

(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:

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

milligrams per capsule

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.