§ 73.1326(b) by revising the specification for boron to read as follows:

§ 73.1326 Chromium hydroxide green.

* * * * *

(b) * * *

Boron (as B_2O_3), not more than 8 percent.

* * * * *

Effective dates: (1) The amendments promulgated by the regulation of July 15, 1977 became effective on August 16, 1977; (2) the amendment set forth above is effective November 22, 1977.

Dated: November 16, 1977.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc.77-33677 Filed 11-21-77;8:45 am]

[6560-01]

SUBCHAPTER B—FOOD AND FOOD PRODUCTS

[FRL 818-3; FAP6H5119/R30]

PART 193—TOLERANCES FOR PESTICIDES IN FOOD ADMINISTERED BY THE ENVIRONMENTAL PROTECTION AGENCY

Propylene Oxide

AGENCY: Office of Pesticide Programs, Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This rule amends 21 CFR 193.380 by establishing a regulation providing for the safe use of the fumigant propylene oxide on cocoa, gums, processed nutmeats (except peanuts), spices, and starch for up to 48 hours at 125 degrees F.

EFFECTIVE DATE: Effective November 22, 1977.

FOR FURTHER INFORMATION CONTACT:

Mr. William Miller, Product Manager (PM) 11, Registration Division (WN-567), Office of Pesticide Programs, Environmental Protection Agency, 401 M Street SW., Washington D.C. 20460 (202/755-9315).

SUPPLEMENTARY INFORMATION: On March 12, 1976, notice was given (41 FR 10709) that Union Carbide Corp., Linde Div., PO Box 372, 51 Cragwood Road, Plainfield NJ 07080, had filed a petition (FAP 6H5119) with the Environmental Protection Agency (EPA). This petition proposed that 21 CFR 193.380 be amended by establishing a regulation providing for the safe use of the fumigant propylene oxide and carbon dioxide in the ratio of 8 parts propylene oxide to 92 parts carbon dioxide by weight for the fumigation of cocoa, gums, processed nutmeats (except peanuts), spices, and starch for periods up to 48 hours at 125 degrees F. No comments were received by the Agency in response to this notice of filing.

The food additive propylene oxide is currently used as a package fumigant in or on dried prunes and glacé-fruit and as a fumigant in or on bulk quantities of cocoa, gums, processed spices, starch, and processed nutmeats (except peanuts), when such bulk foods are to be further processed into a final food form. Except in the fumigation of packaged dried prunes and glacé-fruits, it is applied in fumigation chambers not more than one time at a temperature not in excess of 125° F. The maximum period of fumigation shall not exceed 4 hours for cocoa, processed nutmeats (except peanuts), processed spices, and starch. It is also used on edible gums with a maximum duration of 24 hours. When used in accordance with the prescribed conditions of use in 21 CFR 193.380, residue limitations are as follows: 300 parts per million (ppm) of ethylene oxide for cocoa, gums, processed nutmeats (except peanuts), processed spices, and starch; 700 ppm (as propylene glycol) for glacé-fruit and dried prunes. Carbon dioxide, when used to dilute propylene oxide, is essentially a chemically inactive gas, and therefore, the Agency has determined that there would be no adverse effect regarding possible residues resulting from its use.

The data submitted in the petition indicate that this amendment to 21 CFR 193.380 is not expected to increase exposure to propylene oxide or its metabolites. The present level of exposure to propylene oxide was evaluated by the Food and Drug Administration when the food additive of 300 ppm for propylene oxide was established. Based on that review and the fact that exposure to propylene oxide will not be increased, it is concluded that the pesticide may be safely used in the prescribed manner when such use is in accordance with the label and labeling registered pursuant to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (86 Stat. 873; 7 U.S.C. 136 et seq.). Therefore, the regulation is being established as proposed.

Any person adversely affected by this regulation may, by December 22, 1977, file written objections with the Hearing Clerk, EPA, Rm. 1019, East Tower, 401 M St. SW., Washington, D.C. 20460. Such objections should be submitted in quintuplicate and specify the provisions of the regulation deemed to be objectionable and the grounds for the objections. If a hearing is requested, the objections must state the issues for the hearing. A hearing will be granted if the objections are supported by the grounds legally sufficient to justify the relief sought.

Effective November 22, 1977, 21 CFR Part 193 is amended as set forth below.

(Section 409(c)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 343(c)(1)).)

Dated: November 14, 1977.

EDWIN L. JOHNSON,
Deputy Assistant Administrator for Pesticide Programs.

Section 193.380 is amended by adding a new paragraph at (d) and redesignating (d) as (e) to read as follows:

* * * * *

§ 193.380 Propylene oxide.

* * * * *

(d) When used as a mixture with carbon dioxide (92 parts of carbon dioxide to 8 parts of propylene oxide on a weight/weight basis), all commodities listed in paragraph (c) of this section, except glace fruit and dried prunes, may be processed not more than one time for a period not to exceed 48 hours and at a temperature not to exceed 125 degrees F.

(e) To assure safe use of the additive, the label and labeling of the pesticide formulation containing the food additive shall conform to the label and labeling registered by the U.S. Environmental Protection Agency.

* * * * *

[FR Doc.77-33414 Filed 11-21-77;8:45 am]

[4110-03]

SUBCHAPTER D—DRUGS FOR HUMAN USE

[Docket No. 75N-0020]

PENICILLIN

Updating and Technical Revisions

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This document updates and revises the antibiotic drug regulations that provide for certification of penicillin drug products. The numerous revisions are made to: (1) revoke inactive sections; (2) change nomenclature for consistency with the policy of the current official compendia; (3) reindex Part 440 to make it consistent in structure with other updated parts of Subchapter D that provide for antibiotic drugs; and (4) provide technical changes.

DATES: Effective December 22, 1977, except that the effective date for revising the nonproprietary names is May 22, 1978.

FOR FURTHER INFORMATION CONTACT:

Joan M. Eckert, Bureau of Drugs (HFD-140), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-4292.

SUPPLEMENTARY INFORMATION: The Commissioner of Food and Drugs proposed, in the FEDERAL REGISTER of March 19, 1976 (41 FR 11533), as corrected in the FEDERAL REGISTER of April 5, 1976 (41 FR 14384), to update and revise regulations for penicillin drugs intended for human use. Interested persons were given 60 days to comment.

Comments were received from four manufacturers. The comments and the Commissioner's conclusions follow:

1. One firm objected to the revised wording of the potency statement in §§ 440.255b *Sterile penicillin G benzathine suspension*, 440.255c *Sterile penicillin G benzathine-penicillin G procaine suspension*, and 440.274b *Sterile penicillin G procaine suspension*. The firm, which manufactures penicillin suspen-

sions in prefilled disposable units, said that the revised statement would not provide an appropriate standard for its products.

The Commissioner concludes that the objection is valid. The current regulations specify that "each container or each milliliter" contains a specified dosage. The reference to "container" was deleted in the proposed amendment. Although the prefilled units produced by the firm are filled to deliver the dosage specified in the labeling, the total volume delivered may not be exactly 1 milliliter. The regulations are therefore revised to retain the original language, specifying that "each container or each milliliter" contains the specified dosage.

In the same comment, some typographical errors were noted—the minimum potency for sterile penicillin G potassium, in § 440.80a(a)(1)(i), should be 1,440 units per milligram instead of 1,400; and § 440.155d for penicillin G benzathine tablets should have designated the iodometric assay as the conclusive potency assay, in accordance with the statement in the preamble to the proposal.

The Commissioner agrees, and the regulations are revised accordingly.

The comment also noted that the minimum potency limit for penicillin G potassium tablets was incorrectly published as "9" instead of "90." This error was corrected in a correction document published in the FEDERAL REGISTER of April 5, 1976 (41 FR 14384).

2. One comment made several objections and requests:

a. The firm asked that the concentration of the solution used to determine penicillin V content be lowered from 50 milligrams per 100 milliliters of diluent to 20 milligrams per 100 milliliters of diluent. The firm said that the higher concentration yields absorbance values that are too high to provide accurate readings on most nonrecording instruments.

The Commissioner finds that the requested change is an improvement over the proposed method, and the regulations are revised accordingly.

b. The firm asked that the Karl Fischer moisture test remain as an alternative method for determining the moisture of penicillin V potassium, sterile penicillin G potassium, and penicillin G potassium for injection.

The Commissioner finds it preferable to designate one method as official for determining moisture. Based on the experience of FDA, the Commissioner concludes that the loss-on-drying method is more appropriate than the Karl Fischer method for these drug products. But a manufacturer may prefer to use the Karl Fischer method, which can give satisfactory results. Section 436.2 (21 CFR 436.2) allows use of alternative assay methods provided the results are as accurate as the official method. In case of dispute, however, the results obtained from the designated official method would be conclusive.

c. The firm asked that the hydroxylamine colorimetric assay be included as an alternative potency assay in several dosage form monographs.

The Commissioner agrees that a hydroxylamine colorimetric assay is appropriate as an alternative potency assay for several penicillin drug products. But because the general method in § 436.205 (21 CFR 436.205) is not entirely suitable for dosage form drugs, such alternative potency assay cannot be adopted at this time. The Food and Drug Administration is currently developing an appropriate hydroxlamine colorimetric assay procedure for certain penicillin dosage forms and plans to publish the procedure in the FEDERAL REGISTER in the near future.

d. The firm also asked that the lower pH limit in § 440.171b(a)(1) be 2.0 instead of 3.0, as proposed.

In light of information submitted as part of the comment, the Commissioner has no objection to adopting the limit requested, and the regulation is revised accordingly.

e. The firm objected to the deletion of the provision, under certain circumstances, for a 3 percent moisture limit for penicillin V potassium tablets.

The Commissioner has considered this objection and finds that the 3 percent exemption for moisture is inappropriate for penicillin V potassium tablets currently being certified. According to FDA records, the only tablet that has been the subject of such an exemption from the 1.5 percent limit is V-Kor Tablets, which consisted of three separate compressed layers containing penicillin, antihistamines, and analgesics. Drying of these tablets after compression to reduce the moisture content to a limit of 1.5 percent or less could cause a separation at the point of lamination. Therefore, the 3 percent limit was approved for this product only. V-Kor Tablets were removed from the market as a result of the Drug Efficacy Study Implementation notice, published in the FEDERAL REGISTER of November 17, 1971 (36 FR 21879). This exemption has never applied to any other penicillin V potassium tablet.

On the basis of FDA certification records for the past 2 years, the Commissioner finds that the 1.5 percent limit for penicillin V potassium tablets is reasonable.

3. Comments were received from two manufacturers concerning the proposed revocation of § 440.81 *Buffered crystalline penicillin.* Both firms produce a product containing penicillin G potassium or penicillin G sodium blended with buffers, which they manufacture for sale in bulk to other firms that package it for dispensing. They questioned whether their products are adequately provided for under the proposed regulations.

The Commissioner has considered the comments and agrees that some revisions are necessary to the proposed regulations. He finds that the regulations should provide for certification of these drug products without requiring sampling of the unbuffered bulk during an early stage of processing. Because of the method of manufacturing the buffered bulk product, it is impractical to sample the unbuffered bulk penicillin G potassium or penicillin G sodium for certification testing. Since it is the policy of FDA that, in the antibiotic regulations, each Subpart A is reserved for bulk drugs containing no added substances such as buffers and excipients, it is necessary to establish a new subpart to provide for buffered bulks that are intended for further manufacturing or repacking. The Commissioner is therefore adding new Subpart K—Bulk Drug Formulations for Repacking or for Manufacturing Use to Part 440. The new subpart contains new § 440.1080a *Sterile penicillin G potassium, buffered and new* § 440.1081a *Sterile penicillin G sodium, buffered.* Sections 440.280b and 440.281b as proposed are further revised to provide that the antibiotic drugs used in the manufacture of these dosage forms conform to the requirements of §§ 440.1080a and 440.1081a, respectively. Because §§ 440.280b and 440.281b are now intended only for dosage forms, the references in these monographs, as proposed, to use in manufacturing or repacking are being deleted.

4. One firm asked that sufficient time be provided to permit orderly changes in labeling in accordance with the revised nomenclature.

The Commissioner finds that additional time for revising labeling to reflect the name changes is justified and that use of labeling that complies with all other requirements is not contrary to the public health. Therefore, the effective date is revised, as set forth below, to allow 6 months for revising nomenclature.

In addition, Part 460 (21 CFR Part 460) currently has no authority citation. An authority citation is being added.

In the proposed document, the names of the penicillins which included waters of hydration were amended to delete the hydrate except for ampicillin trihydrate. Since that time, the Commissioner has reconsidered this action and feels that it is scientifically correct to include the water of hydration. Therefore the final rule making document has been revised to include monohydrate wherever the drug contains one water of hydration.

Therefore, under 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 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)), Parts 430,

436, 440, and 460 are being amended, as follows:

PART 430—ANTIEIOTIC DRUGS: GENERAL

a. Part 430 is amended as follows:

1. In § 430.5 the following amendments are made: Paragraph (a)(1)(ii) is revoked and reserved; in paragraph (a)(1)(iii), the term "phenoxymethyl penicillin" is revised to read "penicillin V" wherever it appears; paragraph (b)(1)(ii) is revoked and reserved; in paragraph (b)(1)(iii), the term "phenoxymethyl penicillin" is revised to read "penicillin V"; in paragraph (b)(1)(x), the term "procaine penicillin G" is revised to read "penicillin G procaine" wherever it appears. As amended, the affected text in paragraphs (a)(1) and (b)(1) reads as follows:

§ 430.5 Definitions of master and working standards.

(a) * * *

(1) * * *

(ii) [Reserved]

(iii) *Penicillin V.* The term "penicillin V master standard" means a specific lot of crystalline penicillin V that is designated by the Commissioner as the standard of comparison in determining the potency of the penicillin V working standard.

* * * * *

(b) * * *

(1) * * *

(ii) [Reserved]

(iii) The term "penicillin V working standard" means a specific lot of a homogeneous preparation of penicillin V.

* * * * *

(x) The term "penicillin G procaine working standard" means a specific lot of a homogeneous preparation of penicillin G procaine.

* * * * *

2. Section 430.6 is amended as follows: Paragraph (a)(1)(ii) is revoked and reserved; in paragraph (a)(1)(iii), the term "phenoxymethyl penicillin" is revised to read "penicillin V" wherever it appears. The amended paragraphs read as follows:

§ 430.6 Definitions of the terms "unit" and "microgram" as applied to antibiotic substances.

(a) * * *

(1) * * *

(ii) [Reserved]

(iii) *Penicillin V.* The term "unit" applied to penicillin V means the penicillin activity (potency) contained in 0.590 microgram of the penicillin V master standard.

* * * * *

PART 436—TESTS AND METHODS OF ASSAY OF ANTIBIOTIC AND ANTIBIOTIC-CONTAINING DRUGS

b. The following amendments are made to Part 436:

1. Section 436.33(b) table is amended as follows:

A. The following items are deleted: "Aluminum penicillin," "Chloroprocaine penicillin O," "Clemizole penicillin G," "Diethylaminoethyl ester penicillin G hydriodide," "Hydrabamine penicillin G [3]" and "Sodium nafcillin."

B. The following names are rearranged and reinserted alphabetically into the table: Benzathine cloxacillin is revised to read "Cloxacillin benzathine"; "Benzathine penicillin G" is revised to read "Penicillin G benzathine"; "Benzathine phenoxymethyl penicillin" is revised to read "Penicillin V benzathine"; "Calcium chlortetracycline syrup" is revised to read "Chlortetracycline calcium syrup"; "Calcium novobiocin" is revised to read "Novobiocin calcium"; "Calcium oxytetracycline" is revised to read "Oxytetracycline calcium"; "Disodium carbenicillin" is revised to read "Carbenicillin disodium"; "Hydrabamine phenoxymethyl penicillin [3]" is revised to read "Penicillin V hydrabamine [3]"; "Phenoxymethyl penicillin" is revised to read "Penicillin V"; "Potassium hetacillin" is revised to read "Hetacillin potassium"; "Potassium penicillin G" is revised to read "Penicillin G potassium"; "Potassium phenethicillin" is revised to read "Phenethicillin potassium"; "Potassium phenoxymethyl penicillin" is revised to read "Penicillin V potassium"; "Procaine penicillin G" is revised to read "Penicillin G procaine"; "Sodium ampicillin" is revised to read "Ampicillin sodium"; "Sodium cephalothin" is revised to read "Cephalothin sodium"; "Sodium colistimethate" is revised to read "Colistimethate sodium"; "Sodium novobiocin" is revised to read "Novobiocin sodium"; "Sodium cloxacillin monohydrate" is revised to read "Cloxacillin sodium monohydrate"; "Sodium dicloxacillin monohydrate" is revised to read "Dicloxacillin sodium monohydrate"; "Sodium methicillin" is revised to read "Methicillin sodium monohydrate"; "Sodium nafcillin monohydrate" is revised to read "Nafcillin sodium monohydrate"; "Sodium oxacillin" is revised to read "Oxacillin sodium monohydrate"; and "Sodium penicillin G" is revised to read "Penicillin G sodium"; "Zinc bacitracin" is revised to read "Bacitracin zinc."

As amended, the table in paragraph (b) reads as follows:

§ 436.33 Safety test.

* * * * *

(b) * * *

Antibiotic drug	Diluent (diluent number as listed in § 436.31)	Test dose: Concentration in units or milligrams of activity per milliliter	Test dose: Volume in milliliters to be administered to each mouse	Route of administration as described in paragraph (c) of this section
Amoxicillin trihydrate	9	20 mg	0.5	Intravenous.
Amphotericin B	6	50 mg	.4	Oral.
Amphotericin B for injection	3	0.05 mg	.3	Intravenous.
Ampicillin	9	20 mg	.5	Do.
Ampicillin sodium	3	40 mg	.5	Do.
Ampicillin trihydrate	9	20 mg	.5	Do.
Bacitracin	4	200 units	.5	Do.
Bacitracin methylene disalicylate	5	1,000 units	1.0	Oral.
Bacitracin zinc	3	4,000 units	.5	Do.
Benzylpenicilloyl-polylysine injection	(1)	4 mg	.5	Do.
Capreomycin sulfate	4	3.0 mg	.5	Intravenous.
Carbenicillin disodium	3	40 mg	.5	Do.
Carbenicillin indanyl sodium	3	100	.5	Oral.
Cefazolin sodium	3	50 mg	.5	Intravenous.
Cephacetrile sodium	3	60 mg	.5	Do.
Cephalexin monohydrate [3]	12	10 mg	.5	Oral.
Cephaloglycin [3]	5	120.0 mg	.5	Do.
Cephaloridine	3	50 mg	.5	Intravenous.
Cephalothin sodium	3	40 mg	.5	Do.
Cephapirin sodium	3	40 mg	.5	Do.
Cephradine	10	40 mg	.5	Oral.
Cephradine Sterile	14	23 mg	.5	Intravenous.
Cephradine for injection	1	23 mg	.5	Do.
Chloramphenicol	4	5 mg*	.5	Do.
Chloramphenicol palmitate	5	60 mg	1.0	Oral.
Chloramphenicol sodiumsuccinate	4	20 mg	.5	Intravenous.
Chlortetracycline	(1)	2 mg	.5	Do.
Chlortetracycline bisulfate	3	2 mg	.4	Do.
Chlortetracycline calcium syrup	3	25 mg	.5	Oral.
Chlortetracycline hydrochoride	3	2 mg	.5	Intravenous.
Clindamycin hydrochloride hydrate	4	4 mg	.5	Do.
Clindamycin palmitate hydrochloride	3	50 mg	1.0	Oral.
Clindamycin phosphate	4	20 mg	.5	Intravenous.
Cloxacillin benzathine	10	10 mg	.5	Do.
Cloxacillin sodium monohydrate	3	16 mg	.5	Do.
Colistin sulfate	3	0.6 mg	.5	Oral.
Colistimethate sodium	3	1.5 mg	.5	Intravenous.
Cycloserine	4	32 mg	.5	Do.
Demeclocycline	(1)	2mg	.5	Do.
Demeclocycline hydrochloride	3	2mg	.5	Do.
Dicloxacillin sodium monohydrate	4	20 mg	.5	Do.
Dihydrostreptomycin sulfate	3	2 mg	.5	Do.
Doxycycline hyclate	4	5 mg	.5	Do.
Doxycycline hyclate for injection	4	2 mg	.5	Do.
Doxycycline monohydrate	(1)	100 mg	.5	Oral.
Erythromycin	5	30 mg	1.0	Do.
Erythromycin estolate	5	40mg	.5	Do.
Erythromycin ethylcarbonate	5	100 mg	.5	Do.
Erythromycin ethylsuccinate	3	80 mg	.5	Do.
Erythromycin gluceptate	3	2 mg	.5	Intravenous.
Erythromycin lactobionate for injection	3	3 mg	.5	Do.
Erythromycin stearate	(1)	80 mg	.5	Oral.
Gentamicin sulfate	4	1 mg	.5	Intravenous.
Gramicidin [3]	5	5 mg	.5	Subcutaneous.
Griseofulvin	5	200 mg	.5	Oral.
Hetacillin	11	45 mg [2]	.4	Intravenous.
Hetacillin potassium	4	8 mg [2]	.5	Do.
Kanamycin sulfate	3	2 mg	.5	Do.
Lincomycin hydrochloride monohydrate	4	4 mg	.5	Do.
Methacycline hydrochloride	3	2 mg	.5	Do.
Methicillin sodium monohydrate	4	100 mg	.5	Do.
Minocycline hydrochloride	3	2 mg	.5	Do.
Mitomycin [3]	3	0.2 mg	.5	Do.
Nafcillin sodium monohydrate	4	16 mg	.5	Do.
Neomycin sulfate	4	0.2 mg	.5	Do.
Novobiocin calcium	4	2 mg	.5	Do.
Novobiocin sodium	4	4 mg	.5	Do.
Nystatin	6	1,200 units	.5	Intraperitoneal.
Oleandomycin phosphate	4	8 mg	.5	Intravenous.
Oxacillin sodium monohydrate	4	20 mg	.5	Do.
Oxytetracycline	(1)	2 mg	.5	Do.
Oxytetracycline calcium	5	25 mg	.5	Oral.
Oxytetracycline hydrochloride	3	2 mg	.5	Do.
Paromomycin sulfate	3	8 mg	.5	Do.
Penicillamine	10	100 mg	1.0	Do.
Penicillin G benzathine	4	4,000 units	.25	Intravenous.
Penicillin G potassium	3	4,000 units	.5	Do.
Penicillin G procaine	4	2,000 units	.5	Do.
Penicillin G sodium	3	4,000 units	.5	Do.
Penicillin V	4	2,000 units	.5	Do.
Penicillin V benzathine	4	4,000 units	.25	Do.
Penicillin V hydrabamine [3]	(1)	100 mg	.5	Oral.
Penicillin V potassium	4	2,000 units	.5	Intravenous.
Phenethicillin potassium	4	4,000 units	.5	Do.
Polymyxin B sulfate	4	1,200 units	.5	Do.
Rifampin	10	6 mg	1.0	Oral.
Rolitetracycline	3	2 mg	.5	Intravenous.
Rolitetracycline nitrate	3	2 mg	.5	Do.
Spectinomycin hydrochloride	4	16 mg	.5	Do.
Streptomycin sulfate	3	2 mg	.5	Do.
Streptonicozid sulfate	3	1 mg	.5	Do.
Tetracycline	(1)	2 mg	.5	Do.
Tetracycline hydrochloride	3	2 mg	.5	Do.
Tetracycline phosphate	(1)	2 mg	.5	Do.
Troleandomycin	4	200 mg	.5	Oral.
Vancomycin hydrochloride	4	4 mg	.5	Intravenous.
Viomycin sulfate	4	2 mg	.5	Do.

[1] To prepare the sample solution, proceed as directed in the individual section of the antibiotic drug regulations in this chapter for the antibiotic to be tested.

[2] Ampicillin activity.

[3] Use the observation period specified in the individual section of the antibiotic drug regulations in this chapter for the antibiotic to be tested in lieu of the 48-hr-observation period specified in par. (d) of this section.

§ 436.105 [Amended]

2. Section 436.105 *Microbiological agar diffusion assay* is amended in the tables in paragraphs (a) and (b) by revising the name "phenoxymethyl penicillin" to read "Penicillin V" and reinserting the item alphabetically into the tables.

3. Section 436.204 is amended as follows:

a. In the table in paragraph (b)(1), the item "Penicillin O" is deleted, the name "Phenoxymethyl penicillin" is revised to read "Penicillin V", and the name "Potassium L-phenethicillin" is revised to read "L-phenethicillin potassium" and the last item is reinserted alphabetically into the table.

b. In paragraph (b)(2), the table is revised. The amended text reads as follows:

§ 436.204 Iodometric assay.

* * * * *

(b) * * *

(1) * * *

Antibiotic	Initial solvent	Diluent (solution number as listed in § 436.101(a))	Final concentration in units or milligrams of activity per milliliter of standard solution
Amoxicillin	None	Distilled water	1.0 mg.
Ampicillin	do	do	1.25 mg.
Cephalexin	do	do	2 mg.
Cephaloridine	do	do	2 mg.
Cephalothin	do	do	2 mg.
Cephapirin	do	do	2 mg.
Cloxacillin	do	do	1.25 mg.
Dicloxacillin	do	do	1.25 mg.
L-phenethicillin potassium	do	1	2,000 units.
Methicillin	do	1	1.25 mg.
Nafcillin	do	1	1.25 mg.
Oxacillin	do	1	1.25 mg.
Penicillin G	do	1	2,000 units.
Penicillin V	2 ml methyl alcohol.	1	2,000 units.

(2) * * *

Antibiotic	Initial solvent	Diluent (solution number as listed in § 436.101(a))	Final concentration in units or milligrams of activity per milliliter of sample
Amoxicillin trihydrate	None	Distilled water	1.0 mg.
Ampicillin	do	do	1.25 mg.
Ampicillin sodium	do	1	1.25 mg.
Ampicillin trihydrate	do	Distilled water	1.25 mg.
Cephalexin	do	do	2 mg.
Cephaloridine	do	do	2 mg.
Cephalothin sodium	do	do	2 mg.
Cephapirin sodium	do	do	2 mg.
Cloxacillin sodium monohydrate	do	do	1.25 mg.
Dicloxacillin sodium monohydrate	do	1	1.25 mg.
Methicillin sodium monohydrate	do	1	1.25 mg.
Nafcillin sodium monohydrate	do	1	1.25 mg.
Oxacillin sodium monohydrate	do	1	1.25 mg.
Penicillin G benzathine blank solution	do	Distilled water	2,000 units.
Penicillin G benzathine inactivated solution	do	1*N* NaOH	2,000 units; allow to stand in 1*N* NaOH for 15 min. before assaying.
Penicillin G potassium	do	1	2,000 units.
Penicillin G procaine	2 ml methyl alcohol.	1	2,000 units.
Penicillin G sodium	None	1	2,000 units.
Penicillin V	2 ml methyl alcohol.	1	2,000 units.
Penicillin V benzathine blank solution	None	Distilled water	2,000 units.
Penicillin V benzathine inactivated solution	do	1*N* NaOH	2,000 units; allow to stand in 1*N* NaOH for 15 min. before assaying.
Penicillin V hydrabamine	do	Chloroform	2,000 units.
Penicillin V potassium	do	1	2,000 units.
Phenethicillin potassium	do	1	2,000 units.

4. Section 436.205 is amended as follows:

a. In the table in paragraph (b) by changing the name "Phenoxymethyl penicillin" to read "Penicillin V" and the name "Procaine penicillin G" to read "Penicillin G procaine," and both items are reinserted alphabetically into the table.

b. In paragraph (c), the table is revised. The amended text reads as follows:

§ 436.205 Hydroxylamine colorimetric assay.

* * * * *

(b) * * *

Antibiotic	Diluent (solution number as listed in § 436.101(a))	Final concentration in milligrams per milliliter of standard
Amoxicillin	Distilled water.	1.0
Ampicillin	do	1.25
Cefazolin [1]		1.0
Cephacetrile	Distilled water.	2.0
Cephaloridine	do	1.0
Cephalothin	do	2.0
Cephapirin	do	1.0
Cloxacillin	1	1.25
Dicloxacillin	1	1.25
Methicillin	1	1.25
Nafcillin	1	1.25
Oxacillin	1	1.25
Penicillin G	1	1.25
Penicillin G procaine	17	2.0
Penicillin V	17	1.25
Phenethicillin	1	1.25

[1] To prepare the working standard solution, proceed as directed in the individual section of the antibiotic drug regulation in this chapter for the antibiotic to be tested.

(c) * * *

Antibiotic	Diluent (solution number as listed in § 436.101(a))	Final concentration in units or milligrams of activity per milliliter of sample
Amoxicillin trihydrate	Distilled water.	1.0
Ampicillin:	do	1.25
Ampicillin sodium	do	1.25
Ampicillin trihydrate	do	1.25
Cefazolin sodium	1	1.0
Cephacetrile sodium	Distilled water.	2.0
Cephaloridine	do	1.0
Cephalothin sodium	do	2.0
Cephapirin sodium	do	1.0
Cloxacillin sodium monohydrate.	1	1.25
Dicloxacillin sodium monohydrate.	Distilled water.	1.25
Methicillin sodium monohydrate.	1	1.25
Nafcillin sodium monohydrate.	1	1.25
Oxacillin sodium monohydrate.	1	1.25
Penicillin G potassium	1	1.25
Penicillin G procaine	17	2.0
Penicillin G sodium	1	1.25
Penicillin V	17	1.25
Penicillin V potassium	1	1.25
Phenethicillin potassium	1	1.25

* * * * *

5. In Subpart E, the following new § 436.214 is added.

§ 436.214 Heat stability.

Store an accurately weighed portion of the sample of approximately 30 milligrams in an unstoppered 50-milliliter Erlenmeyer flask for 4 days in an electric oven at 100° C±1° C. At the end of this period, remove the flask from the oven and allow to cool in a desiccator. Accurately weigh an unheated portion of the original sample of approximately 30 milligrams. Assay both the heated and unheated samples for potency as directed

in § 436.204 or § 436.205 of this chapter. Determine the percent loss from the difference in potency between the unheated original sample and the heat-treated sample.

6. In Subpart F, the following new § 436.316 is added.

§ 436.316 Determination of penicillin G content.

(a) *Reagents.* The reagents are freshly prepared every three days and are of such quality that when used in this procedure with an authentic sample of penicillin G, not less than 97 percent of penicillin G is recovered.

(1) *Amyl acetate (iso-amyl acetate) solution.* Saturate the amyl acetate (boiling range 138.5° C—141.5° C) with the *N*-ethyl piperidine salt of penicillin G by adding 2 milligrams of the salt for each 1.0 milliliter of the solvent. Cool this solution to 0° C—8° C and filter it through a sintered-glass filter immediately before use.

(2) *Acetone solution.* Saturate reagent grade acetone with the *N*-ethyl piperidine salt of penicillin G using 3 milligrams of salt for each 1 milliliter of acetone. Cool this solution to 0° C—8° C and filter it through a sintered-glass filter immediately before use.

(3) *N-ethyl piperidine solution.* *N*-ethyl piperidine (boiling range 129.5° C—131.0° C) should be stored in brown bottles in a refrigerator. Dilute 1.0 milliliter of this reagent with 4.0 milliliters of amyl acetate. Saturate this solution with the *N*-ethyl piperidine salt of penicillin G, using about 3 milligrams of the salt for each 1.0 milliliter of solution. Cool this solution to 0° C—8° C and filter it through a sintered-glass filter immediately before use.

(4) *Phosphoric acid solution.* Prepare by dissolving 1.0 milliliter of reagent grade phosphoric acid (85 percent) in 4.0 milliliters of water. Cool to 0° C—8° C and shake before using.

(5) *Silica gel.* Use dry silica gel (mesh size 6–16, Tyler standard). Place about 0.5 gram of the silica gel in a micro filter funnel (approximately 10-millimeter diameter) having a fritted-glass disc of medium porosity.

(b) *Procedure.* Accurately weigh from 60 to 70 milligrams of the sample to be tested, except if penicillin G procaine is to be tested weigh 90 to 100 milligrams of sample, into a glass test tube or glass vial of approximately 10-milliliter capacity. Add 2.0 milliliters of water to dissolve or suspend (procaine) the penicillin and cool to 0° C—5° C. Add 2.0 milliliters of amyl acetate solution and 0.5 milliliter of phosphoric acid solution, stopper and shake the container vigorously for approximately 15 seconds. For penicillin G procaine, add a second 0.5-milliliter portion of phosphoric acid solution and shake vigorously. Centrifuge to obtain a clear separation of the two layers (approximately 20 seconds). If any penicillin procaine remains undissolved, add a third 0.5-milliliter portion of phosphoric acid solution, shake the container vigorously, and centrifuge. After centrifuging, remove as much of the amyl acetate layer as possible, usually about 1.7 milliliters to 1.8 milliliters, with a suitable hypodermic needle and syringe and place the portion removed into the filter funnel containing silica gel, described in paragraph (a)(5) of this section. Allow the amyl acetate to remain in contact with the silica gel for exactly 20 seconds, then apply suction and collect the filtrate in a small test tube placed in a suction flask surrounded by cracked ice. Pipet a 1.0-milliliter aliquot of the amyl acetate filtrate into a tared flat-bottom glass tube (approximately 15 x 50 millimeters) containing 1.0 milliliter of acetone solution and 0.5 milliliter of *N*-ethyl piperidine solution. The time elapsing between accidification and the addition of the filtrate to the above reagents should not be more than 3 minutes. Place the glass tube containing the mixture into a large weighing bottle, stopper the bottle and allow to stand for not less than 2 hours in a refrigerator at 0° C—8° C. Remove the liquid from the precipitate by means of a tared micro filter stick and wash with a total of 1.0 milliliter of acetone solution adding the latter by means of a hypodermic syringe equipped with a fine needle. Place the filter stick inside the glass tube, dry under vacuum at room temperature for not less than 1 hour, and weigh. (The *N*-ethyl piperidine penicillin G residues can be saved for saturating reagents).

(c) *Calculations.* Calculate the percent penicillin G content as follows:

$$\text{Percent penicillin G content} = \frac{\text{Milligrams } N\text{-ethyl piperidine penicillin precipitate} \times 149.4}{\text{Weight of sample in milligrams}}$$

PART 440—PENICILLIN ANTIBIOTIC DRUGS

c. Part 440 is amended as follows:

§ 440.9a [Amended]

1. Section 440.9a *Sterile sodium ampicillin* is amended by changing the name "sodium ampicillin" to read "ampicillin sodium" in the heading and in paragraphs (a)(1) and (a)(1)(x).

§ 440.13a [Amended]

2. Section 440.13a *Sterile disodium carbenicillin* is amended by changing the name "disodium carbenicillin" to read "carbenicillin disodium" in the section heading and in paragraphs (a)(1) and (a)(1)(vii).

§ 440.15 [Amended]

3. Section 440.15 *Sodium cloxacillin* is amended as follows:

a. By changing the name "sodium cloxacillin" to read "cloxacillin sodium monohydrate" in the section heading and in paragraph (a)(1).

b. By revising the text of paragraph (a)(1)(v) to read "Its cloxacillin content is not less than 82.5 percent."

c. By changing "sodium cloxacillin content," to read "cloxacillin content," in paragraph (a)(3)(i).

d. By deleting the word "sodium" the four times it appears with "sodium cloxacillin" in the heading, text, and formula in paragraph (b)(5).

§ 440.19 [Amended]

4. Section 440.19 *Nonsterile sodium dicloxacillin mononhydrate* is amended as follows:

a. By changing the name "sodium dicloxacillin monohydrate" to read "dicloxacillin sodium monohydrate" in the section heading and in paragraphs (a)(1) and (a)(1)(viii).

b. By deleting the word "nonsterile" from the section heading and first sentence of paragraph (a)(1).

§ 440.19a [Amended]

5. Section 440.19a *Sterile sodium dicloxacillin monohydrate* is amended as follows:

a. By changing the name "sodium dicloxacillin monohydrate" to read "dicloxacillin sodium monohydrate" in the section heading and in paragraphs (a)(1) and (a)(1)(x).

b. By revising the text of paragraph (a)(2) to read "If this drug is packaged for dispensing, in addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'sterile dicloxacillin sodium'."

§ 440.25 [Amended]

6. Section 440.25 *Nonsterile hetacillin* is amended by deleting the word "Nonsterile" from the section heading.

§ 440.29 [Amended]

7. Section 440.29 is amended as follows:

a. By revising the section heading to read § 440.29 *Hetacillin potassium.*

b. By changing the name "potassium hetacillin" to read "hetacillin potassium" in paragraphs (a)(1) and (a)(1)(vi).

c. By revising the text of paragraph (a)(1)(v) to read "Its hetacillin content is not less than 82 percent and not more than 95.5 percent".

d. By changing "postassium hetacillin content," to read "hetacillin content," in paragraph (a)(3)(i).

e. By deleting the word "potassium" the four times its appears in paragraph (b)(5).

f. By deleting the figures "X 427.57" and "X 389.48" from the formula therein, and as amended the formula reads:

$$\text{Percent hetacillin} = \frac{c \times 5{,}000 \times 100}{\text{weight of sample in milligrams}}$$

§ 440.29a [Amended]

8. Section 440.29a *Sterile potassium hetacillin* is amended as follows:

a. By changing the name "potassium hetacillin" to read "hetacillin potassium" in the section heading and in paragraphs (a)(1) and (a)(1)(viii).

b. By revising the text of paragraph (a)(1)(vii) to read "Its hetacillin content is not less than 82 percent and not more than 95.5 percent."

c. By changing "potassium hetacillin content," to read "hetacillin content," in paragraph (a)(3)(i).

By changing "potassium hetacillin content," to read "hetacillin content," in the heading and text in paragraph (b)(7).

d. By changing "potassium hetacillin and X 389.48" from the formula therein, and as amended the formula reads:

$$\text{Percent hetacillin} = \frac{c \times 500}{\text{Weight of sample in milligrams}}$$

§ 440.36a [Amended]

9. Section 440.36a *Sterile sodium methicillin* is amended as follows:

a. By changing the name "sodium methicillin" to read "methicillin sodium monohydrate" in the section heading and in paragraph (a)(1).

b. By revising the text of paragraph (a)(1)(vii) to read "Its methicillin content is not less than 81.5 percent."

c. By changing "sodium methicillin content," to read "methicillin content," in paragraph (a)(3)(i).

d. By deleting the word "sodium" from the heading, text, and two places in the formula in paragraph (b)(7).

§ 440.41 [Amended]

10. Section 440.41 *Nonsterile sodium nafcillin monohydrate* is amended as follows:

a. By deleting the word "Nonsterile" from the section heading and by changing the name "sodium nafcillin monohydrate" to read "nafcillin sodium monohydrate" in the section hearing and in paragraph (a)(1).

b. By revising the text of paragraph (a)(1)(vi) to read "Its nafcillin content is not less than 82.7 percent."

c. By changing "sodium nafcillin monohydrate content," to read "nafcillin content," in paragraph (a)(3)(i).

d. By changing "sodium nafcillin monohydrate" to read "nafcillin" in the heading, text, and two places in the formula in paragraph (b)(6).

§ 440.41a [Amended]

11. Section 440.41a *Sterile sodium nafcillin monohydrate* is amended as follows:

a. By changing the name "sodium nafcillin monohydrate" to read "nafcillin sodium monohydrate" in the section heading and in paragraph (a)(1).

b. By revising the text of paragraph (a)(1)(viii) to read "Its nafcillin content is not less than 82.0 percent."

c. By changing "sodium nafcillin monohydrate content," to read "nafcillin content," in paragraph (a)(3)(i).

d. By changing the heading of paragraph (b)(3) to read *"Nafcillin content."*

§ 440.49 [Amended]

12. Section 440.49 *Sodium oxacillin* is amended as follows:

a. By changing the name "sodium oxacillin" to read "oxacillin sodium monohydrate" in the section heading and in paragraph (a)(1).

b. By revising the text of paragraph (a)(1)(v) to read "Its oxacillin content is not less than 81.5 percent and not more than 95.0 percent."

c. By changing "sodium oxacillin content," to read "oxacillin content," in paragraph (a)(3)(i).

d. By deleting the word "sodium" from the heading and the two times it appears in the formula in paragraph (b)(5).

§ 440.49a [Amended]

13. Section 440.49a *Sterile sodium oxacillin* is amended as follows:

a. By changing the name "sodium oxacillin" to read "oxacillin sodium monohydrate" in the section heading and in paragraph (a)(1).

b. By revising the text of paragraph (a)(1)(vii) to read "Its oxacillin content is not less than 81.5 percent and not more than 95.0 percent."

c. By changing "sodium oxacillin content," to read "oxacillin content," in paragraph (a)(3)(i).

d. By deleting the word "sodium" from the heading of paragraph (b)(7).

§ 40.53a [Revoked]

14. Section 440.53a *Sterile aluminum penicillin (aluminum penicillin salt)* is revoked.

15. Section 440.55a is revised to read as follows:

§ 440.55a Sterile penicillin G benzathine.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Penicillin G benzathine is the *N,N'*-dibenzylethylenediamine salt of penicillin G. It is so purified and dried that:

(i) Its potency is not less than 1,090 units and not more than 1,272 units per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) It passes the safety test.

(v) Its moisture content is not less than 5.0 percent and not more than 8.0 percent.

(vi) Its pH in a saturated aqueous solution (about 100 milligrams per milliliter) is not less than 5.0 and not more than 7.5.

(vii) Its penicillin G content is not less than 57.9 percent and not more than 71.6 percent.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, safety, moisure, pH, penicillin G content, and crystallinity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay—*(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately measured representative portion of the sample in sufficient absolute methyl alcohol to give a solution of convenient concentration. Immediately, further dilute with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(2) of that section, except use medium C in lieu of medium A, medium F in lieu of medium E, and during the period of incubation shake the tubes at least once daily.

(3) *Pyrogens.* Proceed as directed in § 436.32(d) of this chapter, using a solution containing 4,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using a saturated aqueous solution prepared by suspending about 100 milligrams of sample per milliliter.

(7) *Penicillin G content.* Accurately weigh approximately 50 milligrams of the sample, dissolve in absolute methyl alcohol, and dilute to 100 milliliters with absolute methyl alcohol. Treat a portion of the working standard in the same manner. Using a suitable spectrophotometer equipped with a quartz cell and absolute methyl alcohol as the blank, determine the absorbence at 263 nanometers. Calculate the percent penicillin G as follows:

$$\text{Percent penicillin G} = \frac{\text{Absorbance of sample} \times \text{weight in milligrams of standard} \times \text{percent penicillin G in standard}}{\text{Absorbance of standard} \times \text{weight in milligrams of sample}}$$

(8) *Crystallinity.* Proceed as directed in § 436.203 of this chapter.

§ 440.57 [Amended]

16. Section 440.57 *Benzathine phenoxymethyl penicillin* is amended as follows:

a. By changing "benzathine phenoxymethyl penicillin" to read "penicillin V benzathine" in the section heading and paragraph (a)(1).

b. By changing "phenoxymethyl penicillin" to read "penicillin V" in paragraphs (a)(1), (a)(1)(v), (a)(3)(i), (b)(1)(i) and (b)(5), including the formula therein.

§ 440.59a [Revoked]

17. Section 440.59a *Sterile chloroprocaine penicillin O (penicillin O chloroprocaine* salt) is revoked.

§ 440.60a [Revoked]

18. Section 440.60a *Sterile dibenzylamine penicillin G (dibenzylamine penicillin G salt)* is revoked.

§ 440.61a [Revoked]

19. Section 440.61a *Sterile diethylaminoethyl ester penicillin G hydriodide (penicillin G diethylaminoethyl ester hydriodide)* is revoked.

§ 440.63a [Revoked]

20. Section 440.63a *Sterile ephedrine penicillin (penicillin ephedrine salt), ephedrine penicillin G (penicillin G ephedrine salt)* is revoked.

§ 440.65a [Revoked]

21. Section 440.65a *Sterile l-ephenamine penicillin G (penicillin G l-ephenamine salt)* is revoked.

§ 440.66 [Revoked]

22. Section 440.66 *Hydrabamine penicillin G (hydrabamine penicillin G salt)* is revoked.

§ 440.69 [Amended]

23. Section 440.69 *Hydrabamine phenoxymethyl penicillin* is amended as follows:

a. By changing "hydrabamine phenoxymethyl penicillin" to read "penicillin V hydrabamine" in the section heading and paragraph (a)(1).

b. By changing "phenoxymethyl penicillin" to read "penicillin V" in paragraphs (a)(1), (a)(1)(vi), (a)(3)(i), (b)(1) and (b)(1)(i), and (b)(6), including the formula therein.

24. Section 440.71 is revised to read as follows:

§ 440.71 Penicillin V.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Penicillin V is 3,3-dimethyl - 7-oxo-6-(2-phenoxyacetamido) - 4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 1,525 units nor more than 1,780 units per milligram.

(ii) It passes the safety test.

(iii) Its moisture content is not more than 2.0 percent.

(iv) Its pH in a saturated aqueous solution is not less than 2.5 and not more than 4.0.

(v) Its penicillin V content is not less than 90 percent and not more than 105 percent.

(vi) It is crystalline.

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, each package shall bear on its outside wrapper or container and the immediate container the statement "For use in the manufacture of nonparenteral drugs only."

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, safety, moisture, pH, penicillin V content, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay—*(1) *Potency.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample (aproximately 30 milligrams) in 2.0 milliliters of absolute methyl alcohol. Further dilute an aliquot of this solution with sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) *Safety.* Proceed as directed in § 436.33 of this chapter.

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using a saturated aqueous solution prepared by adding approximately 30 milligrams per milliliter.

(5) *Penicillin V content.* Accurately weigh approximately 20 milligrams of sample, dissolve in absolute methyl alcohol, and dilute to 100 milliliters with absolute methyl alcohol. Treat a portion of the working standard in the same manner. Using a suitable spectrophotometer equipped with a quartz cell and absolute methyl alcohol as the blank, determine the absorbance of the peak at 276 nanometers. Calculate the percent penicillin V as follows:

$$\text{Percent penicillin V} = \frac{\text{Absorbance of sample} \times \text{weight in milligrams of standard} \times \text{percent penicillin V in standard}}{\text{Absorbance of standard} \times \text{weight in milligrams of sample}}$$

(6) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

25. Section 440.73 is revised to read as follows:

§ 440.73 Penicillin V potassium.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Penicillin V potassium is the potassium salt of 3,3-dimethyl-7-oxo-6-(2-phenoxyacetamido) - 4 - thia - 1 - azabicyclo[3.2.0]heptane - 2 - carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 1,380 units nor more than 1,610 units per milligram.

(ii) It passes the safety test.

(iii) Its loss on drying is not more than 1.5 percent.

(iv) Its pH in an aqueous solution containing 30 milligrams per milliliter is not less than 4.0 and not more than 7.5.

(v) Its penicillin V content is not less than 81.2 percent and not more than 94.7 percent.

(vi) It is crystalline.

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, each package shall bear on its outside wrapper or container and the immediate container the statement "For use in the manufacture of nonparenteral drugs only."

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, safety, loss on drying, pH, penicillin V content, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay—*(1) *Potency.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) *Safety.* Proceed as directed in § 436.33 of this chapter.

(3) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 30 milligrams per milliliter.

(5) *Penicillin V content.* Dissolve and dilute approximately 20 milligrams of the sample, accurately weighed to 100 milliliters with 0.1*N* sodium hydroxide solution. Treat a portion of the penicillin V working standard in the same manner. Using a suitable spectrophotometer equipped with a quartz cell and 0.1*N* sodium hydroxide solution as the blank, determine the absorbance of the peak at 275 nanometers. Calculate the percent penicillin V as follows:

$$\text{Percent penicillin V} = \frac{\text{Absorbance of sample} \times \text{weight in milligrams of standard} \times \text{percent penicillin V in standard}}{\text{Absorbance of standard} \times \text{weight in milligrams of sample}}$$

(6) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

26. Section 440.74a is revised to read as follows:

§ 440.74a Sterile penicillin G procaine.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Penicillin G procaine is 3,3 - dimethyl - 7 - oxo - 6 - (2 - phenyl - acetamido) - 4 - thia - 1 - azabicyclo [3.2.0]heptane-2-carboxylic acid 2-(diethylamino) ethyl *p*-aminobenzoate compound (1:1). It is so purified and dried that:

(i) Its potency is not less than 900 and not more than 1,050 units per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) It passes the safety test.

(v) Its moisture content is not less than 2.8 percent and not more than 4.2 percent.

(vi) Its pH in a saturated aqueous solution (about 300 milligrams per milliliter) is not less than 5 and not more than 7.5.

(vii) Its penicillin G content is not less than 51.0 percent and not more than 59.6 percent.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, safety, moisture, pH, penicillin G content, and crystallinity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay—*(1) *Potency.* Use any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed § 436.205 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except add sufficient penicillinase to diluting fluid A and swirl the flask to completely solubilize the sample before filtration. If the product contains lecithin, use diluting fluid D in lieu of A.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, using a solution containing 2,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using a saturated solution prepared by suspending 300 milligrams of sample per milliliter.

(7) *Penicillin G content.* Proceed as directed in § 436.316 of this chapter.

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

27. Section 440.80a is revised to read as follows:

§ 440.80a Sterile penicillin G potassium.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Penicillin G postassium is potassium 3,3 - dimethyl - 7 - oxo-6-(2 - phenylacetamido) - 4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate. It is so purified and dried that:

(i) Its potency is not less than 1,440 units and not more than 1,680 units per milligram. If it is packaged for dispensing, its potency is satifactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) It passes the safety test.

(v) Its loss on drying is not more than 1.5 percent.

(vi) Its pH in an aqueous solution containing 60 milligrams per milliliter is not less than 5.0 and not more than 7.5.

(vii) Its penicillin G content is not less than 80.8 percent and not more than 94.3 percent.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, safety, loss on drying, pH, penicillin G content, and crystallinity.

(ii) Samples required:

(*a*) If the batch is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams

(*2*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay—*(1) *Potency—*(i) *Sample preparation.* Dissolve an accurately weighed portion of the sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration; also, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with solution 1 to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Use any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(*c*) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 2,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

(7) *Penicillin G content.* Proceed as directed in § 436.316 of this chapter.

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

§ 440.81 [Revoked]

28. Section 440.81 *Buffered crystalline penicillin* is revoked.

29. The following § 440.81a is added to read as follows:

§ 440.81a Sterile penicillin G sodium.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Penicillin G sodium is sodium 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate. It is so purified and dried that:

(i) Its potency is not less than 1,500 units and not more than 1,750 units per milligram. If it is packaged for dispensing, its content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) It passes the safety test.

(v) Its loss on drying is not more than 1.5 percent.

(vi) Its pH in an aqueous solution containing 60 milligrams per milliliter is not less than 5.0 and not more than 7.5.

(vii) Its penicillin G content is not less than 84.5 percent and not more than 98.5 percent.

(viii) It is crystalline.

(ix) It passes the test for heat stability if it does not show a loss of more than 10 percent of its original potency.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, safety, loss on drying, pH, penicillin G content, crystallinity, and heat stability.

(ii) Samples required:

(*a*) If the batch is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*2*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(*b*) If the batch is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay—*(1) *Potency—*(i) *Sample preparation.* Dissolve an accurately weighed portion of the sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration; also, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative aliquot from each container. Dilute with solution 1 to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Use any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(*c*) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 2,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

(7) *Penicillin G content.* Proceed as directed in § 436.316 of this chapter.

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(9) *Heat stability.* Proceed as directed in § 436.214 of this chapter.

§ 440.82 [Amended]

30. Section 440.82 *Potassium phenethicillin* is amended by changing the name "potassium phenethicillin" to read "phenethicillin potassium" in the section heading and in paragraph (a)(1) and by changing the name "Phenoxymethyl penicillin" to read "Penicillin V" in the last sentence of paragraph (b)(8).

§ 440.115 [Amended]

31. Section 440.115 is amended by revising the section headiing to read § 440.115 *Cloxacillin sodium monohydrate oral dosage forms.*

§ 440.115a [Amended]

32. Section 440.115a *Sodium cloxacillin capsules* is amended as follows:

a. By changing "sodium cloxacillin" to read "cloxacillin sodium monohydrate" in the section heading and wherever it appears in paragraphs (a)(1) and (a)(3)(ii)(*a*).

b. By reviising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'cloxacillin sodium capsules'."

c. By revising the text of paragraph (a)(3)(i)(*a*) to read "The cloxacillin sodium monohydrate used in making the batch for potency, safety, moisture, pH, cloxacillin content, identity, and crystallinity."

§ 440.115b [Amended]

33. Section 440.115b *Sodium cloxacillin for oral solution* is amended as follows:

a. By changing "sodium cloxacillin" to read "cloxacillin sodium monohydrate" in the section heading and wherever it appears in paragraph (a)(1) and (a)(3)(ii)(*a*).

b. By revising the second sentence of paragraph (a)(1) to read "When reconstituted as directed in the labeling, each milliliter contains the equivalent of 25 milligrams or 50 milligrams of cloxacillin."

c. By revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'cloxacillin sodium for oral solution'."

d. By revising the text of paragraph (a)(3)(i)(*a*) to read "The cloxacillin sodium monohydrate used in making the batch for potency, safety, moisture, pH, cloxacillin content, identity, and crystallinity."

§ 440.119 [Amended]

34. Section 440.119 is amended by revising the section heading to read § 440.119 *Dicloxacillin sodium monohydrate oral dosage forms.*

§ 440.119a [Amended]

35. Section 440.119a *Sodium dicloxacillin monohydrate capsules* is amended as follows:

a. By changing "sodium dicloxacillin monohydrate" to read "dicloxacillin sodium monohydrate" in the section heading and wherever it appears in paragraphs (a)(1), (a)(3)(i)(*a*), and (a)(3)(ii)(*a*).

b. By revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'dicloxacillin sodium capsules'."

§ 440.119b [Amended]

36. Section 440.119b *Sodium dicloxacillin monohydrate for oral suspension* is amended by changing "sodium dicloxacillin monohydrate" to read "dicloxacillin sodium monohydrate" in the section heading and wherever it appears in paragraphs (a)(1), (a)(3)(i)(*a*), and (a)(3)(ii)(*a*) and by revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'dicloxacillin sodium for oral suspension'."

§ 440.129 [Amended]

37. Section 440.129 *Potassium hetacillin capsules* is amended as follows:

a. By changing "potassium hetacillin" to read "hetacillin potassium" in the sec-

tion heading and wherever it appears in paragraphs (a)(1) and (a)(3)(ii)(*a*).

b. By revising the text of paragraph (a)(3)(i)(*a*) to read "The hetacillin potassium used in making the batch for potency, safety, moisture, pH, hetacillin content, identity, and crystallinity."

§ 440.141 [Amended]

38. Section 440.141 is amended by revising the section heading to read § 440.141 *Nafcillin sodium monohydrate oral dosage forms.*

§ 440.141a [Amended]

39. Section 440.141a *Sodium nafcillin monohydrate tablets* is amended as follows:

a. By changing "sodium nafcillin monohydrate" to read "nafcillin sodium monohydrate" in the section heading and in paragraph (a)(1).

b. By revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'nafcillin sodium tablets'."

c. By revising the text of paragraph (a)(3)(i)(*a*) to read "The nafcillin sodium monohydrate used in making the batch for potency, safety, moisture, pH, crystallinity, nafcillin content, and identity."

§ 440.141b [Amended]

40. Section 440.141b *Sodium nafcillin monohydrate capsules* is amended as follows:

a. By changing "sodium nafcillin monohydrate" to read "nafcillin sodium monohydrate" in the section heading and wherever it appears in paragraphs (a)(1) and (a)(3)(ii)(*a*).

b. By revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'nafcillin sodium capsules'."

c. By revising the text of paragraph (a)(3)(i)(*a*) to read "The nafcillin sodium monohydrate used in making the batch for potency, safety, moisture, pH, crystallinity, nafcillin content, and identity."

§ 440.141c [Amended]

41. Section 440.141c *Sodium nafcillin monohydrate for oral solution* is amended as follows:

a. By changing "sodium nafcillin monohydrate" to read "nafcillin sodium monohydrate" in the section heading and wherever it appears in paragraphs (a)(1) and (a)(3)(ii)(*a*).

b. By revising the second sentence of paragraph (a)(1) to read "When reconstituted as directed in the labeling, each milliliter contains the equivalent of 50 milligrams of nafcillin."

c. By revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'nafcillin sodium for oral solution'."

d. By revising the text of paragraph (a)(3)(i)(*a*) to read "The nafcillin sodium monohydrate used in making the batch for potency, safety, moisture, pH, crystallinity, nafcillin content, and identity."

§ 440.149 [Amended]

42. Section 440.149 is amended by revising the section heading to read § 440.149 *Oxacillin sodium monohydrate oral dosage forms.*

§ 440.149a [Amended]

43. Section 440.149a *Sodium oxacillin capsules* is amended as follows:

a. By changing "sodium oxacillin" to read "oxacillin sodium monohydrate" in the section heading and wherever it appears in paragraph (a)(1) and (a)(3)(ii)(*a*).

b. By revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'oxacillin sodium capsules'."

c. By revising the text of paragraph (a)(3)(i)(*a*) to read "The oxacillin sodium monohydrate used in making the batch for potency, safety, moisture, pH, oxacillin content, crystallinity, and identity."

§ 440.149b [Amended]

44. Section 440.149b *Sodium oxacillin for oral solution* is amended as follows:

a. By changing "sodium oxacillin" to read "oxacillin sodium monohydrate" in the section heading and wherever it appears in paragraph (a)(1) and (a)(3)(ii)(*a*).

b. By revising the second sentence of paragraph (a)(1) to read "When reconstituted as directed in the labeling, each milliliter contains the equivalent of either 25 milligrams or 50 milligrams of oxacillin."

c. By revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'oxacillin sodium for oral solution'."

d. By revising the text of paragraph (a)(3)(i)(*a*) to read "The oxacillin sodium monohydrate used in making the batch for potency, safety, moisture, pH, oxacillin content, crystallinity, and identity."

§ 440.153 [Revoked]

45. Section 440.153 *Aluminum penicillin tablets* is revoked.

§ 440.155 [Amended]

46. Section 440.155 is amended by revising the section heading to read § 440.155 *Penicillin G benzathine oral dosage forms.*

§ 440.155a [Revoked]

47. Section 440.155a *Benzathine penicillin G and crystalline penicillin tablets* is revoked.

§ 440.155b [Revoked]

48. Section 440.155b *Benzathine penicillin G and phenoxymethyl penicillin tablets* is revoked.

49. Section 440.155c is revised to read as follows:

§ 440.155c Penicillin G benzathine oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G benzathine oral suspension contains penicillin G benzathine with one or more suitable dispersing agents, buffer substances, preservatives, colorings, and flavorings. Each milliliter contains penicillin G benzathine equivalent to 30,000 units or 60,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. Its pH is not less than 6.0 and not more than 7.0. The penicillin G benzathine used conforms to the standards prescribed by § 440.55a (a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G benzathine used in making the batch for potency, safety, moisture, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency and pH.

(ii) Samples required:

(*a*) The penicillin G benzathine used in making the batch: 10 packages, each containing approximately 300 miligrams.

(*b*) The batch: A minimum of 5 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately measured representative volume of the sample in sufficient absolute methyl alcohol to give a solution of convenient concentration. Immediately further dilute with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, using a representative aliquot of the drug prepared for assay as described in paragraph (b)(2) of that section.

(2) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted sample.

50. Section 440.155d is added to read as follows:

§ 440.155d Penicillin G benzathine tablets.

(a)) *Requirements for certification*—(1) *Standards of identity, strength quality, and purity.* Penicillin G benzathine tablets contain penicillin G benzathine with one or more suitable and harmless diluents, binders, lubricants, colorings, and flavorings. Each tablet

contains penicillin G benzathine equivalent to 200,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. Its moisture content is not more than 8.0 percent. The tablets shall disintegrate within 1 hour. The penicillin G benzathine used conforms to the standards prescribed by § 440.55a(a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G benzathine used in making the batch for potency, safety, moisture, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, moisture, and disintegration time.

(ii) Samples required:

(*a*) The penicillin G benzathine used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency.* Using the penicillin G working standard as the standard of comparison, assay for potency by either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of tablets into a high-speed glass blender jar containing 200 milliliters of absolute methyl alcohol. Blend for 1 minute. Add an additional 300 milliliters of absolute methyl alcohol and blend again for 2 to 3 minutes. Immediately further dilute an aliquot with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, preparing the sample as follows: Weigh and finely powder six tablets. Transfer two accurately weighed portions of the tablets, each equivalent to 200,000 units of penicillin G, to two separate 100-milliliter volumetric flasks. Dilute one flask, which is to be used as the blank, to volume with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), and proceed as directed in § 436.204(d) of this chapter. In lieu of directions in § 436.204(e)(1), (2), and (3), to the other flask add 10 milliliters of 1.0*N* NaOH and mix well. Allow to stand for 15 minutes, then add 10 milliliters of 1.2*N* HCl, and dilute to volume with distilled water. Pipette a 2.0-milliliter aliquot into a 125-milliliter glass-stoppered Erlenmeyer flask and proceed as directed in § 436.204(c)(4) of this chapter.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Disintegration time.* Proceed as directed in § 436.212 of this chapter.

§ 440.157 [Amended]

51. Section 440.157 *Benzathine phenoxymethyl penicillin oral suspension* is amended as follows:

a. By changing "benzathine phenoxymethyl penicillin" to read "penicillin V benzathine" in the section heading, wherever it appears in paragraphs (a)(1), (a)(3)(i)(*a*), and (a)(3)(ii)(*a*).

b. By changing "phenoxymethyl penicillin" in paragraphs (a)(1), (a)(3)(i)(*a*), and (b)(1)(i) to read "penicillin V".

§ 440.160 [Revoked]

52. Section 440.160 *Dibenzylamine penicillin and potassium penicillin powder, buffered* is revoked.

§ 440.166 [Revoked]

53. Section 440.166 *Hydrabamine penicillin G oral suspension* is revoked.

§ 440.169 [Amended]

54. Section 440.169 is amended by revising the section heading to read § 440.169 *Penicillin V hydrabamine oral dosage forms.*

§ 440.169a [Amended]

55. Section 440.169a *Hydrabamine phenoxymethyl penicillin chewable tablets* is amended as follows:

a. By changing "hydrabamine phenoxymethyl penicillin" to read "penicillin V hydrabamine" in the section heading and wherever it appears in paragraphs (a)(1), (a)(2), (a)(3)(i)(*a*), (a)(3)(ii)(*a*).

b. By changing "phenoxymethyl penicillin" to read "penicillin V" in paragraphs a)(1), (a)(3)(i)(*a*), (b)(1), and (b)(1)(i).

§ 440.169b [Amended]

56. Section 440.169b *Hydrabamine phenoxymethyl penicillin oral suspension* is amended as follows:

a. By changing "hydrabamine phenoxymethyl penicillin" to read "pencillin V hydrabamine" in the section heading and wherever it appears in paragraphs (a)(1), (a)(3)(i)(*a*), and (a)(3)(ii)(*a*).

b. By changing "phenoxymethyl penicillin" to read "penicillin V" in paragraphs (a)(1), (a)(3)(i)(*a*), (b)(1), and (b)(1)(i).

§ 440.171 Penicillin V oral dosage forms.

57. Section 440.171 *Phenoxymethyl penicillin oral dosage forms* is revised to read as set forth above.

58. Section 440.171a is revised to read as follows:

§ 440.171a Penicillin V capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin V capsules are composed of penicillin V with one or more suitable and harmless lubricants. Each capsule contains either 125 milligrams (200,000 units) or 250 milligrams (400,000 units) of penicillin V. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its moisture content is not more than 2 percent. The penicillin V used conforms to the standards prescribed by § 440.71(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin V used in making the batch for potency, safety, moisture, pH, penicillin V content, and crystallinity.

(*b*) The batch for potency and moisture.

(ii) Samples required:

(*a*) The penicillin V used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of capsules into a high-speed glass blender jar containing sufficient absolute methyl alcohol to give a solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter. Immediately dilute an aliquot of the methyl alcohol solution with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the methyl alcohol with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

59. Section 440.171b is revised to read as follows:

§ 440.171b Penicillin V for oral suspension.

(a) *Requirements for certificatiton*—(1) *Standards of identity, strength, quality, and purity.* Penicillin V for oral suspension is composed of penicillin V with or without one or more suitable and harmless suspending agents, colorings, flavorings, and buffer substances. When reconstituted as directed in the labeling, each milliliter contains 25 milligrams (40,000 units), 50 milligrams (80,000 units) or 208.3 milligrams (333,333 units) of penicillin V. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its moisture content is not more than 1 percent. When reconstituted as directed in the labeling, its pH is not less than 2.0

and not more than 4.0. The penicillin V used conforms to the standards prescribed by § 440.71(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin V used in making the batch for potency, safety, moisture, pH, penicillin V content, and crystallinity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The penicillin V used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute as directed in the labeling. Dissolve an accurately measured representative volume of the sample in sufficient absolute methyl alcohol to give a solution of convenient concentration. Immediately further dilute an aliquot with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin V (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, preparing the sample as follows: Reconstitute as directed in the labeling. Dissolve an accurately measured representative portion of the sample in absolute methyl alcohol and dilute with 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the sample reconstituted as directed in the labeling.

60. The following new § 440.171c is added:

§ 440.171c Penicillin V tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin V tablets are composed of penicillin V with or without one or more suitable and harmless diluents, binders, lubricants, and colorings. Each tablet contains 125 milligrams (200,000 units), 300 milligrams (500,000 units), or 500 milligrams (800,000 units) of penicillin V. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its moisture content is not more than 3 percent. It shall disintegrate within 1 hour. The penicillin V used conforms to the standards prescribed by § 440.71(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin V used in making the batch for potency, safety, moisture, pH, penicillin V content, and crystallinity.

(*b*) The batch for potency, moisture, and disintegration time.

(ii) Samples required:

(*a*) The penicillin V used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of tablets into a high-speed glass blender jar containing sufficient absolute methyl alcohol to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter. Immediately dilute an aliquot of the methyl alcohol solution with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the methyl alcohol solution with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Disintegration time.* Proceed as directed in § 436.212 of this chapter.

§ 440.173 Penicillin V potassium oral dosage forms.

61. Section 440.173 *Potassium phenoxymethyl penicillin oral dosage forms* is revised to read as set forth above.

62. Section 440.173a is revised to read as follows:

§ 440.173a Penicillin V potassium capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin V potassium capsules are composed of penicillin V potassium and one or more suitable lubricants and fillers. Each capsule contains penicillin V potassium equivalent to 250 milligrams (400,000 units) or 500 milligrams (800,000 units) of penicillin V. The potency is satisfactory if it is not less than 90 percent and more than 115 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its loss on drying is not more than 2.0 percent. The penicillin V potassium used conforms to the standards prescribed by § 440.73(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin V potassium used in making the batch for potency, safety, loss on drying, pH, crystallinity, and penicillin V content.

(*b*) The batch for potency and loss on drying.

(ii) Samples required:

(*a*) The penicillin V potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of capsules into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Using the penicillin V working standard as the standard of comparison, assay by either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

63. Section 440.173b is revised to read as follows:

§ 440.173b Penicillin V potassium chewable tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin V potassium chewable tablets are composed of penicillin V potassium with suitable diluents, binders, buffers, colorings, and flavorings. Each tablet contains penicillin V potassium equivalent to 125 milligrams (200,000 units) or 250 milligrams (400,000 units) of penicillin V. Its potency is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams or units of penicillin V that it is represented to contain. The loss on drying is not more than 1.5 percent. The penicillin V potassium used conforms to the standards prescribed by § 440.73(a)(1).

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5 of this chapter, this drug shall be labeled "penicillin V potassium tablets".

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter,

each such request shall contain:

(i) Results of tests and assays on: (*a*) The penicillin V potassium used in making the batch for potency, safety, loss on drying, pH, penicillin V content, and crystallinity.

(*b*) The batch for potency and loss on drying.

(ii) Samples required:

(*a*) The penicillin V potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 30 tablets.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in §436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

64. The following § 440.173c is added:

§ 440.173c Penicillin V potassium tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin V potassium tablets are composed of penicillin V potassium with or without one or more suitable and harmless buffer substances, diluents, binders, lubricants, colorings, and flavorings. Each tablet contains penicillin V potassium equivalent to 125 milligrams (200,000 units), 250 milligrams (400,000 units), or 500 milligrams (800,000 units) of penicillin V. Its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its loss on drying is not more than 1.5 percent. It shall disintegrate within 1 hour. The penicillin V potassium used conforms to the standards prescribed by § 440.73(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on: (*a*) The penicillin V potassium used in making the batch for potency, safety, loss on drying, pH, penicillin V content and crystallinity.

(*b*) The batch for potency, loss on drying, and disintegration time.

(ii) Samples required:

(*a*) The penicillin V potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 36 tablets.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(3) *Disintegration time.* Proceed as directed in § 436.212 of this chapter.

65. The following new § 440.173d is added:

§ 440.173d Penicillin V potassium for oral solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin V potassium for oral solution is composed of penicillin V potassium with or without one or more suitable and harmless suspending agents, colorings, flavorings, buffer substances, and preservatives. When reconstituted as directed in the labeling, each milliliter contains penicillin V potassium equivalent to either 25 milligrams (40,000 units) or 50 milligrams (80,000 units) of penicillin V. Its potency is satisfactory if it contains not less than 90 percent and not more than 135 percent of the number of milligrams or units of penicillin V that it is represented to contain. Its moisture content is not more than 1 percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.5. The penicillin V potassium used conforms to the standards prescribed by § 440.73(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on: (*a*) The penicillin V potassium used in making the batch for potency, safety, loss on drying, pH, penicillin V content, and crystallinity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The penicillin V potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Dilute an accurately measured representative portion of the suspension with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin V per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the sample when reconstituted as directed in the labeling.

§ 440.174 [Revoked]

66. Section 440.174 *Procaine penicillin in oil capsules* is revoked.

§ 440.180 Penicillin G potassium oral dosage forms.

67. Section 440.180 *Penicillin oral dosage forms* is revised to read as set forth above.

68. Section 440.180a is revised to read as follows:

§ 440.180a Penicillin G potassium tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium tablets are composed of penicillin G potassium with or without one or more suitable and harmless buffer substances, dilutents, binders, lubricants, colorings, and flavorings. Each tablet contains penicillin G potassium equivalent to 100,000 units, 200,000 units, 250,000 units, 400,000 units, 500,000 units, 800,000 units or 1,000,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. Its loss on drying is not more than 1 percent. The tablets shall disintegrate within 1 hour. The penicillin G potassium used conforms to the standards prescribed by § 440.80a(a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeded in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G potassium used in making the batch for potency, safety, loss on drying, pH, penicillin G content, and crystallinity.

(*b*) The batch:

(*1*) If the person who requests certification is the manufacturer of the batch: Potency, loss on drying, and disintegration time of tablets collected during the time of tableting the batch; and, unless the tablets are packaged into dispensing-size containers immediately after they are compressed or the manufacturer has submitted to the Commissioner, and it has been accepted, information adequate to prove that such tests are not necessary, loss on drying of the tablets collected during each day of packaging the batch.

(*2*) If the person who requests certification is not the manufacturer of the batch: Potency, loss on drying, and disintegration time of tablets collected during each day the tablets are being packaged into dispensing-size containers.

(ii) Samples required:

(*a*) The penicillin G potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) If the person who requests certification is the manufacturer of the batch: A minimum of 36 tablets. If, after tableting, such person packaged the batch into dispensing-size containers: 20 tablets, collected at equal intervals during each day the tablets are being packaged, except that this sample is not required if the tablets are packaged immediately after they are compressed or if the manufacturer has been exempted by the Commissioner from such requirement.

(*2*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of tablets filled by such person into dispensing-size containers during each day's packaging operations): A minimum of 36 tablets collected by taking single tablets at such intervals throughout each day of packaging the tablets so that the quantities packaged during the intervals are approximately equal.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(3) *Disintegration time.* Proceed as directed in § 436.212 of this chapter.

§ 440.180b [Revoked]

69. Section 440.180b *Penicillin-streptomycin tablets; penicillin-dihydrostreptomycin tablets* is revoked.

70. Section 440.180c is revised to read as follows:

§ 440.180c Penicillin G potassium capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium capsules are composed of penicillin G potassium and a suitable and harmless diluent. Each capsule contains penicillin G potassium equivalent to 250,000 units or 400,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. Its loss on drying is not more than 1.5 percent. The penicillin G potassium used conforms to the standards prescribed by § 440.80a(a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G potassium used in making the batch for potency, safety, loss on drying, pH, pencillin G content, and crystallinity.

(*b*) *The batch:*

(*1*) If the person who requests certification is the manufacturer of the batch: Potency and loss on drying of capsules collected during the time of encapsulating the batch; and, unless the capsules are packaged into dispensing-size containers immediately after they are encapsulated or the manufacturer has submitted to the Commissioner, and it has been accepted, information adequate to prove that such tests are not necessary, loss on drying of capsules collected during each day of packaging the batch.

(*2*) If the person who requests certification is not the manufacturer of the batch: Potency and loss on drying of capsules collected during each day the capsules are being packaged into dispensing-size containers.

(ii) Samples required:

(*a*) The penicillin G potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) If the person who requests certification is the manufacturer of the batch: A minimum of 30 capsules. If after encapsulating, such person packaged the batch into dispensing-size containers: 20 capsules collected at equal intervals during each day the capsules are being packaged, except that this sample is not required if the capsules are packaged immediately after they are filled or if the manufacturer has been exempted by the Commissioner from such requirement.

(*2*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of capsules filled by such person into dispensing-size containers during each day's packaging operations): A minimum of 30 capsules collected by taking single capsules at such intervals throughout each day of packaging the capsules that the quantities packaged during the intervals are approximately equal.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of capsules into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

§ 440.180d [Revoked]

71. Section 440.180d *Penicillin and novobiocin capsules* is revoked.

§ 440.180e [Revoked]

72. Section 440.180e *Crystalline penicillin G oral suspension, crystalline penicillin G sodium oral suspension, potassium penicillin G oral suspension* is revoked.

73. Section 440.180f is revised to read as follows:

§ 440.180f Penicillin G potassium for oral solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium for oral solution contains penicillin G potassium and one or more suitable and harmless buffers, colorings, flavorings, diluents, and preservatives. Each milliliter contains penicillin G potassium equivalent to 20,000 units, 25,000 units, 40,000 units, 50,000 units, 80,000 units, or 100,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of units of penicillin G that it is represented to contain. Its moisture

content is not more than 1 percent. When reconstituted as directed in the labeling, its pH is not less than 5.5 and not more than 7.5. The penicillin G potassium used conforms to the standards prescribed by § 440.80a(a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G potassium used in making the batch for potency, safety, loss on drying, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(*a*) The penicillin G potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Transfer an accurately measured representative portion into a suitable volumetric flask and dilute to volume with 1 percent potassium phosphate buffer, pH 6.0 (solution 1).

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the solution obtained after reconstituting the drug as directed in the labeling.

74. The following § 440.180g is added to read as follows:

§ 440.180g Penicillin G potassium tablets for solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium tablets for solution are composed of penicillin G potassium. Each tablet contains penicillin G potassium equivalent to 100,000 units, 200,000 units, or 250,000 units of penicillin G. The potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. Its loss on drying is not more than 1 percent. The penicillin G potassium used conforms to the standards prescribed by § 440.80a(a)(1), except sterility and pyrogens.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to compling with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G potassium used in making the batch for potency, safety, loss on drying, pH, penicillin G content, and crystallinity.

(*b*) The batch:

(*1*) If the person who requests certification is the manufacturer of the batch: Potency and loss on drying of tablets collected during the time of tableting the batch; and, unless the tablets are packaged into dispensing-size containers immediately after they are compressed, or the manufacturer has submitted to the Commissioner, and it has been accepted, information adequate to prove that such tests are not necessary, loss on drying of the tablets collected during each day of packaging the batch.

(*2*) If the person who requests certification is not the manufacturer of the batch: Potency and loss on drying of the tablets collected during each day the tablets are being packaged into dispensing-size containers.

(ii) Samples required:

(*a*) The penicillin G potassium used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) If the person who requests certification is the manufacturer of the batch: A minimum of 30 tablets. If, after tableting, such person packaged the batch into dispensing-size containers: 20 tablets collected at equal intervals during each day the tablets are packaged, except that this sample is not required if the tablets are packaged immediately after they are compressed or if the manufacturer has been exempted by the Commissioner from such requirement.

(*2*) If the person who requests certification is not the manufacturer of the batch (for the purposes of certification, a batch shall be that number of tablets filled by such person into dispensing-size containers during each day's packaging operations): A minimum of 30 tablets collected by taking single tablets at such intervals throughout each day of packaging the tablets that the quantities packaged during the intervals are approximately equal.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Place a representative number of tablets into a high-speed glass blender jar containing sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Blend for 3 to 5 minutes.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

§ 440.209 [Amended]

75. Section 440.209 *Sterile sodium ampicillin* is amended by changing "sodium ampicillin" to read "ampicillin sodium" in the section heading and the text.

§ 440.213 [Amended]

76. Section 440.213 *Sterile disodium carbenicillin* is amended by changing "disodium carbenicillin" to read "carbenicillin disodium" in the section heading and the text.

§ 440.219 Dicloxacillin sodium monohydrate injectable dosage forms.

77. Section 440.219 *Sodium dicloxacillin monohydrate injectable dosage forms* is revised to read as set forth above.

§ 440.219a [Amended]

78. Section 440.219a *Sterile sodium dicloxacillin monohydrate* is amended by changing "sodium dicloxacillin monohydrate" to read "dicloxacillin sodium monohydrate" in the section heading and the text.

§ 440.219b [Amended]

79. Section 440.219b *Sodium dicloxacillin monohydrate for injection* is amended as follows:

a. By changing "sodium dicloxacillin monohydrate" to read "dicloxacillin sodium monohydrate" in the section heading and in paragraphs (a)(1), (a)(3)(i)(*a*) and (a)(3)(ii)(*a*).

b. By revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'dicloxacillin sodium for injection'."

§ 440.229 Hetacillin potassium injectable dosage forms.

80. Section 440.229 *Potassium hetacillin injectable dosage forms* is revised to read as set forth above.

§ 440.229a [Amended]

81. Section 440.229a *Sterile potassium hetacillin* is amended by changing "potassium hetacillin" to read "hetacillin potassium" in the section heading and the text.

§ 440.229b [Amended]

82. Section 440.229b *Potassium hetacillin for injection* is amended as follows:

a. by changing "potassium hetacillin" to read "hetacillin potassium" in the section heading and wherever it appears in paragraphs (a)(1), (a)(3)(ii)(*a*) and (b)(4).

b. By revising the text of paragraph (a)(3)(i)(*a*) to read "The hetacillin potassium used in making the batch for potency, moisture, pH, hetacillin content, identity, and crystallinity."

§ 440.236 [Amended]

83. Section 440.236 *Sodium methicillin for injection* is amended as follows:

a. By changing "sodium methicillin" to read "methicillin sodium monohydrate" in the section heading and wherever it appears in paragraphs (a)(1) and (a)(3)(ii)(*a*).

b. By revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'methicillin sodium for injection'."

c. By revising the text of paragraph (a)(3)(i)(*a*) to read "The methicillin sodium monohydrate used in making the batch for potency, moisture, pH, methicillin content, crystallinity, and identity."

§ 440.241 [Amended]

84. Section 440.241 *Sodium nafcillin monohydrate for injection* is amended as follows:

a. By changing "sodium nafcillin monohydrate" to read "nafcillin sodium monohydrate" in the section heading and wherever it appears in paragraph (a)(1) and (a)(3)(ii)(*a*).

b. By revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'nafcillin sodium for injection'."

c. By revising the text of paragraph (a)(3)(i)(*a*) to read "The nafcillin sodium monohydrate used in making the batch for potency, moisture, pH, crystallinity, nafcillin content, and identity."

§ 440.249 [Amended]

85. Section 440.249 *Sodium oxacillin for injection* is amended as follows:

a. By changing "sodium oxacillin" to read "oxacillin sodium monohydrate" in the section heading and wherever it appears in paragraphs (a)(1) and (a)(3)(ii)(*a*).

b. By revising the text of paragraph (a)(2) to read "In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled 'oxacillin sodium for injection'."

c. By revising paragraph (a)(3)(i)(*a*) to read "The oxacillin sodium monohydrate used in making the batch for potency, moisture, pH, oxacillin content, crystallinity, and identity."

§ 440.253 [Revoked]

86. Section 440.253 *Aluminum penicillin in oil* is revoked.

§ 440.255 Penicillin G benzathine injectable dosage forms.

87. Section 440.255 *Benzathine penicillin G injectable dosage forms* is revised to read as set forth above.

§ 440.255a [Revoked]

88. Section 440.255a *Benzathine penicillin G in oil* is revoked.

89. Section 440.255b is revised to read as follows:

§ 440.255b Sterile penicillin G benzathine suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile penicillin G benzathine suspension is an aqueous suspension of penicillin G benzathine and one or more suitable suspending or dispersing agents, buffer substances, and preservatives. Each container or each milliliter contains penicillin G benzathine equivalent to 300,000 units or 600,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. It passes the safety test. Its pH is not less than 5.0 and not more than 7.5. The penicillin G benzathine used conforms to the standards prescribed by § 440.55a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G benzathine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, sterility, pyrogens, safety, and pH.

(ii) Samples required:

(*a*) The penicillin G benzathine used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or if the labeling specifies the amount of potency in a given volume, remove an accurately measured representative portion from each container. Dilute the portion thus obtained with sufficient absolute methyl alcohol to give a solution of convenient concentration. Immediately further dilute with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single-dose container; or if the labeling specifies the amount of potency in a given volume, remove an accurately measured representative portion from each container. Using the sample thus obtained, proceed as directed in § 436.204(b)(2) of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(2) of that section, except use medium C in lieu of medium A, and medium F in lieu of medium E. During the period of incubation, shake the tubes at least once daily.

(3) *Pyrogens.* Proceed as directed in § 436.32(d) of this chapter, using a solution containing 4,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *pH* Proceed as directed in § 436.202 of this chapter, using the undiluted sample.

90. Section 440.255c is revised to read as follows:

§ 440.255c Sterile penicillin G benzathine-penicillin G procaine suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile penicillin G benzathine-penicillin G procaine suspension is an aqueous mixture of penicillin G benzathine and penicillin G procaine with or without suitable and harmless buffer substances, suspending agents, and preservatives. Each container or each milliliter contains penicillin G benzathine and penicillin G procaine each equivalent to either 150,000 units or 300,000 units. Its penicillin G benzathine content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. Its penicillin G procaine content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. It passes the safety test. Its pH is not less than 5.0 and not more than 7.5. The penicillin G benzathine used conforms to the standards prescribed by § 440.55a(a)(1). The penicillin G procaine used conforms to the standards prescribed by § 440.74a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G benzathine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(*b*) The penicillin G procaine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(*c*) The batch for penicillin G benzathine content, penicillin G procaine content, sterility, pyrogens, safety, and pH.

(ii) Samples required:

(*a*) The penicillin G benzathine used in making the batch: 10 packages, each

containing approximately 500 milligrams.

(b) The penicillin G procaine used in making the batch: 10 packages, each containing approximately 500 milligrams.

(c) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Total potency.* Assay for total potency by either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(a) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Using a suitable hypodermic needle and syringe, place one dose of the drug in a 100-milliliter volumetric flask and add sufficient methyl alcohol to dissolve the benzathine penicillin G. Dilute to volume with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), and shake well. Immediately further dilute an aliquot with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(b) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, preparing the sample as follows: Using a suitable hypodermic needle and syringe, withdraw 2 one-dose portions of sample. Place one portion into an appropriate-sized volumetric flask and add 20 milliliters of 0.5*N* NaOH for each 300,000 units of benzathine penicillin G, mix well, being sure that all penicillin is in solution, and allow to stand for 15 minutes. Add 1 milliliter of 1.2*N* HCl for each 2 milliliters of 0.5*N* NaOH, mix, and dilute with distilled water to obtain a concentration of 2,000 units per milliliter. Dilute the other portion, which is to be used as the blank solution, with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a concentration of approximately 2,000 units per milliliter.

(ii) *Penicillin G procaine content*—(a) *Reagents*—(1) *Sodium nitrite solution.* Dissolve 0.1 gram of sodium nitrite in 100 milliliters of distilled water. Prepare a fresh solution every week and store under refrigeration.

(2) *Ammonium sulfamate solution.* Dissolve 0.5 gram of ammonium sulfamate in 100 milliliters of distilled water and store under refrigeration.

(3) *N-(1-naphthyl)-ethylenediamine solution.* Dissolve 0.1 gram of *N*-(1-naphthyl) - ethylenediamine dihydrochloride in 100 milliliters of distilled water. Prepare fresh solutions every week and store under refrigeration.

(4) *Standard procaine solution.* Prepare a standard solution containing 27.55 milligrams of procaine hydrochloride U.S.P. in a liter of distilled water (each milliliter of the standard solution is equivalent to 60 units of penicillin G procaine).

(b) *Preparation of sample solution.* Using a suitable hypodermic needle and syringe, withdraw a one dose portion of the sample and place it into an appropriate-sized volumetric flask. Add 20 milliliters of 0.5*N* NaOH for each 300,000 units of penicillin G benzathine, mix well, being sure that all penicillin is in solution, and allow to stand for 15 minutes. Add 1 milliliter of 1.2*N* HCl for each 2 milliliters of 0.5*N* NaOH, mix, and dilute with distilled water to obtain a concentration of 60 units of penicillin G procaine per milliliter. Transfer a 3.0-milliliter aliquot of this solution to a 50-milliliter volumetric flask and add 2 milliliters of water to give a volume of 5 milliliters.

(c) *Procedure.* Transfer respectively, 1.0, 2.0, 3.0, 4.0, and 5.0 milliliters of the standard procaine solution to each of five 50-milliliter volumetric flasks and transfer 5.0 milliliters of distilled water to a sixth 50-milliliter volumetric flask. Add 4.0, 3.0, 2.0, and 1.0 milliliters of water to the first four flasks, respectively, to give each a volume of 5 milliliters. To each flask of the standard and sample solutions, add 0.5 milliliter of 4*N* HCl, 1.0 milliliter of sodium nitrite solution, 1.0 milliliter of ammonium sulfamate solution, and 1.0 milliliter of *N*-(1-naphthyl)-ethylenediamine solution. Mix and wait two minutes after each addition. Dilute each flask to volume with distilled water. Using a sutable photoelectric colorimeter, determine the absorbancy of each solution at 550 nanometers. The instrument is balanced so that the zero concentration reads 0 absorbancy. Plot the standard curve on coordinate graph paper. Obtain the procaine penicillin content of the solution for assay directly from the point on the standard curve corresponding to its absorbancy.

(iii) *Penicillin G benzathine content.* The sum of the penicillin G procaine content determined as directed in paragraph (b)(1)(ii) of this section subtracted from the total potency determined as directed in paragraph (b)(1)(i) of this section represents the penicillin G benzathine content.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(2) of that section, except use medium C in lieu of medium A, medium F in lieu of medium E, and during the period of incubation, shake the tubes at least once daily.

(3) *Pyrogens.* Proceed as directed in § 436.32(d) of this chapter, using a solution containing 4,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted aqueous suspension.

91. Section 440.255d is added to read as follows:

§ 440.255d Sterile penicillin G benzathine for suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile penicillin G benzathine for suspension is a dry mixture of penicillin G benzathine and one or more suitable suspending or dispersing agents, and with or without one or more suitable preservatives and buffer substances. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. It passes the safety test. Its moisture content is not less than 5.0 percent and not more than 8.0 percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.5. The penicillin G benzathine used conforms to the standards prescribed by § 440.55a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The penicillin G benzathine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(b) The batch for potency, sterility, pyrogens, safety, moisture, and pH.

(ii) Samples required:

(a) The penicillin G benzathine used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch:

(1) If the batch is packaged for repacking:

(i) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(ii) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(2) If the batch is packaged for dispensing:

(i) For all tests except sterility: A minimum of 10 immediate containers.

(ii) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dissolve the portion thus obtained with sufficient absolute methyl alcohol to give a solution of convenient concentration. Immediately, further dilute with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the

reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, preparing the sample as follows: Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Using the sample thus obtained, proceed as directed in § 436.204(b)(2) of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(2) of that section, except use medium C in lieu of medium A, and medium F in lieu of medium E. During the period of incubation shake the tubes at least once daily.

(3) *Pyrogens.* Proceed as directed in § 436.32(d) of this chapter, using a solution containing 4,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using the suspension obtained when the product is reconstituted as directed in the labeling.

§ 440.259 [Revoked]

92. Section 440.259 *Chloroprocaine pencillin O for aqueous injection* is revoked.

§ 440.261 [Revoked]

93. Section 440.261 *Diethylaminoethyl ester penicillin G hydriodide for aqueous injection (penicillin G diethylaminoethyl ester hydriodide for aqueous injection)* is revoked.

§ 440.265 [Revoked]

94. Section 440.265 *1-ephenamine penicillin G injectable dosage forms* is revoked.

§ 440.265a [Revoked]

95. Section 440.265a *1-ephenamine penicillin G in oil* is revoked.

§ 440.265b [Revoked]

96. Section 440.265b *1-ephenamine penicillin G for aqueous injection* is revoked.

§ 440.274 Penicillin G procaine injectable dosage forms.

97. Section 440.274 *Procaine penicillin G injectable dosage forms* is revised to read as set forth above.

98. Section 440.274a is revised to read as follows:

§ 440.274a Sterile penicillin G procaine with aluminum stearate suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile penicillin G procaine with aluminum stearate suspension is penicillin G procaine in a refined vegetable oil with one or more suitable and harmless dispersing agents and hardening agents. Each milliliter contains penicillin G procaine equivalent to 300,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. Its moisture content is not more than 1.4 percent. The penicillin G procaine used conforms to the standards prescribed by § 440.74a(a)(1). If the hardening agent is a refined hydrogenated and deodorized peanut oil, it is free from rancidity; it has an iodine value of not more than 10; its free fatty acid content as oleic acid is not more than one-tenth of 1 percent and its melting point is 64° C±2° C.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G procaine used in making the batch for potency, pyrogens, safety, moisture, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, sterility, and moisture.

(ii) Samples required:

(*a*) The penicillin G procaine used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 5 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place an accurately measured representative portion of the sample or the entire contents of a single dose container into a 50-milliliter volumetric flask. Add 4 milliliters of chloroform and mix thoroughly. Dilute to volume with absolute ethyl alcohol. Mix well. Immediately further dilute with sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to the reference concentration of 1 unit of penicillin G per milliliter (estimated).

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(2) of that section, except use medium B in lieu of medium A.

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter.

99. Section 440.274b is revised to read as follows:

§ 440.274b Sterile penicillin G procaine suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile penicillin G procaine suspension is an aqueous mixture of penicillin G procaine and one or more suitable suspending or dispersing agents, buffer substances, and preservatives. It may contain procaine hydrochloride in a concentration not exceeding 2.0 percent and one or more suitable stabilizing agents. Each container or each milliliter contains penicillin G procaine equivalent to 300,000 units, 500,000 units, or 600,000 units of penicillin G. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. It passes the safety test. Its pH is not less than 5.0 and not more than 7.5. The penicillin G procaine used conforms to the standards prescribed by § 440.74a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G procaine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, sterility, pyrogens, safety, and pH.

(ii) Samples required:

(*a*) The penicillin G procaine used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of 10 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents, if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume, remove an accurately measured representative portion from each container. Dissolve the sample thus obtained in 50 to 100 milliliters of absolute methyl alcohol and add sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Immediately further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, preparing the sample as follows: Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents, if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume, remove an accurately measured representative portion from each container. Dissolve and dilute the sample thus obtained with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to be prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except add sufficient penicillinase to diluting fluid A and swirl the flask to completely solubilize the procaine penicillin before filtration. If the product contains lecithin, use diluting fluid D in lieu of diluting fluid A. If the product contains sodium carboxymethylcellulose, add sufficient sterile carboxymethylcellulase to diluting fluid A or D to completely solubilize the sodium carboxymethylcellulose before filtration. If the preparation contains homogenizers or suspending agents that prevent solubilization, proceed as directed in paragraph (e)(2) of that section, except use medium B in lieu of medium A.

(3) *Pyrogens.* Proceed as directed in § 436.32(a), using a solution containing 2,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted drug.

100. The following new § 440.274c is added:

§ 440.274c Sterile penicillin G procaine for suspension.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Sterile penicillin G procaine for suspension is a dry mixture of penicillin G procaine and one or more suitable suspending or dispersing agents, buffer substances, and preservatives. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. It passes the safety test. Its moisture content is not less than 2.8 and not more than 4.2 percent. When reconstituted as directed in the labeling, its pH is not less than 5.0 and not more than 7.5. The penicillin G procaine used conforms to the standards prescribed by § 440.74a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The penicillin G procaine used in making the batch for potency, moisture, pH, penicillin G content, and crystallinity.

(*b*) The batch for potency, sterility, pyrogens, safety, moisture, and pH.

(ii) Samples required:

(*a*) The penicillin G procaine used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) If the batch is packaged for repacking:

(*i*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*ii*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(*2*) If the batch is packaged for dispensing:

(*i*) For all tests except sterility: A minimum of 10 immediate containers.

(*ii*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay—*(1) *Potency.* Use either of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(i) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: If it is packaged for repacking, dissolve an accurately weighed sample, equivalent to one dose, in 50 to 100 milliliters of absolute methyl alcohol and add sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. If it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic syringe and needle, remove all of the withdrawable contents, if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dissolve the sample thus obtained in 50 to 100 milliliters of absolute methyl alcohol and add sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration. Immediately further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, preparing the sample as follows: If it is packaged for repacking, dissolve and dilute an accurately weighed sample, equivalent to one dose, with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the prescribed concentration. If it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents, if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume, remove an accurately measured representative portion from each container. Dissolve and dilute the sample thus obtained with 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except add sufficient penicillinase to diluting fluid A and swirl the flask to completely solubilize the procaine penicillin before filtration. If the product contains lecithin, use diluting fluid D in lieu of diluting fluid A. If the product contains sodium carboxymethylcellulose, add sufficient sterile carboxymethylcellulose to diluting fluid A or D to completely solubilize the sodium carboxymethylcellulose before filtration. If the preparation contains homogenizers or suspending agents that prevent solubilization, proceed as directed in paragraph (e)(2) of that section, except use medium B in lieu of medium A.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) using a solution containing 2,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using the suspension obtained when reconstituted as directed in the labeling.

§ 440.280 Penicillin G potassium injectable dosage forms.

101. Section 440.280 *Penicillin injectable dosage forms* is revised to read as set forth above.

§ 440.280a [Amended]

102. Section 440.280a *Sterile sodium penicillin, calcium penicillin, crystalline penicillin (crystalline penicillin sodium, crystalline penicillin potassium, crystalline penicillin G sodium, crystalline penicillin G potassium, crystalline penicillin O sodium, crystalline penicillin O potassium)* is amended by changing the name to read "Sterile penicillin G potassium" in the section heading and in the text.

103. Section 440.280b is revised to read as follows:

§ 440.280b Penicillin G potassium for injection.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium for injection is a dry mixture of penicillin G potassium and the buffer sodium citrate in a quantity not less than 4.0 percent and not more than 5.0 percent by weight of its total solids. It may contain citric acid in a quantity not more than 0.15 percent of its total solids in place of a corresponding amount of sodium citrate. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. It passes the safety test. Its loss on drying is not more than 1.5 percent. Its pH is not less than 6.0 and not more than 8.5. The penicillin G potassium, buffered, used conforms to the standards prescribed by § 440.1080a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on: (*a*) The penicillin G potassium, buffered, used in making the batch for potency,

loss on drying, pH, penicillin G content, and crystallinity.

(b) The batch for potency, sterility, pyrogens, safety, loss on drying, and pH.

(ii) Samples required: (a) The penicillin G potassium, buffered, used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Then, using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove or expel an accurately measured representative portion from each container. Dilute with solution 1 to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(a) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(b) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(c) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 2,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter or, if the diluent is included in a disposable syringe combination, use the solution obtained when the drug is reconstituted as directed in the labeling.

§ 440.280c [Revoked]

104. Section 440.280c *Crystalline penicillin and bacitracin* is revoked.

§ 440.280d [Revoked]

105. Section 440.280d *Crystalline penicillin and epinephrine in oil* is revoked.

§ 440.281 Penicillin G sodium injectable dosage forms.

106. Section 440.281 *Buffered crystalline penicillin* is revised to read as set forth above.

107. The following new section § 440.281a is added to read as follows:

§ 440.281a Sterile penicillin G sodium.

The requirements for certification and the tests and methods of assay for sterile penicillin G sodium packaged for dispensing are described in § 440.81a.

108. Section 440.281b is added to read as follows:

§ 440.281b Penicillin G sodium for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G sodium for injection is a dry mixture of penicillin G sodium and the buffer sodium citrate in a quantity not less than 4.0 percent and not more than 5.0 percent by weight of its total solids. It may contain citric acid in a quantity not more than 0.15 percent of its total solids in place of a corresponding amount of sodium citrate. Its potency is satisfactory if it is not less than 6.0 and not more than than 120 percent of the number of units of penicillin G that it is represented to contain. It is sterile. It is nonpyrogenic. It passes the safety test. Its loss on drying is not more than 1.5 percent. Its pH is not less than 6.0 and not more than 7.5. The penicillin G sodium, buffered, used conforms to the standards prescribed by § 440.1081a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on: (a) The penicillin G sodium, buffered, used in making the batch for potency, loss on drying, pH, penicillin G content, crystallinity, and heat stability.

(b) The batch for potency, sterility, pyrogens, safety, loss on drying, and pH.

(ii) Samples required: (a) The penicillin G sodium, buffered, used in making the batch: 10 packages, each containing approximately 60 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents if it is represented as a single dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. Dilute with solution 1 to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(a) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(b) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(c) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 2,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of thischapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

Subparts D–J—[Reserved]

§ 440.563 [Revoked]

109. Subpart F, consisting of § 440.563 *Ephedrine penicillin tablets,* is revoked.

110. New Subpart K, consisting of new §§ 440.1080a and 440.1081a, is added to Part 440 to read as follows:

Subpart K—Bulk Drug Formulations for Repacking or for Manufacturing Use

§ 440.1080a Sterile penicillin G potassium buffered.

(a) *Requirements for certification.*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G potassium, buffered, is a dry mixture of penicillin G potassium and the buffer sodium citrate in a quantity not less than 4.0 percent and not more than 5.0 percent by weight of its total solids. It may contain citric acid in a quantity not more than 0.15 percent of its total solids in place of a corresponding amount of sodium citrate. The sodium citrate and citric acid used in making the batch must conform to all U.S.P. specifications. It is so purified and dried that:

(i) Its potency is not less than 1,355 units and not more than 1,595 units per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) It passes the safety test.

(v) Its loss on drying is not more than 1.5 percent.

(vi) Its pH is not less than 6.0 and not more than 8.5.

(vii) Its penicillin G content is not less than 76.3 percent and not more than 89.8 percent.

(viii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, safety, loss on drying, pH, penicillin G content, and crystallinity.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay.*—(1) *Potency.*—(i) *Sample preparation.* Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(*c*) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 2,000 units of penicillin G per milliliter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

(7) *Penicillin G content.* Proceed as directed in § 436.316 of this chapter.

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

§ 440.1081a Sterile penicillin G sodium, buffered.

(a) *Requirements for certification.*—(1) *Standards of identity, strength, quality, and purity.* Penicillin G sodium, buffered, is a dry mixture of penicillin G sodium and the buffer sodium citrate in a quantity not less than 4.0 percent and not more than 5.0 percent by weight of its total solids. It may contain citric acid in a quantity not more than 0.15 percent of its total solids in place of a corresponding amount of sodium citrate. The sodium citrate and citric acid used in making the batch must conform to all U.S.P. specifications. It is so purified and dried that:

(i) Its potency is not less than 1,420 units and not more than 1,667 units per milligram.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) It passes the safety test.

(v) Its loss on drying is not more than 1.5 percent.

(vi) Its pH is not less than 6.0 and not more than 7.5.

(vii) Its penicillin G content is not less than 80 percent and not more than 93.8 percent.

(viii) It is crystalline.

(ix) It passes the test for heat stability if it does not show a loss of more than 10 percent of its original potency.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, safety, loss on drying, pH, penicillin G content, crystallinity, and heat stability.

(ii) Samples required:

(*a*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(*b*) For sterility testing: 20 packages, each containing approximately 600 milligrams.

(b) *Tests and methods of assay.*—(1) *Potency.*—(i) *Sample preparation.* Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration.

(ii) *Assay procedures.* Assay for potency by any of the following methods; however, the results obtained from the iodometric assay shall be conclusive.

(*a*) *Microbiological agar diffusion assay.* Proceed as directed in § 436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 unit of penicillin G per milliliter (estimated).

(*b*) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(*c*) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter, diluting an aliquot of the stock solution with solution 1 to the prescribed concentration.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 2,000 units of penicillin G per millimeter.

(4) *Safety.* Proceed as directed in § 436.33 of this chapter.

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

(7) *Penicillin G content.* Proceed as directed in § 436.316 of this chapter.

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(9) *Heat stability.* Proceed as directed in § 436.214 of this chapter.

PART 460—ANTIBIOTIC DRUGS INTENDED FOR USE IN LABORATORY DIAGNOSIS OF DISEASE

d. In Part 460, the following authority citation is added to precede the "source" note in the table of contents:

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

Effective date: This amendment shall become effective December 22, 1977 except that the effective date for revising the nonproprietary names (e.g., "phenoxymethyl penicillin to penicillin V" and "Sodium penicillin G to penicillin G sodium" shall be May 22, 1978. Any preparation under this order that is labeled after May 22, 1978 and does not bear the appropriate revised name is misbranded.

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

Dated: November 11, 1977.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc.77-33332 Filed 11-21-77;8:45 am]

[4110-03]

SUBCHAPTER F—BIOLOGICS

[Docket No. 75N-0312]

BLOOD PRODUCTS

Single Donor Plasma (Human)

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This document issues Additional Standards for Single Donor Plasma (Human) products. These standards contain many of the provisions of the "Minimum Requirements: Single Donor Plasma (Human)," which were developed in 1954 and published in uncodified form by the Department of Health, Education, and Welfare, together with changes and additions that reflect more recent experience and scientific knowledge.

DATES: Effective November 22, 1977, except that the effective date for labeling requirements is May 22, 1978.

FOR FURTHER INFORMATION CONTACT:

Al Rothschild, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, Md. 20014, 301-443-1920.

SUPPLEMENTARY INFORMATION: The Commissioner of Food and Drugs proposed in the FEDERAL REGISTER of November 11, 1975 (40 FR 52619) to amend Part 640 (21 CFR Part 640) by adding new Subpart D to prescribe Additional Standards for Single Donor Plasma (Human) products. The shipping temperatures and dating periods for Single Donor Plasma (Human) products including Recovered Plasma (Human) were also proposed as amendments to §§ 600.15 and 610.53, (21 CFR 600.15 and 610.53) respectively.

Single Donor Plasma (Human) is the fluid portion of one unit of human blood intended for intravenous use which, in a closed system, has been collected, stabilized against clotting, and separated from the cells. The manner in which the Single Donor Plasma (Human) is processed determines the uses and names by which it is known.

Interested persons were given until January 12, 1976 to file written comments with the Hearing Clerk, Food and Drug Administration. Fifty-nine letters, each containing a number of comments, were received. The comments and the Commissioner's responses are as follows:

1. Ten comments on the proposal's preamble questioned the indication for use of Single Donor Plasma (Human) for the treatment of hypovolemia (abnormally decreased volume of circulating fluid [plasma] in the body); the use of plasma separated from blood 26 days after blood collection; and the use of freshly frozen Single Donor Plasma (Human) for the treatment of Factor IX deficiencies, since Factor IX is not labile. In addition, the comments suggested other uses of Single Donor Plasma (Human) products, such as for clotting defects associated with liver disease and hemorrhagic disorders. These additional uses were not identified in the proposal.

The Commissioner recognizes that there are differences of opinion in the medical community concerning uses of Single Donor Plasma (Human) products, as suggested by the comments. For this reason, and in accordance with § 601.25 (21 CFR 601.25), he has requested that the Panel on Review of Blood and Blood Derivatives review available data and recommend appropriate uses for each Single Donor Plasma (Human) product. In the interim, the Commissioner advises that FDA will continue to approve labeling for those indications for which the products have been routinely used in the past. The Commissioner will propose to amend the additional standards for Single Donor Plasma (Human), if necessary, in implementing the Panel recommendations.

2. Three comments on proposed §§ 600.15 and 610.53 asked why Single Donor Plasma (Human) and Single Donor Plasma (Human) with factors removed should be required to be shipped and stored at −18° C and suggested that ambient temperature is adequate.

The Commissioner advises that the −18° C shipping and storage temperature is necessary to prevent degradation and leaching of the phthalate plasticizer from the plasma container during the 5-year dating period. Such leaching may occur at higher temperatures, particularly above freezing. Additionally, −18° C is a temperature at which cold-growing and other microbial organisms do not multiply should there be any contamination during collection of the source material. Accordingly, the comments are rejected.

3. Seventeen comments on proposed §§ 600.15 and 610.53 said that the categories of Single Donor Plasma (Human) products are excessive. Three of these comments questioned the need for Single Donor Plasma (Human), Platelet Rich, since it is now seldom used because of the availability of the platelet concentrate preparation. The majority of the comments suggested that there is no justification for labeling units as having had Platelet Concentrate (Human) Removed, since this component would not be present in a viable condition in the plasma, unless specifically processed as required for Single Donor Plasma (Human), Platelet Rich. Six comments questioned the need for the label Single Donor Plasma (Human), Cryoprecipitated Antihemophilic Factor Removed, since, unless the plasma was separated and frozen as required for Single Donor Plasma (Human), Fresh Frozen, the antihemophilic factor would not be available for therapeutic use. Six comments recommended that the categories of products include liquid Single Donor Plasma (Human) with suggested dating periods of 26 days, 30 days, 90 days, or 1 year.

The Commissioner advises that the need to include Single Donor Plasma (Human), Platelet Rich, as a specific category has been reviewed by the Panel on Review of Blood and Blood Derivatives. It is their opinion that Single Donor Plasma (Human), Platelet Rich, is a useful product, and although it does not offer the advantage of the concentrate, there is no reason not to designate it as an acceptable category of Single Donor Plasma (Human).

It has been the practice to use descriptive terms, in addition to the proper name, to advise users that a component has been removed by physical means, to differentiate it from a final product not subjected to this additional processing. However, with the publication of Current Good Manufacturing Practices for Blood and Blood Components (21 CFR Part 606), products must be processed according to published Additional Standards, thereby standardizing production techniques. Accordingly, the Commissioner accepts the comments, and §§ 600.15 and 610.53 are revised to delete all categories except Single Donor Plasma (Human); Single Donor Plasma (Human), Fresh Frozen; and Single Donor Plasma (Human), Platelet Rich.

On the other hand, the Commissioner is also adding to §§ 600.15 and 610.53 a fourth category, Single Donor Plasma (Human), Liquid, with a dating period of 26 days. This is consistent with the requirement that Single Donor Plasma (Human) be separated from whole blood within 26 days after collection, thereby limiting the exposure of Single Donor Plasma (Human), Liquid, to any additional extraction of phthalate from the polyvinyl chloride containers currently in use. In addition, § 600.15(a) is being amended for Single Donor Plasma (Human), Platelet Rich to be consistent with the amendment published in the FEDERAL REGISTER of February 25, 1977 (42 FR 10982) modifying the shipping temperature for Platelet Concentrate (Human).

4. Five comments on proposed § 610.53 recommended that Single Donor Plasma (Human), Fresh Frozen, be stored at −30° C or colder for the best preservation of the antihemophilic factor.

The Commissioner is aware that the stability of the product is slightly increased at the colder temperature. However, he believes that the slight increase in stability obtained with −30° C is outweighed by the consequent burden on processors and users to purchase additional freezers capable of maintaining −30° C storage temperature. The Panel on Review of Blood and Blood Derivatives also considered this question and agreed that existing data demonstrate adequate stability with −18° C storage. Accordingly, the comments are rejected.

5. One comment on proposed § 610.53 asked why Single Donor Plasma (Human) was given a dating period of 5 years, while Single Donor Plasma (Human), Fresh Frozen, was given a dating period of only 1 year.

The Commissioner advises that the labile clotting factor, Factor VIII, which is present in Single Donor Plasma (Human), Fresh Frozen, may not be stable when stored for more than 1 year. To assure satisfactory potency of this factor, the fresh frozen product must be stored for not more than 1 year at the required storage temperature.

6. One comment on proposed § 640.30 (a) suggested that the definition be changed to state that the plasma has been separated from red blood cells rather than from "cells."

The Commissioner agrees that the term "cells" is intended to mean red blood cells. The comment is accepted, and § 640.30(a) of the final regulations is amended accordingly.

7. Three comments on proposed § 640.-30(a) objected to the requirement that a closed system be used to separate Single quires use of blood collection containers with attached satellites. One of these comments said there are occasional needs to prepare Cryoprecipitated Antihemo-

philic Factor (Human) from a unit of Single Donor Plasma (Human) that has no satellite container and questioned what could be done with the remaining plasma.

Blood intended for processing into Single Donor Plasma (Human) must be collected in a closed system requiring containers with attached satellites to preclude the possibility of contamination of the plasma and the red blood cells during separation. The Commissioner concludes that the benefits obtained from collection in a closed system far outweigh the extra cost of using the required containers with satellites. Accordingly, the comment objecting to the use of a closed system is rejected.

For clarification, it should be noted that Whole Blood (Human) may be collected in containers without satellites. However, plasma separated from such containers of blood may not be labeled as Single Donor Plasma (Human), but must be labeled as Recovered Human Plasma for further manufacturing. The regulations concerning Cryoprecipitated Antihemophilic Factor (Human), §§ 640.50 through 640.56 as amended in the FEDERAL REGISTER of April 29, 1977 (42 FR 21772), require that it must be collected and processed in a closed system. The plasma remaining after separation of Cryoprecipitated Antihemophilic Factor (Human) may be labeled as Single Donor Plasma (Human). If a unit of Single Donor Plasma (Human) has, for any reason, been entered during processing, the plasma must be labeled Recovered Human Plasma and not Single Donor Plasma (Human).

8. One comment on proposed § 640.30 (b) suggested revision to reverse the sequence of the wording since more Single Donor Plasma (Human) is collected from whole blood donors than is collected by plasmapheresis.

The Commissioner agrees with this comment, and the sequence is reversed accordingly.

9. Three comments on proposed § 640.31(c) questioned the intent of the paragraph and suggested that if it was to eliminate donors who might transmit hepatitis B surface antigen (HB_sAg) due to recent exposure to blood products, this prohibition should be stated directly. Two of these comments said the paragraph is unnecessarily restrictive since immunized individuals would be prevented from being Single Donor Plasma (Human) donors even though they may be free of demonstrable antibodies. One of these comments suggested that a test for unexpected antibodies be required of all donors or that the units of Single Donor Plasma (Human) be crossmatched.

The Commissioner agrees that eliminating all donors who have ever been immunized is not necessary, since some individuals may not have developed significant titers of antibody. Accordingly, § 640.31(c) is clarified to eliminate only those donors who may have been immunized with human red cells within 6 months to preclude transmission of hepatitis viruses. Similarly, donors who have been immunized with blood group substances need not be eliminated as satisfactory donors since these substances are derived from nonhuman sources and do not carry any hepatitis viruses. Accordingly, the Commissioner is also amending § 640.31(c) to delete the phrase "or blood group substances." Until agreement can be reached by blood-banking experts regarding the need to test all Whole Blood (Human) donors for unexpected antibodies, it is not appropriate to require such testing. Therefore, § 640.35 is amended to delete paragraph (h) which referenced the test for unexpected antibodies, which is no longer required.

10. Two comments on proposed § 640.32 suggested that all whole blood be stored at 20° to 24° C until the plasma is separated, regardless of whether Platelet Concentrate (Human) or Single Donor Plasma (Human) is to be prepared.

The Commissioner concedes that storage of all units of whole blood at 20° to 24° C prior to separation of plasma may provide greater flexibility and reduce the necessity for two different methods of storage. However, since the requested change would involve a change in the Whole Blood (Human) regulations, and since this change was not proposed, it would be inappropriate to make the change without opportunity for interested persons to comment. The Commissioner will consider, at another time, a proposal to amend the Whole Blood (Human) regulations. In the interim, interested persons are invited to submit data and information concerning amendment of the Whole Blood (Human) regulations to require that whole blood be stored at 20° to 24° C until removal of the plasma, after which the red blood cells shall be stored at 1° to 6° C. Accordingly, the comments are rejected.

11. One comment on proposed § 640.32 said Single Donor Plasma (Human) standards should include provisions for transportation, as provided in § 640.4(i) concerning Whole Blood (Human).

The Commissioner advises that proposed § 640.32(a) includes, through reference to § 640.4, provisions for transportation and storage. For clarification, § 640.32(a) is amended in the final rule by adding the phrase "transported and stored" after the reference to collection.

12. One comment on proposed § 640.32 said the "12° range" limitation in the storage of red blood cells should be deleted.

The Commissioner proposed the 2-degree range to be consistent with the existing requirements for Whole Blood (Human) and Red Blood Cells (Human). It is recognized that the 2-degree range is unnecessarily restrictive and that any variation within the 1° to 6° C storage temperature will adequately protect the safety, purity, potency, and effectiveness of the product during its dating period. Accordingly, the comment is accepted, and § 640.32 is amended to delete the 2-degree range requirement.

Having reconsidered this matter, the Commissioner is also deleting the 2-degree range prescribed for Whole Blood (Human) in § 640.4(i), Red Blood Cells (Human) in § 640.11(a), and Platelet Concentrate (Human) in §§ 640.24(d)(2) and 640.25(a) since it is unnecessarily restrictive. Section 610.53 is changed to reflect these amendments. Additionally, it has come to the Commissioner's attention that the storage temperature prescribed in § 610.53 for Whole Blood (Human) and Red Blood Cells (Human) is erroneously stated to be 1° to 10° C, and that § 640.2(e)(3) should be clarified. These regulations are being amended to read 1° to 6° C for storage and, in § 640.2(e)(3), to read 1° to 6° C for storage and 1° to 10° C for shipping.

13. One comment on proposed § 640.33(a) said Rh grouping required by § 640.5(c) should not be required for this product. Four additional comments recommended that the test results for blood group designations be deleted from § 640.35(c) of the labeling requirements because the test is not medically important.

The Commissioner agrees that only the ABO group designation is necessary since it has clinical importance. The remaining blood group designations of the source blood were proposed because tests to identify the blood groups are routinely performed, and the results may be of some interest to the patient's physician. Accordingly, the Commissioner accepts the comments, and § 640.33(a) is amended to delete reference to § 640.5(c). In addition, § 640.35(c) is revised to require that only the ABO group designation of the source blood be identified in the labeling of Single Donor Plasma (Human) products.

14. Four comments on proposed § 640.33(b) questioned the requirement that pilot samples must accompany the final product. One additional comment suggested that only integrally attached samples, such as segments, be permitted as pilot samples.

The Commissioner proposed that pilot samples accompany the final product to provide the user the opportunity to do compatibility testing, if desired. However, since compatibility testing is not required, the Commissioner has decided to delete this provision. Accordingly, paragraph (b) is deleted and paragraph (c) is redesignated as paragraph (b).

15. The Commissioner is revising proposed § 640.34, which describes the categories of Single Donor Plasma (Human) products, to be consistent with the amendments to §§ 600.15 and 610.53 discussed in item 3 above. Paragraphs (d), (e), and (f) of proposed § 640.34 are deleted. Section 640.34 is amended to describe the products in the same order as now listed in proposed §§ 600.15 and 610.53. In addition, new paragraphs are added to describe Single Donor Plasma (Human), Liquid and to clarify that Platelet Concentrate (Human) and Cryoprecipitated Antihemophilic Factor (Human), or both, may be removed from Single Donor Plasma (Human), with

appropriate labeling for the remaining product.

16. One comment on proposed § 640.34(a) questioned the requirement of limiting to 4 hours the time for transfer of Single Donor Plasma (Human) to the final container and placing it at −18° C storage.

The Commissioner advises that it is necessary to restrict the time to accomplish the transfer. The 4-hour limit was selected as a reasonable length of time. However, after further consideration, the Commissioner concludes that the transfer time should be extended to 6 hours to be consistent with the requirement that Single Donor Plasma (Human), Fresh Frozen be transferred and frozen solid within 6 hours. Accordingly, the final regulation is amended in § 640.34(a) to change the "4 hours" to read "6 hours."

17. Four comments on proposed § 640.34 said the proper names should be changed. One comment suggested the name Single Donor Plasma (Human) be changed to "intravenous plasma" to distinguish the plasma products from recovered plasma intended for further manufacture. One comment suggested that "Fresh Frozen Plasma (Human)" be used as a substitute for Single Donor Plasma (Human), Fresh Frozen. One comment suggested that the name Single Donor Plasma (Human), Frozen, should be used for plasma with Cryoprecipitated Antihemophilic Factor (Human) Removed, to distinguish it from Single Donor Plasma (Human), Fresh Frozen. One comment recommended that "(Human)" should be deleted from all the proper names.

The Commissioner rejects the comments on revising the proper names of these Single Donor Plasma (Human) products, other than to eliminate the need to indicate the removal of components, when components have been removed. The categories are recognized in the blood-banking field and are self-descriptive.

The Commissioner advises that changes in proper names, including deletion of the term ("Human"), are being reviewed for all licensed biologics. If the term ("Human") is deleted, it will be removed from all products at one time.

18. One comment on proposed § 640.34(b) concerning Single Donor Plasma (Human), Fresh Frozen, questioned the wording "frozen within 6 hours after phlebotomy" and asked if this meant that the product must be placed in a —18° C freezer within 6 hours, or must be frozen within 6 hours.

The Commissioner intended that the unit reach a frozen state within 6 hours and not merely placed in a freezer. For clarification, the word "solid" is added.

19. Three comments on proposed § 640.34(c) (redesignated § 640.34(d) in the final regulations) concerned the allowable level of red blood cells that could remain in Single Donor Plasma (Human), Platelet Rich. Two of the comments said the level is to restrictive. One comment said the presence of red blood cells has not been convincingly shown to be harmful. The comments also noted that the regulation regarding Platelet Concentrate (Human) standard does not have a limit for red blood cells.

The Commissioner advises that the proposed requirement that Single Donor Plasma (Human) Platelet Rich contain no more than 20,000 red blood cells per cubic millimeter is intended to prevent unexpected high levels of red blood cells. As noted in the comments, the standard for Platelet Concentrate (Human) does not contain such a requirement. Moreover, § 640.34(h) (redesignated § 640.34(g) in the final regulations) provides for gross visual inspection to determine the presence of red blood cells. For these reasons, the Commissioner agrees that it is not necessary to specify a specific upper limit for red blood cell contamination. Accordingly, the comments are accepted, and the limitation on the number of red blood cells is eliminated.

20. One comment on proposed § 640.34(c) (redesignated § 640.34(d) in the final regulations) noted that agitation of Single Donor Plasma (Human), Platelet Rich during storage was not required, but made no recommendation.

The Commissioner requested the Panel on Review of Blood Derivatives to consider this question. The Panel stated that recent studies suggest that the product will be more effective if it is agitated during storage at 20° to 24° C. Accordingly, § 640.34(d) is amended, and a new paragraph (n) is added to § 640.35 of the final regulations to require gentle and continuous agitation of the product during storage at 20° to 24° C.

21. Three comments on proposed § 640.34(c) (redesignated § 640.34(d) in the final regulations) protested that 250,000 platelets per cubic millimeter is too high, especially when one takes into account the dilution of the plasma with anticoagulant.

The Commissioner advises that the proposed standard was reviewed by the Panel on Review of Blood and Blood Derivatives. The Panel concluded that the count is achievable provided monitoring of the procedure is adequate, including monitoring the centrifuge equipment during operation. The count is also consistent with that required for Platelet Concentrate (Human), which has been shown by analyses of samples submitted to the Bureau to be readily attainable. Accordingly, the comments are rejected.

22. One comment on proposed § 640.34(g) (redesignated § 640.34(f) in the final regulations) suggested that the regulation should make provision for reasonable discoloration of the plastic.

The Commissioner recognizes that the method of fabricating plastic film may produce some discoloration. Accordingly, the comment is accepted, and § 640.34(f) is amended in the final regulations to replace the phrase "be colorless" with the phrase "have no color added to the plastic."

23. One comment on proposed § 640.34(h) (redesignated § 640.34(g) in the final regulations) said the requirement to determine the amount of hemoglobin in the product by visual inspetcion is unusual. The comment offered no objections or alternative suggestion.

The Commissioner advises that the amount of hemoglobin in the final product can easily be determined by comparing the product with a known control sample and not issuing it if more than 25 milligrams of hemoglobin per 100 milliliters of plasma is present. This gross inspection provides reasonable quality control to assure that there will be no gross contamination with red blood cells.

24. Three comments on proposed §§ 640.34(h)(3) (redesignated § 640.34(g)(3) in the final regulations) said the anticoagulant in the source blood is transferred with the plasma at the time of separation and could be considered an unpermitted preservative.

The intent of the prohibition was to prevent the addition of a preservative to the plasma after its separation. For clarification, § 640.34(g)(3) is amended in the final regulations by replacing the phrase "shall not contain a preservative" with "no preservative shall be added to the final product."

25. One comment on proposed § 640.35 said the labeling requirements for Whole Blood (Human) and Red Blood Cells (Human) indicating whether the donor was "paid" or "volunteer" should apply to Single Donor Plasma (Human).

In the FEDERAL REGISTER of February 25, 1977 (42 FR 11019), the Commissioner proposed to amend the biologics regulations to require that each container of whole blood and blood components (red blood cells, cryoprecipitated antihemophilic factor, platelet concentrate, and single donor plasma) intended for transfusion shall bear the label statement "Paid Donor", or "Volunteer Donor", as applicable. When a final order based upon the February 25 proposal is promulgated, it will apply to Single Donor Plasma (Human) and these regulations will be amended.

26. Five comments on proposed § 640.35(b) said the volume of source blood and the volume of anticoagulant have no clinical applicability and should be deleted. Three additional comments noted that only the volume of Single Donor Plasma (Human) has clinical applicability.

The Commissioner agrees that the volume of source blood has little clinical applicability, and therefore the requirement is deleted in the final regulation. However, the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(e)) and the regulations promulgated thereunder (21 CFR 201.10) require complete listing of all active ingredients, and the quality of contents of the final product. These regulations are applicable to blood products, which are also drugs. Accordingly, the volume of plasma and volume and type of anticoagulant are retained in the final regulations.

27. Seven comments concerning § 640.35 (f) and (g) said identification of the type of serological tests for syphilis is unnecessary, the type of test for HB_sAg is

redundant since third generation testing is required by law, and the word "results" should be eliminated and "interpretation" or "result" should be substituted as a more accurate requirement.

The Commissioner concludes that the label should state that the Single Donor Plasma (Human) is nonreactive for syphilis, since this is clinically important information. The Commissioner accepts the suggestion to delete identification of the type of serological test for syphilis since this is of almost no medical importance. Similarly, § 640.35(g) is amended to delete the requirement to state the type of test for HB_sAg, since § 610.40 requires third generation testing for HB_sAg. The Commissioner agrees with the comment suggesting use of the term "result" rather than "results," and § 640.35(f) of the final regulations is amended accordingly. Consistent with the labeling requirements for other blood products as revised in the FEDERAL REGISTER of August 19, 1976 (41 FR 35062), the Commissioner is also amending § 640.35 (f) and (g) to provide alternative label statements concerning the tests for syphilis and hepatitis, respectively.

28. One comment on proposed § 640.35 (k) (redesignated § 640.35(j) in the final regulations) recommended that the range of 30° to 37° C be omitted in order to provide for thawing at room temperature. The comment said this would enable multiple units to be thawed at one time in anticipation of use during subsequent days.

The Commissioner advises that the 30° to 37° C range was proposed to provide a reasonable time for thawing while minimizing the time the product is exposed to room temperature or higher. Accordingly, the comment is rejected.

29. Twelve comments on proposed § 640.35(l) (redesignated § 640.35(k) in the final regulations) objected to the requirement to use the product within 2 hours after thawing. Four comments suggested that the time be extended from 4 to 12 hours. One comment proposed that the product be used immediately after thawing.

The 2-hour limitation was proposed as a reasonable length of time after thawing. However, data now show that even the labile clotting factor is stable for 6 hours thereafter. For this reason, the additional standards for Cryoprecipitated Antihemophilic Factor (Human) provide for a 6-hour interval. The Commissioner concludes that the same interval would not result in excessive leaching of phthalates for the Single Donor Plasma (Human) products, and § 640.35 (k) of the final regulations is amended accordingly.

30. One comment on proposed § 640.35 (m) (redesignated § 640.35(l) in the final regulations) said the instructions to use a filter in the administration set should indicate the kind of filter and mesh size.

The Commissioner advises that the requirement was proposed to alert users that specially designed filtering equipment is necessary. However, data upon which the Commissioner would designate one specific filter type or mesh size are currently inadequate. Accordingly, the comment is rejected. However, the Commissioner invites the submission of data or information on types and sizes of filters. At such time as adequate data are available, the regulation will be amended to specify a type and size of filter.

31. One comment on proposed § 640.35 (n) (redesignated § 640.35(m) in the final regulations) suggested that the term "ABO Group" be used in place of the phrase "compatible recipients" if that was intended.

The Commissioner advises that this is the intent of the requirement, and § 640.35(m) is amended in the final regulations to use the phrase "ABO group compatible." "This conforms with the elimination of the Rh testing requirement discussed in item 13 of this preamble.

32. One comment on proposed § 640.35 (n) (redesignated § 640.35(m) in the final regulations) expressed concern that the statement "recommendation for" was not strong enough and suggested that the statement read "for administration to ABO group compatible recipients only" or "assure absence of lytic A, and/or B."

The Commissioner agrees that the instruction should be strengthened. Accordingly, the comment is accepted and the final order is amended to read, "Instructions to administer to ABO group compatible recipients."

33. One comment on proposed § 640.35 (o) said this paragraph concerning use of the product in certain coagulation defects should be a part of the circular, where it could be more fully developed.

The Commissioner agrees with this comment, and paragraph (o) is deleted in the final regulation.

34. One comment on proposed § 640.35 (r) and (s) (redesignated § 640.35 (q) and (r), respectively, in the final regulations) objected to including the names, addresses, and license numbers of all locations involved in the processing of Single Donor Plasma (Human).

The Commissioner does not consider the requirement to be unduly burdensome. Under normal circumstances, the label would include two establishments at most, the establishment collecting the blood and the establishment separating the plasma. Accordingly, the comment is rejected.

35. Twenty-one comments concerned § 640.36—plasma diverted for further manufacturing. Most objected to the proposed requirement to ship this plasma at −18° C, the prohibition against pooling the plasma prior to shipment, and the required use of a closed system.

The Commissioner did not intend that this regulation apply to all plasma intended for further manufacture. Rather, it would have permitted a manufacturer, to divert units originally processed as Single Donor Plasma (Human) for either blood derivatives or reagent use by relabeling them for such use. Since the product was prepared in a closed system, is pyrogen-free, and has been stored as a single donor product, it is an excellent resource for further manufacturing.

The proposal was not intended to apply to plasma that is recovered from outdated units of whole blood, with no intermediate step of preparing a transfusible product (Single Donor Plasma (Human)). Recovered plasma intended for a licensed final product is presently separated, pooled, and shipped in a liquid state to a manufacturer of derivatives or reagents under the short supply provisions. Further, this plasma does not require a closed system for separation. However, because of the confusion resulting from proposed § 640.36, the Commissioner has determined that separate additional standards proposed for all recovered plasma would be useful, and he will issue these for comment in the near future. Accordingly, section 640.36 is deleted in the final rule.

Additional background data and information on which the Commissioner relies in promulgating these regulations are on public display in the office of the Hearing Clerk (HFC–20), Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, Md. 20857.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner (21 CFR 5.1), Parts 600, 610, and 640 are amended as follows:

PART 600—BIOLOGICAL PRODUCTS: GENERAL

1. In Part 600, § 600.15(a) is amended by deleting the entry "Single donor plasma (human), frozen" and adding alphabetically the following new entries, to read as follows:

§ 600.15 Temperatures during shipment.

* * * * *

(a) *Products.*

Product	*Temperature*
* * *	* *
Single donor plasma (human).	−18° C or colder.
Single donor plasma (human), fresh frozen.	−18° C or colder.
Single donor plasma (human), liquid.	1° to 10° C.
Single donor plasma (human), platelet rich.	Between 1° and 10° C or all reasonable methods to maintain the temperature as close as possible to a range between 20° and 24° C.

* * * * *

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

2. In Part 610, § 610.53 is amended by deleting the 2-degree range from the storage temperature requirements for the entry "Platelet Concentrate (Human)", by changing the storage temperatures for entries "Red Blood Cells (Human)" and "Whole Blood (Human)" to 1° to 6° C, by revising the dating period and storage temperature requirements for the entry "Single Donor Plasma (Human)", and by

adding alphabetically four new entries, to read as follows:

§ 610.53 Dating periods for specific products.

* * * * *	
Platelet concentrate (human).	72 hours from time of collection of source blood, provided labeling recommmends storage at 20° to 24° C or between 1° to 6° C.
* * * * *	
Red blood cell (human).	(a) Twenty-one days from date of collection of source blood, provided labeling recommends storage between 1° and 6° C and the hermetic seal is not broken during processing. Section 610.51 does not apply.
	Twenty-four hours after plasma removal, provided labeling recommends storage between 1° and 6° C, if the hermetic seal is broken during processing. Section 610.51 does not apply.
	(b) *Frozen:* 3 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 6° C. Section 610.51 does not apply.
* * * * *	
Single donor plasma (human).	5 years (−18° C or colder). Section 610.51 does not apply.
Single donor plasma (human), fresh frozen.	1 year (−18° C or colder). Section 610.51 does not apply.
Single donor plasma (human), liquid.	26 days (1° and 6° C).
Single donor plasma (human), platelet rich.	72 hours (20° to 24° C or between 1° and 6° C). Section 610.51 does not apply.
* * * * *	
Whole blood (human) collected in.	(a) ACD solution—21 days, provided labeling recommends storage between 1° and 6° C. Section 610.51 does not apply.
	(b) Heparin solution—48 hours provided labeling recommends storage between 1° and 6° C. Section 610.51 does not apply.
	(c) CPD solution—21 days, provided labeling recommends storage between 1° and 6° C. Section 610.51 does not apply.
* * * * *	

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

3. Part 640 is amended as follows:

a. In § 640.2, by revising paragraph (e)(3) to read as follows:

§ 640.2 General requirements.

* * * * *

(e) * * *

(3) The blood has been stored continuously at 1° to 6° C and shipped between 1° and 10° C;

* * * * *

b. In § 640.4 by revising paragraph (i) to read as follows:

§ 640.4 Collection of the blood.

* * * * *

(i) *Storage.* Immediately after collection, unless the blood is to be used as a source for Platelet Concentrate (Human), it shall be placed in storage at a temperature 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 range between 1° and 6° C until it arrives at the processing laboratory, where it shall be stored at a temperature between 1° and 6° C. Blood from which Platelet Concentrate (Human) is to be prepared shall be held in an environment maintained at a temperature range of 20° to 24° C until the platelet concentrates are separated. The red blood cells shall be placed in storage at a temperature between 1° and 6° C immediately after the platelet concentrates are separated.

c. In § 640.11 by revising paragraph (a) to read as follows:

§ 640.11 General requirements.

(a) *Storage.* Immediately after processing, the Red Blood Cells (Human) shall be placed in storage and maintained at a temperature between 1° and 6° C.

* * * * *

d. In § 640.24 by revising paragraph (d)(2) to read as follows:

§ 640.24 Processing.

* * * * *

(d) * * *

(2) 1° to 6° C resuspended in 20 to 30 milliliters of plasma.

e. In § 640.25 by revising paragraph (a) to read as follows:

* * * * *

§ 640.25 General requirements.

(a) *Storage.* Immediately after processing, Platelet Concentrate (Human) shall be placed in storage at the temperature range suitable to the volume of resuspension plasma. If stored at 20° to 24° C, a continuous gentle agitation of the platelet concentrate shall be maintained throughout the storage period. Agitation is optional if stored at a temperature between 1° and 6° C.

* * * * *

f. New Subpart D—Single Donor Plasma (Human)—is added to read as follows:

Subpart D—Single Donor Plasma (Human)

Sec.

640.30 Single Donor Plasma (Human).
640.31 Suitability of donors.
640.32 Collection of source material.
640.33 Testing the blood.
640.34 Processing.
640.35 Labeling.

* * * * *

Subpart D—Single Donor Plasma (Human)

§ 640.30 Single Donor Plasma (Human).

(a) *Proper name and definition.* The proper name of this product shall be Single Donor Plasma (Human). The product is defined as the fluid portion of one unit of human blood intended for intravenous use, which, in a closed system, has been collected, stabilized against clotting, and separated from the red blood cells.

(b) *Source.* (1) Single Donor Plasma (Human) shall be obtained by separating plasma from blood collected from blood donors or by plasmapheresis.

(2) Single Donor Plasma (Human) may be obtained from a unit of Whole Blood (Human) collected by another licensed establishment.

§ 640.31 Suitability of donors.

(a) Whole blood donors shall meet the criteria for donor suitability prescribed in § 640.3.

(b) Plasmapheresis donors shall meet the criteria for donor suitability prescribed in § 640.63, excluding the phrase "other than malaria" in paragraph (c)(9) of that section. Informed consent shall be required as prescribed in § 640.61.

(c) Donors shall not be suitable if they are known to have been immunized within the past 6 months by injection with human red blood cells.

§ 640.32 Collection of source material.

(a) Whole blood shall be collected, transported, and stored as prescribed in § 640.4, except that paragraphs (d)(2) and (h) of that section shall not apply. When whole blood is intended for Single Donor Plasma (Human); Single Donor Plasma (Human), Fresh Frozen; and Single Donor Plasma (Human), Liquid, it shall be maintained at a temperature between 1° and 6° C until the plasma is removed. Whole blood intended for Single Donor Plasma (Human), Platelet Rich shall be maintained as prescribed in § 640.24 until the plasma is removed. The red blood cells shall be placed in storage at a temperature between 1° and 6° C immediately after the plasma is separated.

(b) Plasma obtained by plasmapheresis shall be collected as prescribed in

§§ 640.62, 640.64 (except that paragraph (c)(3) of § 640.64 shall not apply), and 640.65.

§ 640.33 Testing the blood.

(a) Blood from which plasma is separated shall be tested as prescribed in § 610.40 of this chapter and § 640.5 (a), (b), and (e).

(b) Manufacturers of Single Donor Plasma (Human) collected by plasmapheresis shall have testing and recordkeeping responsibilities equivalent to those prescribed in §§ 640.71 and 640.72.

§ 640.34 Processing.

(a) *Single Donor Plasma (Human).* Single Donor Plasma (Human) shall be separated from the red blood cells within 26 days after phlebotomy, and shall be stored at −18° C or colder within 6 hours after transfer to the final container, unless the product is to be stored as Single Donor Plasma (Human), Liquid.

(b) *Single Donor Plasma (Human), Fresh Frozen.* Single Donor Plasma (Human), Fresh Frozen shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and minimal manipulation of the donor's tissue. The plasma shall be separated from the red blood cells, frozen solid within 6 hours after phlebotomy, and stored at −18° C or colder.

(c) *Single Donor Plasma (Human), Liquid.* Single Donor Plasma (Human), Liquid shall be separated from the red blood cells within 26 days after phlebotomy and shall be stored at a temperature of 1° to 6° C within 4 hours after filling the final container.

(d) *Single Donor Plasma (Human), Platelet Rich.* Single Donor Plasma (Human), Platelet Rich shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and manipulation of the donor's tissue. The plasma shall be separated from the red blood cells by centrifugation within 4 hours after phlebotomy. The time and speed of centrifugation shall have been shown to produce a product with at least 250,000 platelets per cubic milliliter. The plasma shall be stored at a temperature between 20° to 24° C or between 1° and 6° C, immediately after filling the final container. A gentle and continuous agitation of the product shall be maintained throughout the storage period, if stored at a temperature of 20° to 24° C.

(e) *Modifications of Single Donor Plasma (Human).* It is possible to separate Platelet Concentrate (Human) and/or Cryoprecipitated Antihemophilic Factor (Human) from Single Donor Plasma (Human). When these components are to be separated, the plasma shall be collected as described in § 640.32 for Single Donor Plasma (Human).

(1) Platelet Concentrate (Human) shall be separated as prescribed in Subpart C of Part 640, prior to freezing the plasma. The remaining plasma may be labeled as Single Donor Plasma (Human), Fresh Frozen, if frozen solid within 6 hours after phlebotomy.

(2) Cryoprecipitated Antihemophilic Factor (Human) shall be removed as prescribed in Subpart F of Part 640. The remaining plasma may be labeled Single Donor Plasma (Human).

(3) Plasma remaining after both Platelet Concentrate (Human) and Cryoprecipitated Antihemophilic Factor (Human) have been removed may be labeled Single Donor Plasma (Human).

(f) *The final container.* (1) The final container shall have no color added to the plastic and shall be transparent to permit visual inspection of the contents; any closure shall maintain a hermetic seal and prevent contamination of the contents.

(2) The final 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, potency, and effectiveness of the product.

(3) Prior to filling, the final container shall be identified by number so as to relate it to the donor.

(g) *The final product.* (1) The final product shall be inspected immediately after separation of the plasma and shall not be issued for transfusion if there is (i) any abnormality in color or physical appearance, (ii) any indication of contamination, or (iii) more than 25 milligrams hemoglobin per 100 milliliters of plasma as determined by visual inspection.

(2) With the exception of Single Donor Plasma (Human), Platelet Rich; and Single Donor Plasma (Human), Liquid, the final product shall be stored in a manner that will show evidence of thawing and shall not be issued if there is any evidence of thawing of the product during storage or breakage of the container.

(3) No preservative shall be added to the final product.

§ 640.35 Labeling.

In addition to the applicable labeling requirements of § 610.62 of this chapter and in lieu of the requirements of §§ 610.60 and 610.61 of this chapter, the container labels for Single Donor Plasma (Human) products shall bear the following information:

(a) The proper name of the product, using the nomenclature as set forth in § 640.34.

(b) The volume of plasma, and the volume and type of anticoagulant present in the source blood from which the product was prepared.

(c) ABO blood group designation of the source blood.

(d) Donor number.

(e) Expiration date.

(f) The result of the serologic test for syphilis or the statement, "Nonreactive for Syphilis by STS".

(g) The result of the test for hepatitis B surface antigen or the statement "Nonreactive for HBsAg by FDA Required Test".

(h) Instructions to store the product as prescribed in § 610.53 of this chapter.

(i) A warning against further processing of the frozen proudct if there is evidence of breakage or thawing.

(j) Instructions to thaw the frozen product at a temperature between 30° and 37° C.

(k) Instructions to use the frozen product within 6 hours after thawing.

(l) Instructions to use a filter in the administration equipment.

(m) Instructions to administer ABO group compatible recipients.

(n) When applicable, a statement that the product should be gently and continuosuly agitated during storage.

(o) A statement to see the instruction circular for directions for use.

(p) The statement, "Caution: Federal Law Prohibits Dispensing Without a Prescription".

(q) Name, address and license number of the manufacturer.

(r) Where plasma has been prepared from Whole Blood (Human) processed by another licensed establishment, such fact, and the name, address, and license number of the other establishment.

Effective date: This regulation becomes effective November 22, 1977, except requirements for labeling changes shall become effective May 22, 1978.

(Sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262).)

Dated: November 11, 1977.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc. 77-33413 Filed 11-21-77;8:45 am]

[1505-01]

Title 7—Agriculture

CHAPTER II—FOOD AND NUTRITION SERVICE, DEPARTMENT OF AGRICULTURE

PART 271—PARTICIPATION OF STATE AGENCIES AND ELIGIBLE HOUSEHOLDS

Food Stamp Program

Correction

In FR Doc.77-32309, appearing at page 58153 in the issue of Tuesday, November 8, 1977, the 16th entry in the next to last column of the table on page 58154, now reading "51", should read, "50".

[3410-05]

CHAPTER VII—AGRICULTURAL STABILIZATION AND CONSERVATION SERVICE (AGRICULTURAL ADJUSTMENT), DEPARTMENT OF AGRICULTURE

SUBCHAPTER B—FARM MARKETING QUOTAS AND ACREAGE ALLOTMENT

[Amdt. 9]

PART 729—PEANUTS

Subpart—Regulations for Determination of Acreage Allotments and Marketing Quotas for 1972 and Subsequent Crops of Peanuts

AGENCY: Agricultural Stabilization and Conservation Service, Department of Agriculture.

ACTION: Final rule.