

**PART 453—LINCOMYCIN
ANTIBIOTIC DRUGS**

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Subpart A—Bulk Drugs

§ 453.20 Clindamycin hydrochloride hydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Clindamycin hydrochloride hydrate is the hydrated hydrochloride salt of clindamycin. It is so purified and dried that:

(i) Its clindamycin content is not less than 800 micrograms of clindamycin per milligram.

(ii) Its microbiological activity is not less than 800 micrograms of clindamycin per milligram.

(iii) [Reserved]

(iv) Its moisture content is not less than 3.0 percent and not more than 6.0 percent.

(v) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 3.0 and not more than 5.5.

(vi) It is crystalline.

(vii) It passes the identity test for clindamycin hydrochloride hydrate.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5(b) 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 clindamycin content, microbiological activity, moisture, pH, crystallinity, and identity.

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

(b) *Tests and methods of assay*—(1) *Clindamycin content (vapor phase chromatography).* Proceed as directed in § 436.302 of this chapter.

(2) *Microbiological activity (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 sterile distilled water to give a stock solution of convenient concentration. Further dilute the stock solution with 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of clindamycin per milliliter (estimated).

(3) [Reserved]

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

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

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

(7) *Identity.* Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(2) of that section.

[39 FR 19161, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§ 453.21 Clindamycin palmitate hydrochloride.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Clindamycin palmitate hydrochloride is the white to off-white amorphous powder of the hydrochloride salt of the palmitic acid ester of clindamycin. It is freely soluble in water, ethanol, chloroform, and ether. It is so purified and dried that:

(i) It contains not less than 540 micrograms of clindamycin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not more than 3.0 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 2.8 and not more than 3.8.

(v) It passes the identity test for clindamycin palmitate hydrochloride.

(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 clindamycin content, moisture, pH, and identity.

(ii) Samples required: 10 packages, nine containing not less than 300 milligrams and one package containing not less than 2 grams.

(b) *Tests and methods of assay—(1) Clindamycin content.* Proceed as directed in § 436.303 of this chapter.

(2) [Reserved]

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

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(5) *Identity.* Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(2) of that section.

[39 FR 19161, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§ 453.22 Clindamycin phosphate.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Clindamycin phosphate is a water-soluble ester of clindamycin and

phosphoric acid. It occurs as a white to off-white powder. It is so purified and dried that:

(i) Its clindamycin content is not less than 758 micrograms of clindamycin per milligram calculated on an anhydrous basis.

(ii) Its microbiological activity is not less than 758 micrograms of clindamycin per milligram calculated on an anhydrous basis.

(iii) [Reserved]

(iv) Its moisture content is not more than 6.0 percent.

(v) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 3.5 and not more than 4.5.

(vi) It is crystalline.

(vii) It passes the identity test for clindamycin phosphate.

(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 clindamycin content, microbiological activity, moisture, pH, crystallinity, and identity.

(ii) Samples required: 10 packages, nine containing approximately 300 milligrams and one containing 1.5 grams.

(b) *Tests and methods of assay—(1) Clindamycin content (vapor phase chromatography).* Proceed as directed in § 436.304 of this chapter.

(2) *Microbiological activity (microbiological agar diffusion assay).* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Accurately weigh approximately 12 milligrams of the clindamycin phosphate sample into a 50-milliliter glass-stoppered centrifuge tube. Pipet 25 milliliters of the pH 9.0 borate buffer into the centrifuge tube. Add 10 milliliters of chloroform and shake vigorously for 15 minutes. Centrifuge the resulting mixture and pipet a 20-milliliter aliquot of the aqueous phase into a 35-milliliter centrifuge tube. Add a weighed amount of intestinal alkaline phosphatase equivalent to 50 units of

activity¹ and allow the solution to stand until the enzyme has completely dissolved. Place the tube into a water bath at 37° C ±2° C for 2.5 hours. After the 2.5-hours hydrolysis, allow the solution to cool. Further dilute an aliquot of the solution with 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of clindamycin per milliliter (estimated).

(3) [Reserved]

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

(5) *pH*. Proceed as directed in §436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

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

(7) *Identity*. Proceed as directed in §436.211 of this chapter, using the sample preparation method described in paragraph (b)(2) of that section, except dry the sample for 2 hours at 100° C and allow to equilibrate with the atmosphere for 1 hour.

[46 FR 2996, Jan. 13, 1981, as amended at 50 FR 19921, May 13, 1985]

§ 453.22a Sterile clindamycin phosphate.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Sterile clindamycin phosphate is a water-soluble ester of clindamycin and phosphoric acid. It occurs as a white to off-white powder. It is so purified and dried that:

(i) Its clindamycin content is not less than 758 micrograms of clindamycin per milligram calculated on an anhydrous basis.

(ii) Its microbiological activity is not less than 758 micrograms of clindamycin per milligram calculated on an anhydrous basis.

(iii) It is sterile.

(iv) It is nonpyrogenic.

(v) [Reserved]

(vi) It contains no depressor substances.

(vii) Its moisture content is not more than 6 percent.

¹Defined such that 50 units hydrolyzes at least 20 micromoles of a clindamycin phosphate authentic sample under the assay conditions described in this section.

(viii) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 3.5 and not more than 4.5.

(ix) It is crystalline.

(x) It passes the identity test for clindamycin phosphate.

(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 clindamycin content, microbiological activity, sterility, pyrogens, depressor substances, moisture, pH, crystallinity, and identity.

(ii) Samples required:

(a) For all tests except sterility: 10 packages, nine containing approximately 300 milligrams and one containing 1.5 grams.

(b) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay—(1) Clindamycin content (vapor phase chromatography)*. Proceed as directed in §436.304 of this chapter.

(2) *Microbiological activity (microbiological agar diffusion assay)*. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Accurately weigh approximately 12 milligrams of the clindamycin phosphate sample into a 50-milliliter glass-stoppered centrifuge tube. Pipet 25 milliliters of the pH 9.0 borate buffer into the centrifuge tube. Add 10 milliliters of chloroform and shake vigorously for 15 minutes. Centrifuge the resulting mixture and pipet a 20-milliliter aliquot of the aqueous phase into a 35-milliliter centrifuge tube. Add a weighed amount of intestinal alkaline phosphatase equivalent to 50 units of activity¹ and allow the solution to stand until the enzyme has completely dissolved. Place the tube into a water bath at 37° C.±2° C. for 2.5 hours. After the 2.5-hour hydrolysis, allow the solution to cool. Further dilute an aliquot of the solution with

¹Defined such that 50 units hydrolyzes at least 20 micromoles of a clindamycin phosphate authentic sample under the assay conditions described in this section.

0.1M potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of clindamycin per milliliter (estimated).

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

(4) *Pyrogens*. Proceed as directed in § 436.32(a) of this chapter, using a solution containing 24 milligrams of clindamycin per milliliter.

(5) [Reserved]

(6) *Depressor substances*. Proceed as directed in § 436.35 of this chapter.

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

(8) *pH*. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

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

(10) *Identity*. Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(2) of that section, except dry the sample for 2 hours at 100° C. and allow to equilibrate with the atmosphere for 1 hour.

[39 FR 19161, May 30, 1974, as amended at 46 FR 60568, Dec. 11, 1981; 50 FR 19921, May 13, 1985]

§ 453.30 Lincomycin hydrochloride monohydrate.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Lincomycin hydrochloride monohydrate is the monohydrated hydrochloride salt of lincomycin. It is freely soluble in water and soluble in acetone and dimethylformamide. It is so purified and dried that:

(i) Its potency is not less than 790 micrograms of lincomycin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not less than 3.0 percent and is not more than 6.0 percent.

(iv) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 3.0 and not more than 5.5.

(v) Its specific rotation in an aqueous solution at 25° C. is not less than +135° and not more than +150°.

(vi) It passes the infrared identity test.

(vii) Its content of lincomycin B is not more than 5 percent.

(viii) It passes the identity test if the elution pattern of the lincomycin sample compares quantitatively to that of the lincomycin working standard under identical conditions of gas liquid chromatography.

(ix) It is crystalline.

(2) *Labeling*. It shall be labeled in accordance with the requirements of § 432.5(b) 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, moisture, pH, specific rotation, infrared absorption spectrum, lincomycin B content, crystallinity, and identity.

(ii) Samples of the batch: 10 packages, each containing approximately 300 milligrams.

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

(i) *Microbiological turbidimetric assay*. Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient sterile distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with sterile distilled water to the reference concentration of 0.5 microgram of lincomycin per milliliter (estimated).

(ii) *Gas liquid chromatography assay*. Proceed as directed in § 436.306 of this chapter.

(2) [Reserved]

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

(4) *pH*. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(5) *Specific rotation*. Accurately weigh 500 milligrams of lincomycin hydrochloride monohydrate in a 25-milliliter, glass stoppered volumetric flask and fill to volume with distilled water. Proceed as directed in § 436.210 of this

chapter, using a 2.0-decimeter polarimeter tube and calculate the specific rotation on an anhydrous basis.

(6) *Infrared absorption spectrum.* Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(2) of that section.

(7) *Lincomycin B content.* Proceed as directed in § 436.306 of this chapter.

(8) *Identity.* Proceed as described in § 436.306 of this chapter.

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

[39 FR 19161, May 30, 1974, as amended at 46 FR 3839, Jan. 16, 1981; 50 FR 19921, May 13, 1985]

§ 453.30a Sterile lincomycin hydrochloride monohydrate.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Lincomycin hydrochloride monohydrate is the monohydrated hydrochloride salt of lincomycin. It is freely soluble in water and soluble in acetone and dimethylformamide. It is so purified and dried that:

(i) Its potency is not less than 790 micrograms of lincomycin per milligram.

(ii) It is sterile.

(iii) [Reserved]

(iv) It is nonpyrogenic.

(v) It contains no depressor substances.

(vi) Its moisture content is not less than 3.0 percent and not more than 6.0 percent.

(vii) Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 3.0 and not more than 5.5.

(viii) Its specific rotation in an aqueous solution at 25° C. is not less than +135° and not more than +150°.

(ix) It passes the infrared identity test.

(x) Its content of lincomycin B is not more than 5 percent.

(xi) It passes the identity test if the elution pattern of the lincomycin sample compares quantitatively to that of the lincomycin working standard under identical conditions of gas liquid chromatography.

(xii) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5(b) 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, depressor substances, moisture, pH, specific rotation, infrared absorption spectrum, lincomycin B content, identity, 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 300 milligrams.

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

(i) *Microbiological turbidimetric assay.* Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient sterile distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with sterile distilled water to the reference concentration of 0.5 microgram of lincomycin per milliliter (estimated).

(ii) *Gas liquid chromatography assay.* Proceed as directed in § 436.306 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) [Reserved]

(4) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, using a solution containing 0.5 milligram of lincomycin per milliliter.

(5) *Depressor substances.* Proceed as directed in § 436.35 of this chapter.

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

(7) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(8) *Specific rotation.* Accurately weigh 500 milligrams of lincomycin hydrochloride monohydrate in a 25 milliliter, glass-stoppered volumetric flask and fill to lincomycin B content, crystallinity, and volume with distilled water. Proceed as directed in § 436.210, using a 2.0-decimeter polarimeter tube and calculate the specific rotation on an anhydrous basis.

(9) *Infrared absorption spectrum.* Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(2) of that section.

(10) *Lincomycin B content.* Proceed as directed in § 436.306 of this chapter.

(11) *Identity.* Proceed as directed in § 436.306 of this chapter.

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

[39 FR 19161, May 30, 1974, as amended at 46 FR 3839, Jan. 16, 1981; 46 FR 60568, Dec. 11, 1981; 50 FR 19921, May 13, 1985]

Subpart B—Oral Dosage Forms

§ 453.120 Clindamycin hydrochloride hydrate capsules.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Clindamycin hydrochloride hydrate capsules are composed of clindamycin hydrochloride hydrate and one or more suitable and harmless diluents and lubricants. Each capsule contains clindamycin hydrochloride hydrate equivalent to 75, 150, or 300 milligrams of clindamycin. Its content of clindamycin is satisfactory if it is not less than 90 percent and not more than 120 percent of the amount of clindamycin that it is represented to contain. The moisture content is not more than 7.0 percent. The clindamycin hydrochloride hydrate used conforms to the standards prescribed by § 453.20(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 clindamycin hydrochloride hydrate used in making the batch for clindamycin content, microbiological

activity, moisture, pH, crystallinity, and identity.

(b) The batch for clindamycin content and moisture.

(ii) Samples required:

(a) The clindamycin hydrochloride hydrate 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) Clindamycin content (vapor phase chromatography).* Proceed as directed in § 436.302 of this chapter, except:

(i) *Preparation of clindamycin sample and working standard solutions.* Accurately weigh a portion of the clindamycin working standard equivalent to about 45 milligrams of clindamycin and transfer to a 15-milliliter glass-stoppered centrifuge tube. Empty 20 capsules, collecting the contents quantitatively. Weigh the powder and determine the average capsule fill weight. Mix the powder and accurately weigh a portion containing the equivalent of about 45 milligrams of clindamycin into a second 15-milliliter glass-stoppered centrifuge tube. Add 3 milliliters of 1 percent sodium carbonate solution and 3 milliliters of chloroform to each tube. Shake the solution vigorously and then centrifuge. Remove the top aqueous layer and add approximately 1 gram of anhydrous sodium sulfate to dry the chloroform layer. Place a 1-milliliter aliquot of the chloroform solution into a 15-milliliter centrifuge tube, add 1 milliliter of internal standard and 0.6 milliliter of acetic anhydride. Agitate the vials to insure complete mixing of the liquids.

(ii) *Calculations.* Calculate the clindamycin content of the capsules as follows:

$$\text{Milligrams of clindamycin per capsule} = \frac{R_u \times W_s \times f \times W_a}{R_s \times W_u}$$

where:

R_u =Area of the clindamycin sample peak (at a retention time equal to that observed for the clindamycin standard)/Area of internal standard peak;

R_s =Area of the clindamycin standard peak/Area of internal standard peak;

W_s =Weight of clindamycin working standard in milligrams;

W_u =Sample weight in milligrams;

f =Potency of clindamycin working standard in milligrams of clindamycin per milligram;

W_a =Average capsule fill weight in milligrams.

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

[39 FR 19161, May 30, 1974, as amended at 50 FR 19921, May 13, 1985; 54 FR 41824, Oct. 12, 1989; 54 FR 43384, Oct. 24, 1989]

§ 453.121 Clindamycin palmitate hydrochloride oral dosage forms.

§ 453.121a Clindamycin palmitate hydrochloride for oral suspension.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Clindamycin palmitate hydrochloride for oral suspension is composed of clindamycin palmitate hydrochloride with one or more suitable and harmless diluents, buffer substances, colorings, and flavorings. When reconstituted as directed in the labeling, using the accompanying diluent when provided, each milliliter contains clindamycin palmitate hydrochloride equivalent to 15 milligrams of clindamycin. Its clindamycin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the amount of clindamycin that it is represented to contain. The moisture content is not more than 3.0 percent. When reconstituted as directed in the labeling, its pH is not less than 3.0 and not more than 5.0. The clindamycin palmitate hydrochloride used conforms to the standards prescribed by § 453.21(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 clindamycin palmitate hydrochloride used in making the batch for clindamycin content, moisture, pH, and identity.

(b) The batch for clindamycin content, moisture, and pH.

(ii) Samples required:

(a) The clindamycin palmitate hydrochloride used in making the batch: 10 packages, nine containing not less than

300 milligrams, and one containing not less than 2 grams.

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

(b) *Tests and methods of assay—(1) Clindamycin content*. Proceed as directed in § 436.303 of this chapter, except:

(i) *Preparation of clindamycin palmitate hydrochloride sample and working standard solutions*. Accurately weigh about 130 milligrams of the clindamycin palmitate hydrochloride working standard and transfer to a 25-milliliter volumetric flask. Add 5 milliliters of distilled water. Reconstitute the clindamycin palmitate hydrochloride for oral suspension as directed in the labeling, using the accompanying diluent when provided, and transfer exactly 5.0 milliliters to a 25-milliliter volumetric flask. Add exactly 5.0 milliliters of internal standard and 1 milliliter of 30 percent sodium carbonate to each flask. Shake both flasks mechanically for 5 minutes. Transfer the contents of each flask to separate 15-milliliter glass-stoppered centrifuge tubes and centrifuge. Remove the top aqueous layer by suction and transfer exactly 1.0 milliliter of the chloroform layer to separate glass-stoppered, conical, 15-milliliter centrifuge tubes. Add 1 milliliter of pyridine and 0.5 milliliter of acetic anhydride. Agitate the tubes to insure complete mixing of the liquids. Proceed as directed in § 436.303(e) of this chapter.

(ii) *Calculations*: Calculate the clindamycin content as follows:

$$\text{Milligrams of clindamycin per milliliter} = \frac{R_u \times W_s \times f}{R_s \times V}$$

where:

R_u =Area of the sample peak (at a retention time equal to that observed for the clindamycin palmitate hydrochloride standard)/Area of internal standard peak;

R_s =Area of the clindamycin palmitate hydrochloride standard peak/Area of internal standard peak;

W_s =Weight of the clindamycin palmitate hydrochloride working standard in milligrams;

V =Volume of reconstituted sample in milliliters;

f =Milligrams of clindamycin activity per milligram of clindamycin palmitate hydrochloride working standard.

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

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

[39 FR 19161, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§ 453.121b Clindamycin palmitate hydrochloride for oral solution.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Clindamycin palmitate hydrochloride for oral solution is composed of clindamycin palmitate hydrochloride with one or more suitable and harmless diluents, buffer substances, colorings, flavorings, and preservatives. When reconstituted as directed in the labeling, each milliliter contains clindamycin palmitate hydrochloride equivalent to 15 milligrams of clindamycin. Its clindamycin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of clindamycin that it is represented to contain. The moisture content is not more than 3.0 percent. When reconstituted as directed in the labeling, its pH is not less than 2.5 and not more than 5.0. The clindamycin palmitate hydrochloride used conforms to the standards prescribed by § 453.21(a)(1).

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

(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 clindamycin palmitate hydrochloride used in making the batch for clindamycin content, moisture, pH, and identity.

(b) The batch for clindamycin content, moisture, and pH.

(ii) Samples required:

(a) The clindamycin palmitate hydrochloride used in making the batch: 10 packages, nine containing not less than 300 milligrams, and one containing not less than 2 grams.

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

(b) *Tests and methods of assay—(1) Clindamycin content.* Proceed as di-

rected in § 436.303 of this chapter, except:

(i) *Preparation of clindamycin palmitate hydrochloride sample and working standard solutions.* Accurately weigh about 130 milligrams of the clindamycin palmitate hydrochloride working standard and transfer to a 25-milliliter volumetric flask. Add 5 milliliters of distilled water. Reconstitute the clindamycin palmitate hydrochloride for oral solution as directed in the labeling and transfer exactly 5.0 milliliters to a 25-milliliter volumetric flask. Add exactly 5.0 milliliters of internal standard and 1 milliliter of 30-percent sodium carbonate to each flask. Shake both flasks mechanically for 5 minutes. Transfer the contents of each flask to separate 15-milliliter glass-stoppered centrifuge tubes and centrifuge. Remove the top aqueous layer by suction and transfer exactly 1.0 milliliter of the chloroform layer to separate glass-stoppered, conical, 15-milliliter centrifuge tubes. Add 1 milliliter of pyridine and 0.5 milliliter of acetic anhydride. Agitate the tubes to insure complete mixing of the liquids. Proceed as directed in § 436.303(e) of this subchapter.

(ii) *Calculations.* Calculate the clindamycin content as follows:

$$\text{Milligrams of clindamycin per milliliter} = \frac{R_u \times W_s \times f}{R_s \times V}$$

where:

R_u =Area of the sample peak (at a retention time equal to that observed for the clindamycin palmitate hydrochloride standard)/Area of internal standard peak;

R_s =Area of the clindamycin palmitate hydrochloride standard peak;/Area of internal standard peak;

W_s =Weight of the clindamycin palmitate hydrochloride working standard in milligrams;

V =Volume of reconstituted sample in milliliters;

f =Milligrams of clindamycin activity per milligram of clindamycin palmitate hydrochloride working standard.

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

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

[39 FR 19161, May 30, 1974, as amended at 50 FR 19921, May 13, 1985]

§ 453.130 Lincomycin hydrochloride oral dosage forms.

§ 453.130a Lincomycin hydrochloride monohydrate capsules.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Lincomycin hydrochloride monohydrate capsules are composed of lincomycin hydrochloride monohydrate and suitable diluents, enclosed in a gelatin capsule. Each capsule contains 250 milligrams of lincomycin or 500 milligrams of lincomycin. The lincomycin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of lincomycin that it is represented to contain. Its moisture content is not more than 7.0 percent. The lincomycin hydrochloride monohydrate used conforms to the standards prescribed by § 453.30(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 lincomycin hydrochloride monohydrate used in making the batch for potency, moisture, pH, specific rotation, infrared absorption spectrum, and identity.

(b) The batch for potency and moisture.

(ii) Samples required:

(a) The lincomycin hydrochloride monohydrate 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.* Use either of the following methods; however, the results obtained from the gas liquid chromatography assay shall be conclusive.

(i) *Microbiological turbidimetric assay.* Proceed as directed in § 436.106 of this chapter, preparing the sample for assay

as follows: Place a representative number of capsules into a high-speed glass blender jar with sufficient sterile distilled water to obtain a stock solution of convenient concentration. Blend for 3 to 5 minutes. Remove an aliquot of the stock solution and further dilute with sterile distilled water to the reference concentration of 0.5 microgram of lincomycin per milliliter (estimated).

(ii) *Gas liquid chromatography assay.* Proceed as directed in § 436.306 of this chapter, except prepare the sample for assay as follows: Place the contents of 5 capsules in a 100-milliliter volumetric flask and add about 60 milliliters of methanol. Place on a steam bath and allow to boil gently for 5 minutes. Remove from the steam bath, add more methanol, and adjust to mark after cooling to ambient temperature. Dilute an aliquot equivalent to 50 milligrams of lincomycin to 25 milliliters with methanol. Transfer 2 milliliters to a centrifuge tube and evaporate to dryness on a steam bath with a stream of dry air. Dissolve the residue in 1 milliliter of dry pyridine. Calculate the lincomycin content of the capsules as follows:

$$\text{Lincomycin content in} \\ \text{milligrams per capsule} = \frac{R_u \times W_s \times d \times f}{R_s \times N}$$

where:

R_u =Area of lincomycin sample peak/Area of internal standard;

R_s =Area of lincomycin standard peak/Area of internal standard;

W_s =Weight of lincomycin working standard in milligrams;

d =Dilution factor;

f =Potency of lincomycin working standard in milligrams of lincomycin per milligram;

N =Number of capsules used.

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

[39 FR 19161, May 30, 1974, as amended at 46 FR 3839, Jan. 16, 1981; 50 FR 19921, May 13, 1985]

§ 453.130b Lincomycin hydrochloride syrup.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Lincomycin hydrochloride syrup is a syrup containing lincomycin hydrochloride monohydrate, one or

more suitable preservatives, flavorings, sweetening agents, colorings, and purified water. Each milliliter contains lincomycin hydrochloride equivalent to either 25 milligrams or 50 milligrams of lincomycin. Its lincomycin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of lincomycin that it is represented to contain. The pH is not less than 3 and not more than 5.5. The lincomycin hydrochloride monohydrate used conforms to the standards prescribed by § 453.30(a)(1) (i), (iv), (v), (vi), (vii), (viii), and (ix).

(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 lincomycin hydrochloride monohydrate used in making the batch for potency, pH, specific rotation, infrared absorption spectrum, lincomycin B content, crystallinity, and identity.

(b) The batch for potency and pH.

(ii) Samples required:

(a) The lincomycin hydrochloride monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

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

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

(i) *Microbiological turbidimetric assay.* Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Remove an accurately measured representative sample with a suitable hypodermic needle and syringe. Place into a high-speed glass blender jar with sufficient sterile distilled water to give a total volume of 500 milliliters. Blend for 3 to 5 minutes. Further dilute an aliquot with sterile distilled water to the reference concentration of 0.5 microgram of lincomycin per milliliter (estimated).

(ii) *Gas liquid chromatography assay.* Proceed as directed in § 436.306 of this chapter, except prepare the sample for

assay by either of the following methods:

(a) Place an aliquot of syrup, containing the equivalent of 250 milligrams of lincomycin into a 50-milliliter volumetric flask and add 30 milliliters of absolute ethanol. Place on a steam bath and boil gently for 5 minutes. Remove from the steam bath and cool. Add ethanol to prior volume level and let stand overnight. Adjust to mark, shake well, and transfer a 5-milliliter aliquot into a 25-milliliter volumetric flask and make to mark with methanol. Place 4 milliliters of this solution in a 15-milliliter centrifuge tube and evaporate to dryness on a steam bath with a stream of dry air. Dissolve the residue in 1 milliliter of dry pyridine. Calculate the lincomycin content as follows:

$$\text{Lincomycin content in} \frac{R_u \times W_s \times d \times f}{R_s \times M}$$

milligrams per milliliter

where:

R_u = Area of lincomycin sample peak/Area of internal standard;

R_s = Area of lincomycin standard peak/Area of internal standard;

W_s = Weight of lincomycin working standard in milligrams;

d = Dilution factor;

f = Potency of lincomycin working standard in milligrams of lincomycin per milligram;

M = Milliliters of syrup used.

(b) Treat the lincomycin working standard and sample in a similar manner, except lyophilize an aliquot of the sample containing the equivalent of 50 milligrams of lincomycin. To approximately 50 milligrams of the standard, accurately weighed, and to the dried residue of the sample, add 5 milliliters of dry pyridine which contains 10 milligrams of tetraphenylcyclopentadienone per milliliter. Warm on a hot plate for 5 minutes to attain complete solution. Remove from the hot plate and add 5 milliliters of hexamethyldisilazane and 2 milliliters of trimethylchlorosilane. Shake mechanically for 60 minutes, then centrifuge for 15 minutes. Inject 2 microliters of the supernate into the chromatograph. Calculate the lincomycin content as follows:

$$\text{Lincomycin content in milligrams per milliliter of syrup} = \frac{R_u \times W_s \times f}{R_s \times M}$$

where:

R_u =Area of lincomycin sample peak/Area of internal standard;

R_s =Area of lincomycin standard peak/Area of internal standard;

W_s =Weight of lincomycin working standard in milligrams;

f =Potency of lincomycin working standard in milligrams of lincomycin per milligram;

M =Milliliters of syrup used.

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

[39 FR 19161, May 30, 1974, as amended at 46 FR 3840, Jan. 16, 1981; 50 FR 19921, May 13, 1985]

Subpart C—Injectable Dosage Forms

§ 453.222 Clindamycin phosphate injection.

(a)(1) *Standards of identity, strength, quality, and purity*. Clindamycin phosphate injection is an aqueous solution of clindamycin phosphate with one or more suitable and harmless preservatives, sequestering agents, or tonicity agents. It may be frozen. Its clindamycin phosphate content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of clindamycin that it is represented to contain. It is sterile. It is nonpyrogenic. It contains no depressor substances. Its pH is not less than 5.5 and not more than 7. The clindamycin phosphate used conforms to the standards prescribed by § 453.22a(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 clindamycin phosphate used in making the batch for clindamycin content, microbiological activity, moisture, pH, crystallinity, and identity.

(b) The batch for clindamycin content, sterility, pyrogens, depressor substances, and pH.

(ii) Samples required:

(a) The clindamycin phosphate 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) Clindamycin content. Use any of the following methods. However, the results obtained from the high performance liquid chromatographic assay shall be conclusive.

(i) *Vapor phase chromatography*. Proceed as directed in § 436.304 of this chapter, except prepare the sample for assay as follows: Shake the sample and dilute a portion with pH 9.0 borate buffer to obtain a solution containing the equivalent of approximately 0.4 milligrams of clindamycin per milliliter. Place 25 milliliters of this solution into a 50-milliliter stoppered centrifuge tube. Add 10 milliliters of chloroform. Shake vigorously for 15 minutes and centrifuge. There should be no emulsion present after centrifugation. Transfer 20 milliliters of the aqueous phase from the tube into a 35-milliliter stoppered centrifuge tube. Add to the tube a weighed amount of intestinal alkaline phosphatase equivalent to 50 units of activity¹ and allow to stand until the phosphatase has dissolved completely. Place the centrifuge tube into a water bath at 37°C±2°C for 2.5 hours. After the 2.5-hours hydrolysis, allow the solution to cool.

(ii) *High performance liquid chromatographic assay*. Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 210 nanometers, a 25-centimeter long × 4.6 millimeter ID column packed with microparticulate (5 to 10 micrometers in diameter) reversed phase octylsilane hydrocarbon bonded

¹Defined such that 50 units hydrolyzes at least 20 micromoles of a clindamycin phosphate authentic sample under the assay conditions described in § 436.304 of this chapter.

silica packing material, a flow rate of about 1.0 milliliter per minute, and a known injection volume of between 10 and 20 microliters. The retention time of clindamycin phosphate, and clindamycin are approximately 6 and 9 minutes, respectively. Reagents, working standard and sample solutions, resolution test solution, system suitability requirements, and calculations are as follows:

(a) *Reagents*—(1) *0.1M Potassium phosphate monobasic buffer*. Dissolve 13.61 grams of potassium phosphate monobasic in 775 milliliters of water. Adjust the pH to 2.5 with phosphoric acid. Further dilute with water to a volume of 1,000 milliliters.

(2) *Mobile phase*. Mix 225 milliliters of acetonitrile and 775 milliliters of 0.1M potassium phosphate, pH 2.5 buffer (225:775). Filter through a suitable filter capable of removing particulate matter greater than 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(b) *Preparation of working standard, sample, and resolution test solutions*—(1) *Working standard solution*. Dissolve an accurately weighed portion of the clindamycin phosphate working standard with sufficient mobile phase (prepared as directed in paragraph (b)(1)(ii)(a)(2) of this section) to obtain a solution containing 200 micrograms of clindamycin activity per milliliter.

(2) *Sample solution*. Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with sufficient mobile phase (prepared as directed in paragraph (b)(1)(ii)(a)(2) of this section) to obtain a solution containing 200 micrograms of clindamycin per milliliter (estimated).

(3) *Resolution test solution*. Place 15 milligrams each of clindamycin phosphate, and clindamycin hydrochloride in a 25-milliliter volumetric flask and dissolve and dilute with mobile phase and mix well. Use this solution to determine the resolution factor.

(c) *System suitability requirements*—(1) *Asymmetry factor*. Calculate the asymmetry factor (A_s), measured at a point 5 percent of the peak height from the baseline as follows:

$$A_s = \frac{a+b}{2a}$$

where:

a = Horizontal distance from point of ascent to point of maximum peak height; and

b = Horizontal distance from the point of maximum peak height to point of descent.

The asymmetry factor (A_s) is satisfactory if it is not more than 1.3.

(2) *Efficiency of the column*. From the number of theoretical plates (n) calculated as described in §436.216(c)(2) of this chapter calculate the reduced plate height (h_r) as follows:

$$h_r = \frac{(L)(10,000)}{(n)(d_p)}$$

where:

L = Length of the column in centimeters;

n = Number of theoretical plates; and

d_p = Average diameter of the particles in the analytical column packing in micrometers.

The absolute efficiency (h_r) is satisfactory if it is not more than 15.

(3) *Resolution factor*. The resolution factor (R) between the peak for clindamycin phosphate and the peak for clindamycin hydrochloride in the chromatogram of the resolution test solution is satisfactory if it is not less than 6.0.

(4) *Coefficient of variation (relative standard deviation)*. The coefficient of variation (S_R in percent) of 5 replicate injections of the working standard solution (prepared as directed in paragraph (b)(1)(ii)(b)(1) of this section) is satisfactory if it is not more than 2.5 percent.

If the system suitability parameters have been met, then proceed as described in §436.216(b) of this chapter.

(d) *Calculations*. Calculate the clindamycin content as follows:

$$\text{Milligrams of clindamycin per milliliter} = \frac{A_u \times P_s \times d}{A_s \times 1,000}$$

where:

A_u = Area of the clindamycin phosphate peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s = Area of the clindamycin phosphate peak in the chromatogram of the clindamycin

phosphate working standard;
 P_s = Clindamycin activity in the
 clindamycin phosphate working standard
 solution in micrograms per milliliter;
 and
 d = Dilution factor of the sample.

(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(a) of this chapter, using a solution containing the equivalent of 24 milligrams of clindamycin per milliliter.

(4) [Reserved]

(5) *Depressor substances*. Proceed as directed in § 436.35 of this chapter.

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

[39 FR 19161, May 30, 1974, as amended at 46 FR 60568, Dec. 11, 1981; 50 FR 19921, May 13, 1985; 54 FR 43289, Oct. 24, 1989; 55 FR 5842, Feb. 20, 1990]

§ 453.230 Lincomycin hydrochloride injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Lincomycin hydrochloride injection is an aqueous solution of lincomycin hydrochloride monohydrate containing benzyl alcohol as a preservative. Each immediate container contains either 1, 2, or 10 milliliters of a solution containing, in each milliliter, 300 milligrams of lincomycin, and 9 milligrams of benzyl alcohol. The lincomycin content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of lincomycin that it is represented to contain. It is sterile. It is nonpyrogenic. It contains no depressor substances. Its pH is not less than 3.0 and not more than 5.5. The lincomycin hydrochloride monohydrate used conforms to the standards prescribed by § 453.30a(a)(1) (i), (vi), (vii), (viii), (ix), (x), and (xi).

(2) *Labeling*. It shall be labeled in accordance with the requirements of § 432.5 of this chapter. If each immediate container contains only 1 milliliter of the drug, the labeling shall include the statement "For pediatric use".

(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 lincomycin hydrochloride monohydrate used in making the batch for potency, moisture, pH, specific rotation, infrared absorption spectrum, lincomycin B content, identity, and crystallinity.

(b) The batch for potency, sterility, pyrogens, depressor substances, and pH.

(ii) Samples required:

(a) The lincomycin hydrochloride monohydrate 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 gas liquid chromatography assay shall be conclusive.

(i) *Microbiological turbidimetric assay*. Proceed as directed in § 436.106 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 of the resultant preparation, remove an accurately measured representative portion from each container. Place the portion, thus obtained, into a suitably-sized volumetric flask and dilute to volume with sterile distilled water. Remove an aliquot and further dilute with sterile distilled water to the reference concentration of 0.5 microgram of lincomycin per milliliter (estimated).

(ii) *Gas liquid chromatography assay*. Proceed as directed in § 436.306 of this chapter, except prepare the sample for assay as follows: Dilute the equivalent of 300 milligrams of lincomycin to 50 milliliters with methanol and shake. Transfer a 3-milliliter aliquot to a 10-milliliter volumetric flask and make to

mark with methanol. Place a 2-milliliter aliquot into a 15-milliliter centrifuge tube and evaporate to dryness on a steam bath with a stream of dry air. Dissolve the residue in 1 milliliter of dry pyridine. Calculate the lincomycin content as follows:

$$\frac{\text{Lincomycin content in milligrams per milliliter}}{R_u} = \frac{R_s \times W_s \times d \times f}{R_s \times \text{number of milliliters of sample}}$$

where:

$$R_u = \frac{\text{Area of lincomycin sample peak}}{\text{Area of internal standard}}$$

$$R_s = \frac{\text{Area of lincomycin standard peak}}{\text{Area of internal standard}}$$

W_s = Weight of lincomycin working standard in milligrams;

d = Dilution factor;

f = Potency of lincomycin working standard in milligrams of lincomycin per milligram

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

(3) [Reserved]

(4) *Pyrogens*. Proceed as directed in § 436.32(a) of this chapter, using a solution containing 0.5 milligram of lincomycin per milliliter.

(5) *Depressor substances*. Proceed as directed in § 436.35 of this chapter.

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

[39 FR 19161, May 30, 1974, as amended at 46 FR 3841, Jan. 16, 1981; 46 FR 60568, Dec. 11, 1981; 50 FR 19921, May 13, 1985]

Subparts D–E [Reserved]

Subpart F—Dermatologic Dosage Forms

§ 453.522 Clindamycin phosphate dermatologic dosage forms.

§ 453.522a Clindamycin phosphate topical solution.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Clindamycin phosphate is a solution of clindamycin phosphate in a

suitable and harmless vehicle. Each milliliter contains 10 milligrams of clindamycin activity. Its clindamycin content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of clindamycin that it is represented to contain. Its pH is not less than 4.0 and not more than 7.0. The clindamycin phosphate used conforms to the standards prescribed by § 453.22(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 clindamycin phosphate used in making the batch for clindamycin content, microbiological activity, moisture, pH, crystallinity, and identity.

(b) The batch for clindamycin content and pH.

(ii) Samples required:

(a) The clindamycin phosphate used in making the batch: 6 packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of six intermediate containers.

(b) *Tests and methods of assay—(1) Clindamycin content (vapor phase chromatography)*. Proceed as directed in § 436.304 of this chapter, except prepare the sample for assay and calculate the clindamycin content as follows:

(i) *Preparation of the sample*. Accurately transfer a volume of sample equivalent to approximately 20 milligrams of clindamycin activity to a 50-milliliter volumetric flask. Evaporate the sample to near dryness under a stream of nitrogen. Dilute to 50 milliliters with pH 9.0 borate buffer and mix well. Place 25.0 milliliters of this solution into a 50-milliliter stoppered centrifuge tube. Add 10 milliliters of chloroform. Shake vigorously for 15 minutes and centrifuge to obtain adequate phase separation of the chloroform and aqueous phase. Transfer 20 milliliters of the aqueous phase from the tube into a 35-milliliter stoppered centrifuge tube. Add to the tube a weighed

amount of intestinal alkaline phosphatase equivalent to 50 units of activity¹ and allow to stand until the phosphatase has dissolved completely. Place the centrifuge tube into a water bath at 37° C ± 2° C for 2.5 hours. After the 2.5-hours hydrolysis, allow the solution to cool.

(ii) *Calculations.* Calculate the clindamycin content as follows:

$$\text{Clindamycin content per milliliter} = (R_u \times W_s \times d \times f) / (R_s \times V)$$

where:

R_u = Area of clindamycin sample peak/Area of internal standard;

R_s = Area of clindamycin standard peak/Area of internal standard;

W_s = Weight of clindamycin working standard in milligrams;

d = Dilution factor;

f = Potency of clindamycin working standard in milligrams of clindamycin per milligram;

V = Volume of sample in milliliters.

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

[46 FR 2997, Jan. 13, 1981. Redesignated at 54 FR 38224, Sept. 15, 1989]

§ 453.522b Clindamycin phosphate gel.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Clindamycin phosphate gel contains clindamycin phosphate in a suitable and harmless vehicle. Each gram contains clindamycin phosphate equivalent to 10 milligrams of clindamycin activity. Its clindamycin content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of clindamycin that it is represented to contain. Its pH is not less than 4.5 and not more than 6.5. It passes the identity test. The clindamycin phosphate used conforms to the standards prescribed by § 453.22(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 re-

quirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The clindamycin phosphate used in making the batch for clindamycin content, microbiological activity, moisture, pH, crystallinity, and identity.

(B) The batch for clindamycin content, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The clindamycin phosphate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(B) The batch: A minimum of six immediate containers.

(b) *Tests and methods of assay—(1) Clindamycin content (High performance liquid chromatographic assay).* Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 210 nanometers, a 25-centimeter long x 4.6-millimeter ID column packed with microparticulate (5 to 10 micrometers in diameter) reversed phase octylsilane hydrocarbon bonded silica packing material, a flow rate of about 1.0 milliliter per minute, and a known injection volume of between 10 and 20 microliters. The retention time of clindamycin phosphate, and clindamycin are approximately 6 and 9 minutes, respectively. Reagents, working standards and sample solutions, resolution test solution, system suitability requirements, and calculations are as follows:

(i) *Reagents—(A) 0.1M Potassium phosphate monobasic buffer.* Dissolve 13.61 grams of potassium phosphate monobasic in 775 milliliters of water. Adjust the pH to 2.5 with phosphoric acid. Further dilute with water to a volume of 1,000 milliliters.

(B) *Mobile phase.* Mix 225 milliliters of acetonitrile and 775 milliliters of 0.1M potassium phosphate, pH 2.5 buffer (225:775). Filter through a suitable filter capable of removing particulate matter greater than 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) *Preparation of working standard, sample, and resolution test solutions—(A)*

¹Defined such that 50 units hydrolyzes at least 20 micromoles of a clindamycin phosphate authentic sample under the assay conditions described in § 436.304 of this chapter.

Working standard solution. Dissolve an accurately weighed portion of the clindamycin phosphate working standard with sufficient mobile phase (prepared as directed in paragraph (b)(1)(i)(B) of this section) to obtain a solution containing 200 micrograms of clindamycin activity per milliliter.

(B) *Sample solution.* Accurately weigh and transfer approximately 2.0 grams of the sample into a 100-milliliter volumetric flask. Dilute to volume with sufficient mobile phase (prepared as directed in paragraph (b)(1)(i)(B) of this section) and shake vigorously for 30 minutes. Centrifuge a portion of the solution and if necessary filter a few milliliters of the centrifuged solution through a 2-micron millipore filter, type BS.

(C) *Resolution test solution.* Place 15 milligrams each of clindamycin phosphate and clindamycin hydrochloride in a 25-milliliter volumetric flask and dissolve and dilute to volume with mobile phase and mix well. Use this solution to determine the resolution factor.

(iii) *System suitability requirements—*(A) *Asymmetry factor.* Calculate the asymmetry factor (A_s), measured at a point 5 percent of the peak height from the baseline as follows:

$$A_s = \frac{a + b}{2a}$$

where:

a = Horizontal distance from point of ascent to point of maximum peak height; and

b = Horizontal distance from the point of maximum peak height to point of descent.

The asymmetry factor (A_s) is satisfactory if it is not more than 1.3.

(B) *Efficiency of the column.* From the number of theoretical plates (n) calculated as described in §436.216(c)(2) of this chapter calculate the reduced plate height (h_r) as follows:

$$h_r = \frac{(L)(10,000)}{(n)(d_p)}$$

where:

L = Length of the column in centimeters;

n = Number of theoretical plates; and

d_p = Average diameter of the particles in the analytical column packing in micrometers.

The absolute efficiency (h_r) is satisfactory if it is not more than 15.

(C) *Resolution factor.* The resolution factor (R) between the peak for clindamycin phosphate and the peak for clindamycin (hydrochloride) in the chromatogram of the resolution test solution is satisfactory if it is not less than 6.0.

(D) *Coefficient of variation (relative standard deviation).* The coefficient of variation (S_R in percent) of 5 replicate injections of the working standard solution (prepared as directed in paragraph (b)(1)(ii)(A) of this section) is satisfactory if it is not more than 2.5 percent. If the system suitability parameters have been met, then proceed as described in §436.216(b) of this chapter.

(iv) *Calculations.* Calculate the clindamycin content as follows:

$$\text{Milligrams of clindamycin per gram} = \frac{A_u \times P_s \times d}{A_s \times 1,000}$$

where:

A_u = Area of the clindamycin phosphate peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s = Area of the clindamycin phosphate peak in the chromatogram of the clindamycin phosphate working standard;

P_s = Clindamycin activity in the clindamycin phosphate working standard solution in micrograms per milliliter; and

d = Dilution factor of the sample.

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

(B) *Identity.* The high-performance liquid chromatogram of the sample determined in paragraph (b)(1) of this section compares qualitatively to that of the clindamycin phosphate working standard.

[54 FR 38224, Sept. 15, 1989]

§453.522c Clindamycin phosphate lotion.

(a) *Requirements for certification—*(1) *Standards for identity, strength, quality, and purity.* Clindamycin phosphate lotion contains clindamycin phosphate in a suitable and harmless lotion vehicle, with one or more suitable and harmless emollients, buffers, and dispersants. Each milliliter contains clindamycin phosphate equivalent to 10 milligrams

of clindamycin. Its clindamycin content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of clindamycin that it is represented to contain. Its pH is not less than 4.5 and not more than 6.5. It passes the identity test. The clindamycin phosphate used conforms to the standards prescribed by § 453.22(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 clindamycin phosphate used in making the batch for clindamycin content, microbiological activity, moisture, pH, crystallinity, and identity.

(B) The batch for clindamycin content, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The clindamycin phosphate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(B) The batch: A minimum of six immediate containers.

(b) *Tests and methods of assay—(1) Clindamycin content (high performance liquid chromatographic assay).* Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 210 nanometers, a 25-centimeter long x 4.6 millimeter ID column packed with microparticulate (5 to 10 micrometers in diameter) reversed phase octylsilane hydrocarbon bonded silica packing material, a flow rate of about 1.08 milliliter per minute, and a known injection volume of between 10 and 20 microliters. The retention time of clindamycin phosphate and clindamycin are approximately 6 and 9 minutes, respectively. Reagents, working standard and sample solutions, resolution test solution, system suitability requirements, and calculations are as follows:

(i) *Reagents—(A) 0.1M Potassium phosphate monobasic buffer.* Dissolve 13.61 grams of potassium phosphate

monobasic in 775 milliliters of water. Adjust the pH to 2.5 with phosphoric acid. Further dilute with water to a volume of 1,000 milliliters.

(B) *Mobile phase.* Mix 225 milliliters of acetonitrile and 775 milliliters of 0.1M potassium phosphate, pH 2.5 buffer (225:775). Filter through a suitable filter capable of removing particulate matter greater than 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) *Preparation of working standard, sample, and resolution test solutions—(A) Working standard solution.* Dissolve an accurately weighted portion of the clindamycin phosphate working standard with sufficient mobile phase (prepared as directed in paragraph (b)(1)(i)(B) of this section) to obtain a solution containing 200 micrograms of clindamycin activity per milliliter.

(B) *Sample solution.* Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with sufficient mobile phase (prepared as directed in paragraph (b)(1)(i)(B) of this section) to obtain a solution containing 200 micrograms of clindamycin per milliliter (estimated).

(C) *Resolution test solution.* Dissolve 30 milligrams of clindamycin phosphate in 25 milliliters of mobile phase. Dissolve 30 milligrams of clindamycin hydrochloride in 25 milliliters of mobile phase. Combine both solutions in a 50-milliliter volumetric flask and shake or use a vortex shaker to assure mixture of both solutions. Use this solution to determine the resolution factor.

(iii) *System suitability requirements—(A) Asymmetry factor.* Calculate the asymmetry factor (A_s), measured at a point 5 percent of the peak height from the base line as follows:

$$A_s = \frac{a+b}{2a}$$

where:

a =Horizontal distance from point of ascent to point of maximum peak height; and
 b =Horizontal distance from the point of maximum peak height to point of descent.

The asymmetry factor (A_s) is satisfactory if it is not more than 1.3.

(B) *Efficiency of the column.* From the number of theoretical plates (n) calculated as described in § 436.216(c)(2) of this chapter, calculate the reduced plate height (h_r) as follows:

$$h_r = \frac{(L)(10,000)}{(n)(d_p)}$$

where:

L =Length of the column in centimeters;
 n =Number of theoretical plates; and
 d_p =Average diameter of the particles in the analytical column packing in micrometers.

The absolute efficiency (h_r) is satisfactory if it is not more than 15.

(C) *Resolution factor.* The resolution factor (R) between the peak for clindamycin phosphate and the peak for clindamycin (hydrochloride) in the chromatogram of the resolution test solution is satisfactory if it is not less than 6.0.

(D) *Coefficient of variation (relative standard deviation).* The coefficient of variation (S_R in percent) of 5 replicate injections of the working standard solution (prepared as directed in paragraph (b)(1)(ii)(A) of this section) is satisfactory if it is not more than 2.5 percent.

If the system suitability parameters have been met, then proceed as described in § 436.216(b) of this chapter.

(iv) *Calculations.* Calculate the clindamycin content as follows:

$$\text{Milligrams of clindamycin per milliliter} = \frac{A_u \times P_s \times d}{A_s \times 1,000}$$

where:

A_u =Area of the clindamycin phosphate peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s =Area of the clindamycin phosphate peak in the chromatogram of the clindamycin phosphate working standard;

P_s =Clindamycin activity in the clindamycin phosphate working standard solution in micrograms per milliliter; and

d =Dilution factor of the sample.

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

(3) *Identity.* The high-performance liquid chromatogram of the sample determined in paragraph (b)(1) of this sec-

tion compares qualitatively to that of the clindamycin phosphate working standard.

[54 FR 40655, Oct. 3, 1989]

§ 453.522d Clindamycin phosphate vaginal cream.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Clindamycin phosphate vaginal cream contains clindamycin phosphate in a suitable and harmless cream vehicle. Each gram contains clindamycin phosphate equivalent to 20 milligrams of clindamycin activity. Its clindamycin content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of clindamycin that it is represented to contain. Its pH is not less than 3.0 and not more than 6.0. It passes the identity test. The clindamycin phosphate used conforms to the standards prescribed by § 453.22(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 clindamycin phosphate used in making the batch for clindamycin content, microbiological activity, moisture, pH, crystallinity, and identity.

(B) The batch for clindamycin content, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The clindamycin phosphate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(B) The batch: a minimum of six immediate containers.

(b) *Tests and methods of assay—(1) Clindamycin content (high performance liquid chromatography assay).* Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 210 nanometers, a 25-centimeter long x 4.6 millimeter ID column packed with microparticulate (5 to 10 micrometers in diameter) reverse

phase octylsilane hydrocarbon bonded silica packing material, a flow rate of 1.0 milliliter per minute, and a known injection volume of 20 microliters. The retention time of clindamycin phosphate, and clindamycin are approximately 6 and 9 minutes, respectively. Reagents, working standards and sample solutions, resolution test solution, system suitability requirements, and calculations are as follows:

(i) *Reagents*—(A) *0.1M Potassium phosphate monobasic buffer*. Dissolve 13.61 grams of potassium phosphate monobasic in 775 milliliters of water. Adjust the pH to 2.5 with phosphoric acid. Further dilute with water to a volume of 1,000 milliliters.

(B) *Mobile phase*. Mix 225 milliliters of acetonitrile and 775 milliliters of 0.1M potassium phosphate, pH 2.5 buffer (225:775). Filter through a suitable filter capable of removing particulate matter greater than 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) *Preparation of working standard, sample, and resolution test solutions*—(A) *Working standard solution*. Dissolve an accurately weighed portion of the clindamycin phosphate working standard in sufficient mobile phase (prepared as directed in paragraph (b)(1)(i)(B) of this section) to obtain a solution containing 200 micrograms of clindamycin activity per milliliter.

(B) *Sample solutions*. Accurately weigh and transfer approximately 1.0 gram of the sample into a 125-milliliter Erlenmeyer flask. Add 100.0 milliliters of mobile phase (prepared as directed in paragraph (b)(1)(i)(B) of this section), accurately measured, and 8 to 10 glass beads (4 to 5 millimeters). Close the flask securely using a plastic stopper and shake vigorously by mechanical means for 1 hour at 50 °C. Cool in an ice bath for approximately 20 minutes. Centrifuge a portion of the mixture. Use the lower cloudy solution for chromatographic analysis. Filter a few milliliters of the centrifuged solution through an appropriate 2 micron filter.

(C) *Resolution test solution*. Place 15 milligrams each of clindamycin phosphate and clindamycin hydrochloride in a 25-milliliter volumetric flask and dissolve and dilute to volume with mo-

bile phase and mix well. Use this solution to determine the resolution factor.

(iii) *System suitability requirements*—(A) *Asymmetry factor*. Calculate the asymmetry factor (A_s), measured at a point 5 percent of the peak height from the baseline as follows:

$$A_s = \frac{a+b}{2a}$$

where:

a = Horizontal distance from point of ascent to point of maximum peak height; and

b = Horizontal distance from point of maximum peak height to point of descent.

The asymmetry factor (A_s) is satisfactory if it is not less than 1.0 and not more than 1.3.

(B) *Efficiency of the column*. From the number of theoretical plates (n) calculated as described in §436.216(c)(2) of this chapter, calculate the reduced plate height (h_r) as follows:

$$h_r = \frac{(L)(10,000)}{(n)(d_p)}$$

where:

L = Length of the column in centimeters;

n = Number of theoretical plates; and

d_p = Average diameter of the particles in the analytical column packing in micrometers.

The absolute efficiency (h_r) is satisfactory if it is not more than 15.

(C) *Resolution factor*. The resolution factor (R) between the peak for clindamycin phosphate and the peak for clindamycin (hydrochloride) in the chromatogram of the resolution test solution is satisfactory if it is not less than 6.0.

(D) *Coefficient of variation (relative standard deviation)*. The coefficient of variation (S_R in percent) of 5 replicate injections of the working standard solution is satisfactory if it is not more than 2.5 percent. If the system suitability parameters have been met, then proceed as described in §436.216(b) of this chapter.

(iv) *Calculation*. Calculate the clindamycin content as follows:

$$\text{Milligrams of clindamycin per gram} = \frac{A_u \times P_s \times d}{A_s \times 1,000}$$

where:

A_u = Area of the clindamycin phosphate peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s = Area of the clindamycin phosphate peak in the chromatogram of the clindamycin phosphate working standard;

P_s = Clindamycin activity in the clindamycin phosphate working standard solution in micrograms per milliliter; and

d = Dilution factor of the sample.

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

(3) *Identity*. The high-pressure liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the clindamycin phosphate working standard.

[60 FR 49508, Sept. 26, 1995]

PART 455—CERTAIN OTHER ANTIBIOTIC DRUGS

Subpart A—Bulk Drugs

Sec.

- 455.4 Aztreonam.
- 455.4a Sterile aztreonam.
- 455.10 Chloramphenicol.
- 455.10a Sterile chloramphenicol.
- 455.11 Chloramphenicol palmitate.
- 455.12a Sterile chloramphenicol sodium succinate.
- 455.15 Clavulanate potassium.
- 455.15a Sterile clavulanate potassium.
- 455.20 Cycloserine.
- 455.40 Mupirocin.
- 455.50 Calcium novobiocin.
- 455.51 Sodium novobiocin.
- 455.51a Sterile sodium novobiocin.
- 455.70 Rifampin.
- 455.80a Sterile spectinomycin hydrochloride.
- 455.82a Sterile sulbactam sodium.
- 455.85 Vancomycin hydrochloride.
- 455.85a Sterile vancomycin hydrochloride.
- 455.86 Vancomycin.
- 455.88 Rifabutin.
- 455.90a Sterile vidarabine monohydrate.

Subpart B—Oral Dosage Forms

- 455.110 Chloramphenicol capsules.
- 455.111 Chloramphenicol palmitate oral suspension.
- 455.120 Cycloserine capsules.
- 455.150 Calcium novobiocin oral suspension.
- 455.151 Sodium novobiocin oral dosage forms.
- 455.151a Sodium novobiocin tablets.
- 455.151b Sodium novobiocin capsules.
- 455.170 Rifampin oral dosage forms.

- 455.170a Rifampin capsules.
- 455.170b Rifampin-isoniazid capsules.
- 455.185 Vancomycin hydrochloride oral dosage forms.
- 455.185a Vancomycin hydrochloride for oral solution.
- 455.185b Vancomycin hydrochloride capsules.
- 455.188 Rifabutin capsules.

Subpart C—Injectable Dosage Forms

- 455.204 Aztreonam injectable dosage forms.
- 455.204a Aztreonam for injection.
- 455.204b Aztreonam injection.
- 455.210 Chloramphenicol injection.
- 455.212 Sterile chloramphenicol sodium succinate.
- 455.230 Moxalactam disodium for injection.
- 455.251 Sodium novobiocin for injection.
- 455.270 Rifampin for injection.
- 455.280a Sterile spectinomycin hydrochloride.
- 455.285 Vancomycin hydrochloride injectable dosage forms.
- 455.285a Sterile vancomycin hydrochloride.
- 455.285b Vancomycin hydrochloride for injection.
- 455.285c Vancomycin hydrochloride injection.
- 455.290 Vidarabine monohydrate for infusion.

Subpart D—Ophthalmic Dosage Forms

- 455.310 Chloramphenicol ophthalmic dosage forms.
- 455.310a Chloramphenicol ophthalmic solution.
- 455.310b Chloramphenicol for ophthalmic solution.
- 455.310c Chloramphenicol ointment (chloramphenicol cream).
- 455.310d Chloramphenicol-polymyxin ointment.
- 455.310e Chloramphenicol-hydrocortisone acetate for ophthalmic suspension.
- 455.390 Vidarabine monohydrate ophthalmic ointment.

Subpart E—Otic Dosage Forms

- 455.410 Chloramphenicol otic.

Subpart F—Dermatologic Dosage Forms

- 455.510 Chloramphenicol dermatologic dosage forms.
- 455.510a Chloramphenicol ointment (chloramphenicol cream).
- 455.510b [Reserved]
- 455.510c Chloramphenicol-polymyxin ointment.
- 455.510d Fibrinolysin and desoxyribonuclease, combined (bovine) with chloramphenicol ointment.
- 455.540 Mupirocin ointment.

AUTHORITY: 21 U.S.C. 357.