rights and property through the transaction. Applicants' attorneys: Walter Harwood, 1822 Parkway Towers, 404 James Robertson Parkway, Nashville, Tenn. 37218 and Robert M. Pearce, Post Office Box E, Bowling Green, Ky. 42101. Operating rights sought to be controlled and merged: *General commodities,* except those of unusual value, classes A and B explosives, household goods as defined by the Commission, commodities in bulk, and those requiring special equipment, as a *common carrier* over regular routes, between Nashville, Tenn., and Morgantown, Ky., serving those intermediate points which are located in Butler County, Ky., with restriction. BOWLING GREEN EXPRESS, INC., is authorized to operate as a *common carrier* in Kentucky and Tennessee. Application has been filed for temporary authority under section 210a(b).

No. MC-F-10933. Authority sought for purchase by HART MOTOR EXPRESS, INC., 2417 North Cleveland Avenue, St. Paul, Minn. 55113, of a portion of the operating rights of RINGSBY-PACIFIC, LTD., 3201 Ringsby Court, Denver, Colo. 80216, and for acquisition by GEORGE HART also of St. Paul, Minn., of control of such rights through the purchase. Applicants' attorney and representative: Donald A. Morken, 1000 First National Bank Building, Minneapolis, Minn. 55402, and John Miller, 3201 Ringsby Court, Denver, Colo. 80216. Operating rights sought to be purchased: *General commodities,* excepting, among others, classes A and B explosives, household goods and commodities in bulk, as a *common carrier* over regular routes, between Shelby, Mont., and the site of the Glasgow Air Force Base, located approximately 22 miles northeast of Glasgow, Mont., serving all intermediate points, between Glasgow, Mont., and Fort Peck, Mont., serving all intermediate points and those off-route points within 10 miles of Fort Peck, between Havre, Mont., and Great Falls, Mont., serving all intermediate points. Vendee is authorized to operate as a *common carrier* in Illinois, Minnesota, Wisconsin, Montana, North Dakota, Missouri, South Dakota, Iowa, Ohio, Nebraska, and Indiana. Application has been filed for temporary authority under section 210a(b).

No. MC-F-10934. Authority sought for purchase by NORTHEASTERN TRUCKING COMPANY, 2508 Starita Road, Post Office Box 2676, Charlotte, N.C. 28213, of a portion of the operating rights of PARRISH DRAY LINE, INC., 285 South Stratford Road, Winston-Salem, N.C., and for acquisition by JOHN F. GUIGNARD and WILLIAM H. GUIGNARD, also of Charlotte, N.C., of control of such rights through the purchase. Applicants' attorney: Edward G. Villalon, 1735 K Street NW., Washington, D.C. 20006. Operating rights sought to be transferred: *General commodities,* excepting, among others, dangerous explosives, household goods and commodities in bulk, as a *common carrier* over irregular routes, between points and places in Sumter County, S.C., on the one hand, and, on the other, Augusta, Atlanta, and Columbus, Ga. Vendee is authorized to operate as a *common carrier* in Illinois, New York, New Jersey, Pennsylvania, North Carolina, Maryland, South Carolina, Virginia, Florida, Tennessee, Connecticut, New Hampshire, Massachusetts, Rhode Island, Kentucky, Louisiana, Alabama, Georgia, Ohio, Indiana, West Virginia, District of Columbia, Maine, Michigan, Minnesota, Mississippi, Texas, Missouri, and Vermont. Application has been filed for temporary authority under section 210a(b).

MOTOR CARRIER OF PASSENGERS

No. MC-F-10931. Authority sought for control by ARTHUR BERNACCHIA and GEORGE BERNACCHIA, 41 Railroad Avenue, Yonkers, N.Y., of WEST FORDHAM TRANSPORTATION CORP., 110 Edison Avenue, Mount Vernon, N.Y. 10550, and for acquisition by ARTHUR BERNACCHIA and GEORGE BERNACCHIA, also of Yonkers, N.Y., of control of WEST FORDHAM TRANSPORTATION CORP., through the acquisition by ARTHUR BERNACCHIA and GEORGE BERNACCHIA. Applicants' attorney: Samuel B. Zinder, Station Plaza East, Great Neck, N.Y. 11021. Operating rights sought to be controlled: Passengers and their baggage, and newspapers in the same vehicle with passengers, as a common carrier, over regular routes, between New Rochelle, N.Y., and Port Chester, N.Y., between New Rochelle, N.Y., and Stamford, Conn., between New Rochelle, N.Y., and New York, N.Y., between Connecticut Turnpike Exit No. 5 and Greenwich, Conn., between Connecticut Turnpike Exit No. 4 and Greenwich, Conn., between Connecticut Turnpike Exit No. 3 and Greenwich, Conn., between Connecticut Turnpike Exit No. 2 and Greenwich, Conn. (on applicant's presently authorized routes), between junction U.S. Highway 1 (Main Street) and Atlantic Street in Stamford, Conn., and Connecticut Turnpike Entrance No. 7 in Stamford, Conn., between New England Thruway Exit No. 13 in Rye, N.Y., and Port Chester, N.Y., between New England Thruway Exit No. 12 and Rye, N.Y., between New England Thruway Exit No. 11 and Rye, N.Y., between New England Thruway Exit No. 10 and Mamaroneck, N.Y., between New England Thruway Exit No. 9 and Larchmont, N.Y., between New England Thruway Exit No. 8 and New Rochelle, N.Y., between New England Thruway Exit No. 7

and New Rochelle, N.Y., serving all intermediate points, with restriction; passengers and their baggage, in special operations, as a common carrier, over irregular routes, between New York, N.Y., on the one hand, and, on the other, Norwalk, Conn., with restriction. ARTHUR BERNACCHIA and GEORGE BERNACCHIA hold no authority from this Commission. However, they are affiliated with the following carriers: (A) CONNECTICUT-NEW YORK AIRPORT BUS CO. INC., 1503 Post Road, Milford, Conn. 06460, which is authorized to operate as a *common carrier* in Connecticut, and New York. (B) RESORT BUS LINES, INC., 31 Edgecomb Place, Yonkers, N.Y. 10710, which is authorized to operate as a *common carrier* in New York, and Massachusetts. (C) CROSS COUNTY COACH CORPORATION, 152 Downing Street, Yonkers, N.Y. 10705, which is authorized to operate as a *common carrier* in New York, New Jersey, Connecticut, and Pennsylvania. Application has been filed for temporary authority under section 210a(b).

By the Commission.

[SEAL] JOSEPH M. HARRINGTON,
Acting Secretary.

[F.R. Doc. 70-11586; Filed, Sept. 1, 1970; 8:49 a.m.]

NOTICE OF FILING OF MOTOR CARRIER INTRASTATE APPLICATIONS

AUGUST 28, 1970.

The following applications for motor common carrier authority to operate in intrastate commerce seek concurrent motor carrier authorization in interstate or foreign commerce within the limits of the intrastate authority sought, pursuant to section 206(a)(6) of the Interstate Commerce Act, as amended October 15, 1962. These applications are governed by § 1.245 of the Commission's rules of practice, published in the FEDERAL REGISTER, issue of April 11, 1963, page 3533, which provides, among other things, that protests and requests for information concerning the time and place of State Commission hearings or other proceedings, any subsequent changes therein, any other related matters shall be directed to the State Commission with which the application is filed and shall not be addressed to or filed with the Interstate Commerce Commission.

State Docket No. 4354, filed July 14, 1970. Applicant: ALLISON-LOGAN FREIGHT LINE, INC., 106 West High Street, Terrell, Tex. 75160. Applicant's representative: Tom M. Snow (same address as applicant). Certificate of public convenience and necessity sought to operate as a freight service as follows: Transportation of *General commodities* (1) between Terrell, Tex., and Kaufman, Tex., over Texas Highway 34 and return over the same route; (2) between Kaufman, Tex., and Dallas, Tex., over U.S. Highway 175, and return over the same route, serving all intermediate points; (3) between Terrell, Tex., and Mineola, Tex., over U.S. Highway 80 and return over the same route, serving all intermediate points; (4) between Mineola, Tex., and Emory, Tex., over U.S. Highway 69 and return over the same route, serving all intermediate points; and (5) between Emory, Tex., and Fruitvale, Tex., over Texas Highway 19 and return over the same route, serving all intermediate points; coordinating this authority with that rendered under other authority. Both intrastate and interstate authority sought.

HEARING: Approximately 20 days after publication in the FEDERAL REGISTER. Requests for procedural information, including the time for filing protests, concerning this application should be addressed to the Railroad Commission of Texas, Capitol Station, Post Office Drawer E. E., Austin, Tex., 78111, and should not be directed to the Interstate Commerce Commission.

State Docket No. MC 5450, filed July 24, 1970. Applicant: PARKHURST MOTOR FREIGHT COMPANY, 235 10th Avenue North, Nashville, Tenn. Applicant's representatives: James Clarence Evans and William G. Womack, 18th Floor, Third National Bank Building, Nashville, Tenn. 37219. Certificate of public convenience and necessity sought to operate a freight service as follows: Transportation of *general commodities* (except used household goods, explosives, commodities in bulk, and commodities requiring specialized equipment), between Nashville, Tenn., and Clarksville, Tenn., as follows: From Nashville over U.S. Highway 41A to Clarksville and return over the same route, serving all intermediate points. Both intrastate and interstate authority sought.

HEARING: September 16, 1970, at 9:30 a.m., C-1-110 Cordell Hull Building, Nashville, Tenn. Requests for procedural information, including the time for filing protests, concerning this application should be addressed to the Tennessee Public Service Commission, Cordell Hull Building, Nashville, Tenn. 37219, and should not be directed to the Interstate Commerce Commission.

State Docket No. A 52064, filed July 22, 1970. Applicant: LOS ANGELES CITY EXPRESS, INC., 2300 East 48th Street, Los Angeles, Calif. 90058. Applicant's representative: Alvin H. Weissman, 9700 Venice Boulevard, Culver City, Calif. 90230. Certificate of public convenience and necessity sought to extend applicant's present authority pursuant to certificate of public convenience and necessity issued by the Public Utilities Commission of the State of California in decision number 73964 dated April 9, 1968, to operate a freight service as follows: Transportation of *General commodities* (except those of unusual value, classes A and B explosives, household goods as defined by the Commission, commodities in bulk, and those requiring special equipment) (a) U.S. Highway 395 between San Bernardino and Kramer Junction, inclusive; (b) U.S. Highway 66 and 91 between San Bernardino and Barstow, inclusive; (c) State Highway 18 between Victorville and Apple Valley, inclusive; (d) Unnumbered highway between Victorville and Barstow, inclusive; (e) U.S. Highway 58 between Barstow and Mojave, inclusive; (f) U.S. Highway 14 between San Fernando and Mojave, inclusive; including the off-route points of Solamint, Forest Park, the Oaks, Acton, Pearblossom, Littlerock, Vincent, Pearland, Palmdale, Lancaster, Rosamond, Newhall, Valencia, and Saugus; (g) Unnumbered Highway between Rosamond and junction with U.S. Highway 58 via Edwards: Service is proposed to, from, and between all points and places hereinabove mentioned. That applicant proposes to use all available public highways between points proposed to be served as hereinabove mentioned, and within the cities hereinabove proposed to be served, and applicant proposes to use such streets and highways as may be necessary to serve consignors and consignees located within said cities. Applicant is transporting and desires to transport general commodities within these areas except for the following:

(a) Used household goods and personal effects not packed in accordance with the crated property requirements set forth in paragraph (d) of Item No. 10-C of Minimum Rate Tariff No. 4-A. (b) Automobiles, trucks, and buses, viz: New and used, finished or unfinished passenger automobiles (including jeeps), ambulances, hearses, and taxis, freight automobiles, automobile chassis, trucks, truck chassis, truck trailers, trucks and trailers combined, buses and bus chassis. (c) Livestock, viz: Bucks, bulls, calves, cattle, cows, dairy cattle, ewes, goats, hogs, horses, kids, lambs, oxen, pigs, sheep, sheep camp outfits, sows, steers, stags, or swine. (d) Liquids, compresses gases, commodities in semiplastic form and commodities in suspension in liquid in bulk, in tank trucks, tank trailers, tank semitrailers or a combination of such highway vehicles. (e) Commodities when transported in bulk in dump trucks or in hopper-type trucks. (f) Commodities when transported in motor vehicles equipped for mechanical mixing in transit. Both intrastate and interstate authority sought.

HEARING: Application has not been assigned for hearing. Requests for procedural information, including the time for filing protests, concerning this application should be addressed to the California Public Utilities Commission, State Building, Civic Center, 455 Golden Gate Avenue, San Francisco, Calif. 94102, and should not be addressed to the Interstate Commerce Commission.

By the Commission.

[SEAL] JOSEPH M. HARRINGTON,
Acting Secretary.

[F.R. Doc. 70-11585; Filed, Sept. 1, 1970; 8:49 a.m.]

CUMULATIVE LIST OF PARTS AFFECTED—SEPTEMBER

The following numerical guide is a list of parts of each title of the Code of Federal Regulations affected by documents published to date during September

3 CFR

Page

PROCLAMATION:

3998 ... 13819

7 CFR

10 ... 13822
52 ... 13822
909 ... 13875
910 ... 13825
932 ... 13877
1099 ... 13826
1138 ... 13826

PROPOSED RULES:

906 ... 13887
1006 ... 13843
1012 ... 13843
1013 ... 13843

8 CFR

103 ... 13828
204 ... 13828
214 ... 13829
223 ... 13829
238 ... 13829
245 ... 13829
247 ... 13829
299 ... 13829
341 ... 13829

9 CFR

76 ... 13878

14 CFR

39 ... 13879
71 ... 13822
385 ... 13822

14 CFR—Continued

Page

PROPOSED RULES:

71 ... 13843, 13889, 13890

19 CFR

PROPOSED RULES:

4 ... 13843
19 ... 13843
111 ... 13843

20 CFR

PROPOSED RULES:

405 ... 13888

21 CFR

3 ... 13880
120 ... 13830
121 ... 13831
141 ... 13881
148i ... 13831

PROPOSED RULES:

3 ... 13887
191 ... 13887

24 CFR

1914 ... 13882
1915 ... 13883

29 CFR

520 ... 13884

39 CFR

531 ... 13831

41 CFR

Page

5A–7 ... 13885

42 CFR

73 ... 13922

43 CFR

PUBLIC LAND ORDERS:

4582 (modified by PLO 4884) ... 13821
4884 ... 13821

PROPOSED RULES:

1850 ... 13887

45 CFR

121 ... 13885

47 CFR

PROPOSED RULES:

73 ... 13890

49 CFR

170 ... 13834
171 ... 13834
172 ... 13834, 13837
173 ... 13834, 13837
174 ... 13834
175 ... 13834
176 ... 13834
177 ... 13834
178 ... 13834
179 ... 13834
1033 ... 13837, 13838

PROPOSED RULES:

1048 ... 13890
1201 ... 13844

50 CFR

32 ... 13838–13842

FEDERAL REGISTER

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PART II

Department of Health, Education, and Welfare

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Public Health Service

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Biological Products

Title 42—PUBLIC HEALTH

Chapter I—Public Health Service, Department of Health, Education, and Welfare

SUBCHAPTER F—QUARANTINE, INSPECTION, LICENSING

PART 73—BIOLOGICAL PRODUCTS

Part 73 of the Public Health Service Regulations (42 CFR Part 73) is hereby recodified and republished as set forth below to reflect the inclusion of subpart designations and renumbering of the sections to allow room for future expansion. This recodification shall be effective upon publication in the FEDERAL REGISTER.

Notice of proposed rule making, public rule making procedures and delay in effective date have been omitted as unnecessary in the issuance of this recodification, since it contains no substantive changes, in existing regulations, and otherwise relates to agency management. Interested persons may obtain a reprint of Part 73, as recodified, upon request from the Division of Biologics Standards, National Institutes of Health, 9000 Rockville Pike, Bethesda, Md. 20014.

The following redesignation table gives the new section derivation from the old section in Part 73:

New section	*Old section*	*New section*	*Old section*
73.101	73.1	73.830	73.82
73.200	73.2	73.840	73.83
73.201	73.3	73.850	73.84
73.202	73.4	73.860	73.85
73.203	73.5	73.870	73.86
73.204	73.6	73.1000	73.100
73.210	73.7	73.1001	73.101
73.220	73.8	73.1002	73.102
73.230	73.9	73.1003	73.103
73.231	73.10	73.1004	73.104
73.232	73.11	73.1005	73.105
73.233	73.12	73.1020	73.110
73.234	73.13	73.1021	73.111
73.235	73.14	73.1022	73.112
73.236	73.15	73.1023	73.113
73.240	73.16	73.1024	73.114
73.300	73.20	73.1025	73.115
73.301	73.21	73.1026	73.116
73.302	73.22	73.1027	73.117
73.303	73.23	73.1028	73.118
73.400	73.30	73.1040	73.130
73.401	73.31	73.1041	73.131
73.402	73.32	73.1042	73.132
73.500	73.35	73.1043	73.133
73.501	73.36	73.1044	73.134
73.502	73.37	73.1045	73.135
73.503	73.38	73.1060	73.140
73.504	73.39	73.1061	73.141
73.505	73.40	73.1062	73.142
73.600	73.50	73.1063	73.143
73.601	73.51	73.1064	73.144
73.602	73.52	73.1065	73.145
73.603	73.53	73.1066	73.146
73.604	73.54	73.1080	73.150
73.605	73.55	73.1081	73.151
73.700	73.70	73.1082	73.152
73.710	73.71	73.1083	73.153
73.720	73.72	73.1084	73.154
73.730	73.73	73.1085	73.155
73.740	73.74	73.1100	73.160
73.750	73.74a	73.1101	73.161
73.760	73.75	73.1102	73.162
73.770	73.76	73.1103	73.163
73.780	73.77	73.1104	73.164
73.790	73.78	73.1105	73.165
73.800	73.79	73.1106	73.166
73.810	73.80	73.1120	73.190
73.820	73.81	73.1121	73.191
73.1122	73.192	73.3500	73.355
73.1123	73.193	73.3501	73.356
73.1124	73.194	73.3502	73.357
73.1125	73.195	73.3503	73.358
73.1126	73.196	73.3504	73.359
73.2000	73.600	73.3520	73.350
73.2001	73.601	73.3521	73.351
73.2002	73.602	73.3522	73.352
73.2003	73.603	73.3523	73.353
73.2004	73.604	73.3524	73.354
73.2005	73.605	73.4000	73.400
73.2006	73.606	73.4001	73.401
73.2020	73.610	73.4002	73.402
73.2021	73.611	73.4003	73.403
73.2022	73.612	73.4004	73.404
73.2023	73.613	73.4005	73.405
73.2024	73.614	73.4006	73.406
73.2025	73.615	73.4020	73.410
73.3000	73.300	73.4021	73.411
73.3001	73.301	73.4022	73.412
73.3002	73.302	73.4023	73.413
73.3003	73.303	73.4024	73.414
73.3004	73.304	73.4025	73.415
73.3005	73.305	73.9000	73.500
73.3020	73.320	73.9001	73.501
73.3021	73.321	73.9002	73.502
73.3022	73.322	73.9020	73.90
73.3023	73.323	73.9021	73.91
73.3024	73.324	73.9022	73.92
73.3025	73.325	73.9023	73.93
73.3026	73.326	73.9024	73.94
73.3027	73.327	73.9025	73.95
73.3028	73.328	73.9026	73.96

Subpart A—General Standards

DEFINITIONS

LICENSES: PROCEDURE

FOREIGN ESTABLISHMENTS AND PRODUCTS

ESTABLISHMENT INSPECTION

ESTABLISHMENT STANDARDS

STANDARDS FOR PRODUCTS: LABELS

STANDARDS FOR PRODUCTS: GENERAL

Subpart B—Additional Standards for Viral Vaccines

POLIOMYELITIS VACCINE

POLIOVIRUS VACCINE, LIVE, ORAL

ADENOVIRUS VACCINE

MEASLES VIRUS VACCINE, LIVE, ATTENUATED

MEASLES VIRUS VACCINE, INACTIVATED

MUMPS VIRUS VACCINE, LIVE

AUTHORITY: The provisions of this Part 73 issued under sec. 215, 58 Stat. 690, as amended; 42 U.S.C. 216. Sec. 351, 58 Stat. 702; 42 U.S.C. 262, unless otherwise noted.

CROSS REFERENCES: For Department of Health, Education, and Welfare regulations relating to drugs as defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), see 21 CFR, Subchapter C. For exemption from section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) of new drugs licensed under the Public Health Service Act, see 21 CFR 130.2. For Bureau of Customs regulations relating to viruses, serums and toxins, see 19 CFR 12.21–12.23. For Post Office regulations relating to the admissibility to the United States mails see 39 CFR Parts 124 and 125, esp. § 125.2.

Subpart A—General Standards

DEFINITIONS

§ 73.101 Definitions.

As used in this part:

(a) "Act" means the Public Health Service Act (58 Stat. 682), approved July 1, 1944.

(b) "Secretary" means the Secretary of Health, Education, and Welfare and any other officer or employee of the Department of Health, Education, and Welfare to whom the authority involved has been delegated.

(c) "Director, National Institutes of Health" means the Director of the National Institutes of Health of the U.S. Public Health Service.

(d) "Institutes" means the National Institutes of Health in the Public Health Service.

(e) "Division of Biologics Standards" means the Division of Biologics Standards of the National Institutes of Health.

(f) "State" means a State or the District of Columbia, Puerto Rico, or the Virgin Islands.

(g) "Possession" includes among other possessions, Puerto Rico and the Virgin Islands.

(h) "Products" includes biological products and trivalent organic arsenicals.

(i) "Biological product" means any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man:

(1) A virus is interpreted to be a product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa.

(2) A therapeutic serum is a product obtained from blood by removing the clot or clot components and the blood cells.

(3) A toxin is a product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less (or equivalent in weight) of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized.

(4) An antitoxin is a product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune.

(5) A product is analogous:

(i) To a virus if prepared from or with a virus or agent actually or potentially infectious, without regard to the degree of virulence or toxicogenicity of the specific strain used.

(ii) To a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.

(iii) To a toxin or antitoxin, if intended, irrespective of its source of origin, to be applicable to the prevention, treatment, or cure of disease or injuries of man through a specific immune process.

(j) "Trivalent organic arsenicals" means arsphenamine and its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man.

(k) A product is deemed "applicable to the prevention, treatment, or cure of diseases or injuries of man" irrespective of the mode of administration or application recommended, including use when intended through administration or application to a person as an aid in diagnosis, or in evaluating the degree of susceptibility or immunity possessed by a person, and including also any other use for purposes of diagnosis if the diagnostic substance so used is prepared from or with the aid of a biological product.

(l) "Proper name", as applied to a product, means the name designated in the license for use upon each package of the product.

(m) "Dating period" means the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results.

(n) "Expiration date" means the calendar month and year, and where applicable, the day and hour, that the dating period ends.

(o) The word "standards" means specifications and procedures applicable

to an establishment or to the manufacture or release of products, which are prescribed in this part and which are designed to insure the continued safety, purity and potency of such products.

(p) The word "continued" as applied to the safety, purity and potency of products is interpreted to apply to the dating period.

(q) The word "safety" means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.

(r) The word "sterility" is interpreted to mean freedom from viable contaminating microorganisms, as determined by the tests prescribed in § 73.730.

(s) "Purity" means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. "Purity" includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances.

(t) The word "potency" is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

(u) "Manufacturer" means any legal person or entity engaged in the manufacture of a product subject to license under the act.

(v) "Manufacture" means all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer.

(w) "Location" includes all buildings, appurtenances, equipment and animals used, and personnel engaged by a manufacturer within a particular area designated by an address adequate for identification.

(x) "Establishment" includes all locations.

(y) "Lot" means that quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single vessel.

(z) A "filling" refers to a group of final containers identical in all respects, which have been filled with the same product from the same bulk lot without any change that will affect the integrity of the filling assembly.

(aa) "Process" refers to a manufacturing step that is performed on the product itself which may affect its safety, purity or potency, in contrast to such manufacturing steps which do not affect intrinsically the safety, purity or potency of the product.

(bb) "Selling agent" or "distributor" means any person engaged in the unrestricted distribution, other than by sale at retail, of products subject to license.

(cc) "Container" (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

(dd) "Package" means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package.

(ee) "Label" means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

LICENSES: PROCEDURE

§ 73.200 Two forms of licenses.

There shall be two forms of licenses: establishment and product.

§ 73.201 Application for establishment and product licenses; procedure for filing.

To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Division of Biologics Standards, on forms prescribed for such purpose, and in the case of an application for a product license, shall submit data derived from laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity and potency, a full description of manufacturing methods, data establishing stability of the product through the dating period, sample(s) representative of the product to be sold, bartered or exchanged or offered, sent, carried or brought for sale, barter or exchange, summaries of results of tests performed on the lot(s) represented by the submitted sample(s), and specimens of the labels, enclosures and containers proposed to be used for the product. An application for license shall not be considered as filed until all pertinent information and data shall have been received from the manufacturer by the Division of Biologics Standards.

§ 73.202 Establishment licenses; issuance and conditions.

(a) *Inspection—compliance with standards.* An establishment license shall be issued only after inspection of the establishment and upon a determination that the establishment complies with the applicable standards prescribed in the regulations in this part.

(b) *Availability of product; simultaneous request for and issuance of product license.* No establishment license shall be issued unless (1) a product intended for sale, barter or exchange or intended to be offered, sent, carried or brought for sale, barter or exchange is available for examination, (2) such product is available for inspection during all phases of manufacture and (3) a product license is requested and issued simultaneously with the establishment license.

(c) *One establishment license to cover all locations.* One establishment license shall be issued to cover all locations meeting the establishment standards.

§ 73.203 Product licenses; issuance and conditions.

(a) *Examination—compliance with standards.* A product license shall be issued only upon examination of the product and upon a determination that the product complies with the standards prescribed in the regulations in this part: *Provided,* That no product license shall be issued except upon a determination that the establishment complies with the establishment standards prescribed in the regulations contained in this part, applicable to the manufacture of such product.

(b) *Manufacturing process—impairment of assurances.* No product shall be licensed if any part of the process of or relating to the manufacture of such product, in the judgment of the Director, National Institutes of Health, would impair the assurances of continued safety, purity and potency as provided by the regulations contained in this part.

§ 73.204 License forms.

(a) *Establishment license.* The establishment license form shall be prescribed by the Director, National Institutes of Health and shall include:

(1) The name and address of the manufacturer.

(2) The name and address of the establishment.

(3) The names and addresses of all locations of the establishment.

(4) The license number.

(5) The date of issuance.

(b) *Product license.* The product license form shall be prescribed by the Director, National Institutes of Health and shall include:

(1) The name and address of the manufacturer.

(2) The name and address of the establishment.

(3) The name and address of each location at which the product is manufactured.

(4) The license number of the establishment.

(5) The proper name of the product, with additional specifications, if any, which may be approved or required for additional labeling purposes.

§ 73.210 Changes to be reported.

(a) *General.* Important proposed changes in location, equipment, management and responsible personnel, or in manufacturing methods and labeling, of any product for which a license is in effect or for which an application for license is pending, shall be reported to the Director, Division of Biologics Standards, by the manufacturer, and unless in case of an emergency, not less than 30 days in advance of the time such changes are intended to be made.

(b) *Manufacturing methods and labeling.* Proposed changes in manufacturing methods and labeling may not become effective until notification of acceptance is received from the Director, Division of Biologics Standards.

(c) *Failure to report.* Failure to report a change as required shall constitute a

ground for summary suspension of a license.

§ 73.220 Products under development.

A biological product or trivalent organic arsenical undergoing development, but not yet ready for a product license, may be shipped or otherwise delivered from one State or possession into another State or possession provided such shipment or delivery is not for sale, barter or exchange and is in accordance with section 505 of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder.

§ 73.230 Issuance, revocation or suspension.

A license shall be issued by the Secretary upon the recommendation of the Director, National Institutes of Health and upon the determination by the Director, National Institutes of Health that the establishment or the product, as the case may be, meets the standards established by the regulations in this part as herein prescribed or hereafter amended. Licenses shall be valid until suspended or revoked. An establishment or product license shall be revoked upon application of the manufacturer giving notice of intention to discontinue the manufacture of all products or of intention to discontinue the manufacture of a particular product for which a license is held. The Director, National Institutes of Health shall recommend to the Secretary that a license be suspended or revoked whenever he finds, after notice and opportunity for hearing, that (a) Public Health Service inspectors after reasonable efforts have been unable to gain access to an establishment or a location for the purpose of carrying out the inspection required under § 73.401, or that (b) manufacturing of products or of a product has been discontinued to an extent that a meaningful inspection cannot be made, or (c) the establishment or any location thereof, or the product for which the license has been issued, fails to conform to the standards in the regulations in this part, as herein prescribed or as hereafter amended, designed to insure the continued safety, purity, and potency of the manufactured product. In case of suspension, unless assurances satisfactory to the Director, National Institutes of Health (a) that access will be permitted or (b) that manufacturing will be resumed, have been provided or (c) if the faulty condition is not corrected within 60 days or within such other period as may be specified in the notice of suspension, whichever is applicable, he shall recommend that the license be revoked. Except as provided in § 73.232, prior to the institution of proceedings looking to the suspension or revocation of a license the licensee shall be advised in writing of the facts or conduct which may warrant such action and shall be accorded opportunity within a reasonable period prescribed by the Director, National Institutes of Health to demonstrate or achieve compliance with the regulations in this part.

§ 73.231 Licenses heretofore issued.

Any license heretofore issued and in effect upon the effective date of the regulations in this part shall remain in effect unless and until superseded by a new license, or suspended or revoked, pursuant to the regulations in this part.

§ 73.232 Summary suspension.

Whenever the Director, National Institutes of Health has reasonable ground to believe that an establishment or product for which a license has been issued fails to conform to the standards prescribed in the regulations in this part, and that by reason of such failure and of failure of the manufacturer to take prompt corrective measures on notice thereof, the distribution or sale of a licensed product would constitute a danger to health, or that the establishment and manufacturing methods have been so changed as to require in order to protect the public health a new showing that the establishment or product meets the standards prescribed in the regulations in this part, he may recommend to the Secretary that the license for the establishment or the product be summarily suspended and the manufacturer be required (a) to notify the selling agents and distributors to whom such product or products have been delivered of such suspension, (b) to furnish complete records of such deliveries and notice of suspension, and (c) to show cause within 60 days or such other period as may be specified in the order why the license should not be revoked.

§ 73.233 Review Board.

When deemed advisable by the Director, National Institutes of Health, in matters involving the safety, purity, and potency of licensed products or products for which an application for license is pending, the reports of inspection and laboratory examinations, together with any pertinent data the establishment may submit, shall be passed upon by a special board of three officers appointed by the Director, National Institutes of Health for that purpose. The board shall report its findings to the Director, National Institutes of Health who will forward its report, together with his findings and recommendations, to the Secretary.

§ 73.234 Opportunity for hearing.

Any manufacturer whose application for a license has been denied, or whose establishment or product license has been summarily suspended, without prior opportunity for hearing, may appeal from such denial or suspension and shall be entitled to a hearing thereon before a review body constituted as provided in § 73.233. The Director, National Institutes of Health, upon review of the record, may affirm, reverse, or modify the findings of the review board, or may direct the taking of further testimony, and shall forward his determinations and recommendations to the Secretary.

§ 73.235 Suspension and revocation; publication.

Notice of suspension or revocation of license, with statement of cause therefor, may be published by the Secretary.

§ 73.236 Licenses; reissuance.

(a) *Compliance with standards.* An establishment or product license, previously suspended or revoked, whether upon application, or for failure to comply with standards or changes in standards prescribed in the regulations in this part, may be reissued or reinstated upon a showing of compliance with required standards and upon such inspection and examination as may be considered necessary by the Director of the Division of Biologics Standards.

(b) *Exclusion of noncomplying location.* An establishment or product license, excluding a location or locations that fail to comply with prescribed standards, may be issued without further application and concurrently with the suspension or revocation of the license for noncompliance at the excluded location or locations.

§ 73.240 Products in short supply; initial manufacturing at other than licensed establishment.

Licenses issued to a manufacturer for an establishment shall authorize persons other than such manufacturer to conduct at places other than such establishment the initial, and partial manufacturing of a product for shipment solely to such manufacturer only to the extent that the names of such persons and places are registered with the Director, National Institutes of Health and he finds, upon application of such manufacturer, that (a) the product is in short supply due either to the peculiar growth requirements of the organism involved or to the scarcity of the animal required for manufacturing purposes, and (b) such manufacturer has established with respect to such persons and places such procedures, inspections, tests or other arrangements as will assure full compliance with the applicable regulations of this part related to continued safety, purity, and potency. Such persons and places shall be subject to all regulations of this part except §§ 73.200 to 73.236, 73.300 to 73.303, and 73.600 to 73.605. Failure of such manufacturer to maintain such procedures, inspections, tests, or other arrangements, or failure of any person conducting such partial manufacturing to comply with applicable regulations shall constitute a ground for summary suspension or revocation of the authority conferred pursuant to this section on the same basis as provided in §§ 73.232, 73.234, and 73.235 with respect to the summary suspension and the revocation of licenses.

FOREIGN ESTABLISHMENTS AND PRODUCTS

§ 73.300 Licenses required; products for controlled investigation only.

Any biological or trivalent organic arsenical manufactured in any foreign

country and intended for sale, barter or exchange shall be refused entry by collectors of customs unless manufactured in an establishment holding an unsuspended and unrevoked establishment license and license for the product. Unlicensed products which are not imported for sale, barter or exchange and which are intended solely for purposes of controlled investigation are admissible only if in accord with section 505 of the Federal Food, Drug, and Cosmetic Act, as amended, and the regulations thereunder.

§ 73.301 Procedure.

Except as otherwise provided in this part, licenses for foreign establishments and products shall be issued, suspended, and revoked in the same manner as licenses for domestic establishments and products. Each foreign establishment holding a license and sending, carrying, or bringing any licensed product into any State or possession for sale, barter, or exchange shall file with the Director, Division of Biologics Standards, the name and address of each person to whom such a product is thus sent, carried, or brought. Foreign licensees shall notify each person in the United States to whom such a product is thus sent, carried, or brought, to keep such records of distribution as are required of domestic licensed establishments. Failure to give such notice to maintain records shall constitute ground for revocation of license.

§ 73.302 Form of license.

Licenses for establishments located in foreign countries shall be in form similar to that for domestic establishments except that they shall authorize manufacture for sending, carrying, or bringing for sale, barter or exchange from the foreign country designated in the license into any State or possession of the United States and shall specify that it is issued upon the condition that the licensee will permit the inspection during all reasonable hours of the establishment by any officer, agent, or employee of the Department of Health, Education, and Welfare authorized by the Secretary for such purpose.

§ 73.303 Samples for each importation.

Random samples of each importation, obtained by the Collector of Customs and forwarded to the Director, Division of Biologics Standards, shall be at least two final containers of each lot of product. A copy of the associated documents which describe and identify the shipment shall accompany the shipment for forwarding with the samples to the Director, Division of Biologics Standards. For shipments of 20 or less final containers, samples need not be forwarded, provided a copy of an official release from the Division of Biologics Standards accompanies each shipment.

ESTABLISHMENT INSPECTION

§ 73.400 Inspectors.

Inspections shall be made by an officer of the Public Health Service having special knowledge of the methods used in the manufacture and control of products and designated for such purpose by the Director, National Institutes of Health or by any officer, agent, or employee of the Department of Health, Education, and Welfare specifically designated for such purpose by the Secretary.

§ 73.401 Time of inspection.

The inspection of an establishment for which a license is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a product license is desired. In case the license is denied following inspection for the original license, no reinspection need be made until assurance has been received that the faulty conditions which were the basis of the denial have been corrected. An inspection of each licensed establishment shall be made at least once each year. Inspections may be made with or without notice, and shall be made during regular business hours unless otherwise directed.

§ 73.402 Duties of inspector.

The inspector shall:

(a) Call upon the active head of the establishment, stating the object of his visit,

(b) Interrogate the proprietor or other personnel of the establishment as he may deem necessary,

(c) Examine the details of location, construction, equipment and maintenance, including stables, barns, warehouses, manufacturing laboratories, bleeding clinics maintained for the collection of human blood, shipping rooms, record rooms, and any other structure or appliance used in any part of the manufacture of a product,

(d) Investigate as fully as he deems necessary the methods of propagation, processing, testing, storing, dispensing, recording, or other details of manufacture and distribution of each licensed product, or product for which a license has been requested, including observation of these procedures in actual operation,

(e) Obtain and cause to be sent to the Director, Division of Biologics Standards, adequate samples for the examination of any product or ingredient used in its manufacture,

(f) Bring to the attention of the manufacturer any fault observed in the course of inspection in location, construction, manufacturing methods, or administration of a licensed establishment which might lead to impairment of a product,

(g) Inspect and copy, as circumstances may require, any records required to be kept pursuant to § 73.502,

(h) Certify as to the condition of the establishment and of the manufacturing methods followed and make recommendations as to action deemed appropriate with respect to any application for license or any license previously issued.

ESTABLISHMENT STANDARDS

§ 73.500 Personnel.

(a) *Responsible head.* A person shall be designated as the responsible head who shall exercise control of the establishment in all matters relating to compliance with the provisions of this part, with authority to represent the manufacturer in all pertinent matters with the Division of Biologics Standards, and with authority to enforce or to direct the enforcement of discipline and the performance of assigned functions by employees engaged in the manufacture of products. The responsible head shall have an understanding of the scientific principles and the techniques involved in the manufacture of products. The responsible head shall have the responsibility for the training of employees in manufacturing methods and for their being informed concerning the application of the pertinent provisions of this part to their respective functions.

(b) *Other personnel.* Personnel shall have capabilities commensurate with their assigned functions, a thorough understanding of the manufacturing operations which they perform, the necessary training and experience relating to individual products, and adequate information concerning the application of the pertinent provisions of this part to their respective functions. Personnel shall include such professionally trained persons as are necessary to insure the competent performance of all manufacturing processes.

(c) *Restrictions on personnel*—(1) *Specific duties.* Persons whose presence can affect adversely the safety and purity of a product shall be excluded from the room where the manufacture of a product is in progress.

(2) *Sterile operations.* Personnel performing sterile operations shall wear clean or sterilized protective clothing and devices to the extent necessary to protect the product from contamination.

(3) *Pathogenic viruses and spore-bearing organisms.* Persons working with viruses pathogenic for man or with spore-bearing microorganisms, and persons engaged in the care of animals or animal quarters, shall be excluded from areas where other products are manufactured, or such persons shall change outer clothing, including shoes, or wear protective covering prior to entering such areas.

(4) *Live vaccine work areas.* Persons may not enter a live vaccine processing area after having worked with other infectious agents in any other laboratory during the same working day. Only persons actually concerned with propagation of the culture, production of the vaccine, and unit maintenance, shall be allowed in live vaccine processing areas when active work is in progress. Casual visitors shall be excluded from such units at all times and all others having business in such areas shall be admitted only under supervision. Street clothing, including shoes, shall be replaced or covered by suitable laboratory clothing before entering a live vaccine processing unit. Persons caring for animals used in the manufacture of live vaccines shall be excluded from other animal quarters and from contact with other animals during the same working day.

§ 73.501 **Physical establishment, equipment, animals, and care.**

(a) *Work areas.* All rooms and work areas where products are manufactured or stored shall be kept orderly, clean, and free of dirt, dust, vermin and objects not required for manufacturing. Precautions shall be taken to avoid clogging and back-siphonage of drainage systems. Precautions shall be taken to exclude extraneous infectious agents from manufacturing areas. Work rooms shall be well lighted and ventilated. The ventilation system shall be arranged so as to prevent the dissemination of microorganisms from one manufacturing area to another and to avoid other conditions unfavorable to the safety of the product. Filling rooms, and other rooms where open, sterile operations are conducted, shall be adequate to meet manufacturing needs and such rooms shall be constructed and equipped to permit thorough cleaning and to keep air-borne contaminants at a minimum. If such rooms are used for other purposes, they shall be cleaned and prepared prior to use for sterile operations. Refrigerators, incubators and warm rooms shall be maintained at temperatures within applicable ranges and shall be free of extraneous material which might affect the safety of the product.

(b) *Equipment.* Apparatus for sterilizing equipment and the method of operation shall be such as to insure the destruction of contaminating microorganisms. The effectiveness of the sterilization procedure shall be no less than that achieved by an attained temperature of 121.5°C. maintained for twenty minutes by saturated steam or by an attained temperature of 170°C. maintained for two hours with dry heat. Processing and storage containers, filters, filling apparatus and other pieces of apparatus and accessory equipment, including pipes and tubing, shall be designed and constructed to permit thorough cleaning and, where possible, inspection for cleanliness. All surfaces that come in contact with products shall be clean and free of extraneous material. For products for which sterility is a factor, equipment shall be sterile unless sterility of the product is assured by subsequent procedures.

(c) *Laboratory and bleeding rooms.* Rooms used for the processing of products, including bleeding rooms, shall be effectively fly-proofed and kept free of flies and vermin. Such rooms shall be so constructed as to insure freedom from dust, smoke and other deleterious substances and to permit thorough cleaning and disinfection. Rooms for animal injection and bleeding, and rooms for smallpox vaccine animals, shall be disinfected and be provided with the necessary water, electrical and other services.

(d) *Animal quarters and stables.* Animal quarters, stables and food storage areas shall be of appropriate construction, fly-proofed, adequately lighted and ventilated, and maintained in a clean, vermin-free and sanitary condition. No manure or refuse shall be stored as to permit the breeding of flies on the premises, nor shall the establishment be located in close proximity to off-property manure or refuse storage capable of engendering fly breeding.

(e) *Restrictions on building and equipment use*—(1) *Work of a diagnostic nature.* Laboratory procedures of a clinical diagnostic nature involving materials that may be contaminated, shall not be performed in space used for the manufacture of products except that manufacturing space which is used only occasionally may be used for diagnostic work provided spore-bearing pathogenic microorganisms are not involved and provided the space is thoroughly cleaned and disinfected before the manufacture of products is resumed.

(2) *Spore-bearing organisms for supplemental sterilization procedure control test.* Spore-bearing organisms used as an additional control in sterilization procedures may be introduced into areas used for the manufacture of products, only for the purposes of the test and only immediately before use for such purposes: *Provided*, That (i) the organism is not pathogenic for man and does not produce pyrogens or toxins, (ii) the organism does not grow at or below 37° C. within a two-week period, (iii) the culture is demonstrated to be pure, (iv) test cultures are not transferred to culture media in areas used for the manufacture of products, (v) each culture be labeled with the name of the microorganism and the statement "Caution: microbial spores. See directions for storage, use and disposition", and (vi) the container of each such culture is designed to withstand handling without breaking.

(3) *Work with spore-bearing organisms.* Except as provided in the previous paragraph, all work with spore-bearing microorganisms shall be done in an entirely separate building: *Provided*, That such work may be done in a portion of a building used in the manufacture of products not containing spore-bearing microorganisms if such portion is completely walled-off and is constructed so as to prevent contamination of other areas and if entrances to such portion are independent of the remainder of the building. All vessels, apparatus and equipment used for spore-bearing microorganisms shall be permanently identified and reserved exclusively for use with those organisms. Materials destined for further manufacturing may be removed from such an area only under conditions which will prevent the introduction of spores into other manufacturing areas.

(4) *Live vaccine processing.* Space used for processing a live vaccine shall not be used for any other purpose during the processing period for that vaccine and such space shall be decontaminated prior to initiation of the processing. Live vaccine processing areas shall be isolated from and independent of any space used for any other purpose by being either in a separate building, in a separate wing of a building, or in quarters at the blind end of a corridor and shall include adequate space and equipment for all processing steps up to filling into final containers. Test procedures which potentially involve the presence of microorganisms other than the vaccine strains, or the use of tissue culture cell lines other than primary cultures, shall not be conducted in space used for processing live vaccine.

(5) *Equipment and supplies—contamination.* Equipment and supplies used in work on or otherwise exposed to any pathogenic or potentially pathogenic agent shall be kept separated from equipment and supplies used in the manufacture of products to the extent necessary to prevent cross-contamination.

(f) *Animals used in manufacture*—(1) *Care of animals used in manufacturing.* Caretakers and attendants for animals used for the manufacture of products shall be sufficient in number and have adequate experience to insure adequate care. Animal quarters and cages shall be kept in sanitary condition. Animals on production shall be inspected daily to observe response to production procedures. Animals that become ill for reasons not related to production shall be isolated from other animals and shall not be used for production until recovery is complete. Competent veterinary care shall be provided as needed.

(2) *Quarantine of animals*—(i) *General.* No animal shall be used in processing unless kept under competent daily inspection and preliminary quarantine for a period of at least 7 days before use, or as otherwise provided in this part. Only healthy animals free from detectable communicable diseases shall be used. Animals must remain in overt good health throughout the quarantine periods and particular care shall be taken during the quarantine periods to reject animals of the equine genus which may be infected with glanders and animals which may be infected with tuberculosis.

(ii) *Quarantine of monkeys.* In addition to observing the pertinent general quarantine requirements, monkeys used as a source of tissue in the manufacture of vaccine shall be maintained in quarantine for at least 6 weeks prior to use, except when otherwise provided in this part. Only monkeys that have reacted negatively to tuberculin at the start of the quarantine period and again within 2 weeks prior to use shall be used in the manufacture of vaccine. Due precaution shall be taken to prevent cross-infection from any infected or potentially infected monkeys on the premises. Monkeys to be used in the manufacture of a live vaccine shall be maintained throughout the quarantine period in cages closed on all sides with solid materials except the front which shall be screened, with no more than two monkeys housed in one cage. Cage mates shall not be interchanged.

(3) *Immunization against tetanus.* Horses and other animals susceptible to tetanus, that are used in the processing steps of the manufacture of biological products, shall be treated adequately to maintain immunity to tetanus.

(4) *Immunization and bleeding of animals used as a source of products.* Toxins or other nonviable antigens administered in the immunization of animals used in the manufacture of products shall be sterile. Viable antigens, when so used,

shall be free of contaminants, as determined by appropriate tests prior to use. Injections shall not be made into horses within 6 inches of bleeding site. Horses shall not be bled for manufacturing purposes while showing persistent general reaction or local reaction near the site of bleeding. Blood shall not be used if it was drawn within 5 days of injecting the animals with viable microorganisms. Animals shall not be bled for manufacturing purposes when they have an intercurrent disease. Blood intended for use as a source of a biological product shall be collected in clean, sterile vessels. When the product is intended for use by injection, such vessels shall also be pyrogen-free.

(5) *Smallpox vaccine production animals.* Animals used for the manufacture of smallpox vaccine shall be thoroughly cleaned with soap and water at the beginning of the quarantine and at its conclusion. The animals shall not be vaccinated in areas most likely to be contaminated with feces.

(6) *Reporting of certain diseases.* In cases of actual or suspected infection with foot and mouth disease, glanders, tetanus, anthrax, gas gangrene, equine infectious anemia; equine encephalomyelitis, or any of the pock diseases among animals intended for use or used in the manufacture of products, the manufacturer shall immediately notify the Director, Division of Biologics Standards.

(7) *Monkeys used previously for experimental or test purposes.* Monkeys that have been used previously for experimental or test purposes with live microbiological agents shall not be used as a source of kidney tissue for the manufacture of vaccine. Except as provided otherwise in this part, monkeys that have been used previously for other experimental or test purposes may be used as a source of kidney tissue upon their return to a normal condition, provided all quarantine requirements have been met.

(8) *Necropsy examination of monkeys.* Each monkey used in the manufacture of vaccine shall be examined at necropsy under the direction of a qualified pathologist, physician, or veterinarian having experience with diseases of monkeys, for evidence of ill health, particularly for (i) evidence of tuberculosis, (ii) presence of herpes-like lesions, including eruptions or plaques on or around the lips, in the buccal cavity or on the gums, and (iii) signs of conjunctivitis. If there are any such signs or other significant gross pathological lesions, the tissue shall not be used in the manufacture of vaccine.

(g) *Filling procedures.* Filling procedures shall be such as will not affect adversely the safety, purity or potency of the product.

(h) *Containers and closures.* All final containers and closures shall be made of material that will not hasten the deterioration of the product or otherwise render it less suitable for the intended use. All final containers and closures shall be clean and free of surface solids, leachable contaminants and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use. After filling, sealing shall be performed in a manner that will maintain the integrity of the product during the dating period. In addition, final containers and closures for products intended for use by injection shall be sterile and free from pyrogens. Except as otherwise provided in the regulations of this part, final containers for products intended for use by injection shall be colorless and sufficiently transparent to permit visual examination of the contents under normal light. As soon as possible after filling, final containers shall be labeled as prescribed in § 73.600 et seq., except that final containers may be stored without such prescribed labeling provided they are stored in a sealed receptacle labeled both inside and outside with at least the name of the product, the lot number, and the filling identification.

§ 73.502 Records.

(a) *Maintenance of records.* Records shall be made, concurrently with the performance, of each step in the manufacture and distribution of products, in such a manner that at any time successive steps in the manufacture and distribution of any lot may be traced by an inspector. Such records shall be legible and indelible, shall identify the person immediately responsible, shall include dates of the various steps, and be as detailed as necessary for clear understanding of each step by one experienced in the manufacture of products.

(b) *Records retention*—(1) *General.* Records shall be retained for such interval beyond the expiration date as is necessary for the individual product, to permit the return of any clinical report of unfavorable reactions. The retention period shall be no less than five years after the records of manufacture have been completed or six months after the latest expiration date for the individual product, whichever represents a later date.

(2) *Records of recall.* Complete records shall be maintained pertaining to the recall from distribution of any product upon notification by the Director, Division of Biologics Standards, to recall for failure to conform with the standards prescribed in the regulations of this part, because of deterioration of the product or for any other factor by reason of which the distribution of the product would constitute a danger to health.

(3) *Suspension of requirement for retention.* The Director, Division of Biologics Standards, may authorize the suspension of the requirement to retain records of a specific manufacturing step upon a showing that such records no longer have significance for the purposes for which they were made: *Provided,* That a summary of such records shall be retained.

(c) *Records of sterilization of equipment and supplies.* Records relating to the mode of sterilization, date, duration, temperature and other conditions relating to each sterilization of equipment and supplies used in the processing of products shall be made by means of automatic recording devices or by means of a system of recording which gives equivalent assurance of the accuracy and reliability of the record. Such records shall be maintained in a manner that permits an identification of the product with the particular manufacturing process to which the sterilization relates.

(d) *Animal necropsy records.* A necropsy record shall be kept on each animal from which a biological product has been obtained and which dies or is sacrificed while being so used.

(e) *Records in case of divided manufacturing responsibility.* If two or more establishments participate in the manufacture of a product, the records of each such establishment must show plainly the degree of its responsibility. In addition, each participating manufacturer shall furnish to the manufacturer who prepares the product in final form for sale, barter or exchange, a copy of all records relating to the manufacturing operations performed by such participating manufacturer insofar as they concern the safety, purity and potency of the lots of the product involved, and the manufacturer who prepares the product in final form shall retain a complete record of all the manufacturing operations relating to the product.

§ 73.503 Retention samples.

Manufacturers shall retain for a period of at least 6 months after the expiration date, a quantity of representative material of each lot of each product, sufficient for examination and testing for safety and potency, except Whole Blood (Human), Antihemophilic Plasma (Human), Red Blood Cells (Human), Single Donor Plasma (Human), Normal Human Plasma and Allergenic Products prepared to physician's prescription. Samples so retained shall be selected at random from either final container material, or from bulk and final containers, provided they include at least one final container as a final package, or package-equivalent of such filling of each lot of the product as intended for distribution. Such sample material shall be stored at temperatures and under conditions which will maintain the identity and integrity of the product. Samples retained as required in this section shall be in addition to samples of specific products required to be submitted to the Division of Biologics Standards. Exceptions may be authorized by the Director, Division of Biologics Standards, when the lot yields relatively few final containers and when such lots are prepared by the same method in large number and in close succession.

§ 73.504 Reporting of errors.

The Director, Division of Biologics Standards, shall be notified promptly of errors or accidents in the manufacture of products that may affect the safety, purity, or potency of any product.

§ 73.505 Temperatures during shipment.

The following products shall be maintained during shipment at the specified temperatures:

Product	Temperature
Poliovirus Vaccine, Live, Oral, Type 1 Poliovirus Vaccine, Live, Oral, Type 2 Poliovirus Vaccine, Live, Oral, Type 3 Poliovirus Vaccine, Live, Oral, Trivalent	A temperature which will maintain ice continuously in a solid state.
Red Blood Cells (Human), Frozen.	—65° C. or colder.
Red Blood Cells (Human), Liquid.	Between 1° and 10° C.
Single Donor Plasma (Human), Frozen.	—18° C. or colder.
Smallpox Vaccine, Liquid.	A temperature which will maintain ice continuously in a solid state.
Whole Blood (Human).	Between 1° and 10° C.
Yellow Fever Vaccine.	A temperature which will maintain ice continuously in a solid state.

STANDARDS FOR PRODUCTS: LABELS

§ 73.600 Container label.

(a) *Full label.* The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product;

(2) The name, address, and license number of manufacturer;

(3) The lot number or other lot identification;

(4) The expiration date;

(5) The recommended individual dose, for multiple dose containers.

(b) *Package label information.* If the container is not enclosed in a package, all the items required for a package label shall appear on the container label.

(c) *Partial label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.

(d) *No container label.* If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label.

(e) *Visual inspection.* When the label has been affixed to the container a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents.

§ 73.601 Package label.

The following items shall appear on the label affixed to each package containing a product:

(a) The proper name of the product;

(b) The name, address, and license number of manufacturer;

(c) The lot number or other lot identification;

(d) The expiration date;

(e) The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative";

(f) The number of containers, if more than one;

(g) The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;

(h) The recommended storage temperature;

(i) The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product;

(j) The recommended individual dose if the enclosed container(s) is a multiple-dose container;

(k) The route of administration recommended, or reference to such directions in an enclosed circular;

(l) Known sensitizing substances, or reference to an enclosed circular containing appropriate information;

(m) The type and calculated amount of antibiotics added during manufacture;

(n) The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;

(o) The adjuvant, if present;

(p) The source of the product when a factor in safe administration;

(q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information;

(r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency."

§ 73.602 Proper name; package label; legible type.

(a) *Position.* The proper name of the product on the package label shall be placed above any trade-mark or trade name identifying the product and symmetrically arranged with respect to other printing on the label.

(b) *Prominence.* The point size and type-face of the proper name shall be at least as prominent as the point size and type-face used in designating the trademark and trade name. The contrast in color value between the proper name and the background shall be at least as great as the color value between the trade-mark and trade name and the background. Typography, layout, contrast, and other printing features shall not be used in a manner that will affect adversely the prominence of the proper name.

(c) *Legible type.* All items required to be on the container label and package label shall be in legible type. "Legible type" is type of a size and character which can be read with ease when held in a good light and with normal vision.

§ 73.603 Divided manufacturing responsibility to be shown.

If two or more establishments participate in the manufacture of a product, the name, address, and license number of each must appear on the package label, and on the label of the container if capable of bearing a full label.

§ 73.604 Name of selling agent or distributor.

The name and address of the selling agent or distributor of a product may appear on the label under the designation of "selling agent" or "distributor" provided that the name and address of the manufacturer is given precedence in prominence.

§ 73.605 Products for export.

Labels on packages or containers of products for export may be adapted to meet specific requirements of the regulations of the country to which the product is to be exported provided that in all such cases the minimum label requirements prescribed in § 73.600 are observed.

STANDARDS FOR PRODUCTS: GENERAL

§ 73.700 Tests prior to release required for each lot.

No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product. Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies. The results of all tests performed shall be considered in determining whether or not the test results meet the test objective, except that a test result may be disregarded when it is established that the test is invalid due to causes unrelated to the product.

§ 73.710 Potency.

Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in § 73.101(t).

§ 73.720 General safety.

In addition to specified safety tests prescribed in this part for individual products, a general safety test shall be performed in final container material, from each filling of each lot of all products intended for administration to man, either after the labels have been affixed to the final container, or affixed, both outside and inside, to the multiple container storage receptacle just prior to its sealing for storage purposes. Exceptions to this procedure may be authorized by the Director, Division of Biologics Standards, when more than one lot is processed each day. The general safety test shall consist of the parenteral injection of the maximum volume tolerated into each of two mice weighing approximately 20 gms. each

and into each of two guinea pigs weighing approximately 350 gms. each but no more than 0.5 ml. need be inoculated into each mouse and no more than 5.0 ml. need be inoculated into each guinea pig. After injection the animals shall be observed for a period of no less than seven days and if neither significant symptoms nor death results during the observation period, the product meets the requirements for general safety. Variations of this test, either in the volume injected or in the species of test animal used shall be made whenever required because of the human dose level demanded of the product or because of any individual demands of the product itself.

§ 73.730 Sterility.

Except as provided in paragraph (f), the sterility of each lot of each product shall be demonstrated by the performance of the tests prescribed in paragraphs (a) and (b) of this section for both bulk and final container material. Bulk material shall be tested spearately from final container material and material from each final container shall be tested in individual test vessels.

(a) *The test*—(1) *Using Fluid Thioglycollate Medium.* The volume of product, as required by paragraph (d) of this section (hereinafter referred to also as the "inoculum"), from samples of both bulk and final container material, shall be inoculated into test vessels of Fluid Thioglycollate Medium. The inoculum and medium shall be mixed thoroughly and incubated at a temperature of 30° to 32° C. for a test period of no less than seven days and examined visually for evidence of growth on the third or fourth or fifth day and on the seventh or eighth day. If incubation is continued beyond eight days, an additional examination shall be made on the last day of the test period. If the inoculum renders the medium turbid so that the absence of growth cannot be determined reliably by visual examination, portions of this turbid medium in amounts of no less than 1.0 ml. shall be transferred on the third or fourth or fifth day of incubation, from each of the test vessels and inoculated into additional vessels of medium. The material in the additional vessels shall be incubated at a temperature of 30° to 32° C. for no less than seven days. Notwithstanding such transfer of material, examination of the original vessels shall be continued as prescribed above. The additional test vessels shall be examined visually for evidence of growth on the third or fourth or fifth day of incubation and on the seventh or eighth day and if incubation is continued beyond a period of eight days, an additional examination shall be made on the last day of the incubation period. If growth appears, repeat tests may be performed as prescribed in paragraph (b) of this section and interpreted as specified in paragraph (c) of this section.

(2) *Using Fluid Sabouraud Medium.* except for dried products, a test for fungi and yeast shall be made on final container material, following the procedures prescribed in subparagraph (1) of this paragraph except that (i) the medium shall be Fluid Sabouraud Medium; (ii) the incubation shall be at a temperature of 20° to 25° C.; (iii) the period of incubation shall be no less than ten days and an examination shall be made on the tenth or eleventh or twelfth day in lieu of an examination on the seventh or eighth day.

(b) *Repeat tests*—(1) *Repeat bulk test.* If growth appears in the test of the bulk material, the test may be repeated to rule out faulty test procedures by testing at least the same volume of material.

(2) *First repeat final container test.* If growth appears in any test (thioglycollate or Sabouraud) of final container material, that test may be repeated to rule out faulty test procedures by testing material from a sample of at least the same number of final containers.

(3) *Second repeat final container test.* If growth appears in any first repeat final container test (thioglycollate or Sabouraud), that test may be repeated provided there was no evidence of growth in any test of the bulk material and material from a sample of twice the number of final containers used in the first test is tested by the same method used in the first test.

(c) *Interpretation of test results.* The results of all tests performed on a lot shall be considered in determining whether or not the lot meets the requirements for sterility, except that tests may be excluded when demonstrated by adequate controls to be invalid. The lot meets the test requirements if no growth appears in the tests prescribed in paragraph (a) of this section. If repeat tests are performed, the lot meets the test requirements if no growth appears in the tests prescribed in paragraph (b)(2) or (b)(3) of this section, whichever is applicable.

(d) *Test samples and volumes*—(1) *Bulk.* Each sample for the bulk sterility test shall be representative of the bulk material and the volume tested shall be no less than 10 ml. (Note exceptions in paragraph (f) of this section.)

(2) *Final containers.* The sample for the final container and first repeat final container tests shall be no less than 20 final containers from each filling of each lot, selected to represent all stages of filling from the bulk vessel. If the amount of material in the final container is 1.0 ml. or less, the entire contents shall be tested. If the amount of material in the final container is more than 1.0 ml., the volume tested shall be the largest single dose recommended by the manufacturer or 1.0 ml., whichever is larger, but no more than 10 ml. of material or the entire contents from a single final container need be tested. (Note exceptions in paragraph (f) of this section.)

(e) *Culture medium*—(1) *Formulae.* (i) The formula for Fluid Thioglycollate Medium is as follows:

Fluid Thioglycollate Medium

1-cystine	0.5 gm.
Sodium chloride	2.5 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	5.5 gm.
Granular agar (less than 15% moisture by weight).	0.75 gm.
Yeast extract (water-soluble)	5.0 gm.
Pancreatic digest of casein	15.0 gm.
Purified water	1,000.0 ml.
Sodium thioglycollate (or thioglycollic acid—0.3 ml.).	0.5 gm.
Resazurin (0.10% solution, freshly prepared).	1.0 ml.

Final pH 7.1±0.1.

(ii) The formula for Fluid Sabouraud Medium is as follows:

Fluid Sabouraud Medium

Dextrose	20 gm.
Pancreatic digest of casein	5 gm.
Peptic digest of animal tissue	5 gm.
Purified water	1,000 ml.

Final pH 5.7±0.1.

(2) *Culture medium requirements*—(i) *Quality and condition of medium and design of test vessel.* The growth promoting qualities and conditions of the culture medium, and the design of the test vessel, shall be such as are shown to provide conditions favorable to aerobic and anaerobic growth of microorganisms throughout the test period.

(ii) *Ratio of inoculum to culture medium.* The ratio of the volume of the inoculum to the volume of culture medium shall be such as will dilute the preservative in the inoculum to a level that does not inhibit growth of contaminating microorganisms. Inhibitors or neutralizers of preservative may be considered in determining the proper ratio.

(f) *Exceptions.* Bulk and final container material shall be tested for sterility as described above in this section except as follows:

(1) *Different sterility tests prescribed.* When different sterility tests are prescribed for a product in this part.

(2) *Alternate incubation temperatures.* Two tests may be performed, in all respects as prescribed in paragraph (a)(1) of this section, one test using an incubation temperature of 18° to 22° C., the other test using an incubation temperature of 35° to 37° C., in lieu of performing one test using an incubation temperature of 30° to 32° C.

(3) *Different tests equal or superior.* A different test may be performed provided that prior to the performance of such a test a manufacturer submits data which the Director, National Institutes of Health finds adequate to establish that the different test is equal or superior to the tests described in paragraphs (a) and (b) of this section in detecting contamination and makes the finding a matter of official record.

(4) *Test precluded or not required.* The tests prescribed in this section need not be performed for Whole Blood (Human), Red Blood Cells (Human), Single Donor Plasma (Human), Smallpox Vaccine and other similar products concerning which the Director, National Institutes of Health, finds that the mode

of administration, the method of preparation or the special nature of the product precludes or does not require a sterility test.

(5) *Viscous biological products.* Thioglycollate Broth Medium may be used in lieu of Fluid Thioglycollate Medium to test viscous biological products. The formula for Thioglycollate Broth Medium is as follows:

Thioglycollate Broth Medium. Certain biological products are turbid or otherwise do not lend themselves readily to culturing in Fluid Thioglycollate Medium because of its viscosity. In such instances, the following broth is acceptable in place of the Fluid Thioglycollate Medium, provided it is used in Smith fermentation tubes which have been heated within four hours in a boiling water bath or in free-flowing steam so as to drive the dissolved oxygen out of the medium in the closed arm:

l-cystine	0.5 gm.
Sodium chloride	2.5 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	5.5 gm.
Yeast extract (water-soluble)	5.0 gm.
Pancreatic digest casein	15.0 gm.
Purified water	1,000.0 ml.
Sodium thioglycollate (or thioglycollic acid—0.3 ml.).	0.5 gm.

Final pH 7.1±0.1.

(6) *Number of final containers more than 20, less than 200.* If the number of final containers in the filling is more than 20 or less than 200, the sample shall be no less than 10 percent of the containers.

(7) *Number of final containers—20 or less.* If the number of final containers in a filling is 20 or less, the sample shall be two final containers, or the sample need be no more than one final container, provided (i) the bulk material met the sterility test requirements and (ii) after filling, it is demonstrated by testing a simulated sample that all surfaces to which the product was exposed were free of contaminating microorganisms. The simulated sample shall be prepared by rinsing the filling equipment with sterile 1.0 percent peptone solution, pH 7.1±0.1, which shall be discharged into a final container by the same method used for filling the final containers with the product.

(8) *Samples—large volume of product in final containers.* For Normal Serum Albumin (Human), Normal Human Plasma, Antihemophilic Plasma (Human), Plasma Protein Solution (Human) and Fibrinogen (Human), when the volume of product in the final container is 50 ml. or more, the final containers selected as the test sample may contain less than the full volume of product in the final containers of the filling from which the sample is taken: *Provided,* That the containers and closures of the sample are identical with those used for the filling to which the test applies and the sample represents all stages of that filling.

(9) *Diagnostic products not intended for injection.* For diagnostic products not intended for injection, (i) only the Thioglycollate Medium test is required, (ii) the volume of material for the bulk test shall be no less than 2.0 ml., and (iii) the sample for the final container test shall be no less than three final containers if the total number filled is 100 or less, and, if greater, one additional container for each additional 50 containers or fraction thereof, but the sample need be no more than 10 containers.

(10) *Human immune globulin preparations.* For human immune globulin preparations, the test samples from the bulk material and from each final container need be no more than 2.0 ml.

§ 73.740 Purity.

Products shall be free from extraneous material. In addition, products shall be tested as provided in paragraphs (a) and (b) of this section.

(a) *Test for residual moisture.* Each lot of dried product shall be tested for residual moisture and other volatile substances.

(1) *Procedure.* The test for dried products shall consist of measuring the maximum loss of weight in a weighed sample equilibrated over anhydrous P_2O_5 at a pressure of not more than one mm. of mercury, and at a temperature of 20° to 30° C. for as long as it has been established is sufficient to result in a constant weight.

(2) *Test results; standard to be met.* The residual moisture and other volatile substances shall not exceed 1 percent except that for BCG Vaccine they shall not exceed 1½ percent, for Measles Virus Vaccine, Live, Attenuated; Rubella Virus Vaccine, Live and Antihemophilic Factor (Human), they shall not exceed 2 percent, and for Modified Plasma (Bovine); Thrombin; Fibrinogen; Streptokinase; Streptokinase - Streptodornase; and Anti-Influenza Virus Serum for the Hemagglutination Inhibition Test, they shall not exceed 3 percent.

(b) *Test for pyrogenic substances.* Each lot of any product intended for use by injection shall be tested for pyrogenic substances by intravenous injection into rabbits as provided in subparagraphs (1) and (2) of this paragraph: *Provided,* That notwithstanding any other provision of this part, the test for pyrogenic substances is not required for the following products: Products containing formed blood elements; Single Donor Plasma (Human); Normal Horse Serum; Normal Rabbit Serum; bacterial, viral and rickettsial vaccines and antigens; toxoids; toxins, allergenic extracts; venoms; diagnostic substances and trivalent organic arsenicals.

(1) *Test dose.* The test dose for each rabbit shall be at least 3 milliliters per kilogram of body weight of the rabbit and also shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended, but need not exceed 10 ml. per kilogram of body weight of the rabbit, except that: (i) Regardless of the human dose recommended, the test dose per kilogram of body weight of each rabbit shall be, at least 1 milliliter for immune globulins derived from human blood, at least 3 milliliters for Normal Human Plasma, and at least 30 milligrams for Fibrinogen (Human); (ii) for Streptokinase, Streptokinase-Streptodornase, Aggregrated Radio-Iodinated (I^{131}) Albumin (Human), Radio-Chromated (Cr^{51}) Serum Albumin (Human), Radio-Iodinated (I^{125}) Serum Albumin (Human) and Radio-Iodinated (I^{131}) Serum Albumin (Human), the test dose shall be at least equivalent proportionately on a body weight basis to the maximum single human dose recommended.

(2) *Procedure.* Products shall be tested for freedom from pyrogenic substances by intraveneous injection of the test dose into three or more rabbits in overt good health and by recording for each rabbit a control temperature taken within one hour prior to injection, and three additional temperatures taken one, two, and three hours after injection. For purposes of subparagraph (3) of this paragraph, if there is no temperature increase over the control temperature (i.e. where the temperature remains unchanged or falls), the temperature rise shall be considered as zero. If there is an increase in temperature over the control temperature, the temperature rise shall be the difference between the highest of the three hourly readings and the control temperature reading.

(3) *Test results; standards to be met.* The results recorded for all rabbits used in all tests of a lot of a product shall be included in determining whether the standard for purity is met. The product fails to meet test requirements if one-half or more of all rabbits show a temperature rise of 0.6° C. or more or if the average temperature rise of all rabbits is 0.5° C. or more.

(c) *Different tests equal or superior.* A different test for residual moisture may be performed provided that prior to its performance the manufacturer submits data which the Director, National Institutes of Health finds adequate to establish that the different test is equal or superior to the test described in paragraph (a) of this section and makes the finding a matter of official record.

§73.750 Test for *Mycoplasma.*

Except as provided otherwise in this part, prior to clarification or filtration in the case of live virus vaccines produced from in-vitro living cell cultures, and prior to inactivation in the case of inactivated virus vaccines produced from such living cell cultures, each virus harvest pool and control fluid pool shall be tested for the presence of *Mycoplasma,* as follows:

Samples of the virus for this test shall be stored either (1) between 2° and 8° C. for no longer than 24 hours, or (2) at −20° C. or lower if stored for longer than 24 hours. The test shall be performed on samples of the viral harvest pool and on control fluid pool obtained at the time of viral harvest, as follows: No less than 2.0 ml. of each sample shall be inoculated in evenly distributed amounts over the surface of no less than 10 plates of at least two agar media. No less than 1.0 ml. of sample shall be inoculated into each of four tubes containing 10 ml. of a semisolid broth medium. The media shall be such as have been shown to be capable of detecting known *Mycoplasma* and each test shall include control cultures of at least two known strains of *Mycoplasma,* one of which must be *M. pneumoniae.* One half of

the plates and two tubes of broth shall be incubated aerobically at 36° C. ±1° C. and the remaining plates and tubes shall be incubated anaerobically at 36° C. ±1° C. in an environment of 5–10 percent CO_2 in N_2. Aerobic incubation shall be for a period of no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml. of broth from each of the two tubes shall be combined and subinoculated on to no less than 4 additional plates and incubated aerobically. Anaerobic incubation shall be for no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml. of broth from each of the two tubes shall be combined and subinoculated on to no less than four additional plates and incubated anaerobically. All inoculated plates shall be incubated for no less than 14 days, at which time observation for growth of *Mycoplasma* shall be made at a magnification of no less than 300×. If the Dienes Methylene Blue-Azure dye or an equivalent staining procedure is used, no less than a one square cm. plug of the agar shall be excised from the inoculated area and examined for the presence of *Mycoplasma*. The presence of the *Mycoplasma* shall be determined by comparison of the growth obtained from the test samples with that of the control cultures, with respect to typical colonial and microscopic morphology. The virus pool is satisfactory for vaccine manufacture if none of the tests on the samples show evidence of the presence of *Mycoplasma*.

§ 73.760 Identity.

The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.

§ 73.770 Requests for samples and protocols; official release.

Samples of any lot of any licensed product, together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Division of Biologics Standards. Upon notification by the Director, Division of Biologics Standards, a manufacturer shall not distribute a lot of a product until the lot is released by the Director, Division of Biologics Standards: *Provided*, That the Director shall not issue such notification except when deemed necessary for the safety, purity or potency of the product.

§ 73.780 Cultures.

(a) *Storage and maintenance.* Cultures used in the manufacture of products shall be stored in a secure and orderly manner, at a temperature and by a method that will retain the initial characteristics of the organisms and insure freedom from contamination and deterioration.

(b) *Identity and verification.* Each culture shall be clearly identified as to source strain. A complete identification of the strain shall be made for each new stock culture preparation. Primary and subsequent seed lots shall be identified by lot number and date of preparation. Periodic tests shall be performed as often as necessary to verify the integrity of the strain characteristics and freedom from extraneous organisms. Results of all periodic tests for verification of cultures and determination of freedom from extraneous organisms shall be recorded and retained.

§ 73.790 Constituent materials.

(a) *Ingredients, preservative, diluents, adjuvants.* All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used shall not denature the specific substances in the product below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine, Pollovirus Vaccine, Live, Oral, or to viral vaccines labeled for use with the jet injector, or to dried vaccines when the accompanying diluent contains a preservative. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. In no event shall the recommended individual dose of a biological product contain more than 0.85 milligram of aluminum, determined by assay, or more than 1.14 milligrams of aluminum, determined by calculation on the basis of the amount of aluminum compound added.

(b) *Extraneous protein; cell culture produced vaccines.* Extraneous protein known to be capable of producing allergenic effects in human subjects shall not be added to a final virus medium of cell culture produced vaccines intended for injection. If serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000.

(c) *Antibiotics.* A minimum concentration of antibiotics, other than penicillin, may be added to the production substrate of viral vaccines.

§ 73.800 Total solids in serums.

Except as otherwise provided by regulation, no liquid serum or antitoxin shall contain more than 20 percent total solids.

§ 73.810 Permissible combinations.

Licensed products may not be combined with other licensed products, either therapeutic, prophylactic or diagnostic, except as a license is obtained for the combined product. Licensed products may not be combined with nonlicensable therapeutic, prophylactic, or diagnostic substances except as a license is obtained for such combination.

§ 73.820 Standard preparations.

Standard preparations made available by the Division of Biologics Standards shall be applied in testing, as follows:

(a) *Potency standards.* Potency standards shall be applied in testing for potency all forms of the following:

ANTIBODIES

Botulism Antitoxin, Type A.
Botulism Antitoxin, Type B.
Botulism Antitoxin, Type E.
Diphtheria Antitoxin.
Dysentery Antitoxin (Shiga).
Anti-Hemophilus Influenzae Type b Serum.
Histolyticus Antitoxin.
Oedematiens Antitoxin.
Perfringens Antitoxin.
Antipertussis Serum.
Antirabies Serum.
Scarlet Fever Streptococcus Antitoxin.
Sordellii Antitoxin.
Staphylococcus Antitoxin.
Tetanus Antitoxin.
Vibrion Septique Antitoxin.

ANTIGENS

Diphtheria Toxin for Schick Test.
Pertussis Vaccine.
Scarlet Fever Streptococcus Toxin.
Tuberculin, Old.
Tuberculin, Purified Protein Derivative.
Typhoid Vaccine.

BLOOD DERIVATIVE

Thrombin.

(b) *Opacity standard.* The U.S. Opacity Standard shall be applied in estimating the bacterial concentration of all bacterial vaccines. The assigned value of the standard when observed visually is 10 units. The assigned value of the standard when observed with a photometer is (i) 10 units when the wavelength of the filter is 530 millimicrons, (ii) 10.6 units when the wavelength of the filter is 650 millimicrons, and (iii) 9 units when the wavelength of the filter is 420 millimicrons.

§ 73.830 Limits of potency.

The potency of the following products shall be not less than that set forth below and products dispensed in the dried state shall represent liquid products having the stated limitations.

ANTIBODIES

Diphtheria Antitoxin, 500 units per milliliter.
Scarlet Fever Streptococcus Antitoxin, 400 units per milliliter.
Tetanus Antitoxin, 400 units per milliliter.
Tetanus Immune Globulin (Human), 50 units of tetanus antitoxin per milliliter.

ANTIGENS

Pertussis Vaccine, 12 units per total human immunizing dose.
Typhoid Vaccine, 8 units per milliliter.

§ 73.840 Date of manufacture.

The date of manufacture shall be determined as follows:

(a) For products for which an official standard of potency is prescribed in either § 73.820 or § 73.830, or which are subject to official potency tests, the date of initiation by the manufacturer of the last valid potency test.

(b) For products which are not subject to official potency tests, (1) the date of removal from animals, (2) the date of extraction, (3) the date of solution,

or (4) the date of cessation of growth, whichever is applicable.

§ 73.850 Periods of cold storage.

Except as otherwise provided in the regulations of this part, products may be held in cold storage by the manufacturer as follows:

At a temperature not above 5°C.—1 year.
At a temperature not above 0°C.—2 years.

§ 73.860 Dating period.

The dating period for a combination of two or more products shall be no longer than the dating period of the component product with the shortest dating period. The dating period for a product shall begin on the date of manufacture, except that the dating period may begin on the date of issue from the manufacturer's cold storage, provided the product was maintained as prescribed in § 73.850. If held in the manufacturer's cold storage beyond the period prescribed, the dating period shall be reduced by a corresponding period.

§ 73.870 Dating periods for specific products.

The following dating periods are based on data relating to usage, clinical experience or laboratory tests that establish the period beyond which the product cannot be expected beyond reasonable doubt to yield its specific results and retain its safety, purity, and potency, provided the product is maintained at the recommended temperatures. The standards prescribed by the regulations in this part, designed to insure continued safety, purity, and potency of the products, are based on the dating periods set forth below. Cold storage periods and temperatures prescribed in § 73.850 shall apply and outside labels shall recommend storage between 2° C. and 8° C., except when specifically provided otherwise. (Storage temperatures and storage periods are given in parentheses after the dating periods below when they differ from those specified in § 73.850.)

Adsorbed Anti-A Serum	One year.
Adenovirus and Influenza Virus Vaccines Combined Aluminum Hydroxide Adsorbed.	Six months (5° C., six months).
Adenovirus and Influenza Virus Vaccines Combined Aluminum Phosphate Adsorbed.	Six months (5° C., six months).
Adenovirus Vaccine	Six months (5° C., six months).
Aggregated Radio-Iodinated (I^{131}) Albumin (Human).	Thirty days. § 73.850 does not apply.
Allergenic Extracts	With 50 percent or more glycerin, three years (5° C., three years). With less than 50 percent glycerin, eighteen months (5° C., eighteen months). Products for which cold storage conditions are inappropriate, eighteen months, provided labeling recommends storage at no warmer than 30° C. § 73.850 does not apply. Powders and tablets, five years, provided labeling recommends storage at no warmer than 30° C. § 73.850 does not apply. Freeze dried products, five years (5° C., three years).
Allergenic Extracts, Alum Precipitated	Eighteen months (5° C., eighteen months).
Anthrax Vaccine, Adsorbed	One year (5° C., two years). § 73.850 does not apply.
Anti-A Blood Grouping Serum	*Liquid:* One year. *Dried:* Five years.
Anti-A, B Blood Grouping Serum	*Liquid:* One year. *Dried:* Five years.
Anti-B Blood Grouping Serum	*Liquid:* One year. *Dried:* Five years.
Anti-Di^a Serum (Anti-Diego)	One year.
Anti-Fy^a Serum (Anti-Duffy)	One year.
Anti-Fy^b Serum	One year.
Anti-Gr (Vw) Serum	One year.
Antihemophilic Factor (Human)	One year. § 73.850 does not apply.
Antihemophilic Globulin (Human)	One year.
Antihemophilic Plasma (Human)	Five years.
Anti-*Hemophilus influenzae* Type b Serum.	*Liquid:* Two years. *Dried:* Five years.
Anti-Human Chorionic Gonadotropic Serum.	One year. § 73.850 does not apply.
Anti-Human Serum	*Liquid:* One year. *Dried:* Five years.
Anti-I Serum	One year.
Anti-Influenza Virus Serum for the Hemagglutination Inhibition Test.	Two years.
Anti-Jk^a Serum (Anti-Kidd)	One year.
Anti-Jk^b Serum	One year.
Anti-Js^a Serum (Anti-Sutter)	One year.
Anti-k Serum (Anti-Cellano)	One year.
Anti-K Serum (Anti-Kell)	One year.
Anti-Kp^a Serum (Anti-Penney)	One year.
Anti-Kp^b and Anti-K Serum (Anti-Rautenberg and Anti-Kell).	One year.
Anti-Kp^b Serum (Anti-Rautenberg)	One year.
Anti-Le^a Serum (Anti-Lewis)	*Liquid:* One year. *Dried:* Five years.
Anti-Le^b Serum	*Liquid:* One year. *Dried:* Five years.
Anti-Lu^a Serum (Anti-Lutheran)	One year.
Anti-M Serum	One year.
Anti-M^g Serum	One year.
Anti-Mi^a Serum (Anti-Miltenberger)	One year.
Anti-N Serum	One year.
Anti-P Serum	One year.
Antirabies Serum	Two years.
Anti-Rh Typing Serum, Anti-hr′ (Anti-c).	One year.
Anti-Rh Typing Serum, Anti-hr″ (Anti-e).	One year.
Anti-Rh Typing Serum, Anti-hr^v (Anti-V).	One year.
Anti-Rh Typing Serum, Anti-rh′ (Anti-C).	*Liquid:* One year. *Dried:* Five years.
Anti-Rh Typing Serum, Anti-rh″ (Anti-E).	*Liquid:* One year. *Dried:* Five years.
Anti-Rh Typing Serum, Anti-Rh_o (Anti-D).	*Liquid:* One year. *Dried:* Five years.
Anti-Rh Typing Serum, Anti-Rh_o′ (Anti-CD).	*Liquid:* One year. *Dried:* Five years.
Anti-Rh Typing Serum, Anti-Rh_o″ (Anti-DE).	One year.
Anti-Rh Typing Serum, Anti-$Rh_o rh′ rh″$ (Anti-CDE).	One year.
Anti-Rh Typing Serum, Anti-Rh_o+Rh^o (Anti-D+D^u).	One year.
Anti-Rh Typing Serum, Anti-rh^w (Anti-C^w).	One year.
Anti-rh^w and Anti-K Serum (Anti-(C^w+Kell)).	One year.
Anti-s Serum	*Liquid:* One year. *Dried:* Five years.
Anti-S Serum	One year.

Antivenin (*Crotalidae*) Polyvalent	Five years with an initial 10 percent excess of potency, provided labeling recommends storage at no warmer than 37° C.
Antivenin (*Latrodectus mactans*)	Five years with an initial 10 percent excess of potency.
Antivenin (*Micrurus fulvius*)	Five years with an initial 10 percent excess of potency.
Anti-U Serum (Anti-Ss)	One year.
Anti-Wr^a Serum (Anti-Wright)	One year.
B. histolyticus Antitoxin	Five years with an initial 20 percent excess of potency.
B. oedematiens Antitoxin	Five years with an initial 20 percent excess of potency.
B. sordellii Antitoxin	Five years with an initial 20 percent excess of potency.
BCG Vaccine	Six months (5° C., one year).
Blastomycin	Two years (5° C., one year).
Blood Group Specific Substances A and B.	Two years.
Blood Group Specific Substance A	Two years.
Blood Group Specific Substance B	Two years.
Botulism Antitoxin	Five years with an initial 20 percent excess of potency.
Chicken Pox Immune Serum (Human)	*Liquid:* One year. *Dried:* Five years.
Cholera Vaccine	Eighteen months (5° C., one year).
Cobra Venom with Silicic and Formic Acids.	Eighteen months (5° C., one year).
Cobra Venom Solution	Eighteen months (5° C., one year).
Coccidioidin	Three years (5° C., one year).
Collagenase	Eighteen months, provided labeling recommends storage at no warmer than 25° C. § 73.850 does not apply.
Diphtheria Antitoxin	*Liquid:* Five years with an initial 20 percent excess of potency. *Dried:* Five years with an initial 10 percent excess of potency.
Diphtheria and Tetanus Toxoids and Pertussis and Poliomyelitis Vaccines Adsorbed.	Four months (5° C., two months).
Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and Poliomyelitis Vaccine.	(a) Four months (5° C., two months). (b) One year, provided the pertussis and poliomyelitis components unmixed when issued (5° C., one year).
Diphtheria and Tetanus Toxoids and Pertussis Vaccine.	Eighteen months (5° C., one year).
Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed.	Eighteen months (5° C., one year).
Diphtheria and Tetanus Toxoids and Poliomyelitis Vaccine.	One year (5° C., one year).
Diphtheria and Tetanus Toxoids	Two years (5° C., one year).
Diphtheria and Tetanus Toxoids Adsorbed.	Two years (5° C., one year).
Diphtheria Toxin for Schick Test	One year (5° C., one year).
Diphtheria Toxoid	Two years (5° C., one year).
Diphtheria Toxoid Adsorbed	Two years (5° C., one year).
Diphtheria Toxoid and Pertussis Vaccine	Eighteen months (5° C., one year).
Diphtheria Toxoid and Pertussis Vaccine Adsorbed.	Eighteen months (5° C., one year).
Dysentery Antitoxin, Shiga	Five years with an initial 20 percent excess of potency.
Equine Encephalomyelitis Vaccine (Eastern).	One year.
Equine Encephalomyelitis Vaccine (Western).	One year.
Fibrinogen (Human)	Five years.
Fibrinogen with Antihemophilic Factor (Human).	Five years.
Fibrinolysin (Human)	Two years.
Fibrinolysin and Desoxyribonuclease Combined (Bovine).	Three years, provided labeling recommends storage at no warmer than 30° C.
Fibrinolysin and Desoxyribonuclease Combined (Bovine) with Chloramphenical.	Three years, provided labeling recommends storage at no warmer than 30° C.
Gas Gangrene Polyvalent Antitoxin	Five years with an initial 20 percent excess of potency.
Haemophilus influenzae Typing Serum	One year.
Histamine Azoprotein	Two years.
Histoplasmin	Two years (5° C., one year).
Immune Serum Globulin (Human)	Three years (5° C., three years).
Influenza Virus Hemagglutinating Antigen.	Two years (5° C., one year).
Influenza Virus Vaccine	Eighteen months (5° C., one year).
Lymphogranuloma Venereum Antigen	One year (5° C., one year).
Measles Immune Serum (Human)	*Liquid:* One year. *Dried:* Five years.
Measles Immune Globulin (Human)	Three years (5° C., three years).
Measles-Smallpox Vaccine, Live	One year. § 73.850 does not apply.
Measles Virus Vaccine, Inactivated	One year (5° C., one year).
Measles Virus Vaccine, Live, Attenuated	One year. § 73.850 does not apply.
Modified Plasma (Bovine)	Twenty months. § 73.850 does not apply.
Mumps Immune Serum (Human)	*Liquid:* One year. *Dried:* Five years.
Mumps Immune Globulin (Human)	Three years from date the dried or frozen bulk product is placed in final solution (5° C., three years).
Mumps Skin Test Antigen	Eighteen months (5° C., one year).
Mumps Vaccine	Eighteen months (5° C., one year).
Mumps Virus Vaccine, Live	One year. § 73.850 does not apply.
Normal Bovine Serum	Five years.
Normal Horse Serum	Five years.
Normal Human Plasma	*Liquid*: Three years provided product is maintained between 15° and 30° C., and labeling recommends storage between 15° and 30° C. § 73.850 does not apply. *Dried*: Seven years provided labeling recommends storage not above 37° C. § 73.850 does not apply.
Normal Human Serum	*Liquid:* Eighteen months. *Dried:* Five years. *Frozen:* Three years, provided labeling recommends storage at no warmer than −18° C. § 73.850 does not apply. *Melted:* One year after the date of melting. § 73.850 does not apply.
Normal Rabbit Serum	Five years.

Normal Serum Albumin (Human)	(a) Five years, provided labeling recommends storage between 2° and 10° C. (5° C., three years). or (b) Three years, provided labeling recommends storage at room temperature, no warmer than 37° C. (5° C., three years). or (c) Ten years, if in an hermetically sealed metal container and provided labeling recommends storage between 2° and 10° C. § 73.850 does not apply.
Oxophenarsine Hydrochloride	Three years (5° C., one year).
Perfringens Antitoxin	Five years with an initial 20 percent excess of potency.
Pertussis Immune Serum (Human)	Three years from date the dried or frozen bulk product is placed in final solution (5° C., three years).
Pertussis Immune Globulin (Human)	*Liquid:* One year. *Dried:* Five years.
Pertussis Vaccine	Eighteen months (5° C., one year).
Plague Vaccine	Eighteen months (5° C., one year).
Plasma Protein Fraction (Human)	(a) Five years (5° C., one year). (b) Three years, provided labeling recommends storage at no warmer than 30° C. (5° C., one year).
Pneumococcus Typing Serum	One year.
Poliomyelitis Immune Globulin (Human).	Three years (5° C., three years).
Poliomyelitis Vaccine	One year (5° C., one year).
Poliomyelitis Vaccine Adsorbed	One year (5° C., one year).
Poliovirus Vaccine, Live, Oral, Trivalent	*Frozen:* One year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state (−10° C., one year). *Liquid:* Thirty days, provided labeling recommends storage between 2° and 8° C. § 73.850 does not apply.
Poliovirus Vaccine, Live, Oral, Type I	*Frozen:* One year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state (−10° C., one year). *Liquid:* Thirty days, provided labeling recommends storage between 2° and 8° C. § 73.850 does not apply.
Poliovirus Vaccine, Live, Oral, Type II	*Frozen:* One year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state (−10° C., one year). *Liquid:* Thirty days, provided labeling recommends storage between 2° and 8° C. § 73.850 does not apply.
Poliovirus Vaccine, Live, Oral, Type III	*Frozen:* One year, provided labeling recommends storage at a temperature which will maintain ice continuously in a solid state (−10° C., one year). *Liquid:* Thirty days, provided labeling recommends storage between 2° and 8° C. § 73.850 does not apply.
Polyvalent bacterial antigens with "No U.S. Standard of Potency."	*Liquid:* Eighteen months (5° C., one year). *Dried:* Five years (5° C., one year).
Polyvalent bacterial vaccines with "No U.S. Standard of Potency."	*Liquid:* Eighteen months (5° C., one year). *Dried:* Five years (5° C., one year).
Polyvalent modified bacterial antigens with "No U.S. Standard of Potency."	*Liquid:* Eighteen months (5° C., one year). *Dried:* Five years (5° C., one year).
Polyvalent sensitized bacterial vaccines with "No U.S. Standard of Potency."	*Liquid:* Eighteen months (5° C., one year). *Dried:* Five years (5° C., one year).
Profibrinolysin (Human)	Two years.
Pseudomonas Polysaccharide	Eighteen months.
Q Fever Vaccine	One year (5° C., one year).
Rabies Vaccine	*Liquid:* Six months (5° C., three months). *Dried:* Eighteen months.
Radio-Chromated (Cr^{51}) Serum Albumin (Human).	Sixty days from the date chromium is added. § 73.850 does not apply.
Radio-Iodinated (I^{128}) Serum Albumin (Human).	120 days from date iodination is completed. § 73.850 does not apply.
Radio-Iodinated (I^{131}) Serum Albumin (Human).	Thirty days from date iodination is completed. § 73.850 does not apply.
Reagent Red Blood Cells (Human)	Twenty-one days. § 73.850 does not apply.
Reagent Blood Group Specific Substances A and B.	Two years.
Red Blood Cells (Human)	(a) Twenty-one days from date of collection of source blood, provided labeling recommends storage between 1° and 10° C. and the hermetic seal is not broken during processing. § 73.850 does not apply. Twenty-four hours after plasma removal, provided labeling recommends storage between 1° and 10° C., if the hermetic seal is broken during processing. § 73.850 does not apply. (b) *Frozen:* Three years, provided labeling recommends storage at −65° C. or colder. Twenty-four hours after removal from storage at −65° C. or colder, provided labeling recommends storage between 1° and 10° C. § 73.850 does not apply.
Resuspended Red Blood Cells (Human)	Ten days. § 73.850 does not apply.
Rh_o (D) Immune Globulin (Human)	Six months (5° C., six months).
Rocky Mountain Spotted Fever Vaccine	Eighteen months (5° C., one year).
Rubella Virus Vaccine, Live	One year. § 73.850 does not apply.
Russell Viper Venom	Five years.
Scarlet Fever Immune Serum (Human)	*Liquid:* One year. *Dried:* Five years.
Scarlet Fever Streptococcus Toxin for Dick Test.	One year (5° C., one year).
Scarlet Fever Streptococcus Toxin for Immunization.	One year (5° C., one year).
Shick Test Control	One year (5° C., one year).
Single Donor Plasma (Human)	(a) Five years, provided labeling recommends storage at not above −18° C. § 73.850 does not apply. (b) If used in coagulation defects, one year, provided labeling recommends storage at not above −18° C. § 73.850 does not apply.
Smallpox Vaccine	*Liquid:* Three months, provided labeling recommends storage at no warmer than 0° C. (−10° C., nine months, if product is maintained as glycerinated or equivalent vaccine in bulk or final containers). *Dried:* Eighteen months (5° C., six months).
Staphylococcus Antitoxin	Five years with an initial 20 percent excess of potency.

Staphylococcus Toxoid	Two years (5° C., one year).
Staphylococcus Toxoid and Bacterial Antigen made from Staphylococcus (Albus and Aureus).	Eighteen months (5° C., one year).
Staphylococcus Toxoid and Bacterial Vaccine made from Staphylococcus (Aureus).	Eighteen months (5° C., one year).
Staphylococcus Toxoid, Streptococcus Toxin, and Bacterial Vaccine made from Staphylococcus (Aureus), Streptococcus (Hemolyticus), Pneumococcus, *Hemophilus influenzae*.	One year (5° C., one year).
Streptococcus Erythrogenic Toxin	One year (5° C., one year).
Streptokinase	Eighteen months.
Streptokinase-Streptodornase	*Dried:* Two years (5° C., one year). *Tablets:* Eighteen months, provided labeling recommends storage at no warmer than 30° C. (5° C., six months).
Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use).	Two years (5° C., one year).
Tetanus and Gas Gangrene Polyvalent Antitoxin.	Five years with an initial 20 percent excess of potency.
Tetanus Immune Globulin (Human)	Three years with an initial 10 percent excess of potency (5° C., one year).
Tetanus Antitoxin	*Liquid:* Five years with an initial 20 percent excess of potency. *Dried:* Five years with an initial 10 percent excess of potency.
Tetanus Toxoid	Two years (5° C., one year).
Tetanus Toxoid Adsorbed	Two years (5° C., one year).
Tetanus Toxoid and Pertussis Vaccine	Eighteen months (5° C., one year).
Thrombin	Three years.
Trichinella Extract	Eighteen months (5° C., one year).
Tuberculin	*Old, concentrated:* Containing 50 percent glycerin, five years. *Old diluted:* One year. *Purified Protein Derivative, concentrated:* Two years containing 50 percent glycerin (5° C., one year). *Purified Protein Derivative, diluted:* One year. § 73.850 does not apply. *Purified Protein Derivative, dried:* Five years. *Old, dried on multiple puncture device:* Two years, provided labeling recommends storage at no warmer than 30° C. (30° C., one year).
Typhoid and Paratyphoid Vaccine	Eighteen months (5° C., one year).
Typhoid Vaccine	Eighteen months (5° C., one year).
Typhus Vaccine	Eighteen months (5° C., one year).
Vibrion Septique Antitoxin	Five years with an initial 20 percent excess of potency.
Whole Blood (Human)* collected in	(a) ACD solution—Twenty-one days, provided labeling recommends storage between 1° and 10° C. § 73.850 does not apply. (b) Heparin solution—Forty-eight hours, provided labeling recommends storage between 1° and 10° C. § 73.850 does not apply. (c) CPD solution—Twenty-one days, provided labeling recommends storage between 1° and 10° C. § 73.850 does not apply.
Yellow Fever Vaccine	One year, provided labeling recommends storage at no warmer than 5° C. (−20° C., one year).

NOTE: Changes in labeling necessitated by changes of proper names in this section published at 35 F.R. 4941 shall be effective when the manufacturer's current supply of labels has been exhausted or March 21, 1971, whichever first occurs.

Subpart B—Additional Standards for Viral Vaccines

POLIOMYELITIS VACCINE

§ 73.1000 The product.

(a) *Proper name and definition.* The proper name of this product shall be "Poliomyelitis Vaccine", which shall consist of an aqueous preparation of poliovirus types 1, 2, and 3, grown in monkey kidney tissue cultures, inactivated by a suitable method.

(b) *Strains of virus.* Strains of poliovirus used in the manufacture of vaccine shall be identified by historical records, infectivity tests and immunological methods. Any strain of virus may be used that produces a vaccine meeting the requirements of §§73.1001, 73.1002, and 73.1003, but the Director, National Institutes of Health may from time to time prohibit the use of any specific strain whenever he finds that it is practicable to use another strain of the same type that is potentially less pathogenic to man and that will produce a vaccine of at least equivalent safety and potency.

(c) *Monkeys; species permissible as source of kidney tissue.* Only Macaca or Cercopithecus monkeys, or a species found by the Director, Division of Biologics Standards, to be equally suitable, which have met all requirements of §§ 73.501(f) (2) and 73.501(f) (8) shall be used as a source of kidney tissue for the manufacture of Poliomyelitis Vaccine.

§ 73.1001 Manufacture.

(a) *Cultivation of virus.* Virus for manufacturing vaccine shall be grown with aseptic techniques in monkey kidney cell cultures. Suitable antibiotics in the minimum concentration required may be used (§ 73.790(c)).

(b) *Filtration.* Within 72 hours preceding the beginning of inactivation, the virus suspensions shall be filtered or clarified by a method having an efficiency equivalent to that of filtration through an S1 Seitz type filter pad.

(c) *Virus titer.* The 50 percent endpoint ($TCID_{50}$) of the virus fluids after filtration shall be $10^{6.5}$ or greater as confirmed by comparison in a simultaneous test (using groups of 10 tubes at 1 log steps or groups of 5 tubes at 0.5 log steps) with a reference virus distributed by the Division of Biologics Standards. Acceptable titrations of the reference virus shall not vary more than ± 0.5 $\log_{10}$ from its labeled titer using 0.5 milliliter inoculum in tissue culture.

(d) *Inactivation of virus.* The virus shall be inactivated, as evidenced by the tests prescribed in § 73.1002, through the use of an agent or method which has been demonstrated to be consistently effective in the hands of the manufacturer in inactivating a series of lots of poliovirus. If formaldehyde is used for inactivation, it shall be added to the virus suspension to a final concentration of U.S.P. solution of formaldehyde of 1:4000, and the inactivation conducted under controlled conditions of pH and time, at a temperature of 36° to 38° C. Three or more virus titers, suitably spaced to indicate rate of inactivation, shall be determined during the inactivation process. Filtration equivalent to that described in paragraph (b) of this section shall be performed after the estimated baseline time (time at which the 50 percent end-point reaches one tissue culture infective dose per milliliter), but prior to sampling for the first single strain tissue culture test required in § 73.1002(b), except that this filtration may be omitted for strains of a virulence for monkeys equal to or less than that of the MEF–1 Type 2 strain of poliovirus.

(e) *Additional processing.* Single strain or trivalent pools that have failed to pass safety tests prescribed in § 73.1002 (b), (c), or (e) may be treated as follows:

(1) Filtration or clarification by a method having an efficiency equivalent to that of filtration through an S1 Seitz type filter pad.

(2) Negative tests performed as described in § 73.1002 (b) and (c) must be obtained on each of two successive samples taken so as to be separated by an interval of at least 3 days while the material is being subjected to treatment with 1: 4000 U.S.P. formaldehyde solution and heat at 36° to 38° C. The first sample may be taken before incubation is begun and the second sample shall be taken after the incubation of at least 3 days is completed. For both single strain and trivalent pools the volume

tested for each tissue culture safety test shall be equivalent to at least 1,500 human doses.

(3) Pools which are positive following such additional processing shall not be used for the manufacture of poliomyelitis vaccine.

(f) *Supplemental inactivation.* Supplemental inactivation employing a method capable of reducing the titer of a similarly produced virus suspension by a factor of 10^{-6} may be applied at any point after the filtration step described in paragraph (d) or (e)(1) of this section.

§ 73.1002 Tests for safety.

In the manufacture of the product, the following tests relating to safety shall be conducted by the manufacturer.

(a) *The virus pool—tests prior to inactivation*—(1) *B virus and Mycobacterium tuberculosis.* Prior to inactivation, each individual virus harvest or virus pool shall be tested for the presence of B virus and Mycobacterium tuberculosis.

(2) *SV–40.* Prior to inactivation, the material shall be tested for the presence of SV–40 as follows (or by any other test producing equally reliable results): A sample of at least 5 ml. from the virus harvest or virus pool shall be neutralized by high titer specific antiserum of other than primate origin. A similar sample from the pool of tissue culture fluids from control vessels representing the tissue from which the virus was prepared may be tested in place of the virus sample. The sample shall be tested in primary cercopithecus tissue cultures or in a cell line demonstrated as at least equally susceptible to SV–40. Each tissue culture system shall be observed for at least 14 days and at the end of the observation period at least one subculture of fluid shall be made in the same tissue culture system and the subculture shall be observed for at least 14 days.

(3) *Test results.* The virus harvest or virus pool is satisfactory for poliomyelitis vaccine only if the tests produce no evidence of the presence of B virus, Mycobacterium tuberculosis or SV–40.

(b) *Single strain pool tissue culture tests for poliovirus.* (1) Before pooling to make the final poliomyelitis vaccine, during inactivation at 36° to 38° C., two samples of each monovalent bulk strain pool shall be tested for the presence of virus by tissue culture methods, the second sample to be taken at least 3 days after taking the first sample.

(2) Each sample shall be no smaller than the equivalent of 1,500 human doses and shall be subjected to the complete testing process and each test shall be performed on a different monkey kidney tissue culture cell preparation. The test sample for one of these tests may be used also for the test prescribed in § 73.1002(f), provided the cell cultures used have been demonstrated as fully susceptible to SV–40 and poliovirus. Each sample shall be inoculated into five or more tissue culture bottles of a suitable capacity, the ratio of the vaccine to the nutrient fluid being approximately 1:1 to 1:3, and the area of the surface growth of cells being at least 3 square centimeters per milliliter of sample. The tissue culture bottles shall be observed for at least 14 days.

(3) A first subculture shall be made at the end of 7 days from date of inoculation by planting at least 2 percent of the volume from each original bottle into suitable tissue culture vessels, followed by refeeding.

(4) A second subculture shall be made from each original bottle in the same manner at the end of 14 days from date of inoculation.

(5) Each of the first and second subcultures shall be observed for at least 7 days.

(6) If cytopathogenic effects occur either in the original bottles of the two tests or in the subcultures from them, or if cellular degeneration appears in the original bottles or in the subcultures before degeneration occurs in uninoculated cultures, the pool shall be held until the matter is resolved. If active poliovirus is indicated, the strain pool shall not be used for inclusion in a final vaccine unless effectively reprocessed as described in § 73.1001(e). If other viruses are present, the pool shall not be used unless it can be demonstrated that such viruses have originated from other than the strain pool being tested.

(c) *Trivalent vaccine pool tissue culture test.* No less than 1,500 human doses of the trivalent vaccine pool, without final preservative, prepared by pooling the three type pools, each of which has passed all tests prescribed in paragraph (b) of this section, shall be subjected to the complete tissue culture test prescribed in such paragraph (b) in at least two approximately equal tests in separate monkey kidney tissue culture preparations. This test sample may be used also for the test prescribed in § 73.1002 (f) provided the cell cultures used have been demonstrated as fully susceptible to SV–40 and poliovirus.

(d) *Trivalent vaccine pool lymphocytic choriomeningitis test.* The final vaccine shall be shown to be free of lymphocytic choriomeningitis virus by intracerebral inoculation of the maximum volume tolerated into 10 or more mice which shall be observed daily for at least 21 days and a negative test shall not be valid unless at least eight mice survive for this period.

(e) *Test in monkeys for active virus.* (1) Vaccine from final containers selected at random from each filling of each lot shall be pooled to provide a test sample of at least 400 milliliters representing the various fillings. An equal volume of bulk vaccine may be substituted for test samples from each filling lot provided the procedure has been approved by the Director, Division of Biologics Standards.

(2) A total of not less than 20 monkeys shall be inoculated with the test sample. A preinjection serum sample from each monkey must not contain neutralizing antibody against the three poliovirus types detectable in a dilution of 1:4 when tested against not more than 1,000 $TCID_{50}$ of virus. At least 80 percent of the test animals representing each filling or each bulk sample must survive the test period without significant weight loss, except that if at least 60 percent of the test animals survive the first 48 hours after injection, those animals which do not survive this 48-hour test period may be replaced by an equal number of test animals. At least 80 percent of the animals used in the test must show microscopic evidence of inoculation trauma in the lumbar region of the spinal cord, and gross or microscopic evidence of inoculation trauma in the thalamic area. If less than 60 percent of the test animals survive the first 48 hours, or if less than 80 percent of the animals fail to meet the other criteria prescribed in this section, the test must be repeated.

(3) Vaccines shall be injected by combined intracerebral, intraspinal, and intramuscular routes into Macaca or Cercopithecus monkeys or a species found by the Director, Division of Biologics Standards, to be equally suitable for the purpose. The animals shall be in overt good health and injected under deep barbiturate anesthesia. The intracerebral injection shall consist of 0.5 milliliter of test sample into the thalamic region of each hemisphere. The intraspinal injection shall consist of 0.5 milliliter of concentrated test sample into the lumbar spinal cord enlargement, the test sample to be concentrated 100 fold in the ultracentrifuge by a method demonstrated to recover at least 90 percent of the virus particles in the sediment after it has been resuspended in the same lot of unconcentrated test sample. The intramuscular injection shall consist of 1.0 milliliter of test sample into the right leg muscles. At the same time, 200 milligrams of cortisone acetate shall be injected into the left leg muscles, and 1.0 milliliter of procaine penicillin (300,000 units) into the right arm muscles. The monkeys shall be observed for 17 to 19 days and signs suggestive of poliomyelitis shall be recorded.

(4) At the end of the observation period, samples of cerebral cortex and of cervical and lumbar spinal cord enlargements shall be taken for virus recovery and identification. Histological sections shall be prepared from both spinal cord enlargements and examined.

(5) Doubtful histopathological findings necessitate (i) examination of a sample of sections from several regions of the brain in question, and (ii) attempts at virus recovery from the nervous tissues previously removed from the animal. The test results must be negative. Test results are negative if the histological and other studies leave no doubt that poliomyelitis infection did not occur.

(f) *Tissue culture safety test for SV–40.* At least 500 human doses of each monovalent or trivalent pool of vaccine shall be tested for the presence of SV–40 using primary cercopithecus monkey tissue cultures or using a cell line demonstrated as at least equally susceptible to SV–40. The test shall be conducted as described in § 73.1002(b), except for the volume of test sample and except that one subculture of at least 2 percent of the volume of the fluids shall be made no less than 14 days from the date of inoculation and examined for at least 14 days from the date of subinoculation.

The vaccine is satisfactory only if there is no evidence of the presence of SV–40 in any of the cultures or subcultures.

§ 73.1003 Potency test.

Each lot of vaccine shall be subjected to a potency test which permits an estimation of the antigenic capacity of the vaccine. This is done by means of a simultaneous comparison of the serum antibody levels produced in monkeys by the vaccine under test with the antibody level of the reference serum distributed by the Division of Biologics Standards. The potency test shall be performed on samples taken after all final processing of the product has been completed, including addition of preservative, except that when the final product contains material having an adjuvant effect an additional test shall be performed with a sample taken before the addition of the adjuvant material. The volume of the test sample for the additional test shall be adjusted to the equivalent volume of poliomyelitis vaccine in the final product. The test shall be conducted as follows:

(a) *Inoculation of monkeys.* A group of 12 or more Macaca monkeys, or a species found by the Director, Division of Biologics Standards, to be equally suitable for the purpose, shall be used. Animals shall weigh between 4 and 8 pounds and shall be in overt good health. Animals that become ill and remain ill during the course of immunization shall be excluded from the group. The test shall not be valid unless at least 10 animals survive the test period and their preinoculation serum antibody levels are as prescribed in paragraph (d) of this section. The test vaccine shall be given intramuscularly to each monkey in 3 doses at 7-day intervals, each dose to be the recommended individual human dose. Only undiluted vaccine shall be used.

(b) *Serum samples.* A blood sample shall be taken from each monkey prior to vaccination and then again 7 days after the last injection. Serum shall be separated aseptically, and stored under refrigeration.

(c) *Serum-virus neutralization test.* The titers of individual monkey serums shall be determined in comparison with the reference serum in tests designed to include controls for all the variables of significance including the following:

(1) Serum toxicity control;

(2) Cell control and cell titration;

(3) Virus titration control (at least 4 tubes for each dilution at 0.5 log steps); and

(4) Serum controls using type-specific serums to identify the type of virus used in the neutralization test.

(d) *Interpretation of the test.* Animals showing preinoculation titers of 1:4 or over when tested against not more than 1,000 $TCID_{50}$ of virus, shall be excluded from the test. The geometric mean titer of antibody induced in the monkeys surviving the course of immunization and bleeding, shall be calculated. A comparison of the value so obtained shall be made with the value for the reference serum that was tested simultaneously and expressed as the ratio between the geometric mean titer value of the serums under test and the mean titer value of the reference serum.

(e) *Potency requirements.* A lot of vaccine tested against the reference serum shall be satisfactory if the geometric mean value of the group of individual monkey serums representing the lot of vaccine tested is at least 1.29 times the mean value of the reference serum for Type 1, at least 1.13 times for Type 2, and at least 0.72 times for Type 3.

§ 73.1004 General requirements.

(a) *Consistency of manufacture.* No lot of final vaccine shall be released unless it is one of a series of five consecutive lots produced by the same manufacturing process, all of which have shown negative results with respect to all tests for the presence of live poliovirus, and unless each of the monovalent pools of which a polyvalent final vaccine is composed similarly is one of a series of five consecutive monovalent pools of the same type of inactivated poliovirus, all of which have shown negative results in all tests for the presence of live poliovirus.

(b) *Dose.* These additional standards are based on a human dose of 1.0 milliliter for a single injection and a total human immunizing dose of three injections of 1.0 milliliter given at appropriate intervals.

(c) *Samples and protocols.* For each lot of vaccine, the following material shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda, Md. 20014:

(1) A 2,500 milliliter sample, neutralized, not dialyzed, and without final preservative, taken at the latest possible stage of manufacturing before the addition of such preservative.

(2) A 200 milliliter bulk sample of the final vaccine containing final preservative.

(3) A total of not less than a 200 milliliter sample of the final vaccine in final labeled containers.

(4) A protocol which consists of a summary of the history of manufacture of each lot including all results of each test for which test results are requested by the Director, Division of Biologics Standards.

§ 73.1005 Equivalent methods.

Modification of any particular manufacturing method or procedure or the conditions under which it is conducted as set forth in the additional standards relating to poliomyelitis vaccine (§§ 73.1000 to 73.1004, inclusive) shall be permitted whenever the manufacturer presents evidence to demonstrate that such modification will provide equal or greater assurances of the safety, purity and potency of the vaccine as the assurances provided by such standards, and the Director, National Institutes of Health so finds and makes such finding a matter of official record.

POLIOVIRUS VACCINE, LIVE, ORAL

§ 73.1020 The product.

(a) *Proper name and definition.* The proper name of this product shall be "Poliovirus Vaccine, Live, Oral", followed by a designation of the form in which the vaccine is distributed by the manufacturer. The vaccine shall be a preparation of one or more live, attenuated polioviruses grown in monkey kidney cell cultures, prepared in a form suitable for oral administration.

(b) *Criteria for acceptable strains and acceptable seed virus.* (1) Strains of attenuated poliovirus Types 1, 2, and 3 used in the manufacture of the vaccine shall be identified by: (i) Historical records including origin and techniques of attenuation, (ii) antigenic properties, (iii) neurovirulence for monkeys, (iv) pathogenicity for other animals and tissue cultures of various cell types, and (v) established virus markers including rct/40, d, and other markers shown to be associated with strain virulence.

(2) Poliovirus strains shall not be used in the manufacture of Poliovirus Vaccine, Live, Oral, unless, (i) data are submitted to the Director, National Institutes of Health which establish that each such strain is free of harmful effect upon administration in the recommended dosage to at least 1 million people susceptible to poliomyelitis, under circumstances where adequate epidemiological surveillance of neurological illness has been maintained, and, (ii) each such strain produces a vaccine meeting the safety and potency requirements of §§ 73.1024(b), 73.1025, and 73.1027. Susceptibility shall be demonstrated by blood tests, stool examinations and other appropriate methods.

(3) Each seed virus used in manufacture shall be demonstrated to be free of extraneous microbial agents.

(4) No seed virus shall be used for the manufacture of poliovirus vaccine unless its neurovirulence in Macaca monkeys is no greater than that of the Reference Attenuated Poliovirus distributed by the Division of Biologics Standards. The neurovirulence of the seed virus shall be demonstrated by the following tests to be performed by the manufacturer: (i) The test prescribed in § 73.1024(b)(1) using seed virus as test material in place of monovalent virus pool material and (ii) the following comparative intramuscular neurovirulence test: Each of at least 10 monkeys shall be injected with a total of 5.0 ml. of the seed virus under test in one or more proximate locations of either a gluteus or gastrocnemius muscle. Similar injections shall be made in another group of 10 monkeys using the Reference Attenuated Poliovirus. Each monkey shall be injected intramuscularly with no less than $10^{7.7}$ $TCID_{50}$ of viral inoculum. All monkeys shall be observed for 17 to 21 days and a comparative evaluation shall be made of the evidence of neurovirulence of the virus under test and the Reference Attenuated Poliovirus, as prescribed in § 73.1024(b)(1)(iii).

(5) Subsequent and identical neurovirulence tests shall be performed in monkeys whenever there is evidence of a change in the neurovirulence of the production virus, upon introduction of a new production seed lot, and as often as necessary otherwise to establish to the satisfaction of the Director, National Institutes of Health that the seed virus strains for vaccine manufacture have maintained their neurovirulence properties as set forth in § 73.1024(b)(1)(iii).

(6) The Director, National Institutes of Health may, from time to time, prohibit the use of a specified strain whenever he finds it is practicable to use another strain of the same type which is potentially less pathogenic for man, and that it will produce a vaccine of greater safety and of at least equivalent potency.

§ 73.1021 Reference strains.

The following reference viruses shall be obtained from the Division of Biologics Standards.

Reference Poliovirus, Live, Attenuated, Type 1, as a control for correlation of virus titers in tissue cultures.

Reference Poliovirus, Live, Attenuated, Type 2, as a control for correlation of virus titers in tissue cultures.

Reference Poliovirus, Live, Attenuated, Type 3, as a control for correlation of virus titers in tissue cultures.

Reference Attenuated Poliovirus, Type 1, as a control for correlation of monkey neurovirulence tests.

§ 73.1022 Animal source; quarantine; personnel.

(a) *Monkeys*—(1) *Species permissible as source of kidney tissue.* Only Macaca or Cercopithecus monkeys, or a species found by the Director, Division of Biologics Standards, to be equally suitable, which have met all the requirements of §§ 73.501(f)(2) and 73.501(f)(8) shall be used as the source of kidney tissue for the manufacture of Poliovirus Vaccine, Live, Oral.

(2) *Experimental and test monkeys.* Monkeys that have been used previously for experimental or test purposes shall not be used as a source of kidney tissue in the processing of vaccine.

(3) *Quarantine; additional requirements.* Excluding deaths from accidents or causes not due to infectious diseases, if the death rate of any group of monkeys being conditioned in accordance with § 73.501(f)(2) exceeds 5 percent per month, the remaining monkeys may be used for the manufacture of Poliovirus Vaccine only if they survive a new quarantine period.

(b) *Personnel.* All possible steps shall be taken to insure that personnel involved in processing the vaccine are immune to poliovirus in order to minimize the possibility that they may become excretors of poliovirus.

§ 73.1023 Manufacture.

(a) *Primary cell cultures.* Only primary monkey kidney tissue cultures may be used in the manufacture of poliovirus vaccine. Continuous line cells shall not be introduced or propagated in vaccine manufacturing areas.

(b) *Virus passages.* Virus in the final vaccine shall represent no more than five tissue culture passages from the original strain, each of which shall have met the criteria of acceptability prescribed in § 73.1020(b).

(c) *Identification of processed kidneys.* The kidneys from each monkey shall be processed and the viral fluid resulting therefrom shall be identified as a separate monovalent harvest and kept separately from other monovalent harvests until all samples for the tests prescribed in the following paragraph relating to that pair of kidneys shall have been withdrawn from the harvest.

(d) *Monkey kidney tissue production vessels prior to virus inoculation.* Prior to inoculation with the seed virus, the tissue culture growth in vessels representing each pair of kidneys shall be examined microscopically for evidence of cell degeneration at least 3 days after complete formation of the tissue sheet. If such evidence is observed, the tissue cultures from that pair of kidneys shall not be used for poliovirus vaccine manufacture. To test the tissue found free of cell degeneration for further evidence of freedom from demonstrable viable microbial agents, the fluid shall be removed from the cell cultures immediately prior to virus inoculation and tested in each of four culture systems; (1) Macaca monkey kidney cells, (2) Cercopithecus monkey kidney cells, (3) primary rabbit kidney cells, and (4) human cells from one of the systems described in § 73.1024(a)(6), in the following manner: Aliquots of fluid from each vessel shall be pooled and at least 10 ml. of the pool inoculated into each system, with ratios of inoculum to medium being 1:1 to 1:3 and with the area of surface growth of cells at least 3 square centimeters per milliliter of test inoculum. The cultures shall be observed for at least 14 days. At the end of the observation period, at least one subculture of fluid from the Cercopithecus monkey kidney cell cultures shall be made in the same tissue culture system and the subculture shall be observed for at least 14 days. If these tests indicate the presence in the tissue culture preparation of any viable microbial agent the tissue cultures so implicated shall not be used for poliovirus vaccine manufacture.

(e) *Control vessels.* Before inoculation with seed virus, sufficient tissue culture vessels to represent at least 25 percent of the cell suspension from each pair of kidneys shall be set aside as controls. The control vessels shall be examined microscopically for cell degeneration for an additional 14 days. The cell fluids from such control vessels shall be tested, both at the time of virus harvest and at the end of the additional observation period, by the same method prescribed for testing of fluids in paragraph (d) of this section. In addition, the cell sheet in each control vessel shall be examined for presence of hemadsorption viruses by the addition of guinea pig red blood cells.

(f) *Virus harvest; interpretation of test results.* If the tissue culture in less than 80 percent of the control vessels is not free of cell degeneration at the end of the observation period, no tissue from the kidneys implicated shall be used for poliovirus vaccine manufacture. If the test results of the control vessels indicate the presence of any extraneous agent at the time of virus harvest, the entire virus harvest from that tissue culture preparation shall not be used for poliovirus vaccine manufacture. If any of the tests or observations described in paragraph (d) or (e) of this section demonstrate the presence in the tissue culture preparation of any microbial agent known to be capable of producing human disease, the virus grown in such tissue culture preparation shall not be used for poliovirus vaccine manufacture.

(g) *Kidney tissue production vessels after virus inoculation—temperature.* After virus inoculation, production vessels shall be maintained at a temperature not to exceed 35.0° C. during the course of virus propagation.

(h) *Kidney tissue virus harvests.* Virus harvested from vessels containing the kidney tissue from one monkey may constitute a monovalent virus pool and be tested separately, or viral harvests from more than one pair of kidneys may be combined, identified and tested as a monovalent pool. Each pool shall be mixed thoroughly and samples withdrawn for testing as prescribed in § 73.1024(a). The samples shall be withdrawn immediately after harvesting and prior to further processing, except that samples of test materials frozen immediately after harvesting and maintained at −60° C. or below, may be tested upon thawing, provided no more than one freeze-thaw cycle is employed.

(i) *Filtration.* After harvesting and removal of samples for the safety tests prescribed in § 73.1024(a), the pool shall be passed through sterile filters having a sufficiently small porosity to assure bacteriologically sterile filtrates.

§ 73.1024 Test for safety.

(a) *Tests prior to filtration.* Monovalent virus pools shall contain no demonstrable viable microbial agent other than the attenuated live polioviruses intended. The vaccine shall be tested for the absence of adventitious and other infectious agents including polioviruses of other types or strains, simian agents, Mycobacterium tuberculosis, pox viruses, lymphocytic choriomeningitis virus, Echo viruses, Coxsackie viruses, and B virus. Testing of each monovalent pool shall include the following procedures:

(1) *Inoculation of rabbits.* A minimum of 100 ml. of each monovalent virus pool shall be tested by inoculation into at least 10 healthy rabbits, each weighing 1,500–2,500 grams. Each rabbit shall be injected intradermally in multiple sites, with a total of 1.0 ml. and subcutaneously with 9.0 ml., of the viral pool, and the animals observed for at least 3 weeks. Each rabbit that dies after the first 24 hours of the test or is sacrificed because of illness shall be necropsied and the brain and organs removed and examined. The virus pool may be used for poliovirus vaccine only if at least 80 percent of the rabbits remain healthy and survive the entire period and if all

the rabbits used in the test fail to show lesions of any kind at the sites of inoculation and fail to show evidence of B virus or any other viral infection.

(2) *Inoculation of adult mice.* Each of at least 20 adult mice, each weighing 15–20 grams, shall be inoculated intraperitoneally with 0.5 ml. and intracerebrally with 0.03 ml. of each monovalent virus pool to be tested. The mice shall be observed for 21 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and examined for evidence of viral infection by direct observation and subinoculation of appropriate tissue into at least five additional mice which shall be observed for 21 days. The monovalent virus pool may be used for poliovirus vaccine only if at least 80 percent of the mice remain healthy and survive the entire period and if all the mice used in the test fail to show evidence of lymphocytic choriomeningitis virus or other viral infection.

(3) *Inoculation of suckling mice.* Each of at least 20 suckling mice less than 24 hours old, shall be inoculated intracerebrally with 0.01 ml. and intraperitoneally with 0.1 ml. of the monovalent virus pool to be tested. The mice shall be observed daily for at least 14 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and all areas examined for evidence of viral infection. Such examination shall include subinoculation of appropriate tissue suspensions into an additional group of at least five suckling mice by the intracerebral and intraperitoneal routes and observed daily for 14 days. In addition, a blind passage shall be made of a single pool of the emulsified tissue (minus skin and viscera) of all mice surviving the original 14-day test. The virus pool under test is satisfactory for poliovirus vaccine only if at least 80 percent of the mice remain healthy and survive the entire period and if all the mice used in the test fail to show evidence of Coxsackie or other viral infection.

(4) *Inoculation of guinea pigs.* Each of at least five guinea pigs, each weighing 350–450 grams, shall be inoculated intracerebrally with 0.1 ml. and intraperitoneally with 5.0 ml. of the monovalent virus pool to be tested. The animals shall be observed for at least 42 days and daily rectal temperatures recorded for the last 3 weeks of the test. Each animal that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and its tissues shall be examined both microscopically and culturally for evidence of tubercle bacilli, and by passage of tissue suspensions into at least three other guinea pigs by the intracerebral and intraperitoneal routes of inoculation for evidence of viral infection. If clinical signs suggest infection with lymphocytic choriomeningitis virus, serological tests shall be performed on blood samples of the test guinea pigs to confirm the clinical observations. Animals that die or are sacrificed during the first 3 weeks after inoculation with poliovirus shall be examined for infection with lymphocytic choriomeningitis virus. Animals that die in the final 3 weeks shall be examined both microscopically and culturally for Mycobacterium tuberculosis. The monovalent virus pool is satisfactory for poliovirus vaccine only if at least 80 percent of all animals remain healthy and survive the observation period and if all the animals used in the test fail to show evidence of infection with Mycobacterium tuberculosis, or any viral infection.

(5) *Inoculation of monkey kidney tissue cultures.* At least 500 doses or 50 ml., whichever represents a greater volume of virus, of each undiluted monovalent virus pool, or in equal proportions from individual harvests or subpools, shall be tested for simiam viruses in Macaca, and the same volume in Cercopithecus, monkey kidney tissue cultures, in a ratio of inoculum to medium of from 1: 1 to 1: 3, and with the area of surface growth of cells at least 3 square centimeters per milliliter of test inoculum, after neutralization of the poliovirus by high titer specific antiserum of nonprimate origin. The immunizing antigens used for the preparation of antisera shall be grown in a human tissue culture cell line. The cultures shall be observed for no less than 14 days. At the end of the observation period at least one subculture of fluid from the Cercopithecus kidney cell culture shall be made in the same tissue culture system and the subculture shall be observed for at least 14 days. The monovalent virus pool is satisfactory for poliovirus vaccine only if all the tissue cultures fail to show evidence of the presence of simian viruses or any other viral infection.

(6) *Inoculation of human cell cultures.* At least 500 doses or 50 ml., whichever represents a greater volume of virus, taken from either a single monovalent pool, or in equal proportions from individual harvests or subpools, shall be tested in a ratio of inoculum to medium of 1:1 to 1:3, and with the area of surface growth of cells at least 3 square centimeters per milliliter of test inoculum, for the presence of measles virus in either (i) primary human amnion cells, (ii) primary human kidney cells, or (iii) any other cell system of comparable susceptibility to unmodified measles virus. The test material shall be neutralized with poliovirus antiserum of other than primate origin if the tissue culture cell system used is susceptible to poliovirus. The culture shall be observed for no less than 14 days. The monovalent virus pool is satisfactory for poliovirus vaccine only if all tissue cultures fail to show evidence of the presence of measles virus or any other viral infection.

(7) *Inoculation of rabbit kidney tissue cultures.* At least 500 ml. of virus pool taken from either a single monovalent pool, or in equal proportions from individual harvests or subpools, shall be tested in a ratio of inoculum to medium of from 1:1 to 1:3, and with the area of surface growth of cells at least 3 square centimeters per milliliter of test inoculum, in primary rabbit kidney tissue culture preparations for evidence of B virus. The culture shall be observed for no less than 14 days. The monovalent virus pool is satisfactory for poliovirus vaccine only if all tissue cultures fail to show evidence of the presence of B virus.

(b) *Tests after filtration.* The following tests relating to safety shall be performed after the filtration process, on each monovalent virus pool or on each multiple thereof (monovalent lot):

(1) *Neurovirulence in monkeys.* Each monovalent virus pool or monovalent lot shall be tested in comparison with the Reference Attenuated Poliovirus for neurovirulence in Macaca mulatta (rhesus) monkeys by both the intrathalamic and intraspinal routes of injection. A preinjection serum sample obtained from each monkey must be shown to contain no neutralizing antibody in a dilution of 1: 4 when tested against no more than 1,000 $TCID_{50}$ of each of the three types of poliovirus. The neurovirulence tests are not valid unless the sample contains at least $10^{7.0}$ $TCID_{50}$ per ml. when titrated in comparison with the Reference Poliovirus, Live, Attenuated of the appropriate type. All monkeys shall be observed for 17 to 21 days, under the supervision of a qualified pathologist, physician or veterinarian, and any evidence of physical abnormalities indicative of poliomyelitis or other viral infections shall be recorded.

(i) *Intrathalamic inoculation.* Each of at least 30 monkeys shall be injected intracerebrally by placing 0.5 ml. of virus pool material into the thalamic region of each hemisphere. Comparative evaluations shall be made with the virus pool under test and the Reference Attenuated Poliovirus. Only monkeys that show evidence of inoculation into the thalamus shall be considered as having been injected satisfactorily. If on examination there is evidence of failure to inoculate virus pool material into the thalamus, additional monkeys may be inoculated in order to reestablish the minimum number of 30 monkeys for the test.

(ii) *Intraspinal inoculation.* Each of a group of at least five monkeys shall be injected intraspinally with 0.2 ml. of virus pool material containing at least $10^{7.0}$ $TCID_{50}$ per ml. and each monkey in additional groups of at least five monkeys shall be injected intraspinally with 0.2 ml of a 1:1,000 and 1:10,000 dilution respectively, of the same virus pool material. Comparative evaluations shall be made with the virus pool under test and the reference material. Only monkeys that show microscopic evidence of inoculation into the gray matter of the lumbar cord shall be considered as having been injected satisfactorily. If on examination there is evidence of failure to inoculate intraspinally, additional animals may be inoculated in order to reestablish the minimum number of five animals per group.

(iii) *Determination of neurovirulence.* At the conclusion of the observation period comparative histopathological examinations shall be made of the lumbar cord, cervical cord, lower medulla, upper medulla, mesencephalon and motor cortex of each monkey in the groups injected with virus under test and those injected with the Reference Attenuated Poliovirus, except that for

animals dying during the test period, these examinations shall be made immediately after death. If at least 60 percent of the animals of a group survive 48 hours after inoculation, those animals which did not survive may be replaced by an equal number of animals tested as prescribed in paragraph (b)(1) of this section. If less than 60 percent of the animals of a group survive 48 hours after inoculation, the test must be repeated. At the conclusion of the observation the animals shall be examined to ascertain whether the distribution and histological nature of the lesions are characteristics of poliovirus infection. A comparative evaluation shall be made of the evidence of neurovirulence of the virus under test and the Reference Attenuated Poliovirus with respect to (a) the number of animals showing lesions characteristic of poliovirus infection, (b) the number of animals showing lesions other than those characteristic of poliovirus infection, (c) the severity of the lesions, (d) the degree of dissemination of the lesions, and (e) the rate of occurrence of paralysis not attributable to the mechanical injury resulting from inoculation trauma. The virus pool under test is satisfactory for poliovirus vaccine only if at least 80 percent of the animals in each group survive the observation period and if a comparative analysis of the test results demonstrate that the neurovirulence of the test virus pool does not exceed that of the Reference Attenuated Poliovirus.

(iv) *Test with Reference Attenuated Poliovirus.* The Reference Attenuated Poliovirus shall be tested as prescribed in § 73.1024(b)(1) (i) and (ii) at least once for every 10 production lots of vaccine, except that the interval between the test of the reference and the test of any lot of vaccine shall not be greater than 3 months. The test procedure shall be considered acceptable only if lesions of poliomyelitis are seen in monkeys inoculated with the reference material at a frequency statistically compatible with all previous tests with this preparation.

(2) *Test for virus titer.* The concentration of living virus in each monovalent virus pool or lot shall be determined, using the Reference Poliovirus Live, Attenuated of the same type as a control. The test shall be a 50 percent end-point titration calculation ($TCID_{50}$), performed with either groups of 10 tubes at 1 log dilution steps or groups of five tubes of 0.5 log dilution steps, or a test of demonstrated equivalent sensitivity. Acceptable titrations of the reference virus shall not vary more than ±0.5 log from its labeled titer.

(3) *Tests for In-Virto Markers.* A test shall be performed on each monovalent virus pool or each monovalent lot resulting therefrom, using the rct/40 Marker. A second test shall be performed using the d Marker or another marker method shown to be of value in identification of the attenuated strain. The test results shall demonstrate that the virus under test and the seed virus have substantially the same marker characteristics.

(i) *rct/40 Marker.* Attenuated strains which grow readily at 40° C. (±0.5° C.) are classified as rct/40 positive (+) in contrast to the rct/40 negative (−) strains which show an increased growth of at least 100,000 fold at 36° C. over that obtained at 40° C. Comparative determinations shall be made in either tube or bottle cultures.

(ii) *d Marker.* Attenuated strains which grow readily at low concentrations of bicarbonate under agar are classified as d positive (+) in contrast to the d negative (−) strains which exhibit delayed growth under the same conditions. The cultures shall be grown in a 36° C. incubator either in stoppered bottles or in plates in an environment of 5 percent CO_2 in air.

§ 73.1025 Potency test.

The concentration of live virus expressed as $TCID_{50}$ of each type in the vaccine shall constitute the measure of its potency. The accuracy of the titration to determine the concentration of live virus in the lot under test shall be confirmed by performing a titration with the Reference Poliovirus, Live, Attenuated of the appropriate type as a check on titration technique. The concentration of each type of live virus contained in the vaccine of the lot under test shall be between 200,000 and 500,000 $TCID_{50}$ per human dose.

§73.1026 General requirements.

(a) *Final container sterility test.* The final container sterility test need not be performed provided aseptic techniques are used in the filling process.

(b) *Consistency of manufacture.* No lot of vaccine shall be released unless each monovalent pool contained therein is one of a series of five consecutive pools of the same type, each pool having been manufactured by the same procedures, and each having met the criteria of neurovirulence for monkeys prescribed in § 73.1024(b)(1), and of in-vitro markers prescribed in § 73.1024(b)(3).

(c) *Dose.* The individual human dose of vaccine shall contain from 200,000 to 500,000 $TCID_{50}$ of each type of virus in the final monovalent vaccine, and for polyvalent vaccine not more than 1,000,000 $TCID_{50}$ of Type 1 virus, 100,000 to 200,000 $TCID_{50}$ of Type 2 virus and 200,000 to 500,000 $TCID_{50}$ of Type 3 virus.

(d) *Labeling.* In addition to the items required by other applicable labeling provisions of this part, the final container label shall bear a statement indicating that liquid vaccine may not be used for more than 7 days after opening the container. Labeling may include a statement indicating that for frozen vaccine a maximum of 10 freeze-thaw cycles is permissible provided the total cumulative duration of thaw does not exceed 24 hours, and provided the temperature does not exceed 8° C. during the periods of thaw.

(e) *Samples and protocols.* For each lot of vaccine, the following materials shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda, Md. 20014:

(1) A protocol which consists of a summary of the history of manufacture of each lot including all results of each test for which test results are requested by the Director, Division of Biologics Standards.

(2) A 500 milliliter bulk sample of each final monovalent pool having a virus titer of no less than $10^{7.5}$ $TCID_{50}$ per milliliter, except that if the titer is greater, a correspondingly smaller volume may be submitted.

(3) A total of no less than 200 doses or no less than six final containers, whichever is the larger amount.

§ 73.1027 Clinical trials to qualify for license.

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design. Such clinical trials shall be conducted with five consecutive lots of poliovirus vaccine which have been manufactured by the same methods, each of which has shown satisfactory results in all prescribed tests. Type specific neutralizing antibody (from less than 1:4 before vaccine treatment, to 1:16 or greater after treatment) shall be induced in 80 percent or more of susceptibles when administered orally as a single dose, or in excess of 90 percent of susceptibles when administered orally after a series of doses. A separate clinical trial shall have been conducted for each monovalent and each polyvalent vaccine for which license application is made.

§ 73.1028 Equivalent methods.

Modification of any particular manufacturing method or process or the conditions under which it is conducted as set forth in the additional standards relating to Poliovirus Vaccine, Live, Oral, shall be permitted whenever the manufacturer presents evidence that demonstrates the modification will provide assurances of the safety, purity, and potency of the vaccine that are equal to or greater than the assurances provided by such standards, and the Director, National Institutes of Health so finds and makes such finding a matter of official record.

Adenovirus Vaccine

§ 73.1040 The product.

(a) *Proper name and definition.* For the purpose of section 351(a)(2) of the act and § 73.101(k), the proper name of this product shall be "Adenovirus Vaccine" with a designation of the types of virus included in the vaccine. Such vaccine shall consist of an aqueous preparation of one or more adenoviruses grown in monkey kidney tissue cultures inactivated by a suitable method. Where more than one type of virus is used in the manufacture of the vaccine, equal proportions of each type shall be combined with a tolerance for each component of 5 percent of the total volume.

(b) *Strains of virus.* Strains of adenovirus used in the manufacture of the vaccine shall be identified by historical

records, infectivity tests, and immunological methods. Only those strains of virus may be used that (1) produce a vaccine meeting the safety and potency requirements in §§ 73.1042 and 73.1043, (2) never had any passage in malignant cells of human or animal origin, and (3) have been maintained in monkey kidney cultures for at least 10 passages prior to use.

(c) *Monkey kidney tissue.* Only cynomolgus or rhesus monkeys or other species of equal suitability, in overt good health, that have reacted negatively to tuberculin within 2 weeks prior to use shall be used as a source of kidney tissue for the production of virus. Each animal shall be examined at necropsy under the supervision of a qualified pathologist for gross signs of disease. If there is any gross pathological lesion of any significance to their use in the manufacture of vaccine, the kidneys shall be discarded. Kidney tissue from monkeys that have been used previously for experimental purposes shall not be used, except that monkeys in overt good health, used for the safety or potency tests of adenovirus vaccines with negative clinical findings (§§ 73.1042 and 73.1043) that have reacted negatively to tuberculin prior to such test, may be used within two weeks of the end of the test period. The monkeys shall not at any time have been housed in the same building where monkeys actually infected with or exposed to poliovirus are housed, and due precautions shall be taken to prevent cross-infection from any infected or potentially infected monkeys on the premises.

§ 73.1041 Manufacture of adenovirus vaccine.

(a) *Cultivation of virus.* Virus for manufacturing vaccine shall be grown with aseptic technique in monkey kidney cell cultures using a synthetic medium. Suitable antibiotics in the minimum concentration required may be used. If penicillin is used, not more than 200 units per milliliter may be added. Phenol red may not exceed a concentration of 0.002 percent.

(b) *Filtration.* Within 72 hours preceding the beginning of inactivation, the virus suspensions shall be filtered or clarified by a method having an efficiency at least equivalent to that of a Selas 02 type filter.

(c) *Virus titer.* The titer of each virus pool after filtration shall be determined by a suitable method. It shall also be demonstrated that each virus pool possesses adenovirus group antigen by the complement-fixing test.

(d) *Inactivation of virus.* The virus shall be inactivated, as evidenced by the test in tissue culture as set forth in § 73.1042, through the use of an agent or method which has been demonstrated to be effective in the hands of the manufacturer in inactivating a series of at least 5 consecutive lots of adenovirus vaccine. If formaldehyde is used for inactivation, it shall be added to the virus suspension to a final concentration of U.S.P. formaldehyde solution of at least 1:4000. The inactivation shall be conducted under controlled conditions of pH and time at a temperature of 36° to 38° C. As an indication of inactivation, not less than two samples shall be removed during the inactivation process and treated as prescribed in § 73.1042(b)(1). Regardless of the concentration of formaldehyde used, the total heating period shall be not less than 20 hours and at least three times the period required for the reduction of live virus to a point where no virus is detected in a 5 milliliter sample when tested in accordance with § 73.1042(b)(1). At the end of the heating period a sample shall be removed for the single strain tissue culture safety test.

§ 73.1042 Tests for safety.

In the manufacture of the product, the following tests relating to safety shall be conducted by the manufacturer:

(a) *The virus pool*—(1) *Tests prior to inactivation*—(i) *B virus and Mycobacterium tuberculosis.* Prior to inactivation, each individual virus harvest or virus pool shall be tested for the presence of B virus and Mycobacterium tuberculosis.

(ii) *SV_{40}.* Prior to inactivation, the material shall be tested for the presence of SV_{40} as follows (or by any other test producing equally reliable results): A sample of at least five ml. from the virus harvest or virus pool or pool of tissue culture fluids from corresponding control vessels shall be neutralized by high titer antiserum of an origin other than human, chicken, or simian. The sample shall be tested in the same tissue culture system used for propagating the virus vaccine, and in primary cercopithecus tissue cultures or in a cell line demonstrated as equally susceptible to SV_{40}. Each tissue culture system shall be observed for at least 14 days and at the end of the observation period at least one subculture of fluid shall be made in the same tissue culture system and observed for an additional 14 days.

(iii) *Test results.* The virus harvest or virus pool is satisfactory for adenovirus vaccine only if the tests produce no evidence of the presence of B virus, Mycobacterium tuberculosis and SV_{40}.

(2) Each single strain virus pool shall be shown to be free of lymphocytic choriomeningitis virus and other mouse pathogens by intracerebral injection into 10 or more mice which shall be observed daily for at least 21 days. All mice which die during the observation period shall be studied as to the possible cause of death. A negative test shall not be valid unless at least 8 mice survive the full observation period and unless the virus pool was found free of agents pathogenic for mice; and

(3) An identity test shall be done on each virus pool using monovalent adenovirus serums free from poliomyelitis antibodies. Such serums shall have been prepared from animals immunized with virus grown in other than the tissue used for the neutralization test. The identity tests shall be done (i) in monkey kidney and (ii) in HeLa or other equally susceptible cells. The tissue cultures shall be observed for 7 days. Those showing cytopathogenic effect in the presence of type specific serum shall be subcultured in monkey kidney cells or HeLa cells. The subcultures shall be maintained for 7 days and observed for cytopathogenic effect. Only virus pools free of unidentified cytopathogenic agents and free of all viruses pathogenic to man other than adenoviruses may be used for vaccine manufacture.

(b) *Single strain tissue culture test for adenovirus.* (1) The samples specified in § 73.1041(d) shall be placed immediately after sampling in contact with sodium bisulfite or a similar formaldehyde neutralizing substance that will stop the inactivation process. Each sample shall be dialyzed or rendered non-toxic to tissue culture cells by an appropriate method which does not affect the detection of live virus. An amount of fluid representing at least 5 milliliters of the original virus pool shall be inoculated into monkey kidney or other equally susceptible tissue cultures. The tissue cultures shall be maintained for 7 to 12 days and examined at intervals. At the end of the above period, the cell sheet shall be removed from each culture vessel, broken up by an appropriate means, suspended in a portion of its culture fluid equal to at least 10 percent of the volume which was present during incubation, and inoculated into corresponding fresh tissue culture preparations. Any fluids recovered prior to refeeding during original observation period shall be held at 2° to 5°C. A volume of each fluid representing at least 10 percent of the total volume shall be subcultured to fresh tissue culture. All subcultures shall be examined for at least 7 days. This test shall be considered negative only if no cellular degeneraton occurs attributable to any virus.

(2) A sample of at least 500 milliliters of each single strain pool shall be fully subjected to the following testing procedure in tissue culture cells, with half the sample in monkey kidney cells and half in suitable human cells of demonstrated high susceptibility to adenovirus and poliovirus. The entire sample shall be dialyzed and rendered non-toxic for tissue culture cells. Each half of the sample shall be inoculated into 4 or more tissue culture bottles of suitable capacity so that direct observation of the culture cells is possible under conditions which assure the growth of adenovirus, poliovirus or simian viruses should infective particles of any of these viruses be present in the vaccine. The monkey kidney cell cultures shall be performed as described in § 73.1002(b) except that a third subculture shall be included after 21 days of incubation of the initial culture and that this subculture shall be made by suspending the cell sheet. The initial human cell cultures shall be observed for at least 12 days. A subculture shall be made on each fluid at each refeeding and on the suspension of each cell sheet in the culture fluid removed at the end of the observation period. The inoculum for the subcultures shall be a volume of at least 2 percent of that of the fluid being studied. The subculture shall be examined frequently and refed

as required, and maintained for a period of at least 12 days. If a cytopathogenic effect occurs during the test, the vaccine pool shall be held until the matter is resolved. If active poliomyelitis virus or adenovirus is indicated, the strain pool shall not be used for inclusion in a final vaccine. If other viruses are present, the pool shall not be used unless it can be demonstrated that such viruses did not originate from the strain pool being tested.

(c) *Final vaccine pool tissue culture test.* No less than 1,500 milliliters of the final vaccine pool without final preservative, prepared by pooling the individual single strain preparations, shall be tested in accordance with § 73.1002 (b) and (c).

(d) *Final vaccine test for active virus in monkeys.* Final bulk vaccine shall be tested in monkeys as prescribed in § 73.1002(e) except that the test may be applied to vaccine before it is placed in final containers, and the sample may be dialyzed in order to remove sodium bisulfite or the sodium bisulfite formaldehyde complex before injection intraspinally and intracerebrally into monkeys. In no case, however, shall dialyzed vaccine be used for the intramuscular injection of the monkeys. The test is considered negative if the histological and other studies leave no doubt that virus infections attributable to the vaccine did not occur.

(e) *Exclusion of certain pools from final vaccine.* Pools which fail to pass the tissue culture safety tests prescribed in this section shall not be included in final vaccine, unless it can be clearly shown that the cytopathogenic agent occurred in the test system and not in the vaccine pool. No pool shall be subjected to reprocessing.

§ 73.1043 Potency test.

Each lot of vaccine shall be subjected to a potency test which permits an estimation of the antigenic capacity of the vaccine in comparison with a reference vaccine distributed by the National Institutes of Health. This shall be done using at least 6 animals for each dilution of each vaccine tested and measuring the neutralizing antibody response of the animals receiving test vaccine and others receiving reference vaccine in simultaneous tests. The average antibody level for each type shall equal or exceed the corresponding value of the reference vaccine.

§ 73.1044 General requirements.

(a) *Separate facilities.* The personnel, equipment and supplies used in the manufacture of adenovirus vaccine shall be separated from personnel, equipment or supplies used in connection with any other pathogenic virus to the extent necessary to prevent cross-contamination.

(b) *Final container tests.* Tests shall be made on final containers for safety, sterility and identity, in accordance with §§ 73.720, 73.730 and 73.760 respectively.

(c) *Release of vaccine.* A lot of vaccine shall not be released unless all required safety tests have given negative results.

(d) *Extraneous protein.* Extraneous protein capable of producing allergenic effects on human subjects shall not be added to the final virus production medium. If animal serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000.

(e) *Nitrogen content.* The final vaccine shall have a protein nitrogen content of less than 0.02 milligram per milliliter.

(f) *Dose.* These additional standards for adenovirus vaccine are based on a human dose not exceeding 1.0 milliliter for a single injection.

(g) *Labeling.* In addition to compliance with the requirements of §§ 73.600 to 73.605, inclusive, the label or package enclosure shall include an appropriate statement indicating the type and amount of each antibiotic added, if any. The preservative used shall be stated on the label, as well as allergenic substances added, if any, and the source, composition, and method of inactivation of the viruses.

(h) [Reserved]

(i) *Requirements for samples and protocols.* For each lot of vaccine, the following material shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda Maryland 20014:

(1) A 2,500-milliliter sample of the final vaccine taken at the latest possible stage of manufacture before the addition of preservative.

(2) A 200-milliliter bulk sample of the final vaccine containing all preservatives.

(3) A total of at least 200-milliliter sample of the final vaccine in final labelled containers.

(4) Protocol showing the history of the lot and the results of all of the tests which were carried out by the manufacturer.

§ 73.1045 Equivalent methods.

The provisions of § 73.1005, permitting modifications in methods if found equivalent in assuring safety, purity, and potency, shall be applicable to the additional standards relating to adenovirus vaccine (§§ 73.1040 to 73.1044, inclusive).

MEASLES VIRUS VACCINE, LIVE, ATTENUATED

§ 73.1060 The product.

(a) *Proper name and definition.* The proper name of this product shall be Measles Virus Vaccine, Live, Attenuated, which shall consist of a preparation of live, attenuated, measles virus.

(b) *Criteria for acceptable strains of attenuated measles virus.* Strains of attenuated measles virus used in the manufacture of vaccine shall be identified by (1) historical records including origin and manipulation during attenuation, (2) antigenic specificity as measles virus as demonstrated by tissue culture neutralization tests. Strains used for the manufacture of Measles Virus Vaccine, Live, Attenuated, shall have been shown to be safe and potent in man by field studies with experimental vaccines. Vaccine prepared from measles virus strains propagated in chick embyro or canine renal tissue cultures shall have been demonstrated as safe and potent in at least 10,000 susceptible persons. Susceptibility shall be shown by the absence of neutralizing or other antibodies against measles virus, or by other appropriate methods. Vaccine prepared from measles virus strains propagated in canine renal tissue cultures shall also have been demonstrated to be free from harmful effects in not less than 100,000 persons. Seed virus used for vaccine manufacture shall be free of all demonstrable extraneous viable microbial agents.

(c) *Neurovirulence safety test of the virus seed strain in monkeys*—(1) *The test.* A demonstration shall be made in monkeys of the lack of neurotropic properties of the seed strain of attenuated measles virus used in manufacture of measles virus vaccine. For this purpose, vaccine from each of the five consecutive lots (§ 73.1065) used by the manufacturer to establish consistency of manufacture of the vaccine, shall be tested for neurovirulence in the following manner:

Samples of each of the five lots of vaccine shall be tested in measles susceptible monkeys. Immediately prior to initiation of a test each monkey shall have been shown to be serologically negative for neutralizing antibodies by means of a tissue culture neutralization test with undiluted serum from each monkey tested at approximately 100 $TCID_{50}$ of Edmonston strain measles virus, or negative for measles virus antibodies as demonstrated by tests of equal sensitivity. Each lot of vaccine shall be tested in 10 monkeys by the intracerebral inoculation of 0.5 ml. into the thalamic region of each hemisphere and an inoculation of 0.25 ml. intracisternally. The combined dose of measles virus inoculated into the central nervous system of each monkey shall be no less than the equivalent of 1,000 $TCID_{50}$ of the NIH standard (§ 73.1061(d)). The monkeys shall be observed for 17 to 21 days and symptoms of paralysis as well as other evidences of neurological disorders shall be recorded. The test must be repeated if more than 20 percent of a group of monkeys die from nonspecific causes. Animals which die within the first 48 hours of initiation of the test may be replaced. At the end of the observation period each surviving monkey shall (a) be bled and the serum tested for evidence of serum antibody conversion to measles virus and (b) be autopsied and histopathological sections prepared of appropriate areas of the brain and spinal cord, and the sections examined microscopically for evidence of central nervous system involvement.

(2) *Wild virus controls.* As a check against the inadvertent introduction of wild measles virus, at least four uninoculated measles susceptible control monkeys shall be maintained as either cage mates to, or within the same immediate area of, the ten inoculated test animals for each lot of vaccine for the entire period of observation (17–21 days) and an additional ten days. Serum samples from these control contact monkeys drawn at the time of seed virus inoculation of the test animals, and again after completion of the test, shall be shown to be free of measles neutralizing antibodies.

(3) *Test results.* (i) For each lot of vaccine under test, at least 80 percent of the monkeys must show measles antibody serological conversion (1:4 or greater) and the control contact monkeys must demonstrate no immunological response indicative of measles virus infection.

(ii) The measles virus seed has acceptable neurovirulence properties for use in vaccine manufacture if for each of the five lots (*a*) 80 percent of the monkeys survive the observation period and (*b*) there is no clinical or histopathological evidence of central nervous system involvement attributable to the inoculated virus.

(4) *New seed lots—test for neurovirulence.* The neurovirulence properties of each new seed shall be tested as prescribed in this paragraph. Only seed lots which meet the neurovirulence requirement shall be used for Measles Virus Vaccine manufacture. The test need not be repeated as long as the same seed lot of virus is used.

§ 73.1061 Manufacture of live, attenuated Measles Virus Vaccine.

(a) *Virus cultures.* Virus shall be propagated in chick embryo tissue cultures or canine renal tissue cultures.

(b) *Virus propagated in chick embryo tissue cultures.* Embryonated chicken eggs used as the source of chick embryo tissue for the propagation of measles virus shall be derived from flocks certified to be free of Salmonella pullorum, avian tuberculosis, fowl pox, Rous sarcoma, avian leucosis and other adventitious agents pathogenic for chickens. If eggs are procured from flocks that are not so certified, tests shall be performed to demonstrate freedom of the vaccine from such agents. (See § 73.1062(a)(8) for test for avian leucosis.)

(c) *Virus propagated in canine renal tissue cultures.* Only dogs in overt good health which have been maintained in quarantine in vermin-proof quarters for a minimum of six months, having had no exposure to other dogs or animals throughout the quarantine period, or dogs born to dogs while so quarantined, provided the progeny have been kept in the same type of quarantine continuously from birth, shall be used as a source of kidney tissue for the propagation of measles virus.

(1) *Dogs used for experimental purposes.* Dogs that have been used previously for experimental or testing purposes with microbiological agents shall not be used as a source of kidney tissue in the manufacture of vaccine.

(2) *Quarantine and necropsy.* Each dog shall be examined periodically during the quarantine period as well as at the time of necropsy under the direction of a qualified pathologist, physician or veterinarian having experience with diseases of dogs, for the presence of signs or symptoms of ill health, particularly for evidence of tuberculosis, infectious canine hepatitis, canine distemper, rabies, leptospirosis, and other diseases indigenous to dogs. If there are any such signs, symptoms, or other significant pathological lesions observed, tissue from such animals shall not be used in the manufacture of Measles Virus Vaccine, Live, Attenuated.

(d) *NIH reference measles virus.* An NIH Reference Measles Virus, Live, Attenuated, shall be obtained from the Division of Biologics Standards as a control for correlation of virus titers.

(e) *Passage of virus strain in vaccine manufacture.* Virus in the final vaccine shall represent no more than ten tissue culture passages beyond the passage used to perform the clinical trials (§ 73.1060 (b)) which qualified the manufacturer's vaccine strain for license.

(f) *Tissue culture preparation.* Only primary cell tissue cultures shall be used in the manufacture of Measles Virus Vaccine. Continuous cell lines shall not be introduced or propagated in Measles Virus Vaccine manufacturing areas.

(g) *Control vessels.* (1) From the tissue used for the preparation of tissue cultures for growing attenuated measles virus, an amount of processed cell suspension equivalent to that used to prepare 500 ml. of tissue culture shall be used to prepare uninfected tissue control materials. This material shall be distributed in control vessels and observed microscopically for a period of no less than 14 days beyond the time of inoculation of the production vessels with measles virus; but if the production vessels are held for use in vaccine manufacture for more than 14 days, the control vessels shall be held and observed for the additional period. At the end of the observation period or at the time of virus harvest, whichever is later, fluids from the control cultures shall be tested for the presence of adventitious agents as follows:

Samples of fluid from each control vessel shall be collected at the same time as fluid is harvested from the corresponding production vessels. If multiple virus harvests are made from the same cell suspension, the control samples for each harvest shall be frozen and stored at −60° C. until the last viral harvest for that cell suspension is completed. The fluid from all the control samples from that suspension shall be pooled in proportionate amounts and at least five ml. inoculated into human and simian cell tissue culture systems and in the tissue culture system used for virus production. The cultures shall be observed for the presence of changes attributable to growth of adventitious viral agents including hemadsorption viral agents.

(2) The cell sheets of one quarter to one third of the control vessels shall be examined at the end of the observation period (14 days or longer) for the presence of hemadsorption viruses by the addition of guinea pig red blood cells. If the chick embryo cultures were not derived from a certified source (§ 73.1061 (b)), the remaining tissue culture controls may be used to test for avian leucosis virus using either Rubin's procedure for detecting Resistance Inducing Factor (RIF) or a method of equivalent effectiveness.

(3) The test is satisfactory only if there is no evidence of adventitious viral agents and if at least 80 percent of the control vessels are available for observation at the end of the observation period (14 days or longer).

(h) *Test samples.* Samples of virus harvests or pools for testing by inoculation into animals, into tissue culture systems, into embryonated hens' eggs, and into bacteriological media, shall be withdrawn immediately after harvesting or pooling but prior to freezing except that samples of test materials frozen immediately after harvesting or pooling and maintained at −60° C. or below, may be tested upon thawing, provided no more than two freeze-thaw cycles are employed. The required tests shall be initiated without delay after thawing.

§ 73.1062 Test for safety.

(a) *Tests prior to clarification of vaccine manufactured in chick embryo tissue cultures.* Prior to clarification, the following tests shall be performed on each virus pool of chick embryo tissue culture:

(1) *Inoculation of adult mice.* Each of at least 20 adult mice each weighing 15–20 grams shall be inoculated intraperitoneally with 0.5 ml. and intracerebrally with 0.03 ml. amounts of each virus pool to be tested. The mice shall be observed for 21 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and examined for evidence of viral infection by direct observation and subinoculation of appropriate tissue into at least five additional mice which shall be observed for 21 days. The virus pool may be used only if at least 80 percent of the original group of mice remain healthy and survive the observation period and if none of the mice show evidence of a transmissible agent or other viral infection, other than measles virus, attributable to the vaccine.

(2) *Inoculation of suckling mice.* Each of at least 20 suckling mice less than 24 hours old shall be inoculated intracerebrally with 0.01 ml. and intraperitoneally with 0.1 ml. of the virus pool to be tested. The mice shall be observed daily for at least 14 days. Each mouse that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied and examined for evidence of viral infection. Such examination shall include subinoculation of appropriate tissue suspensions into an additional group of at least five suckling mice by intracerebral and intraperitoneal routes and observed daily for 14 days. In addition, a blind passage shall be made of a single pool of the emulsified tissue (minus skin and viscera) of all mice surviving the original 14-day test. The virus pool is satisfactory for Measles Virus Vaccine only if at least 80 percent of the original inoculated mice remain healthy and survive the entire observation period, and if none of the mice used in the test show evidence of a transmissible agent or viral infection, other than measles virus, attributable to the vaccine.

(3) *Inoculation of monkey tissue cell cultures.* A volume of virus suspension of each undiluted virus pool, equivalent to at least 500 human doses or 50 ml., whichever represents a greater volume,

shall be tested for adventitious agents in cercopithecus monkey kidney tissue culture preparations, after neutralization of the measles virus by a high titer antiserum of nonhuman, nonsimian, and nonchicken origin. The immunizing antigen used for the preparation of the measles antiserum shall be grown in tissue culture cells that shall be free of extraneous viruses which might elicit antibodies that could inhibit growth of extraneous viruses present in the measles virus pool. The tissue culture of the virus pool shall be observed for no less than 14 days. The virus pool is satisfactory for measles virus vaccine only if all the tissue culture tests fail to show evidence of any extraneous transmissible agent other than measles virus attributable to the vaccine.

(4) *Inoculation of other cell cultures.* The measles virus pool shall be tested in the same manner as prescribed in subparagraph (3) in rhesus or cynomolgus monkey kidney, chick embryo, and human tissue cell cultures.

(5) *Inoculation of embryonated chicken eggs.* A volume of virus suspension of each undiluted virus pool, equivalent to at least 100 doses or 10 ml., whichever represents a greater volume, after neutralization of the measles virus by a high titer antiserum of nonhuman, nonsimian, nonchicken origin, shall be tested in embryonated eggs by the allantoic cavity route of inoculation and a separate group tested by the yolk sac route of inoculation, using 0.5 ml. of inoculum per egg. The virus pool is satisfactory if there is no evidence of adventitious agents.

(6) [Reserved]

(7) *Bacteriological tests.* Each virus pool shall be tested for sterility in accordance with § 73.730. In addition each virus pool shall be tested for the presence of M. tuberculosis, both avian and human, by appropriate culture methods.

(8) *Test for avian leucosis.* If the cultures were not derived from a certified source (§ 73.1061(b)), and the control fluids were not tested for avian leucosis (§ 73.1061(g)), at least 500 doses or 50 ml., whichever represents a greater volume of each undiluted vaccine pool, shall be tested and found negative for avian leucosis, using either Rubin's procedure for detecting Resistance Inducing Factor (RIF) or another method of equivalent effectiveness.

(b) *Tests prior to clarification of vaccine manufactured in canine renal tissue cultures.* Prior to clarification, the following tests shall be performed on each virus pool of canine renal tissue culture:

(1) *Inoculation of adult mice.* Virus grown in canine renal tissue cultures shall be tested in adult mice, as prescribed in paragraph (a)(1) of this section for virus grown in chick embryo tissue cultures. Test result standards are those prescribed therein.

(2) *Inoculation of suckling mice.* Each of at least 20 suckling mice less than 24 hours old shall be inoculated intracerebrally with 0.01 ml. and interperitoneally with 0.1 ml. of the canine renal tissue culture virus pool to be tested. The mice shall be observed daily for at least 28 days. Each mouse that dies after the first 48 hours of the test, or is sacrificed because of illness, shall be necropsied and all areas examined for evidence of viral infection. Such examination shall include subinoculation of appropriate tissue suspensions into an additional group of at least five suckling mice by intracerebral and intraperitoneal routes and observed daily for 28 days. The virus pool is satisfactory for Measles Virus Vaccine only if at least 80 percent of the originally inoculated mice remain healthy and survive the entire observation period, and if none of the mice used in the test show evidence of having been infected with rabies virus or any other transmissible agent or viral infection other than measles virus.

(3) *Inoculation of monkey tissue cell cultures.* Virus grown in canine renal tissue cultures shall be tested in monkey tissue cell cultures as prescribed in paragraph (a)(3) of this section for virus grown in chick embryo tissue cultures. Test result standards are those prescribed therein.

(4) *Inoculation of other cell cultures.* Virus grown in canine renal tissue cultures shall be tested in rhesus or cynomolgus monkey kidney tissue, canine renel tissue and human tissue cell cultures as prescribed in paragraph (a)(3) of this section for testing virus grown in chick embryo tissue culture in cercopithecus monkey kidney tissue culture preparations. Test result standards are those prescribed therein.

(5) *Inoculation of embryonated eggs.* Virus grown in canine renal tissue cultures shall be tested in embryonated eggs as prescribed in paragraph (a)(5) of this section for virus grown in chick embryo tissue cultures. Test result standards are those prescribed therein.

(6) [Reserved]

(7) *Bacteriological test.* Each virus pool shall be tested for sterility in accordance with § 73.730. In addition each virus pool shall be tested for M. tuberculosis, human, by appropriate culture methods.

(8) *Tests for adventitious agents.* Each virus pool shall be tested for the presence of such adventitious agents as canine distemper virus, canine hepatitis virus, leptospira and toxoplasma and the following fungi: coccidiomyces, histoplasma and blastomyces. The virus pool is satisfactory only if the results of all tests show no evidence of any extraneous agent attributable to the canine renal tissue or the vaccine.

(c) *Clarification.* After harvesting and removal of samples for testing as prescribed above in this section, the virus fluids shall be clarified by centrifugation, by passage through filters of sufficiently small porosity, or by any other method that will assure removal of all intact tissue cells which may have been collected in the harvesting process.

(d) *Test after clarification—Neurovirulence safety test in monkeys for neurotropic agents.* Before final dilution for standardization for live measles virus content each lot of measles virus vaccine shall be tested for neurotropic agents following the procedure prescribed in § 73.1002(e), except that antibody determinations for measles need not be performed, the test shall be performed before the product is placed in final containers and prior to the addition of an adjuvant, and that symptoms suggestive of any neurotropic agent, rather than those specifically suggestive of poliomyelitis, shall be recorded during the observation of 17 to 19 days. The lot is satisfactory only if the histological and other studies produce no clinical or histological evidence of central nervous system involvement attributable to the presence of a neurotropic agent in the vaccine.

§ 73.1063 Potency test.

The concentration of live measles virus shall constitute the measure of potency. The titration shall be performed in a suitable cell culture system, free of wild viruses, using either the NIH reference measles virus, live, attenuated or a calibrated equivalent strain as a titration control. The concentration of live measles virus contained in the vaccine of each lot under test shall be no less than the equivalent of 1,000 $TCID_{50}$ of the NIH reference per human dose.

§ 73.1064 General requirements.

(a) *Final container tests.* In addition to the tests required pursuant to § 73.760, an immunological and virological identity test shall be performed on the final container if it was not performed on each pool or the bulk vaccine prior to filling.

(b) [Reserved]

(c) [Reserved]

(d) *Dose.* These standards are based on an individual human immunizing dose of no less than 1,000 $TCID_{50}$ of Measles Virus Vaccine, Live, Attenuated, expressed in terms of the assigned titer of the NIH reference measles virus.

(e) *Labeling.* In addition to the items required by other applicable labeling provisions of this part, single-dose container labeling for vaccine which is not protected against photochemical deterioration shall include a statement cautioning against exposure to sunlight.

(f) *Dried vaccine.* Measles Vaccine, Live, Attenuated, may be dried immediately after completion of processing to final bulk material and stored in the dried state, provided its residual moisture and other volatile substances content is not in excess of 2 percent, as provided in § 73.740(a).

(g) *Photochemical deterioration; protection.* Vaccine in multiple dose final containers shall be protected against photochemical deterioration. Such containers may be colored, or outside coloring or protective covering may be used for this purpose, provided (1) the method used is shown to provide the required protection, and (2) visible examination of the contents is not precluded. Vaccine in single dose containers may be protected in the same manner provided the same conditions are met.

(h) *Samples and protocols.* For each lot of vaccine, the following materials shall be submitted to the Director, Division of Biologics Standards, National

Institutes of Health, Bethesda, Md. 20014:

(1) A protocol which consists of a summary of the history of the manufacture of each lot including all results of each test for which test results are requested by the Director, Division of Biologics Standards.

(2) A total of no less than 120 ml. in 10 ml. volumes, in a frozen state (—60° C.), of preclarification bulk vaccine containing no preservative or adjuvant, and no less than 100 ml. in 10 ml. volumes, in a frozen state (—60° C.), of post-clarification bulk vaccine containing stabilizer but no preservative or adjuvant, taken prior to filling into final containers.

(3) A total of no less than 200 recommended doses of the vaccine in final labeled containers distributed equally between the number of fillings made from each bulk lot, except that the representation of a single filling shall be no less than 30 final containers.

§ 73.1065 Clinical trials to qualify for license.

To qualify for license, the antigenicity of the vaccine shall have been determined by clinical trials of adequate statistical design, by subcutaneous administration of the product. Such clinical trials shall be conducted with five consecutive lots of measles virus vaccine which have been manufactured by the same methods, each of which has shown satisfactory results in all prescribed tests. There shall be a demonstration under circumstances wherein adequate clinical and epidemiological surveillance of illness has been maintained to show that the Measles Virus Vaccine, when administered as recommended by the manufacturer—i.e., either with or without human gamma globulin—is free of harmful effect upon administration to approximately 1,000 susceptible individuals, in that there were no detectable neutralizing antibodies before vaccination and there was serological conversion after vaccination. The five lots of vaccine used to qualify for consistency of vaccine manufacture shall be distributed as evenly as possible among the 1,000 individuals tested. Demonstration shall be made of immunogenic effect by the production of specific measles neutralizing antibodies (i.e., sero-conversion less than 1:4 to 1:8 or greater) in at least 90 percent of each of five groups of measles suspectible individuals, each having received the parenteral administration of a virus vaccine dose which is not greater than that which was demonstrated to be safe in field studies (§ 73.1060(b)) when used under comparable conditions.

§ 73.1066 Equivalent methods.

Modification of any particular manufacturing method or process or the conditions under which it is conducted as set forth in the additional standards relating to Measles Virus Vaccine, Live, Attenuated, shall be permitted whenever the manufacturer presents evidence that demonstrates the modification will provide assurances of the safety, purity, and potency of the vaccine that are equal to or greater than the assurances provided by such standards, and the Director, National Institutes of Health so finds and makes such finding a matter of officials record.

Measles Virus Vaccine, Inactivated

§ 73.1080 The product.

(a) *Proper name and definition.* The proper name of this product shall be Measles Virus Vaccine, Inactivated. The vaccine shall consist of a preparation of measles virus inactivated by an appropriate method.

(b) *Criteria for acceptable strains of measles virus.* Strains of measles virus used in the manufacture of vaccine shall be identified by (1) historical records including origin and manipulation and (2) antigenic specificity as measles virus as demonstrated by tissue culture neutralization tests. Strains used for the manufacture of Measles Virus Vaccine, Inactivated, shall have been shown to be safe and potent in man by field studies with experimental vaccines. Vaccine prepared from measles virus strains propagated in chick embryo tissue cultures, monkey kidney tissue cultures or canine renal tissue cultures, shall have been demonstrated as safe and potent in at least 10,000 susceptible persons. Susceptibility shall be shown by the absence of neutralizing or other antibodies against measles virus, or by other appropriate methods. Vaccine prepared from measles virus strains propagated in canine renal tissue cultures shall also have been demonstrated to be free from harmful effects in not less than 100,000 persons. Seed virus used for vaccine manufacture shall be free of all demonstrable extraneous viable microbial agents.

§ 73.1081 Manufacture of measles virus vaccine, inactivated.

(a) *Virus cultures.* Virus shall be propagated in chick embryo tissue cultures, monkey kidney tissue cultures, or canine renal tissue cultures.

(b) *Virus propagated in chick embryo tissue cultures.* Embryonated chicken eggs used as a source of chick embryo tissue for the propagation of measles virus shall be derived from flocks certified to be free of Salmonella pullorum and avian tuberculosis, fowl pox, Rous sarcoma, avian leucosis and other adventitious agents pathogenic for chickens. If eggs are procured from flocks that are not so certified, tests shall be performed to demonstrate that the virus pool be free from such agents prior to inactivation.

(c) *Virus propagated in monkey kidney tissue cultures.* Only Macaca or Cercopithecus monkeys, or a species found by the Director, Division of Biologics Standards, to be equally suitable, which have met all the quarantine requirements, shall be used as the source of kidney tissue for the manufacture of Measles Virus Vaccine, Inactivated.

(1) *Monkeys used for experimental purposes.* Monkeys that have been used previously for experimental purposes with microbiological agents shall not be used as a source of kidney tissue for the manufacture of vaccine. Monkeys that have been used previously for other experimental purposes may be used upon their return to a normal condition.

(2) *Quarantine.* Only monkeys that during the quarantine period, as provided by § 73.501(f)(2), have been tested with and have reacted negatively to tuberculin shall be used as a source of kidney tissue for vaccine manufacture.

(3) *Necropsy.* Each animal at necropsy shall be examined under the direction of a qualified pathologist, physician or veterinarian having experience with diseases of monkeys, for the presence of signs or symptoms of ill health, particularly for (i) evidence of tuberculosis, (ii) presence of herpes-like lesions, including eruptions or plaques on or around the lips, in the buccal cavity or on the gums and (iii) signs of conjunctivitis. If any such signs or other significant gross pathological lesions are present, the kidney shall not be used in the manufacture of Measles Virus Vaccine, Inactivated.

(d) *Virus propagated in canine renal tissue cultures.* Only dogs in overt good provided the progeny have been kept in quarantine in vermin-proof quarters for a minimum of six months, having had no exposure to other dogs or animals throughout the quarantine period, or dogs born to dogs while so quarantined, provided the progeny have been kept in the same type of quarantine continuously from birth, shall be used as a source of kidney tissue for the propagation of measles virus.

(1) *Dogs used for experimental purposes.* Dogs that have been used previously for experimental or testing purposes with microbiological agents shall not be used as a source of kidney tissue in the manufacture of vaccine.

(2) *Quarantine and necropsy.* Each dog shall be examined periodically during the quarantine period as well as at the time of necropsy under the direction of a qualified pathologist, physician or veterinarian having experience with diseases of dogs, for the presence of signs or symptoms of ill health, particularly for evidence of tuberculosis, infectious canine hepatitis, canine distemper, rabies, leptospirosis, and other diseases indigenous to dogs. If there are any such signs, symptoms, or other significant pathological lesions observed, the kidneys from such animals shall not be used in the manufacture of Measles Virus Vaccine, Inactivated.

(e) *NIH Reference Measles Virus.* The following NIH reference viruses shall be obtained from the Division of Biologics Standards:

(1) NIH Reference Measles Virus for titration.

(2) NIH Reference Measles Vaccine for potency testing.

(f) *Passage of virus strain in vaccine manufacture.* Virus in the final vaccine shall represent no more than ten tissue culture passages beyond the passage used to perform the clinical trials which qualified the vaccine strain for license (§ 73.1080(b)), and the virus of that passage shall represent vaccine that

shall have met the following criteria of acceptability:

(1) *Clinical safety.* The vaccine shall be free from harmful effects. Freedom from harmful effects shall be demonstrated by administration, as recommended by the manufacturer, and while maintaining adequate clinical and epidemiological surveillance of illness, to approximately 1,000 individuals, having no detectable neutralizing antibodies before vaccination and showing serological conversion after vaccination. Five consecutive lots of vaccine shall be used to qualify the vaccine for license and shall be distributed as evenly as possible among the 1,000 individuals tested.

(2) *Clinical potency.* The immunogenic effect (i.e., sero-conversion less than 1: 4 to 1: 8 or greater) shall be demonstrated in at least 90 percent of each of five groups of measles susceptible individuals, each group receiving vaccine from one of the five consecutive lots of vaccine which were used to qualify the vaccine for license, and each of which shall have met the safety standards prescribed in these regulations. The dose of vaccine shall be no greater than that which was demonstrated to be safe pursuant to subparagraph (1) of this paragraph and the vaccine shall be used under comparable conditions.

(g) *Types of tissue culture preparation permissible.* Measles Virus Vaccine, Inactivated, shall be produced only in primary cell tissue culture. Continuous line cells shall not be used and shall not be introduced into vaccine production areas.

(h) *Use of antibiotics.* Virus for manufacturing vaccine may be grown in cultures which contain minimum concentration of suitable antibiotics except that penicillin shall not be used in the tissue culture medium or added to the final product.

(i) *Clarification.* After harvesting, the virus fluids shall be clarified by centrifugation, by passage through filters of sufficiently small porosity, or by any other method that will assure removal of all intact tissue cells which may have been collected in the harvesting process.

§ 73.1082 Test for safety.

(a) *Tests prior to the inactivation process.* Samples of virus pools for testing by inoculation into animals or into bacteriological media shall be withdrawn immediately after pooling but prior to freezing or further processing, and tested, prior to the inactivation process, as provided in paragraphs (b) and (c) of this section except that samples of test materials frozen immediately after pooling and maintained at −60° C. or below, may be tested upon thawing, provided no more than two freeze thaw cycles are employed. The required tests shall be conducted without delay after thawing.

(1) *Measles virus propagated in chick embryo tissue cultures*—(i) *Inoculation of adult mice; test for adventitious agents.* Each chick embryo virus pool shall be shown to be free of contaminating agents pathogenic for mice by the intracerebral inoculation of 0.03 ml. and intraperitoneal inoculation of 0.5 ml. amounts of the pool into each of ten or more adult mice (15–20 gms.). The mice shall be observed for at least 21 days. The virus pool is satisfactory for measles virus vaccine only if at least 80 percent of the inoculated animals survive the observation period and none of the animals inoculated shows evidence of infection with extraneous transmissible agents attributable to the vaccine.

(ii) [Reserved]

(iii) *Bacteriological tests.* Each chick embryo virus pool shall be tested for bacteriological sterility in accordance with the procedures prescribed in § 73.730. In addition each virus pool shall be tested and found negative for the presence of M. tuberculosis, both avian and human, by appropriate culture methods.

(iv) *Test for avian leucosis.* The equivalent of at least 50 doses of final vaccine from each undiluted virus pool, or in proportionate amounts from individual harvests or subpools, shall be tested and found negative for avian leucosis, using either Rubin's procedure for detecting Resistance Inducing Factor (RIF) or a procedure of equivalent effectiveness. These tests may be performed on corresponding amounts of fluids from control vessels instead of on the undiluted virus pool or individual harvests of subpools.

(2) *Measles virus propagated in monkey kidney tissue cultures*—(i) *Inoculation of rabbits; test for B virus and other adventitious agents.* A minimum of 100 ml. of each monkey kidney virus pool shall be tested by inoculation into at least ten healthy rabbits, each weighing 1500–2500 grams. Each rabbit shall be injected intradermally at multiple sites with a total of 1.0 ml. and subcutaneously with 9.0 ml. of the virus, and the animals observed for at least three weeks. Each rabbit that dies after the first 24 hours of the test or is sacrificed because of illness shall be necropsied and the brain and organs removed and examined. The virus pool may be used for measles virus vaccine only if at least 80 percent of the rabbits remain healthy and survive the entire period and if none of the rabbits used in the test shows lesions of any kind at the sites of inoculation or shows evidence of B virus or any other transmissible agent attributable to the vaccine.

(ii) *Inoculation of adult mice; test for adventitious agents.* Each virus pool grown in monkey kidney tissue culture shall be tested in adult mice. The test shall be performed and the results measured against the standards prescribed in subparagraph (1) (i) of this paragraph for chick embryo tissue culture.

(iii) *Inoculation of guinea pigs; test for M. tuberculosis.* Each of at least five guinea pigs, each weighing 350–450 grams shall be inoculated intraperitoneally with 5.0 ml. of the monkey kidney virus pool to be tested. The animals shall be observed for at least 42 days for death or signs of disease. Each animal that dies after the first 24 hours of the test, or is sacrificed because of illness, shall be necropsied. The tissues shall be examined both microscopically and culturally for evidence of M. tuberculosis. The virus pool is satisfactory for measles virus vacine only if at least 80 percent of the original group of guinea pigs remain healthy and survive the observation period, and if none of the animals used in the test shows evidence of infection with M. tuberculosis or any extraneous transmissible agent attributable to the vaccine.

(iv) *Bacteriological tests.* Each monkey kidney virus pool shall be tested for bacteriological sterility in accordance with the procedures prescribed in § 73.730. In addition each virus pool shall be tested for the presence of M. tuberculosis (human) by appropriate culture methods.

(v) *Tissue culture test for SV_{40}.* Each individual harvest or virus pool, or a pool of tissue culture fluids from corresponding control vessels, shall be tested for the presence of SV_{40} either as follows or by a test producing equally reliable results: five ml. of a measles virus pool shall be neutralized by high titer antiserum of an origin other than human, chicken or simian. The sample shall be tested in the same tissue culture system used for propagating the virus vaccine, and in primary cercopithecus tissue cultures or in a cell line of demonstrated equal susceptibility to SV_{40}. The tissue cultures shall be observed for at least 14 days and at the end of the observation period at least one subculture of fluid shall be made in the same tissue culture system and the test continued for an additional 14 days. The virus harvest or virus pool is satisfactory for measles virus vaccine only if the test produces no evidence of the presence of SV_{40}.

(3) *Measles virus propagated in canine renal tissue cultures*—(i) *Inoculation of adult mice; test for adventitious agents.* Each virus pool prepared from canine renal tissue cultures shall be shown to be free from contaminating agents pathogenic for mice by the test prescribed in subparagraph (1) (i) of this section for chick embryo virus pools. Test result standards are those prescribed therein.

(ii) *Inoculation of suckling mice.* Suckling mice shall be inoculated as prescribed in § 73.1062(b) (2) for virus (live, attenuated) grown in canine renal tissue cultures. Test result standards are those prescribed therein.

(iii) *Inoculation of monkey tissue cell cultures.* Monkey tissue cell cultures shall be inoculated as prescribed in § 73.1062(a) (3) for virus (live, attenuated) grown in chick embryo tissue cultures. Test result standards are those prescribed therein.

(iv) *Inoculation of other cell cultures.* Virus grown in canine renal tissue cultures shall be tested in rhesus or cynomolgus monkey kidney tissue, canine renal tissue and human tissue cell cultures as prescribed in § 73.1062(a) (3) for testing virus grown in chick embryo tissue cultures in cercopithecus monkey kidney tissue culture preparations. Test result standards are those prescribed therein.

(v) *Inoculation of embryonated chicken eggs.* Embryonated chicken eggs shall be inoculated as prescribed in § 73.1062(a)(5) for virus (live, attenuated) grown in chick embryo tissue cultures. Test result standards are those prescribed therein.

(vi) [Reserved]

(vii) *Bacteriological test.* Each virus pool shall be tested for sterility in accordance with § 73.730. In addition each virus pool shall be tested for M. tuberculosis, human, by appropriate culture methods.

(viii) *Test for adventitious agents.* Each virus pool shall be tested for the presence of the adventitious agents enumerated in § 73.1062(b)(8) for virus (live, attenuated) grown in canine renal tissue cultures. Test result standards are those prescribed therein.

(b) *Inactivation of virus.* The measles virus shall be inactivated through the use of an agent or method which the manufacturer has demonstrated to be effective in inactivating a series of at least five consecutive lots of measles virus vaccine. If formaldehyde is used for inactivation, it shall be added to the virus suspension to a final concentration of U.S.P. formaldehyde solution of a least 1:4,000. The inactivation shall be conducted under controlled conditions of pH and temperature. As an indication of inactivation, not less than two samples shall be removed at the time of inactivation, and titrated in an appropriate tissue cell culture for viable measles virus. Regardless of the concentration of formaldehyde or other inactivating agent used, the total inactivation period shall be not less than three times the period demonstrated by the manufacturer to be necessary to reduce the concentration of live virus to a point where no virus is detectable in a 5.0 ml. sample.

(c) *Tests after inactivation for viable measles virus and adventitious agents*—(1) *Test in tissue cultures.* A sample representing the equivalent of at least 500 doses of final vaccine of each lot shall be rendered nontoxic for tissue culture cells and tested as follows: One half of the sample shall be tested in the same tissue culture system used for propagating the virus vaccine and one half of the sample shall be tested in primary cercopithecus monkey kidney tissue or another suitable cell line of demonstrated high susceptibility to measles virus, poliovirus, and SV_{40} or other adventitious viral agents. Each half of the sample shall be inoculated so that direct microscopic observation of the culture cells is possible under conditions which assure the growth of measles virus, poliovirus, and simian viruses which might have survived the inactivation procedure. After inoculation of the test sample, the tissue cultures shall be observed for at least 14 days. At the end of the observation period the fluids from all the culture bottles in a system shall be removed and pooled. At least two percent of each pool shall be subinoculated in the same cell system as that from which the pooled sample was drawn. The subcultures shall be observed for a period of at least 14 days and examined for cell changes indicative of viral growth. The lot of final vaccine is satisfactory for measles virus vaccine only if none of the tissue culture tests show evidence of viable measles virus or any extraneous transmissible agents attributable to the vaccine.

(2) *Test in embryonated chicken eggs.* For vaccine produced in chick embryo tissue culture, the equivalent of at least 100 doses of each vaccine lot shall be tested in embryonated eggs by the allantoic cavity route and of 100 doses by the yolk sac route of inoculation, using 0.5 ml. of inoculum per egg, and found negative for the presence of extraneous agents in the vaccine.

(3) *Test in monkeys for neurotropic agents.* Each lot of vaccine shall be tested for neurotropic agents following the procedure prescribed in § 73.1002(e) except that antibody determinations for measles need not be performed, the test shall be performed before the product is placed in final containers and prior to the addition of an adjuvant, and that symptoms suggestive of all neurotropic agents shall be recorded during the observation period of 17 to 19 days. The lot is satisfactory only if the histological and other studies produce no clinical or histological evidence of central nervous system involvement attributable to the presence of a neurotropic agent in the vaccine.

§ 73.1083 Test for potency.

A potency test shall be performed on each lot of vaccine by determining the antigenic capacity of the vaccine under tests in comparison with a reference vaccine of antigenic capacity at least equal to that required for the clinical trials specified in § 73.1081(h)(2). The test shall be performed using at least ten animals for each dilution of the test vaccine and of the reference vaccine. The average antibody levels of the animals injected with the vaccine under test shall equal or exceed the average antibody levels of the animals injected with the reference vaccine.

§ 73.1084 General requirements.

(a) [Reserved]

(b) *Extraneous protein.* The final vaccine shall have a protein nitrogen content of less than 0.02 milligram per individual human dose.

(c) *Dose.* These standards are based on an individual human dose of 1.0 ml. for a single injection.

(d) [Reserved]

(e) [Reserved]

(f) *Requirements for samples and protocols.* For each lot of vaccine, the following material shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda, Md. 20014:

(1) A sample of 1,500 doses of the vaccine taken after the last stage of manufacture before the addition of preservative or adjuvant.

(2) A sample of 100 doses of the final vaccine containing all preservatives.

(3) A sample of 200 doses of the final vaccine in final labeled containers.

(4) A protocol which consists of a summary of the history of the manufacture of each lot including all results of each test for which test results are requested by the Director, Division of Biologics Standards.

§ 73.1085 Equivalent methods.

Modification of any particular method of process or the conditions under which it is conducted as set forth in the additional standards relating to Measles Virus Vaccine, Inactivated, shall be permitted whenever the manufacturer presents evidence that demonstrates the modification will provide assurances of the safety, purity, and potency of the vaccine that are equal to or greater than the assurances provided by such standards, and the Director, National Institutes of Health so finds and makes such finding a matter of official record.

Mumps Virus Vaccine, Live

§ 73.1100 The product.

(a) *Proper name and definition.* The proper name of this product shall be Mumps Virus Vaccine, Live, which shall consist of a preparation of live, attenuated mumps virus.

(b) *Criteria for acceptable strains of attenuated mumps virus.* Strains of attenuated mumps virus used in the manufacture of vaccine shall be identified by (1) historical records including origin and manipulation during attenuation, (2) antigenic specificity as mumps virus as demonstrated by tissue culture neutralization tests. Strains used for the manufacture of Mumps Virus Vaccine, Live, shall have been shown to be safe and potent in at least 5,000 susceptible individuals by field studies with experimental vaccines. Susceptibility shall be shown by the absence of neutralizing or other antibodies against mumps virus, or by other appropriate methods. Seed virus used for vaccine manufacture shall be free of all demonstrable extraneous viable microbial agents.

(c) *Neurovirulence safety test of the virus seed strain in monkeys*—(1) *The test.* A demonstration shall be made in monkeys of the lack of neurotropic properties of the seed strain of attenuated mumps virus used in manufacture of mumps vaccine. For this purpose, vaccine from each of the five consecutive lots (§ 73.1105) used by the manufacturer to establish consistency of manufacture of the vaccine, shall be tested in monkeys shown to be serologically negative for mumps virus antibodies by following the procedures in § 73.1060(c)(1) or in § 73.1102(c).

(2) *Test results.* The mumps virus seed has acceptable neurovirulence properties for use in vaccine manufacture if for each of the five lots (i) 80 percent of the monkeys survive the observation period and (ii) there is no clinical or histopathological evidence of central nervous system involvement attributable to the replication of the virus.

(3) *New seed lots—test for neurovirulence.* The neurovirulence properties of each new seed shall be tested as prescribed in subparagraphs (1) and (2) of this paragraph. Only seed lots which meet the neurovirulence requirement shall be used for mumps vaccine manufacture. The test need not be repeated as long as the same seed lot of virus is used.

§ 73.1101 Manufacture of Mumps Virus Vaccine, Live.

(a) *Virus cultures.* Mumps virus shall be propagated in chick embryo cell cultures. The embryonated chicken eggs used as the source of chick embryo tissue for the propagation of mumps virus shall be derived from flocks certified or tested as prescribed in § 73.1061(b).

(b) *NIH Reference Mumps Virus.* An NIH Reference Mumps Virus, Live, shall be obtained from the Division of Biologics Standards as a control for correlation of virus titers.

(c) *Passage of virus strain in vaccine manufacture.* Virus in the final vaccine shall represent no more than five cell culture passages beyond the passage used to perform the clinical trials (§ 73.1100(b)) which qualified the manufacturer's vaccine strain for license.

(d) *Cell culture preparation.* Only primary cell cultures shall be used in the manufacture of mumps virus vaccine. Continuous cell lines shall not be introduced or propagated in mumps virus vaccine manufacturing areas.

(e) *Control vessels.* From the tissue used for the preparation of cell cultures for growing attenuated mumps virus, an amount of processed cell suspension equivalent to that used to prepare 500 ml. of cell culture shall be used to prepare uninfected tissue control materials which shall be prepared and tested by following the procedures prescribed in 73.1061(g).

(f) *Test samples.* Test samples of mumps virus harvests or pools shall be withdrawn and maintained by following the procedures prescribed in § 73.1061(h).

§ 73.1102 Test for safety.

(a) *Tests prior to clarification.* Prior to clarification, the following tests shall be performed on each mumps virus pool prepared in chick embryo cell culture:

(1) *Inoculation of adult mice.* The test shall be performed in the volume and following the procedures prescribed in § 73.1062(a)(1), and the virus pool is satisfactory only if equivalent test results are obtained.

(2) *Inoculation of suckling mice.* The test shall be performed in the volume and following the procedures prescribed in § 73.1062(a)(2), and the virus pool is satisfactory only if equivalent test results are obtained.

(3) *Inoculation of monkey cell cultures.* A mumps virus pool shall be tested for adventitious agents in the volume and following the procedures prescribed in § 73.1062(a)(3), and the virus pool is satisfactory only if equivalent test results are obtained.

(4) *Inoculation of other cell cultures.* The mumps virus pool shall be tested for adventitious agents in the volume and following the procedures prescribed in § 73.1062(a)(3), in rhesus or cynomolgus monkey kidney, in whole chick embryo and in human cell cultures. In addition, each virus pool shall be tested in chick embryo kidney and in chick embryo liver in the same manner except that the volume tested in each cell culture shall be equivalent to 250 human doses or 25 ml., whichever represents a greater volume. The mumps virus pool is satisfactory only if results equivalent to those in § 73.1062(a)(3) are obtained.

(5) *Inoculation of embryonated chicken eggs.* A neutralized suspension of each undiluted mumps virus pool shall be tested in the volume and following the procedures prescribed in § 73.1062(a)(5), and the virus pool is satisfactory only if there is no evidence of adventitious agents.

(6) *Bacteriological tests.* In addition to the tests for sterility required pursuant to § 73.730, bacteriological tests shall be performed on each mumps virus pool for the presence of M. tuberculosis, both avian and human, by appropriate culture methods. The virus pool is satisfactory only if found negative for M. tuberculosis, both avian and human.

(7) *Test for avian leucosis.* If the cultures were not derived from a certified source and control fluids were not tested for avian leucosis, the vaccine shall be tested in the volume and following the procedures prescribed in § 73.1062(a)(8). The cultures are satisfactory for vaccine manufacture if found negative for avian leucosis.

(b) *Clarification.* The mumps virus fluids shall be clarified by following the procedures prescribed in § 73.1062(c).

(c) *Test after clarification—Neurovirulence safety test in monkeys for neurotropic agents.* Before final dilution for standardization for live mumps virus content each lot of mumps vaccine shall be tested for neurotropic agents following the procedures prescribed in § 73.1002(e) except that antibody determinations for mumps need not be performed. The test shall be performed before the product is placed in final containers and prior to the addition of an adjuvant, and symptoms suggestive of any neurotropic agent, including those suggestive of poliomyelitis, shall be recorded during the observation period of 17 to 19 days. The lot is satisfactory if the histological and other studies produce no evidence of changes in the central nervous system attributable to the presence of an extraneous neurotropic agent in the vaccine.

§ 73.1103 Potency test.

The concentration of live mumps virus shall constitute the measure of potency. The titration shall be performed in a suitable cell culture system, free of wild viruses, using either the Reference Mumps Virus, Live, or a calibrated equivalent strain as a titration control. The concentration of live mumps virus contained in the vaccine of each lot under test shall be no less than the equivalent of 5,000 $TCID_{50}$ of the reference virus per human dose.

§ 73.1104 General requirements.

(a) *Final container tests.* In addition to the tests required pursuant to § 73.760, an immunological and virological identity test shall be performed on the final container if it was not performed on each pool or the bulk vaccine prior to filling.

(b) *Dose.* These standards are based on an individual human immunizing dose of no less than 5,000 $TCID_{50}$ of Mumps Virus Vaccine, Live, expressed in terms of the assigned titer of the Reference Mumps Virus, Live.

(c) *Labeling.* In addition to the items required by other applicable labeling provisions of this part, single dose container labeling for vaccine which is not protected against photochemical deterioration shall include a statement cautioning against exposure to sunlight.

(d) *Dried vaccine.* Mumps Virus Vaccine, Live, may be dried immediately after completion of processing to final bulk material and stored in the dried state provided its residual moisture and other volatile substances content is not in excess of 2 percent when tested as prescribed in § 73.740(a).

(e) *Photochemical deterioration; protection.* Mumps Virus Vaccine, Live, in multiple dose containers, shall be protected against photochemical deterioration in accordance with the procedures prescribed in § 73.1064(g).

(f) *Samples and protocols.* For each lot of vaccine, the following materials shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda, Md. 20014:

(1) A protocol which consists of a summary of the history of manufacture of each lot including all results of each test for which test results are requested by the Director, Division of Biologics Standards.

(2) A total of no less than a 500 ml. sample of bulk vaccine or an equivalent sample prior to addition of any preservative, stabilizer or adjuvant, in the frozen state (−60° C.) prior to filling into final containers.

(3) A total of no less than 200 recommended human doses of the vaccine in final labeled containers.

§ 73.1105 Clinical trials to qualify for license.

To qualify for license, the antigenicity of Mumps Virus Vaccine, Live, shall be determined by clinical trials that follow the procedures prescribed in § 73.1065 except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of mumps susceptible individuals, each having received the parenteral administration of a virus vaccine dose which is not greater than that which was demonstrated to be safe in field studies (§ 73.1100(b)) when used under comparable conditions.

§ 73.1106 Equivalent methods.

Modification of any particular manufacturing method or process or the conditions under which it is conducted as set forth in the additional standards relating to Mumps Virus Vaccine, Live, shall be permitted whenever the manufacturer presents evidence that demonstrates the modification will provide assurances of the safety, purity, and potency of the vaccine that are equal to or greater than the assurances provided by such standards, and the Director, National Institutes of Health so finds and makes such finding a matter of official record.

RUBELLA VIRUS VACCINE, LIVE

§ 73.1120 The product.

(a) *Proper name and definition.* The proper name of this product shall be Rubella Virus Vaccine, Live, which shall consist of a preparation of live, attenuated rubella virus.

(b) *Criteria for acceptable strains of attenuated rubella virus.* Strains of attenuated rubella virus used in the manufacture of vaccine shall be identified by (1) historical records including origin and manipulation during attenuation and (2) antigenic specificity as rubella virus as demonstrated by tissue culture neutralization tests.

(c) *Extraneous agents.* Seed virus used for vaccine manufacture shall be free of all demonstrable extraneous viable microbial agents.

(d) *Field studies with experimental vaccines.* (1) Strains used for the manufacture of Rubella Virus Vaccine, Live, shall have been shown in field studies with experimental vaccines to be safe and potent in the group of individuals inoculated, which must include at least 10,000 susceptible individuals. Susceptibility shall be shown by the absence of neutralizing or hemagglutination-inhibiting antibodies against rubella virus or by other appropriate methods.

(2) The virus strain used in the field studies shall be propagated in the same cell culture system that will be used in the manufacture of the product.

(3) The field studies shall be so conducted that at least 5,000 of the susceptible individuals must reside when inoculated in areas where health related statistics are regularly compiled in accordance with procedures such as those used by the National Center for Health Statistics. Data in such form as will identify each inoculated person shall be furnished to the Director, Division of Biologics Standards.

(4) Inoculated persons shall be shown not to be contagious for contacts through surveillance of rubella susceptible contacts of the inoculated persons.

(e) *Neurovirulence safety test of the virus seed strain in monkeys*—(1) *The test.* A demonstration shall be made in monkeys of the lack of neurotropic properties of the seed strain of attenuated rubella virus used in manufacture of rubella vaccine. For this purpose, vaccine from each of the five consecutive lots used by the manufacturer to establish consistency of manufacture of the vaccine shall be tested in monkeys shown to be serologically negative for rubella virus antibodies by following the procedures prescribed in § 73.1060(c)(1) or § 73.1102(c), except that histologic examination shall be made of appropriate sections of the brain in addition to such examination of the spinal cord.

(2) *Test results.* The rubella virus seed has acceptable neurovirulence properties for use in vaccine manufacture if for each of the five lots: (i) 80 percent of the monkeys survive the observation period and (ii) there is no clinical or histopathologic evidence of central nervous system involvement attributable to the replication of the virus.

(3) *New seed lots—test for neurovirulence.* The neurovirulence properties of each new seed shall be tested as prescribed in subparagraphs (1) and (2) of this paragraph. Only seed lots which meet the neurovirulence requirement shall be used for rubella vaccine manufacture. The test need not be repeated as long as the same seed lot of virus is used.

§ 73.1121 Production.

(a) *Virus cultures.* Rubella virus shall be propagated in duck embryo cell cultures, canine renal cell cultures or rabbit renal cell cultures.

(b) *Virus propagated in duck embryo tissue cell cultures.* Embryonated duck eggs used as a source of duck embryo tissue for the propagation of rubella virus shall be derived from flocks certified to be free of avian tuberculosis, the avian leucosis-sarcoma group of viruses and other agents pathogenic for ducks. Only ducks so certified and in overt good health and which are maintained in quarantine shall be used as a source of duck embryo tissue used in the propagation of rubella virus. Ducks in the quarantined flock that die shall be necropsied and examined for evidence of significant pathologic lesions. If any such signs or pathologic lesions are observed, eggs from that flock shall not be used for the manufacture of Rubella Virus Vaccine, Live. Control vessels shall be prepared, observed and tested as prescribed in § 73.1061(g).

(c) *Virus propagated in canine renal tissue cell cultures.* When canine renal cell cultures are used for the propagation of rubella virus the renal tissue shall be obtained from dogs meeting the requirements specified in § 73.1061(c). Control vessels shall be prepared, observed and tested as prescribed in § 73.1061(g).

(c–1) *Virus propagated in rabbit renal tissue cell cultures.* Only rabbits in overt good health which have been maintained in quarantine individually caged in vermin-proof quarters for a minimum of 6 months, having had no exposure to other rabbits or animals throughout the quarantine period, or rabbits born to rabbits while so quarantined, provided the progeny have been kept in the same type of quarantine continuously from birth shall be used as a source of kidney tissue. Animals shall be free of antibodies for agents potentially pathogenic for man unless it has been demonstrated in the license application that the tests required by § 73.1122(b–1) to be performed on each lot of vaccine are capable of detecting contamination of agents capable of producing such antibodies.

(1) *Rabbits used for experimental purposes.* Rabbits that have been used previously for experimental or testing purposes with microbiological agents shall not be used as a source of kidney tissue in the production of vaccine.

(2) *Quarantine and necropsy.* Each rabbit shall be examined periodically during the quarantine period as well as at the time of necropsy under the direction of a qualified pathologist, physician or veterinarian having experience with diseases of rabbits, for the presence of signs or symptoms of ill health, particularly for evidence of tuberculosis, myxomatosis, fibromatosis, rabbit pox, and other diseases indigenous to rabbits. If there are any such signs, symptoms or other significant pathological lesions observed, tissues from that colony shall not be used in the production of vaccine.

(3) *Control vessels.* Control vessels shall be prepared, observed and tested as prescribed in § 73.1061(g).

(d) *Reference Rubella Virus.* A Reference Rubella Virus, Live, shall be obtained from the Division of Biologics Standards as a control for correlation of virus titers.

(e) *Passage of virus strain in vaccine manufacture.* Virus in the final vaccine shall represent no more than five cell culture passages beyond the passage used as the seed strain for the manufacture of the vaccines used to perform the field studies (§ 73.1120(d)), which qualified the manufacturer's vaccine strain for license.

(f) *Cell cultures in vaccine production areas.* Only the cell cultures used in the propagation of rubella virus vaccine shall be introduced into rubella virus vaccine production areas.

(g) *Test samples.* Test samples of rubella virus harvests or pools shall be withdrawn and maintained by following the procedures prescribed in § 73.1061(h).

§ 73.1122 Test for safety.

(a) *Tests prior to clarification of vaccine manufactured in duck embryo cell cultures.* Prior to clarification, the following tests shall be performed on each rubella virus pool prepared in duck embryo cell cultures:

(1) *Inoculation of adult mice.* The test shall be performed in the volume and following the procedures prescribed in § 73.1062(a)(1), and the virus pool is satisfactory only if equivalent test results are obtained.

(2) *Inoculation of suckling mice.* The test shall be performed in the volume and following the procedures prescribed in § 73.1062(a)(2), and the virus pool is satisfactory only if equivalent test results are obtained.

(3) *Inoculation of monkey tissue cell cultures.* A rubella virus pool shall be

tested for adventitious agents in the volume and following the procedures prescribed in § 73.1062(a)(3), except that the virus need not be neutralized by antiserum. The rubella virus pool is satisfactory only if equivalent test results are obtained.

(4) *Inoculation of other cell cultures.* The rubella virus pool shall be tested for adventitious agents in the volume and following the procedures prescribed in § 73.1062(a)(3), in rhesus or cynomolgus monkey kidney, in chick embryo, duck embryo, and in human cell cultures, except that the virus need not be neutralized by antiserum. The rubella virus pool is satisfactory only if results equivalent to those in § 73.1062(a)(3) are obtained.

(5) *Inoculation of embryonated chicken eggs.* A suspension of each undiluted rubella virus pool shall be tested in the volume and following the procedures prescribed in § 73.1062(a)(5) except that the virus need not be neutralized by antiserum. The virus pool is satisfactory only if there is no evidence of adventitious agents.

(6) *Inoculation of embryonated duck eggs.* A suspension of each undiluted rubella virus pool shall be tested in embryonated duck eggs, in the volume and following the procedures prescribed in § 73.1062(a)(5) except that the virus need not be neutralized by antiserum. The virus pool is satisfactory only if there is no evidence of adventitious agents.

(7) *Bacteriological tests.* In addition to the tests for sterility required pursuant to § 73.730, bacteriological tests shall be performed on each rubella virus pool for the presence of M. tuberculosis, both avian and human, by appropriate culture methods. The virus pool is satisfactory only if found negative for M. tuberculosis, both avian and human.

(8) *Test for avian leucosis.* The vaccine shall be tested for avian leucosis, in the volume and following the procedures prescribed in § 73.1062(a)(8). The cultures are satisfactory for vaccine manufacture if found negative for avian leucosis.

(9) *Inoculation of cell cultures and embryonated eggs after neutralization of the virus with antiserum.* Each of the tests prescribed in subparagraphs (3), (4), (5), and (6) of this paragraph shall be carried out also with rubella virus that has been neutralized by the addition of high titer antiserum of nonhuman, nonsimian and nonavian origin except that the volume of virus suspension of each undiluted virus pool tested shall be no less than 5 ml. The rubella antiserum shall have been prepared by using a rubella virus propagated in a cell culture system other than that used for the manufacture of the vaccine under test, and the cell culture system shall be free of extraneous agents which might elicit antibodies that could inhibit growth of any known extraneous agents which might be present in the vaccine under test. These tests may be performed either before or after clarification of the virus. The virus pool is satisfactory only if the results obtained are equivalent to those required in those subparagraphs.

(b) *Tests prior to clarification of vaccine manufactured in canine renal cell cultures.* Prior to clarification each rubella virus pool prepared in canine renal cell cultures shall be tested as follows:

(1) *Inoculation of adult mice.* The test shall be performed in the volume and following the procedures prescribed in § 73.1062(a)(1), and the virus pool is satisfactory only if equivalent test results are obtained.

(2) *Inoculation of suckling mice.* The test shall be performed in the volume and following the procedures prescribed in § 73.1062(b)(2), and the virus pool is satisfactory only if equivalent test results are obtained.

(3) *Inoculation of monkey tissue cell cultures.* The test shall be performed in the volume and following the procedures prescribed in § 73.1062(a)(3), except that the virus need not be neutralized by antiserum. The rubella virus pool is satisfactory only if equivalent test results are obtained.

(4) *Inoculation of other cell cultures.* The tests shall be performed in the volume and following the procedures prescribed in § 73.1062(a)(3, in rhesus or cynomolgus monkey kidney tissue, canine renal tissue and human tissue cell cultures, except that the virus need not be neutralized by antiserum. The rubella virus pool is satisfactory only if equivalent test results are obtained.

(5) *Inoculation of embryonated chicken eggs.* The tests shall be performed in the volume and following the procedures prescribed in § 73.1062(a)(5) except that the virus need not be neutralized by antiserum. The rubella virus pool is satisfactory only if equivalent test results are obtained.

(6) *Bacteriological tests.* In addition to the tests for sterility required pursuant to § 73.730, bacteriological tests shall be performed on each rubella virus pool for the presence of M. tuberculosis, human, by appropriate culture methods. The rubella virus pool is satisfactory only if found negative for M. tuberculosis, human.

(7) *Tests for adventitious agents.* Tests shall be performed for the presence of adventitious agents as prescribed in § 73.1062(b)(8), and the rubella virus pool is satisfactory only if equivalent test results are obtained.

(8) *Inoculation of cell cultures and embryonated eggs after neutralization of the virus with antiserum.* Each of the tests prescribed in subparagraphs (3), (4), and (5) of this paragraph shall be carried out also with rubella virus that has been neutralized following the procedures and in the volume prescribed in paragraph (a)(9) of this section. The virus pool is satisfactory only if the results obtained are equivalent to those required by that subparagraph.

(b–1) *Tests prior to clarification of vaccine manufactured in rabbit renal cell cultures.* Prior to clarification each rubella virus pool prepared in rabbit renal cell cultures shall be tested as follows:

(1) *Inoculation of adult mice.* The test shall be performed in the volume and following the procedures prescribed in § 73.1062(a)(1), and the virus pool is satisfactory only if equivalent test results are obtained.

(2) *Inoculation of suckling mice.* The test shall be performed in the volume and following the procedures prescribed in § 73.1062(a)(2), and the virus pool is satisfactory only if equivalent test results are obtained.

(3) *Inoculation of monkey tissue cell cultures.* A rubella virus pool shall be tested for adventitious agents in the volume and following the procedures prescribed in § 73.1062(a)(3), except that the virus need not be neutralized by antiserum. The rubella virus pool is satisfactory only if equivalent test results are obtained.

(4) *Inoculation of other cell cultures.* The tests shall be performed in the volume and following the procedures prescribed in § 73.1062(a)(3) in rhesus or cynomolgus monkey kidney tissue, rabbit renal tissue and human tissue cell cultures, except that the virus need not be neutralized by antiserum. The rubella virus pool is satisfactory only if equivalent test results are obtained.

(5) *Inoculation of embryonated chicken eggs.* A suspension of each undiluted rubella virus pool shall be tested in the volume and following the procedures prescribed in § 73.1062(a)(5) except that the virus need not be neutralized by antiserum. The virus pool is satisfactory only if there is no evidence of adventitious agents.

(6) *Inoculation of rabbits.* A minimum of 15 ml. of each virus pool shall be tested by inoculation into at least five healthy rabbits, each weighing 1500–2500 grams. Each rabbit shall be injected intradermally in multiple sites with a total of 1.0 ml. and subcutaneously with 2.0 ml., of the virus pool, and the animals observed for at least 30 days. Each rabbit that dies after the first 24 hours of the test or is sacrificed because of illness shall be necropsied and the brain and organs removed and examined. The virus pool is satisfactory only if at least 80 percent of the rabbits remain healthy and survive the entire period and if all the rabbits used in the test fail to show lesions of any kind at the sites of inoculation and fail to show evidence of any viral infection.

(7) *Inoculation of guinea pigs.* Each of at least five guinea pigs, each weighing 350–450 grams, shall be inoculated intracerebrally with 0.1 ml. and intraperitoneally with 5 ml. of the undiluted virus pool. The animals shall be observed for at least 42 days. Each animal that dies after the first 24 hours of the test or is sacrificed because of illness, shall be necropsied. All remaining animals shall be sacrificed and necropsied at the end of the observation period. The virus pool is satisfactory only if at least 80 percent of all animals remain healthy and survive the observation period and if all the animals used in the test fail to show evidence of infection with *M. tuberculosis* or any viral infection.

(8) *Bacteriological tests.* In addition to the tests for sterility required pursuant to § 73.730, bacteriological tests shall be performed on each rubella virus pool for the presence of *M. tuberculosis*, human, by appropriate culture methods. The rubella virus pool is satisfactory only if found negative for *M. tuberculosis*, human.

(9) *Tests for adventitious agents.* Each virus pool shall be tested for the presence of such known adventitious agents of rabbits as toxoplasma, encephalitozoon, herpes cuniculi, the vacuolating virus of rabbits, rabbit syncytial virus, myxoviruses and reoviruses. The virus pool is satisfactory only if the results of all tests show no evidence of any extraneous agent attributable to the rabbit renal tissue or the vaccine.

(10) *Inoculation of cell cultures and embryonated eggs after neutralization of the virus with antiserum.* Each of the tests prescribed in subparagraphs (3), (4), and (5) of this paragraph shall be carried out also with rubella virus that has been neutralized by the addition of high titer antiserum of nonhuman, nonsimian and nonrabbit origin following the procedures and in the volume prescribed in paragraph (a)(9) of this section. The virus pool is satisfactory only if the results obtained are equivalent to those required by that paragraph.

(c) *Clarification.* The rubella virus fluids shall be clarified by following the procedures prescribed in § 73.1062(c).

(d) *Test after clarification-neurovirulence safety test in monkeys for neurotropic agents.* Before final dilution for standardization for live rubella virus content each lot of rubella vaccine shall be tested for neurotropic agents following the procedures prescribed in § 73.1002(e) except that appropriate sections of the brain and spinal cord shall be examined histologically. The test shall be performed before the product is placed in final containers and prior to the addition of an adjuvant. Signs suggestive of any neurotropic agent shall be recorded during the observation period of 17 to 19 days. The lot is satisfactory if the histologic examinations and other studies produce no evidence of changes in the central nervous system attributable to the presence of an extraneous neurotropic agent in the vaccine.

§ 73.1123 Potency test.

The concentration of live rubella virus shall constitute the measure of potency. The titration shall be performed in a suitable cell culture system, using either the Reference Rubella Virus, Live, or a calibrated equivalent strain as a titration control. The concentration of live rubella virus contained in the vaccine of each lot under test shall be no less than the equivalent of 1,000 $TCID_{50}$ of the reference virus per human dose.

§ 73.1124 General requirements.

(a) *Final container tests.* In addition to the tests required pursuant to § 73.760, an immunological and virological identity test shall be performed on the final container if it was not performed on each pool or on the bulk vaccine prior to filling.

(b) *Dose.* These standards are based on an individual human immunizing dose of no less than 1,000 $TCID_{50}$ of Rubella Virus Vaccine, Live, expressed in terms of the assigned titer of the Reference Rubella Virus, Live.

(c) *Labeling.* In addition to the items required by other applicable labeling provisions of this part, single dose container labeling for vaccine which is not protected against photochemical deterioration shall include a statement cautioning against exposure to light.

(d) *Photochemical deterioration; protection.* Rubella Virus Vaccine, Live, in multiple dose containers, shall be protected against photochemical deterioration in accordance with the procedures prescribed in § 73.1064(g).

(e) *Samples; protocols; official release.* For each lot of vaccine, the following shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda, Md. 20014:

(1) A protocol which consists of a summary of the history of the manufacture of each lot including all results of each test for which test results are requested by the Director, Division of Biologics Standards.

(2) A total of no less than 120 ml. in 10 ml. volumes, in a frozen state (—60° C.), of preclarification bulk vaccine containing no preservative or adjuvant, and no less than 100 ml. in 10 ml. volumes, in a frozen state (—60° C.), of postclarification bulk vaccine containing stabilizer but no preservative or adjuvant, taken prior to filling into final containers.

(3) A total of no less than 200 recommended doses of the vaccine in final labeled containers distributed equally between the number of fillings made from each bulk lot, except that the representation of a single filling shall be no less than 30 single dose final containers or six multiple dose final containers.

The product shall not be issued by the manufacturer until notification of official release of the lot is received from the Director, Division of Biologics Standards.

§ 73.1125 Clinical trials to qualify for license.

To qualify for license, the antigenicity of Rubella Virus Vaccine, Live, shall be determined by clinical trials that follow the procedures prescribed in § 73.1065 except that the immunogenic effect shall be demonstrated by establishing that a protective antibody response has occurred in at least 90 percent of each of the five groups of rubella susceptible individuals, each having received the parenteral administration of a virus vaccine dose which is not greater than that which was demonstrated to be safe in field studies when used under comparable conditions.

§ 73.1126 Equivalent methods.

Modification of any particular manufacturing method or process or the conditions under which it is conducted as set forth in the additional standards relating to Rubella Virus Vaccine, Live, shall be permitted whenever the manufacturer presents evidence that demonstrates the modification will provide assurances of the safety, purity, and potency of the vaccine that are equal to or greater than the assurances provided by such standards, and the Director, National Institutes of Health so finds and makes such finding a matter of official record.

Subpart C—Additional Standards for Diagnostic Substances for Dermal Tests

DIPHTHERIA TOXIN FOR SCHICK TEST

§ 73.2000 Proper name and definition.

The proper name of this product shall be Diphtheria Toxin for Schick Test, which shall be a preparation of a diphtheria toxin obtained from the growth of *Corynebacterium diphtheriae.*

§ 73.2001 U.S. Standard preparation.

The U.S. Standard Diphtheria Toxin for Schick Test shall be used to determine the Schick test dose of the product. The Schick test dose of the standard is that amount of the standard, when mixed with 0.001 unit of the U.S. Standard Diphtheria Antitoxin and injected intradermally in a guinea pig, will induce an erythematous reaction of 10 mm. in diameter.

§ 73.2002 Production of Diphtheria Toxin for Schick Test.

(a) *Propagation of bacteria.* The culture medium for propagation of the *Corynebacterium diphtheriae* for preparation of the parent toxin shall not contain ingredients known to be capable of producing allergenic effects in human subjects.

(b) *The parent toxin.* Diphtheria Toxin for Schick Test shall be prepared from a parent toxin which has been demonstrated to be stable and which contains no less than 400 minimum lethal doses per milliliter or 400,000 minimum reaction doses per milliliter. A minimum lethal dose is the smallest amount of toxin that will kill a guinea pig weighing approximately 250 gm. on the fourth day after its subcutaneous injection. A minimum reaction dose is that amount of toxin which when injected intradermally into a guinea pig induces an erythematous reaction 10 mm. in diameter.

§ 73.2003 Potency test.

The dermal reactivity of each lot of the product shall be determined from the results of simultaneous guinea pig intradermal potency tests of the product under test and of the standard. The test shall be performed as follows:

(a) *Guinea pigs.* At least four healthy female guinea pigs shall be used, all of the same strain and each of a size that will permit a random distribution of eight intradermal injections. The hair shall be removed from the back and both sides of each guinea pig without producing abrasions of the skin. The denuded skin of each animal shall be sectioned into four equal areas at right angles to the vertebral column to provide two injection sites in each of the four areas, one on each side of the vertebra.

The test is not valid if the guinea pigs do not show a graded response to the graded dilutions of the Schick test dose of the standard toxin.

(b) *Preparation of the test doses.* Four dilutions, two of the product under test and two of the U.S. Standard Diptheria Toxin for Schick Test, shall be prepared in sterile buffered saline pH 7.4 containing 0.2 percent gelatin. The low and high dilutions of the standard shall be those amounts of a Schick test dose of the standard which in a dose of 0.1 ml. are capable of eliciting graded erythematous dermal reactions between 10 mm. and 20 mm. in diameter. The low and high dilutions of the Schick test dose of the toxin under test shall be the same as those of the standard toxin and estimated to have the same dermal reactivity.

(c) *Inoculation.* The low and high dilutions of the product (chart designation P_L and P_H) and the low and high dilutions of the standard (chart designations S_L and S_H) shall be injected intradermally in a volume of 0.1 ml. into each of the four guinea pigs according to either the following scheme, or in another scheme, provided it will permit comparable randomization of injection sites:

Area	Guinea Pig Number							
	1		2		3		4	
	Left	Right	Left	Right	Left	Right	Left	Right
A	S_L	S_L	S_H	S_H	P_L	P_L	P_H	P_H
B	S_H	S_H	S_L	S_L	P_H	P_H	P_L	P_L
C	P_L	P_L	P_H	P_H	S_L	S_L	S_H	S_H
D	P_H	P_H	P_L	P_L	S_H	S_H	S_L	S_L

(d) *Calculation of test results.* Between 40 and 66 hours following injection, a diameter of the reaction for each injection site shall be calculated by averaging two diameters of the reaction measured at right angles to each other. The average reaction for each dilution for each animal shall be determined, then the average diameters of the reactions of all of the guinea pigs for each dilution shall be calculated. The ratios of the reactions are determined by dividing the average diameter of the low dilution of the product under test by the average diameter of the low dilution of the standard and by dividing the average diameter of the high dilution of the product by the average diameter of the high dilution of the standard.

(e) *Potency requirement.* The potency of the product under test is satisfactory if each calculated ratio of the reactions of the product under test and of the standard is 1.0. The potency of the lot under test is considered to be equal to that of the standard if the ratios are not lower than 0.77 or higher than 1.30, provided that in a single test the ratios are substantially the same.

§ 73.2004 Stability test.

A sample of each lot of the product shall be held at 37° C. for not less than 24 hours and then tested for potency as prescribed in § 73.2003. The stability of the product is satisfactory if test results of the sample meet the potency requirement prescribed in § 73.2003(e).

§ 73.2005 Samples; protocols; official release.

For each lot of the product, the following material shall be submitted to the Director, Division of Biologics Standards:

(a) A protocol which consists of a summary of the history of manufacture of each lot including all results of all tests for which test results are requested by the Director, Division of Biologics Standards.

(b) A sample of no less than 20 ml. of the product.

No lot of the product shall be issued by the manufacturer until notification of official release is received from the Director, Division of Biologics Standards.

§ 73.2006 Equivalent methods.

Modification of any particular manufacturing method or process or the conditions under which it is conducted as set forth in the additional standards relating to Diphtheria Toxin for Schick Test, shall be permitted whenever the manufacturer presents evidence that demonstrates the modification will provide assurances of the safety, purity, and potency of the product that are equal to or greater than the assurances provided by such standards, and the Director, National Institutes of Health, so finds and makes such findings a matter of official record.

TUBERCULIN

§ 73.2020 Proper name and definition.

The proper name of this product shall be Tuberculin, which shall be a preparation derived from *Mycobacterium tuberculosis* or *M. Bovis*.

§ 73.2021 U.S. Standard preparations.

(a) The U.S. Standard Tuberculin, Old, shall be used for determining the potency of nonfractionated tuberculins, as prescribed in § 73.2023. One U.S. Tuberculin unit is 0.1 ml. of a 1:10,000 dilution of this standard.

(b) The U.S. Standard Tuberculin, Purified Protein Derivative, shall be used in determining the potency of tuberculins made from protein fractions, as prescribed in § 73.2023. One U.S. Tuberculin unit is 0.1 ml. of a 1: 5,000 dilution of this standard.

§ 73.2022 Production.

(a) *Propagation of mycobacteria.* The medium used for production of mycobacteria shall not contain ingredients known to be capable of producing allergenic effects in human subjects.

(b) *Tests for viable mycobacteria.* The culture filtrate from each strain in its most concentrated form shall be shown to be free of viable mycobacteria by the following tests:

(1) *Animal test.* A 1.0 ml. sample of the filtrate shall be injected intraperitoneally into each of at least three healthy guinea pigs weighing between 300 and 400 gm. At least two-thirds of the animals must survive an observation period of at least 6 weeks and must show a normal weight gain. After the observation period the animals shall be necropsied and examined for signs indicative of tuberculosis except that animals that die during the observation period shall be necropsied and examined as soon as feasible after death. The filtrate is satisfactory for Tuberculin manufacture if none of the animals in the test show evidence of tuberculosis infection.

(2) *Culture test.* A 2.0 ml. sample of the filtrate shall be inoculated onto Löwenstein-Jensen's egg medium or other media demonstrated to be equally capable of supporting growth. A control test on the culture medium shall be conducted simultaneously with the sample under test and shall be shown to be capable of supporting the growth of small numbers of the production strain(s). All the test vessels shall be incubated at a suitable temperature for a period of 6 weeks under conditions that will prevent drying of the medium, after which the cultures shall be examined for evidence of mycobacterial colonies. The filtrate is satisfactory for Tuberculin manufacture if the test shows no evidence of mycobacteria.

§ 73.2023 Potency test.

The potency of each lot of Tuberculin shall be estimated from a comparison of the responses obtained by the intradermal injection into sensitized guinea pigs weighing over 500 gm. of a sample of the lot under test and of the appropriate standard preparation. The U.S. Standard Tuberculin, Old, shall be used in determining the potency of tuberculins made from the concentrated filtrate of the soluble products of the growth of the mycobacteria. The U.S. Standard Tuberculin, Purified Protein Derivative, shall be used in determining the potency of tuberculins made from protein fraction of the soluble products of the growth of the mycobacteria. The test shall be performed as follows:

(a) *Sensitization of test animals.* At least four white guinea pigs shall be sensitized with *M. tuberculosis* or *M. bovis*. The degree of sensitivity shall be such that an intradermal injection of one U.S. unit of the appropriate standard preparation will produce in each test animal an erythematous reaction approximately 100 mm^2 within 18–24 hours.

(b) *Test Procedure.* The hair shall be removed from both sides of the sensitized test animals without producing abrasions of the skin. Dilutions of the standard containing 0.5, 1, 2, and 4 U.S. units in the test dose of 0.1 ml. and four comparable levels of activity of the lot under test shall be injected intradermally into opposite and parallel sites of each animal. Only three dilutions need be used when the initial concentration of the lot

under test does not contain four units in 0.1 ml. Within 18–24 hours following injection, measurements of the greater and lesser diameters of erythema measured to the closest millimeter shall be made at each site. The mean value of the product of the diameters for each dilution shall be calculated. The number of U.S. units in the lot under test shall be estimated from its relationship to the reactivity of the appropriate standard preparation.

(c) *Potency.* The potency of the lot is satisfactory if the test results are within limits, as follows:

(1) *Products for Mantoux testing.* ±20 percent of the labeled U.S. units.

(2) *Liquid products for multiple puncture testing.* ±20 percent of the U.S. units claimed by the manufacturer in the license application.

(3) *Products dried on multiple puncture devices.* ±50 percent of the U.S. units claimed by the manufacturer in the license application.

§ 73.2024 General requirements.

(a) *General safety.* Each lot of Tuberculin shall be tested for safety as prescribed in § 73.720, except that the sample of tuberculin from multiple puncture devices shall be obtained by removing the tuberculin in a manner that will permit the injection of material from at least five devices into each of two guinea pigs and from at least two devices into each of two mice.

(b) *Labeling.* In addition to complying with all other applicable labeling provisions of this part, the package label shall state the following:

(1) For Tuberculin for Mantoux testing, the number of U.S. units (TU) per dose.

(2) For Tuberculin for multiple puncture testing, a statement indicating that the activity per test is comparable to a stated number of U.S. units (TU) administered by the Mantoux method.

(3) The applicable type of Tuberculin placed immediately following and of no less prominence than the proper name, as follows:

(i) "Old," or

(ii) "Purified Protein Derivative" or "PPD."

(c) *Samples; protocols; official release.* For each lot of Tuberculin the following shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda, Md. 20014:

(1) A protocol which consists of a summary of the history of manufacture of each lot including all results of each test for which test results are requested by the Director, Division of Biologics Standards.

(2) Tuberculin distributed on a multiple puncture device, as follows:

(i) A total of no less than 100 devices,

(ii) A total of no less than 20 ml. of bulk tuberculin.

(3) A total of no less than 20 ml. of liquid tuberculin.

(4) Sufficient dried tuberculin in final containers so that upon reconstitution as recommended in labeling it will yield at least 20 ml.

The product shall not be issued by the manufacturer until notification of official release of the lot is received from the Director, Division of Biologics Standards.

§ 73.2025 Equivalent methods.

Modification of any particular method or process or the conditions under which it is conducted as set forth in the additional standards relating to Tuberculin, shall be permitted whenever the manufacturer presents evidence that demonstrates the modification will provide assurances of the safety, purity, and potency of the product that are equal to or greater than the assurances provided by such standards, and the Director, National Institutes of Health, so finds and makes such finding a matter of official record.

Subpart D—Additional Standards for Blood and Blood Products

WHOLE BLOOD (HUMAN)

§ 73.3000 Proper name and definition.

The proper name of this product shall be Whole Blood (Human). Whole Blood (Human) is defined as blood collected from human donors for transfusion to human recipients.

§ 73.3001 Suitability of donor.

(a) *Method of determining.* The suitability of a donor as a source of Whole Blood (Human) shall be determined by a qualified physician or by persons under his supervision and trained in determining suitability. Such determination shall be made on the day of collection from the donor by means of medical history, a test for hemoglobin level, and such physical examination as appears necessary to a physician who shall be present on the premises when examinations are made, except that the suitability of donors may be determined when a physician is not present on the premises, provided the establishment (1) maintains on the premises, and files with the Division of Biologics Standards, a manual of standard procedures and methods, approved by the Director of the Division of Biologics Standards, that shall be followed by employees who determine suitability of donors, and (2) maintains records indicating the name and qualifications of the person immediately in charge of the employees who determine the suitability of donors when a physician is not present on the premises.

(b) *Qualifications of donor; general.* Except as provided in paragraph (f), a person may not serve as a source of Whole Blood (Human) more than once in 8 weeks. In addition, donors shall be in good health, as indicated in part by:

(1) Normal temperature;

(2) Demonstration that systolic and diastolic blood pressures are within normal limits, unless the examining physician is satisfied that an individual with blood pressures outside these limits is an otherwise qualified donor under the provisions of this section;

(3) A blood hemoglobin level which shall be demonstrated to be no less than 12.5 gm. of hemoglobin per 100 ml. of blood;

(4) Freedom from acute respiratory diseases;

(5) Freedom from any infectious skin disease at the site of phlebotomy and from any such disease generalized to such an extent as to create a risk of contamination of the blood;

(6) Freedom from any disease transmissible by blood transfusion, insofar as can be determined by history and examinations indicated above; and

(7) Freedom of the arms and forearms from skin punctures or scars indicative of addiction to self-injected narcotics.

(c) *Additional qualifications of donor; viral hepatitis.* No individual shall be used as a source of Whole Blood (Human) if he has—

(1) A history of viral hepatitis;

(2) A history of close contact within six months of donation with an individual having viral hepatitis;

(3) A history of having received within six months human blood, or any derivative of human blood which the National Institutes of Health has advised the licensed establishment is a possible source of viral hepatitis.

(d) *Therapeutic bleedings.* Blood withdrawn in order to promote the health of a donor otherwise qualified under the provisions of this section, shall not be used as a source of Whole Blood (Human) unless the container label conspicuously indicates the donor's disease that necessitated withdrawal of blood.

(e) *Immunized donors.* Blood withdrawn from donors known to have been immunized to human blood cell antigens shall not be used for Whole Blood (Human) unless the container label conspicuously indicates such information.

(f) *Qualifications; donations within less than 8 weeks.* A person may serve as a source of Whole Blood (Human) more than once in 8 weeks only if at the time of donation the person is examined and certified by a physician to be in good health, as indicated in part in paragraph (b).

§ 73.3002 Collection of the blood.

(a) *Supervision.* Blood shall be drawn from the donor by a qualified physician or under his supervision by assistants trained in the procedure. A physician shall be present on the premises when blood is being collected, except that blood may be collected when a physician is not present on the premises, provided the establishment (1) maintains on the premises, and files with the Division of Biologics Standards, a manual of standard procedures and methods, approved by the Director of the Division of Biologics Standards, that shall be followed by employees who collect blood, and (2) maintains records indicating the name and qualifications of the person immediately in charge of the employees who collect blood when a physician is not present on the premises.

(b) *The donor clinic.* The pertinent requirements of §§ 73.500 and 73.501 shall apply at both the licensed establishment

and at any other place where the bleeding is performed.

(c) *Blood containers.* Blood containers and donor sets shall be pyrogen-free, sterile and identified by lot number. The amount of anticoagulant required for the quantity of blood to be collected shall be in the blood container when it is sterilized. In addition, all container and donor set surfaces that come in contact with blood used in the processing of Heparinized Whole Blood (Human) shall be water repellent.

(d) *The anticoagulant solution.* The anticoagulant solution shall be sterile and pyrogen-free. One of the following formulae shall be used in the indicated volumes:

(1) *Anticoagulant acid citrate dextrose solution (ACD).*

	Solution A	Solution B
Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$).	22.0 gm.	13.2 gm.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	8.0 gm.	4.8 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	24.5 gm.	14.7 gm.
Water for injection (U.S.P.) to make.	1,000 ml.	1,000 ml.
Volume per 100 ml. blood	15 ml.	25 ml.

(2) *Anticoagulant heparin solution.*

Heparin sodium (U.S.P.)	75,000 units.
Sodium chloride injection (U.S.P.) to make.	1,000 ml.
Volume per 100 ml. blood	6 ml.

A buffer to maintain stability shall be added, if necessary.

(3) *Anticoagulant citrate phosphate dextrose solution (CPD).*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$).	26.3 gm.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	3.27 gm.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	25.5 gm.
Monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$).	2.22 gm.
Water for injection (U.S.P.) to make.	1,000 ml.
Volume per 100 ml. blood	14 ml.

(e) *Donor identification.* Each unit of blood shall be so marked or identified by number or other symbol as to relate it to the individual donor whose identity shall be established to the extent necessary for compliance with § 73.3001.

(f) *Prevention of contamination of the blood.* The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The blood shall be collected by aseptic methods in a sterile system which may be closed or may be vented if the vent protects the blood against contamination.

(g) *Pilot samples for laboratory tests.* Pilot samples for laboratory tests shall meet the following standards:

(1) One or more pilot samples shall be provided with each unit of blood when issued or reissued except as provided in § 73.3004(e)(2) and all pilot samples shall be from the donor who is the source of the unit of blood.

(2) All samples for laboratory tests performed by the manufacturer and all pilot samples accompanying a unit of blood shall be collected at the time of filling the final container by the person who collects the unit of blood.

(3) All containers for all samples shall bear the donor's identification before collecting the samples.

(4) All containers for pilot samples accompanying a unit of blood shall be attached to the whole blood container before blood collection, in a tamper-proof manner that will conspicuously indicate removal and re-attachment.

(h) *Phlebotomy for Heparinized Whole Blood (Human).* Heparinized Whole Blood (Human) shall be collected with minimal damage to and minimal manipulation of the donor's tissue, and with a single, uninterrupted, free-flowing venipuncture.

(i) *Storage.* Immediately after collection, the blood shall be placed in storage within a 2° range between 1° and 6° C., unless it must be transported from the donor clinic to the processing laboratory. In the latter case the blood shall be placed in temporary storage having sufficient refrigeration capacity to cool the blood continuously toward a 2° range between 1° and 6° C. until it arrives at the processing laboratory where it shall be stored within a 2° range between 1° and 6° C.

§ 73.3003 Testing the blood.

All laboratory tests shall be made on a pilot sample specimen of blood taken from the donor at the time of collecting the unit of blood, and these tests shall include the following:

(a) *Serological test for syphilis.* Whole Blood (Human) shall be negative to a serological test for syphilis.

(b) *Determination of blood group.* Each container of Whole Blood (Human) shall be classified as to ABO blood group. At least two blood group tests shall be made and the unit shall not be issued until grouping tests by different methods or with different lots of antiserums are in agreement. Only those Anti-A and Anti-B Blood Grouping Serums licensed under, or that otherwise meet the requirements of, the regulations of this part shall be used, and the technique used shall be that for which the serum is specifically designed to be effective.

(c) *Determination of the Rh factors.* Each container of Whole Blood (Human) shall be classified as to Rh type on the basis of tests done on the pilot sample. The label shall indicate the extent of typing and the results of all tests performed. If the test, using Anti-Rh_o (Anti-D) Typing Serum, is positive, the container may be labeled "Rh Positive". If this test is negative, the results shall be confirmed by further testing which may include tests for the Rh_o variant (D^u) and for other Rh-Hr factors. Blood may be labeled "Rh Negative" if negative to tests for the Rh_o (D) and Rh_o variant (D^u) factors. If the test using Anti-Rh_o (Anti-D) Typing Serum is negative, but not tested for the Rh_o variant (D^u), the label must indicate that this test was not done. Only Anti-Rh Typing Serums licensed under, or that otherwise meet the requirements of, the regulations of this part shall be used, and the technique used shall be that for which the serum is specifically designed to be effective.

(d) *Sterility test.* Whole Blood (Human) intended for transfusion shall not be tested for sterility by a method that entails entering the final container before the blood is used for transfusion.

(e) *Inspection.* Whole Blood (Human) shall be inspected visually during storage and immediately prior to issue. If the color or physical appearance is abnormal or there is any indication or suspicion of microbial contamination the unit of Whole Blood (Human) shall not be issued for transfusion.

§ 73.3004 General requirements.

(a) *Manufacturing responsibility.* All manufacturing of Whole Blood (Human), including donor examination, blood collection, laboratory tests, labeling, storage and issue, shall be done under the supervision and control of the same licensed establishment except that the Director, National Institutes of Health may approve arrangements, upon joint request of two or more licensed establishments, which he finds are of such a nature as to assure compliance otherwise with the provisions of this part.

(b) *Periodic check on sterile technique.* Within the 18th to 24th day after collection, at least one container of blood that upon visual examination appears normal, shall be tested each month as a continuing check on technique of blood collection. The test shall be performed with a total sample of no less than 10 ml. of blood and a total volume of fluid thioglycollate or thioglycollate broth medium 10 times the volume of the sample of blood. The test sample shall be inoculated into one or more test vessels in a ratio of blood to medium of 1 to 10 for each vessel, mixed thoroughly, incubated for seven to nine days at a temperature of 30° to 32° C., and examined for evidence of growth of microorganisms every workday throughout the test period. On the third, fourth, or fifth day at least 1 ml. of material from each test vessel shall be subcultured in additional test vessels containing the same culture medium and in such proportion as will permit significant visual inspection, mixed thoroughly, incubated for seven to nine days at a temperature of 30° to 32° C. and examined for evidence of growth of microorganisms every workday throughout the test period. If growth is observed in any test vessel, the test shall be repeated to rule out faulty test procedure, using another sample of blood from either, (1) the container from which the initial test sample was taken, (2) the residual cells or plasma from that blood, or (3) two different containers of blood, each 18 to 24 days old and each tested separately. The formula for fluid thioglycollate medium shall be as prescribed in § 73.730(e)(1) and the formula for thioglycollate broth medium shall be as prescribed in § 73.730(f)(5). Media and design of container shall meet the requirements prescribed in § 73.730(e)(2)(i). In lieu of performing one test using an incubation temperature of 30° to 32° C., two tests

may be performed, each in all respects as prescribed in this paragraph, one at an incubation temperature of 18° to 22° C. and one at an incubation temperature of 35° to 37° C. A different test may be performed provided that prior to the performance of such a test a manufacturer submits data which the Director, National Institutes of Health finds adequate to establish that the different test is equal or superior to the test herein prescribed as a check on sterile technique and makes the finding a matter of official record.

(c) *Final container.* The original blood container shall be the final container and shall not be entered prior to issue for any purpose except for blood collection. Such container shall be uncolored and transparent to permit visual inspection of the contents and any closure shall be such as will maintain an hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, or potency of the blood.

(d) [Reserved]

(e) *Reissue of blood.* Blood that has been removed from storage controlled by a licensed establishment shall not be reissued by a licensed establishment unless the following conditions are observed:

(1) The container has a tamper-proof seal when originally issued and this seal remains unbroken;

(2) An original pilot sample is properly attached and has not been removed, except that blood lacking a pilot sample may be reissued in an emergency provided it is accompanied by instructions for sampling and for use within six hours after entering the container for sampling;

(3) The blood has been maintained continuously at 1° to 10° C.;

(4) The blood is held for observation until a significant inspection consistent with the requirements of § 73.3003(e) can be made.

(f) *Issue prior to determination of test results.* Notwithstanding the provisions of § 73.700, blood may be issued by the licensee on the request of a physician, hospital or other medical facility, before results of all tests prescribed in § 73.3003 have been determined where such issue is essential to allow time for transportation to assure arrival of the blood by the time when needed for transfusion of such blood provided (1) the blood is shipped directly to such physician or medical facility, (2) the records of the licensee contain a full explanation of the need for such issue, (3) the label on each container of such blood bears the information required by § 73.3005(e), (4) the label does not bear results of tests other than those made on pilot samples of the blood to be shipped, taken at the time of its collection, and (5) the label does not bear the name or any other identification of the intended recipient.

§ 73.3005 Labeling.

In addition to all other applicable labeling requirements, the following, except as prescribed in paragraph (e) of this section, shall appear on the label of each container:

(a) *Anticoagulant*—(1) *Name.* The name of the anticoagulant immediately preceding and of no less prominence than the proper name, expressed as follows:

(i) either "ACD", or "acid citrate dextrose solution",

(ii) either "Heparinized" or "heparin solution",

(iii) either "CPD" or "citrate phosphate dextrose solution".

(2) *Quantity.* The quantity and kind of anticoagulant used and the volume of blood corresponding with the formula prescribed under § 73.3002(d).

(b) *Serological test.* The serological test for syphilis used and the result.

(c) *Blood group and type.* Designation of blood group and Rh factors:

(1) The blood group and Rh factors shall be designated conspicuously.

(2) If a color scheme for differentiating the ABO blood groups is used, the color used to designate each blood group on the container shall be:

Blood Group A: Yellow.
Blood Group B: Pink.
Blood Group O: Blue.
Blood Group AB: White.

(d) *Additional information for labels of Group O Bloods.* Each Group O blood shall be labeled with a statement indicating whether or not isoagglutinin titers or other tests to exclude so-called "dangerous" Group O bloods were performed, and indicating the classification based on such tests.

(e) *Issue prior to determination of test results.* The label on each container of blood that is issued pursuant to the provisions of § 73.3004(f) shall bear the following information and instructions in lieu of the information specified in paragraphs (b), (c), and (d) of this section.

EMERGENCY SHIPMENT FOR USE ONLY BY

(Name of physician, hospital or other medical facility.)

CAUTION

BEFORE TRANSFUSION

1. Do not use until test results received from (name of licensee).
2. Perform crossmatch.

RED BLOOD CELLS (HUMAN)

§ 73.3020 Proper name and definition.

The proper name of this product shall be Red Blood Cells (Human). The product is defined as red blood cells remaining after separating plasma from human blood.

§ 73.3021 Suitability of donor.

The source blood for Red Blood Cells (Human) shall be obtained from a donor who meets the criteria for donor suitability prescribed in § 73.3001.

§ 73.3022 Collection of the blood.

(a) The source blood shall be collected as prescribed in § 73.3002, except that paragraphs (d)(2), and (g), and (h) shall not apply.

(b) Source blood may also be derived from Whole Blood (Human) manufactured in accordance with applicable provisions of this part.

§ 73.3023 Laboratory tests.

A sample of source blood shall be taken from the donor at the time of collection and it shall be used for a serological test for syphilis, for tests to determine blood group and Rh factors, as prescribed in § 73.3003 (a), (b), and (c).

§ 73.3024 Pilot samples.

Pilot samples collected in integral tubing or in separate pilot tubes shall meet the following standards:

(a) One or more pilot samples of either the original blood or of the Red Blood Cells (Human) being processed shall be provided with each unit of Red Blood Cells (Human) when issued or reissued.

(b) Before they are filled, all pilot sample tubes shall be marked or identified so as to relate them to the donor of that unit of red cells.

(c) Before the final container is filled or at the time the final product is prepared, the pilot sample tubes to accompany a unit of cells shall be attached securely to the final container in a tamper proof manner that will conspicuously indicate removal and reattachment.

(d) All pilot sample tubes accompanying a unit of Red Blood Cells (Human) shall be filled at the time the blood is collected or at the time the final product is prepared, in each instance by the person who performs the collection or preparation.

§ 73.3025 Processing.

(a) *Separation.* Red Blood Cells (Human) may be prepared either by centrifugation done in a manner that will not tend to increase the temperature of the blood, and no later than 6 days after the date of blood collection or by normal, undisturbed sedimentation no later than 21 days after the date of blood collection. A portion of the plasma sufficient to assure optimal cell preservation shall be left with the red cells except when a cryophylactic substance is added for prolonged storage.

(b) *Sterile system.* All surfaces that come in contact with the red cells shall be sterile and pyrogen-free. If an open system is used, that is, where the transfer container is not integrally attached to the blood container, and the blood container is entered after blood collection, the plasma shall be separated from the red blood cells with positive pressure maintained on the original container until completely sealed. If the method of separation involves a vented system, that is, when an airway must be inserted in the container for withdrawal of the plasma, the airway and vent shall be sterile and constructed so as to exclude microorganisms and maintain a sterile system.

(c) *Final containers.* Final containers used for Red Blood Cells (Human) shall be the original blood containers unless the method of processing requires a different container. The final container shall meet the requirements for blood containers prescribed in § 73.3004(c). At the time of filling, if a different container

is used, it shall be marked or identified by number or other symbol so as to relate it to the doner of that unit of red cells.

§ 73.3026 General requirements.

(a) *Check on sterile technique.* If Red Blood Cells (Human) are prepared in a vented or open system, a check on sterile technique shall be made each month by performing a test 20–28 hours after the preparation of at least one container of Red Blood Cells (Human), by the method prescribed in § 73.3004(b).

(b) *Storage.* Immediately after processing, the Red Blood Cells (Human) shall be placed in storage and maintained within a 2° range between 1° and 6° C.

(c) *Inspection.* The product shall be inspected immediately after separation of the plasma, periodically during storage, and at the time of issue. The product shall not be issued if there is any abnormality in color or physical appearance or if there is any indication of microbial contamination.

§ 73.3027 Modifications for specific products.

Red Blood Cells (Human), Frozen: A cryophylactic substance may be added to the Red Blood Cells (Human) for extended manufacturer's storage at −65° C. or colder, provided the manufacturer submits data considered by the Director, Division of Biologics Standards, as adequately demonstrating through in vivo cell survival and other appropriate tests that the addition of the substance, the materials used and the processing methods result in a final product that meets the required standards of safety, purity, and potency for Red Blood Cells (Human), and that the frozen product will maintain those properties for the prescribed dating period. Section 73.3026 (b) and (c) do not apply while a cryophylactic substance is present.

§ 73.3028 Labeling.

In addition to the items required by other applicable labeling provisions of this part, labels for Red Blood Cells (Human) shall bear the following:

(a) The information required by § 73.3005 (a)(2), (b), and (c) for Whole Blood (Human), except the proper name.

(b) Immediately following or immediately below and in no less prominence than the proper name, appropriate words describing each approved variation applicable to the product in the final container; for example, Red Blood Cells (Human), Frozen, and Red Blood Cells (Human), Deglycerolized.

(c) Instructions to use a filter in the administration equipment.

(d) Where source blood has been derived from Whole Blood (Human), such fact and the name, address, and license number of the establishment.

IMMUNE SERUM GLOBULIN (HUMAN)

§ 73.3500 The product.

(a) *Proper name and definition.* The proper name of this product shall be Immune Serum Globulin (Human). The product is defined as a sterile solution containing antibodies derived from human blood.

(b) *Source material.* The source of Immune Serum Globulin (Human) shall be blood, plasma or serum from human donors determined at the time of donation to have been free of causative agents of diseases that are not destroyed or removed by the processing methods, as determined by the donor's history and from such physical examination and clinical tests as appear necessary for each donor at the time the blood was obtained. The source blood, plasma or serum shall not contain a preservative and shall be stored in a manner that will prevent contamination by microorganisms, pyrogens or other impurities.

(c) *Additives in source material.* Source blood, plasma or serum shall contain no additives other than citrate or acid citrate dextrose anticoagulant solution, unless it is shown that the processing method yields a product free of the additive to such an extent that the safety, purity and potency of the product will not be affected adversely.

§ 73.3501 Manufacture of Immune Serum Globulin (Human).

(a) *Processing method.* The processing method shall be one that has been shown: (1) To be capable of concentrating tenfold from source material at least two different antibodies; (2) not to affect the integrity of the globulins; (3) to consistently yield a product which is safe for subcutaneous and intramuscular injection and (4) not to transmit viral hepatitis.

(b) *Microbial contamination.* Low temperatures or aseptic techniques shall be used to minimize contamination by microoganisms. Preservatives to inhibit growth of microoganisms shall not be used during processing.

(c) *Bulk storage.* The globulin fraction may be stored in bulk prior to further processing provided it is stored in clearly identified hermetically closed vessels. Globulin as either a liquid concentrate or a solid and containing alcohol or more than 5 percent moisture shall be stored at a temperature of −10° C. or lower. Globulin as a solid free from alcohol and containing less than 5 percent moisture, shall be stored at a temperature of 0° C. or lower.

(d) *Determination of the lot.* Each lot of Immune Serum Globulin (Human) shall represent a pooling of approximately equal amounts of material from not less than 1,000 donors.

(e) *Sterilization and heating.* The final product shall be sterilized promptly after solution. At no time during processing shall the product be exposed to temperatures above 45° C. and after sterilization the product shall not be exposed to temperatures above 30° to 32° C. for more than 72 hours.

§ 73.3502 The final product.

(a) *Final solution.* The final product shall be a 16.5±1.5 percent solution of globulin containing 0.3 molar glycine and a preservative.

(b) *Protein composition.* At least 90 percent of the globulin shall have an electrophoretic mobility not faster than -2.8×10^{-5} centimeters^2 per volt per second, when measured at a 1 percent protein concentration in sodium diethylbarbiturate buffer at pH 8.6 and 0.1 ionic strength.

§ 73.3503 Potency.

(a) *Antibody levels and tests.* Each lot of final product shall contain at least the minimum levels of antibodies for diphtheria, measles, and for at least one type of poliomyelitis. In the event the final bulk solution is stored at a temperature above 5° C. the antibody level tests shall be performed after such storage with a sample of the stored material.

(b) *Minimum levels.* The minimum antibody levels are as follows:

(1) No less than 2 units of diphtheria antitoxin per ml.

(2) A measles neutralizing antibody level of no less than 0.25 times the level of the reference measles serum, except that when recommended for use with Measles Virus Vaccine, Live, Attenuated, the measles antibody level shall be as prescribed in § 73.3523.

(3) A poliomyelitis neutralizing antibody level of no less than 1.0 for Type 1, 1.0 for Type 2, and 2.5 for Type 3, times the antibody level of the reference poliomyelitis immune globulin.

(c) *Reference materials.* The following reference materials shall be obtained from the Division of Biologics Standards:

(1) NIH reference measles serum for correlation of measles antibody titers.

(2) NIH reference poliomyelitis immune globulin for correlation of poliomyelitis antibody titers, Types 1, 2, and 3.

§ 73.3504 General requirements.

(a) *Heat stability test.* Approximately 2 ml. of completely processed material of each lot shall not show any visible sign of gelation after heating in a 12 x 75 mm. stoppered glass tube at 57° C. for 4 hours.

(b) *Hydrogen ion concentration.* The pH of final container material shall be 6.8±0.4 when measured in a solution diluted to 1 percent protein with 0.15 molar sodium chloride.

(c) *Turbidity.* The product shall be free of turbidity as determined by visual inspection of final containers.

(d) *Date of manufacture.* The date of manufacture is the date of initiating the last valid measles or poliomyelitis antibody test (§ 73.3503(b) (2) and (3)) whichever date is earlier.

(e) *Labeling.* In addition to complying with all applicable labeling required in this part, labeling shall indicate that:

(1) There is no prescribed potency for viral hepatitis antibodies.

(2) The product is not recommended for intravenous administration.

(3) The lot is or is not suitable for use with Measles Virus Vaccine, Live, Attenuated.

(4) The lot is or is not recommended for poliomyelitis.

(f) *Samples and protocols.* For each lot of Immune Serum Globulin (Human) the following material shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda, Md. 20014:

(1) A 50 ml. sample of the final product.

(2) All protocols relating to the history of each lot and all results of all tests prescribed in these additional standards.

MEASLES IMMUNE GLOBULIN (HUMAN)

§ 73.3520 The product.

(a) *Proper name and definition.* The proper name of the product shall be Measles Immune Globulin (Human). It shall consist of a sterile solution of 10 to 18 percent globulin derived from human blood, having a measles antibody level of 0.5 times the level of the NIH measles reference serum. Measles Immune Globulin shall be made from a sterile 16.5±1.5 percent solution of human globulin.

(b) *Source material.* The source of Measles Immune Globulin (Human) shall be blood, plasma or serum from human donors determined at the time of donation to have been free of causative agents of diseases that are not destroyed or removed by the processing method, as determined by the donor's history and from such physical examination and clinical tests as appear necessary for each donor at the time the blood was obtained. The source blood, plasma or serum shall not contain a preservative and shall be stored in a manner that will prevent contamination by microorganisms, pyrogens or other impurities.

(c) *Additives in source material.* Source blood, plasma or serum shall contain no additives other than citrate or acid citrate dextrose anticoagulant solution, unless it is shown that the processing method yields a product free of the additive to such an extent that the safety, purity and potency of the product will not be affected adversely.

§ 73.3521 Manufacture of Measles Immune Globulin (Human).

(a) *Processing method.* The globulin shall be prepared by a processing method that (1) has been shown to be capable of concentrating tenfold from source material at least two different antibodies, (2) does not affect the integrity of the globulins and is capable of consistently yielding a product which is safe for subcutaneous and intramuscular injection and (3) will not transmit viral hepatitis.

(b) *Reference materials.* The following reference material shall be obtained from the Division of Biologics Standards: NIH reference measles serum for correlation of measles antibody titers with globulin products.

(c) *Microbial contamination.* Low temperatures or aseptic techniques shall be used to minimize contamination by microorganisms. Preservatives to inhibit growth of microorganisms shall not be used during processing.

(d) *Bulk storage.* The globulin fraction may be stored in bulk prior to further processing provided it is stored in well-marked hermetically closed vessels. Purified globulin as either a liquid concentrate or a solid and containing alcohol or more than 5 percent moisture shall be stored at a temperature not to exceed −10° C. Purified globulin as a solid free from alcohol and containing less than 5 percent moisture, shall be stored at temperatures not to exceed 0° C.

(e) *Determination of the lot.* Each lot of Measles Immune Globulin (Human) shall represent a pooling of material from not less than 1,000 donors.

(f) *Sterilization and dilution.* The product shall be prepared initially as a 16.5 percent solution and this preparation shall be sterilized promptly after solution. After sterilization the product shall not be exposed to temperatures above 45° C. for more than a total of 72 hours. Dilution of this sterile globulin solution shall be made only to adjust the required measles antibody level.

§ 73.3522 The final product.

(a) *Final solution.* The final product shall be a 10 to 18 percent solution of globulin containing 0.3 molar glycine and a preservative.

(b) *Protein composition.* No less than 90 percent of the globulin shall have an electrophoretic mobility not faster than -2.8×10^{-5} centimeters^2 per volt per second, when measured at a 1 percent protein concentration in sodium diethylbarbiturate at pH 8.6 and 0.1 ionic strength.

§ 73.3523 Potency.

Antibody levels and tests. Each lot of final product shall contain no less than the minimum levels of antibodies for diphtheria and measles as follows:

(a) The product shall contain no less than 2 units of diphtheria antitoxin per ml, adjusted for dilution from the 16.5 percent solution.

(b) Each lot of final product shall contain a measles antibody level of 0.5 times the level of the NIH reference measles serum. The measles antibody potency shall be determined by simultaneous determinations of the neutralizing antibody titers of the globulin on tests and of a reference preparation against 100 $TCID_{50}$ (50–500 $TCID_{50}$ when based upon a single test) of measles virus in a tissue culture system. The potency test shall also include a determination of virus titer and controls for globulin toxicity and cell culture viability. Twofold serial dilutions of the globulin under test and of the reference preparation shall be employed in this determination. In applying these requirements a plus or minus variation of one twofold dilution is acceptable.

§ 73.3524 General requirements.

(a) *Heat stability test.* Approximately 2 ml of final container material of each lot shall not show any visible sign of gelation after heating in a 12 x 75 mm. stoppered glass tube at 57° C. for four hours.

(b) *Hydrogen ion concentration.* The pH of final container material shall be 6.8±0.4 when measured in a solution diluted to 1 percent protein with 0.15 molar sodium chloride.

(c) *Turbidity.* The product shall be free of turbidity as determined by visual inspection of final containers.

(d) *Date of manufacture.* The date of manufacture is the date of initiating the last valid measles antibody test as required in § 73.3523(b).

(e) [Reserved]

(f) [Reserved]

(g) *Samples and protocols.* For each lot of globulin, the following materials shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda, Maryland 20014.

(1) 30 ml of final product.

(2) All protocols relating to the history of the manufacture of each lot and all results of all tests prescribed in these additional standards.

Subpart E—Additional Standards for Bacterial Products

PERTUSSIS VACCINE

§ 73.4000 Proper name and definition.

The proper name of this product shall be "Pertussis Vaccine", which shall be an aqueous preparation of either killed whole *Bordetella pertussis* bacteria or a fraction of *Bordetella pertussis* bacteria. The vaccine may be precipitated or adsorbed and may be combined with other antigens.

§ 73.4001 U.S. Standard preparations.

(a) The U.S. Standard Pertussis Vaccine shall be used for determining the potency of Pertussis Vaccine.

(b) The U.S. Opacity Standard shall be used in estimating the bacterial content of the vaccine and of the challenge culture.

§ 73.4002 Manufacture.

(a) *Propagation of bacteria.* Human blood shall not be used in culture medium for propagating bacteria either for seed or for vaccine. The culture medium for propagating bacteria for vaccine shall not contain ingredients known to be capable of producing allergenic effects in human subjects, except blood or blood products from lower animals other than the horse. When blood or a blood product is used, it shall be removed by washing the harvested bacteria. The bacterial concentrate shall be free of extraneous bacteria, fungi, and yeasts, as demonstrated by microscopic examination and cultural methods.

(b) *Bacterial content.* (1) The opacity of the bacterial concentrate shall be determined in terms of the U.S. Opacity Standard not later than 2 weeks after the harvest of the bacteria and before any treatment capable of altering the opacity of the bacterial concentrate.

(2) The total immunizing dose of a vaccine prepared with whole bacteria shall contain (i) in the case of nonadsorbed vaccine no more bacteria than the equivalent of 60 opacity units and (ii) in the case of adsorbed vaccine no more than the equivalent of 48 opacity units.

(c) *Detoxification.* After removing a sample for purity testing, the bacteria

shall be killed and detoxified either (1) by heating, (2) by addition of a chemical agent and appropriate agin:, or (3) by any combination of the stated procedures. The procedure used shall be one that has been shown to have no adverse effect on required safety, purity, and potency.

(d) *Preservative.* The vaccine shall contain a preservative.

§ 73.4003 Mouse toxicity test.

The final vaccine shall be demonstrated to be free from toxicity by the following test:

A group of no less than 10 mice, each mouse weighing 14 to 16 grams, shall have free access to food and water for no less than 2 hours before injection. The group weight of the mice shall be determined immediately prior to injection. Each mouse shall be injected intraperitoneally with a test dose of one-half of the largest recommended single human dose of the final vaccine in a volume of no less than 0.5 ml. nor more than 0.75 ml. The group weight of the mice shall be determined at the end of 72 hours and at the end of 7 days after injection. At the end of 72 hours the average weight per mouse may be no less than the average weight per mouse immediately preceding the injection; at the end of 7 days the average weight gain per mouse may be no less than 3.0 grams; and at the end of 7 days there may be vaccine-related deaths of no more than 5 percent of the total number of mice in all the toxicity tests performed.

§ 73.4004 Potency test.

The number of protective units of the total human immunizing dose shall be estimated for each lot of vaccine from the results of simultaneous intracerebral mouse protection tests of the vaccine under test and the U.S. Standard Pertussis Vaccine. The potency test shall be performed as follows:

(a) *Mice.* Healthy mice shall be used, all from a single strain and of the same sex, or an equal number of each sex in each group, with individual weight varying no more than 4 grams in a single test. In no event shall any of the mice weigh less than 10 grams or more than 20 grams. A system of randomization shall be used to distribute the mice into the groups, with respect to shelf position and to determine the order of challenge. There shall be at least 3 groups consisting of no less than 16 mice each, for each vaccine. In addition, there shall be at least 4 groups consisting of no less than 10 mice each, for control purposes: one group for the challenge dose and 3 groups for titrating the virulence of the challenge dose.

(b) *Vaccination.* (1) Five-fold serial dilutions of the vaccine to be tested and of the standard vaccine shall be made in 0.85 percent sodium chloride solution. The dilutions of the vaccine under test shall have the same protective unitage, based on an estimate of 12 units per total human immunizing dose, as the unitage of the corresponding dilution of the standard vaccine. Each mouse in each group for vaccination shall be injected intraperitoneally with 0.5 ml. of the appropriate dilution.

(2) The interval between vaccination and challenge shall be 14 to 17 days. At least 87.5 percent of the mice in each group shall survive the period between vaccination and challenge and each mouse challenged shall appear healthy.

(c) *The challenge.* (1) The challenge culture of *Bordetella pertussis* for each test shall be taken from a batch of cultures which have been maintained by a method, such as freeze-drying, that retains constancy of virulence.

(2) The challenge and virulence titration doses shall be prepared as follows: The bacteria shall be harvested from a 20 to 24 hour culture grown on Bordet-Gengou medium seeded from a rapidly growing culture less than 48 hours old and uniformly suspended in a solution containing 1.0 percent casein peptone and about 0.6 percent sodium chloride at pH 7.1±0.1. The suspension, freed from agar particles and clumps of bacteria, and adjusted to an opacity of 10 units, shall be diluted in the solution used for suspending the bacteria, to provide in a volume of 0.03 ml. (i) a challenge dose of 0.0001 opacity units (1: 3000) and (ii) virulence titration doses of $\frac{1}{50}$, $\frac{1}{250}$ and $\frac{1}{1250}$ respectively of the challenge dose.

(3) Each vaccinated mouse shall be injected intracerebrally with the challenge dose. The four groups of control mice shall be injected intracerebrally with the challenge dose and its three dilutions, respectively. The challenge-dose control mice shall be injected last. The interval between the removal of the bacteria from the culture medium and the injection of the last mouse shall not exceed 2½ hours.

(d) *Recording the results.* The mice shall be observed for 14 days. Mice dying within 72 hours after challenge shall be excluded from the test. Records shall be maintained of the number of mice that die after 72 hours and of the number of mice showing both paralysis and enlargement of the head at the end of 14 days. All mice that show both paralysis and enlargement of the head shall be considered as deaths for the purposes of determining the ED_{50}.

(e) *Validity of the test.* The test shall be valid provided (1) the ED_{50} of the vaccine under test and the standard vaccine is between the largest and smallest vaccinating doses; (2) the limits of one standard deviation of each ED_{50} fall within the range of 64 percent to 156 percent; (3) the protective response is graded in relation to the vaccinating doses; (4) the dose-response curves of the vaccine under test and the standard vaccine are parallel; (5) the challenge dose contains approximately 200 LD_{50}; (6) the LD_{50} contains no more than 300 colony forming units; and (7) the $\frac{1}{1250}$ dilution of the challenge dose contains no less than 10 and no more than 50 colony forming units.

(f) *Estimate of the potency.* The ED_{50} of each vaccine shall be calculated by a method that provides an estimate of the standard deviation. The protective unit value per total human immunizing dose of the vaccine under test shall be calculated in terms of the unit value of the standard vaccine.

(g) *Potency requirements.* The vaccine shall have a potency of 12 units per total human immunizing dose based upon either a single test estimate of no less than 8 units or a two-, three- or four-test geometric mean estimate of no less than 9.6, 10.8, or 12 units, respectively, except that for the vaccine in a multiple antigen product containing Poliomyelitis Vaccine, the estimate shall be no less than 14 units. In no event shall the estimate be more than 36 units.

(h) *Test design variation.* Variations in the design of the potency test may be permitted providing the results are demonstrated to be of equal or greater precision.

§ 73.4005 General requirements.

(a) *Safety.* The safety test prescribed in § 73.720 shall be made on final container material except that the test shall consist of the intraperitoneal injection of no less than one-half of the largest individual human dose recommended into each of at least two mice weighing approximately 20 grams each, and either the intraperitoneal injection of no less than 3 times the largest individual human dose recommended or the subcutaneous injection of 5.0 ml., into each of at least two guinea pigs weighing approximately 350 grams each. The last sentence of § 73.720 does not apply.

(b) *Dose.* These additional standards are based on a single injection of 0.5 ml., 1.0 ml., or 1.5 ml., and a total human immunizing dose of three single injections of a nonadsorbed vaccine, and two or three single injections of an adsorbed vaccine.

(c) *Product characteristics.* Recommendations shall be made through appropriate labeling that the product after issue should not be frozen and should be well shaken immediately prior to use.

(d) *Labeling.* In addition to the items required by other applicable labeling provisions of this part, the package label shall give the following information:

1. For a vaccine containing a precipitant or an adsorbent, the word "Adsorbed" shall follow the proper name in the same style of type and prominence as the proper name.
2. The total immunizing dose contains 12 units of pertussis vaccine.

(e) *Multiple antigen products.* The Pertussis Vaccine component of multiple antigen products shall be manufactured pursuant to these additional standards, except that the mouse toxicity test (§ 73.4003) and the potency test (§ 73.4004) shall be performed on the multiple antigen product.

(f) *Adsorbed vaccines.* Only aluminum compound reagents shall be introduced into the product to cause precipitation or adsorption of either Pertussis Vaccine or other antigens incorporated with Pertussis Vaccine.

(g) *Freezing prohibition.* Pertussis Vaccine and multiple antigen products of which Pertussis Vaccine is a component shall not be frozen at any time during storage.

(h) *Samples and protocols.* For each lot of vaccine, the following material

shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda, Md. 20014:

(1) A sample of no less than 20 milliliters of the final product for pertussis vaccine testing.

(2) Protocols showing summaries of the manufacturing processes and the results of all mouse toxicity (§ 73.4003) and potency (§ 73.4004) tests performed.

§ 73.4006 Equivalent methods.

Modification of any particular manufacturing method or process or the conditions under which it is conducted as set forth in the additional standards relating to Pertussis Vaccine shall be permitted whenever the manufacturer presents evidence that demonstrates the modification will provide assurances of the safety, purity, and potency of the vaccine that are equal to or greater than the assurances provided by such standards, and the Director, National Institutes of Health so finds and makes such finding a matter of official record.

TYPHOID VACCINE

§ 73.4020 Proper name and definition.

The proper name of this product shall be Typhoid Vaccine which shall be an aqueous or dried preparation of killed *Salmonella typhosa* bacteria.

§ 73.4021 U.S. Standard preparations.

(a) The U.S. Standard Typhoid Vaccine shall be used for determining the potency of Typhoid Vaccine.

(b) The U.S. Opacity Standard shall be used to adjust the opacity of the suspension from which the challenge culture is prepared.

§ 73.4022 Production.

(a) *Strain of bacteria.* Strain Ty 2 of *Salmonella typhosa* shall be used in the manufacture of Typhoid Vaccine.

(b) *Propagation of bacteria.* The culture medium for propagation of *S. typhosa* shall not contain ingredients known to be capable of producing allergenic effects in human subjects. The harvested bacteria shall be free of extraneous bacteria, fungi and yeasts, as demonstrated by microscopic examination and cultural methods.

(c) *Bacterial content.* (1) The number of bacteria in the concentrate of harvested bacteria shall be estimated not later than 2 weeks after harvest and before any treatment capable of altering the accuracy of the estimate.

(2) The number of *S. typhosa* bacteria in the vaccine shall not exceed 10^9 per ml.

(d) *Nitrogen content.* The total nitrogen content of the vaccine shall not exceed 0.035 mg./ml. for nonextracted bacteria preparations and shall not exceed 0.023 mg./ml. for acetone-extracted bacteria preparations.

(e) *Preservative.* Aqueous vaccine and the solution for reconstitution supplied with dried vaccine shall contain a preservative. Dried vaccine shall not contain a preservative.

§ 73.4023 Potency test.

The number of potency units per milliliter shall be estimated for each lot of vaccine from the results of simultaneous mouse protection tests of the vaccine under test and of the U.S. Standard Typhoid Vaccine. The test shall be performed as follows:

(a) *Mice.* Healthy mice shall be used, all from a single strain and of the same sex, or an equal number of each sex in each group, with individual weights between 13 and 16 grams. A system of randomization shall be used to distribute the mice into the groups, with respect to shelf position and to determine the order of challenge. There shall be at least three groups consisting of no less than 16 mice each, for each vaccine. In addition, there shall be at least four groups consisting of no less than 10 mice each, for control purposes; one group for the challenge dose and three groups for titrating the virulence of the challenge dose.

(b) *Inoculation of vaccine.* (1) Serial dilutions, no greater than 5-fold, of the vaccine to be tested and of the standard vaccine shall be made in saline (0.85 percent sodium chloride solution). The mid-dilution of each vaccine shall contain that amount of vaccine which will afford protection to approximately 50 percent of the mice. Each mouse in each group for inoculation shall be injected intraperitoneally with 0.5 ml. of the appropriate dilution.

(2) The interval between inoculation of the vaccine and challenge shall be no less than 7 days nor more than 14 days. At least 87.5 percent of the mice in each group shall survive the period between vaccine inoculation and challenge and each mouse challenged shall appear healthy.

(c) *The challenge.* (1) The challenge culture of Strain Ty 2 of *S. typhosa* for each test shall be taken from a batch of cultures maintained by a method, such as freeze-drying, that retains constancy of virulence.

(2) The challenge and virulence titration doses shall be prepared as follows: The bacteria shall be harvested from a 5- to 6-hour culture grown at 36°±1° C. on a nutrient agar medium which shall have been seeded from a 16- to 20-hour culture grown at 36°±1° C. on a nutrient agar medium, and the harvested bacteria then shall be uniformly suspended in saline. The suspension, freed from agar particles and clumps of bacteria and adjusted to an opacity of 10 units, shall be diluted in saline by 10-fold increments. The suspensions for the challenge and virulence titration doses shall be put into a sterile gastric mucin preparation. The challenge suspension shall be prepared from whichever bacterial dilution provides about 1,000 colony forming units for an 0.5 ml. challenge dose. The virulence titration suspensions shall be 10^1, 10^2, and 10^3 dilutions respectively of the challenge suspension.

(3) Each mouse inoculated with vaccine shall be injected intraperitoneally with an 0.5 ml. dose of the challenge suspension. Each mouse in the four groups of control mice shall be injected intraperitoneally with an 0.5 ml. dose of the challenge suspension and its three dilutions, respectively. The challenge dose control mice shall be injected last. The interval between removal of the bacteria from the culture medium and the injection of the last mouse shall not exceed 2½ hours.

(d) *Recording the results.* The mice shall be observed daily for 3 days. A record shall be maintained of the number of mice that die. A record of the number of mice that survive shall be made at the end of the observation period.

(e) *Validity of the test.* The test is valid provided: (1) the ED_{50} of the vaccine under test and the Standard Vaccine is between the largest and smallest doses inoculated into the mice; (2) the limits of one standard deviation of the ED_{50} of each vaccine fall within the range of 61 percent to 163 percent; (3) a graded protective response is obtained in relation to the vaccine dilutions; (4) the dose response curves of the vaccine under test and the standard vaccine are parallel; (5) the challenge dose contains approximately 1,000 colony forming units; and (6) the LD_{50} of the challenge dose contains no more than 10 colony forming units.

(f) *Repeat tests.* If the test does not meet the criteria prescribed in paragraph (e) of this section, repeat tests may be performed, and the combined results of all tests shall meet the paragraph (e) criteria, except that the limits of one standard deviation of the ED_{50} shall be reduced in proportion to the total number of mice in a test group. Tests established as invalid pursuant to section 73.700 may be disregarded.

(g) *Estimate of the potency.* The ED_{50} of each vaccine shall be calculated by a method that provides an estimate of the standard deviation. The protective unit value per milliliter of the vaccine under test shall be calculated in terms of the unit value of the standard vaccine.

(h) *Potency requirements.* The vaccine shall have a potency of 8 units per milliliter. Variations in potency unit estimates are acceptable provided the estimate is not less than 5.0 units per milliliter.

§ 73.4024 General requirements.

(a) *Dose.* These standards are based on a human adult dose of 0.5 ml. for a single injection and a total immunizing dose of two injections of 0.5 ml. given at appropriate intervals.

(b) *Labeling.* In addition to the items required by other applicable labeling provisions of this part, the package label shall state that the vaccine contains 8 units per milliliter.

(c) *Samples; protocols; official release.* For each lot of vaccine, the following material shall be submitted to the Director, Division of Biologics Standards, National Institutes of Health, Bethesda, Md. 20014:

(1) A sample of no less than 40 ml. of the product distributed in no less than four containers.

(2) A protocol which consists of a summary of the history of manufacture of each lot including all results of each test for which test results are requested by the Director, Division of Biologics Standards.

The product shall not be issued by the manufacturer until notification of official release is received from the Director, Division of Biologics Standards, for each filling lot of dried vaccine and for each bulk lot of aqueous vaccine.

§ 73.4025 Equivalent methods.

Modification of any particular manufacturing method or process or the conditions under which it is conducted as set forth in the additional standards relating to Typhoid Vaccine, shall be permitted whenever the manufacturer presents evidence that demonstrates the modification will provide assurances of the safety, purity, and potency of the vaccine that are equal to or greater than the assurances provided by such standards, and the Director, National Institutes of Health, so finds and makes such finding a matter of official record.

Subpart F—[Reserved]

Subpart G—[Reserved]

Subpart H—[Reserved]

Subpart I—[Reserved]

Subpart J—Additional Standards For Miscellaneous Products

ALLERGENIC PRODUCTS

§ 73.9000 The product.

(a) *Definition.* Allergenic Products are products that are administered to man for the diagnosis, prevention or treatment of allergies.

(b) *Criteria for source material.* Only specifically identified allergenic source materials which contain no more than 1 percent of detectable foreign materials, shall be used in the manufacture of an Allergenic Product. Source materials such as feathers, hairs, and danders shall be free from blood and serum.

§ 73.9001 Manufacture of Allergenic Products.

(a) *Extraneous allergenic substances.* All manufacturing steps shall be performed so as to insure that the product will contain only the allergenic and other substances intended to be included in the final product.

(b) *Cultures derived from microorganisms.* Culture media into which organisms are inoculated for the manufacture of Allergenic Products shall contain no allergenic substances other than those necessary as a growth requirement. Neither horse protein nor any allergenic derivative of horse protein shall be used in culture media.

(c) *Liquid products for oral administration.* Liquid products intended for oral administration that are filled in multiple dose final containers shall contain a preservative in a concentration adequate to inhibit microbial growth.

(d) *Residual pyridine.* Products for which pyridine is used in manufacturing shall have no more residual pyridine in the final product than 25 micrograms per milliliter.

§ 73.9002 Tests.

(a) *Identity.* When a specific identity test meeting the provisions of § 73.760 cannot be performed, the manufacture of each lot shall be separated from the manufacture of other products in a manner that will preclude adulteration, and records made in the course of manufacture shall be in sufficient detail to verify the identity of the product.

(b) *Safety.* A safety test shall be performed on the contents of a final container of each lot of each product as prescribed in § 73.720 except for the following:

(1) For lots consisting of no more than 20 final containers or 20 sets of individual dilutions, or where the final container contains no more than one intended human dose, the safety test need not be performed on the contents of a final container provided the safety test is performed on each lot of stock concentrate and on each lot of diluent contained in the final product. Only stock concentrates and diluents which have passed the general safety test shall be kept in the work areas used for the manufacture of Allergenic Products. A stock concentrate is an extract derived from a single allergenic source and used in the manufacture of more than one lot of product, and from which final dilutions or mixtures are prepared directly.

(2) For powders for scratch tests, a sample shall be suspended in a suitable diluent and injected into each animal, and the sample size shall be the single human dose recommended.

(c) *Sterility.* A sterility test shall be performed on each lot of each Allergenic Product as prescribed in § 73.730, with the following exceptions:

(1) When bulk material is not prepared, the sterility test prescribed for bulk material shall be performed on each container of each stock concentrate at the time a stock concentrate is prepared, and the test sample shall be no less than 1 ml. from each stock concentrate container.

(2) For lots consisting of no more than 5 final containers, the final container test shall be performed in accordance with § 73.730(f)(7) using the sample therein prescribed or using a sample of no less than 0.25 ml. of product from each final container, divided in approximately equal proportions for testing in Fluid Thioglycollate and Fluid Sabouraud's media. The test sample in the latter alternative method may be an overfill in the final container.

(3) For products prepared in sets of individual dilution series, a test sample of 0.25 ml. shall be taken from a final container of each dilution, which samples may be pooled and one half of the pooled material used for the test with fluid Thioglycollate medium and one-half used for the test with fluid Sabouraud's medium.

(4) Tablets and capsules need not be tested for sterility provided aseptic techniques are employed in their manufacture.

TRIVALENT ORGANIC ARSENICALS

§ 73.9020 Tests prior to release.

Tests required to be made, prior to the release of each lot of a licensed product, shall be supplemented in the case of the trivalent organic arsenicals by tests for:

(a) Stability,
(b) Solubility,
(c) Arsenic content,
(d) Moisture,
(e) Relative non-toxicity.

§ 73.9021 Pretesting by Institute; sample of each lot.

Prior to the release of any lot of the product, the manufacturer shall forward to the Director, Division of Biologics Standards, no less than 15 ampoules of the largest single-dose size in such lot, together with protocols showing the results of each test required prior to release.

§ 73.9022 Expiration date.

Notification from the Director, Division of Biologics Standards, that lot samples forwarded in accordance with § 73.9021 have satisfactorily passed prescribed tests shall indicate a date which may be taken as the date of manufacture for the purpose of fixing the expiration date. The date of issue shall be the same as the date of manufacture.

§ 73.9023 Composition of product.

Solutions or solutions of mixtures in the concentrations recommended for clinical administration shall be of such hydrogen ion value and tonicity as to be physiologically compatible with human blood.

§ 73.9024 Container.

The product shall be hermetically sealed under vacuum or under a dry non-oxidizing gas in glass ampoules. The contents of any final container shall not exceed 10 maximum human doses.

§ 73.9025 Final container label.

In addition to the labeling requirements stated in § 73.600 the final container label of the trivalent organic arsenicals shall bear the statements required in § 73.9026 (b) and (c) and an additional statement giving the amount of the drug contained in the ampoule.

§ 73.9026 Outside label.

The outside label, in addition to the complete proper name and all other items required for products generally shall show conspicuously: (a) If the product is dispensed as a mixture or solution, the name of all admixed substances.

(b) If the ampoule is a multiple dose container, the fact that it is a multiple dose container.

(c) Specific method of preparation, if any, required prior to administration, as, for example, alkalinization.

Dated: August 19, 1970.

ROBERT Q. MARSTON,
Director,
National Institutes of Health.

Approved: August 27, 1970.

JOHN G. VENEMAN,
Acting Secretary.

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