

## Subpart B—Oral Dosage Forms

**§ 455.110 Chloramphenicol capsules.**

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Chloramphenicol capsules are composed of chloramphenicol with or without one or more suitable and harmless diluents and lubricants. Each capsule contains 50, 100, or 250 milligrams of chloramphenicol. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of chloramphenicol that it is represented to contain. The chloramphenicol used conforms to the standards prescribed by § 455.10(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 chloramphenicol used in making the batch for potency, pH, specific rotation, melting range, absorptivity, and crystallinity.

(b) The batch for potency.

(ii) Samples required:

(a) The chloramphenicol 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; potency.* Use either of the following methods; however, the results obtained from the microbiological turbidimetric assay shall be conclusive.

(1) *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 containing 100 milliliters of 95 percent ethyl alcohol. Blend for 2 minutes. Then add 400 milliliters of distilled water and blend again for 2 minutes. Remove an aliquot and further dilute with distilled water to the reference concentration of 2.5 micrograms of chloramphenicol per milliliter (estimated).

(2) *Spectrophotometric assay—(i) Preparation of working standard solution.* Dis-

solve approximately 50 milligrams of the working standard in 100 milliliters of distilled water. Warm if necessary to hasten dissolution. Transfer 10 milliliters into a 250-milliliter volumetric flask and fill to volume with distilled water.

(ii) *Procedure.* Place the contents of 10 capsules into a 250-milliliter volumetric flask. Add 50 milliliters of pure methyl alcohol to the flask and shake for at least 1 minute. Fill to volume with distilled water and mix thoroughly. Withdraw an aliquot and dilute with sufficient distilled water to give a concentration of 20 micrograms per milliliter. Using a suitable spectrophotometer equipped with a 1.0-centimeter cell and distilled water as the blank, determine the absorbance of the working standard and sample solutions at 278 nanometers. Calculate the potency as follows:

$$\text{Milligrams per capsule} = \frac{\text{Absorbance of sample} \times \text{labeled potency per capsule in milligrams}}{\text{Absorbance of standard}}$$

[39 FR 19149, May 30, 1974, as amended at 48 FR 3960, Jan. 28, 1983; 50 FR 19921, May 13, 1985]

**§ 455.111 Chloramphenicol palmitate oral suspension.**

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Chloramphenicol palmitate oral suspension is chloramphenicol palmitate and one or more suitable and harmless buffer substances, suspending agents, preservatives, colorings, and flavorings suspended in a suitable and harmless vehicle. Each milliliter contains chloramphenicol palmitate equivalent to 30.0 milligrams of chloramphenicol. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of chloramphenicol that it is represented to contain. Its pH is not less than 4.5 nor more than 7.0. Its content of polymorph A crystals does not exceed 10 percent. The chloramphenicol palmitate used conforms to the standards prescribed by § 455.11(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 chloramphenicol palmitate used in making the batch for chloramphenicol content, melting range, specific rotation, and crystallinity.

(b) The batch for chloramphenicol content, pH, and content of polymorph A crystals.

(ii) Samples required:

(a) The chloramphenicol palmitate used in making the batch: 10 packages, each containing approximately 500 milligrams.

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

(b) *Tests and methods of assay*—(1) Chloramphenicol content (high-pressure liquid chromatography). Proceed as directed in §436.335 of this chapter, except prepare the sample solution and calculate the chloramphenicol content as follows:

(i) *Preparation of sample solution.* Transfer a portion of the sample equivalent to 150 milligrams of chloramphenicol into a 200-milliliter volumetric flask. Add 100 milliliters of methanol and 4 milliliters of glacial acetic acid. Shake and dilute to volume with methanol. Filter the solution through a glass fiber filter or equivalent that is capable of removing particulate contamination to 1 micron in diameter.

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

$$\frac{\text{Milligrams of chloramphenicol}}{\text{per milliliter}} = \frac{(A)(W_s)(f)(4)}{(B)(1,000)(V)}$$

where:

A=Area of the chloramphenicol palmitate sample peak (at a retention time equal to that observed for the standard);

B=Area of the working standard peak;

W<sub>s</sub>=Weight of standard in milligrams;

f=Micrograms of chloramphenicol activity per milligram of chloramphenicol palmitate working standard; and

V=Volume of sample in milliliters.

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

(3) *Content of polymorph A crystal.*—(i) *Preparation of standards*—(a) *Standard containing 20 percent of polymorph A.*

Prepare a thoroughly mixed, dry powder composed by weight of 1 part of polymorph A crystals of chloramphenicol palmitate and 4 parts of nonpolymorph A crystals of chloramphenicol palmitate.

(b) *Standard containing 10 percent of polymorph A.* Prepare a thoroughly mixed, dry powder composed by weight of 1 part of polymorph A crystals of chloramphenicol palmitate and 9 parts of nonpolymorph A crystals of chloramphenicol palmitate.

(ii) *Preparation of sample.* Place 20 milliliters of thoroughly mixed oral suspension into a 50-milliliter centrifuge tube. Add 20 milliliters of water and mix. Centrifuge for 10 to 15 minutes at a speed not less than 18,000 revolutions per minute. Decant the supernatant liquid. Wash the residue as follows: Add 2 milliliters of water to the residue, mix to make paste, add 18 milliliters of water, and mix thoroughly. Centrifuge, decant the supernatant liquid, and wash the residue two more times. Remove the washed residue from the centrifuge tube and dry it at least 14 hours in a vacuum desiccator at room temperature.

(iii) *Procedure.* Weigh 150 to 200 milligrams of liquid petrolatum into an agate mortar and add about 100 milligrams of standard or sample. Mix with a small spatula and then mull thoroughly with a pestle until a uniform consistency is obtained. Adjust a suitable infrared spectrophotometer so that 100 percent transmittance is recorded over the range of 11.0 to 13.0 microns. Use two rock salt plates as an absorption cell. Place a small drop of the mull in the center of one of the plates. Gently put the other plate on the mull and slowly squeeze the plates together to spread the mull uniformly. Clamp the two plates firmly together in a metal cell holder. Examine the assembled cell by holding it up to the light. It should appear smooth and free of any air bubbles and when placed in the instrument it should give a percent transmittance of 20 to 30 percent at 12.3 microns. Place the cell in the infrared spectrophotometer and record the absorption spectrum from 11.0 to 13.0 microns.

(iv) *Treatment of spectra*—(a) *Standard containing 20 percent of polymorph A.*

Determine by inspection of the recorded spectrum the exact wavelengths of minimum absorption at approximately 11.3 and 12.65 microns. Also determine by inspection the exact wavelengths of maximum absorption at approximately 11.65 and 11.86 microns. In the following subdivision, references to these four nominal wavelengths are to the exact wavelengths observed on the particular instrument being used.

(b) *Standard containing 10 percent of polymorph A.* Draw a straight baseline between the minima occurring at 11.3 and 12.65 microns. Draw straight lines at 11.65 and 11.86 microns intersecting both the recorded spectrum and the baseline. Obtain the corrected absorbances at 11.65 and 11.86 microns and calculate the absorbance ratios as follows:

$$\text{Absorbance ratio} = \frac{S_{11.65} - B_{11.65}}{S_{11.86} - B_{11.86}}$$

where:

$S_{11.65}$  = Absorbance value of recorded spectrum at 11.65 microns;

$B_{11.65}$  = Absorbance value at point of intersection of the 11.65-micron line with the baseline;

$S_{11.86}$  = Absorbance value of recorded spectrum at 11.86 microns;

$B_{11.86}$  = Absorbance value at point of intersection of the 11.86-micron line with the baseline.

(c) *Sample.* Proceed as described in paragraph (b)(3)(iv)(b) of this section.

(v) *Calculation.* The absorbance ratio of the sample must be greater than the absorbance ratio of the standard containing 10 percent of polymorph A.

[39 FR 19166, May 30, 1974, as amended at 49 FR 6093, Feb. 17, 1984; 50 FR 19921, May 13, 1985]

#### § 455.120 Cycloserine capsules.

(a) *Requirements for certification—(1) Standards of identity, quality, and purity.* Cycloserine capsules are capsules composed of crystalline cycloserine, with or without one or more suitable and harmless buffer substances, diluents, binders, and lubricants. Each capsule contains 250 milligrams of cycloserine. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cycloserine that it is represented to contain.

The loss on drying is not more than 1.0 percent. The cycloserine used conforms to the standards prescribed by § 455.20(a)(1).

(2) *Labeling.* In addition to the labeling prescribed by § 432.5 of this chapter, the labeling of each package shall bear a warning to the effect that the drug is to be used in patients with tuberculosis who fail to respond to treatment with isoniazid, streptomycin, paraaminosalicylic acid, viomycin, pyrazinamide, or combinations of these drugs, and that the drug may cause serious reactions such as convulsive seizures and mental disturbances.

(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) Cycloserine used in making the batch for potency, loss on drying, pH, residue on ignition, crystallinity, and identity.

(b) The batch for cycloserine content and loss on drying.

(ii) Samples required:

(a) Cycloserine used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch: Minimum of 30 capsules.

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

(i) *Chemical colorimetric assay—(a) Reagents.* (1) Acetic acid—1.0*N* solution.

(2) Sodium hydroxide—4.0*N* and 0.1*N* solutions.

(3) Sodium nitroprusside—4.0 percent solution: Dissolve 4.0 grams in sufficient distilled water to make 100.0 milliliters. Mix well. Store in amber bottle.

(4) Oxidized nitroprusside reagent—Mix equal parts of the 4.0 percent sodium nitroprusside solution and 4.0*N* sodium hydroxide, and let stand for 1 hour before using. Prepare daily and store in amber bottle.

(5) Cycloserine standard solution—dilute an appropriate-sized aliquot of the