

P_c =Cyclosporine content in the cyclosporine working standard solution in micrograms per milliliter;
 d =Dilution factor of the sample; and
 n =Number of capsules in the sample assayed.

(2) *Disintegration time.* Proceed as directed in §436.212 of this chapter, using the procedure described in §436.212(e)(5).

[55 FR 19873, May 14, 1990; 55 FR 22014, May 30, 1990]

Subpart C—Injectable Dosage Forms

§ 448.210 Sterile bacitracin.

The requirements for certification and the tests and methods of assay for sterile bacitracin packaged for dispensing are described in §448.10a.

§ 448.215 Sterile capreomycin sulfate.

The requirements for certification and the tests and methods of assay for sterile capreomycin sulfate packaged for dispensing are described in §448.15a.

§ 448.220 Colistimethate sodium injectable dosage forms.

§ 448.220a Sterile colistimethate sodium.

The requirements for certification and the tests and methods of assay for sterile colistimethate sodium packaged for dispensing are described in §448.20a.

§ 448.223 Cyclosporine for infusion.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Cyclosporine for infusion is a solution of cyclosporine in a suitable and harmless alcohol derivatized vegetable oil vehicle. Its cyclosporine content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of cyclosporine that it is represented to contain. It is sterile. It contains not more than 42 endotoxin units per milliliter (United States Pharmacopeia endotoxin units). The cyclosporine used conforms to the standards prescribed by §448.23.

(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 cyclosporine used in making the batch for cyclosporine content, loss on drying, heavy metals, and identity.

(b) The batch for cyclosporine content, sterility, and bacterial endotoxins.

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

(a) The cyclosporine used in making the batch: Six packages, each containing approximately 500 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) Cyclosporine content.* Proceed as directed in §436.346 of this chapter, except prepare the working standard and sample solutions and calculate the cyclosporine content as described in paragraphs (b)(1) (i) and (ii) of this section. A typically suitable column for cyclosporine dosage forms is 250 millimeters long having an inside diameter of 4 millimeters packed with dimethyl silane chemically bonded to porous silica particles 10 microns in diameter [RP-2 (E.M. Science, S. Plainfield, NJ)].

(i) *Preparation of working standard and sample solutions.*

NOTE: Prepare working standard and sample solutions immediately before analysis.

(a) *Preparation of working standard solution.* Dissolve an accurately weighed portion of the working standard in ethanol by shaking for at least 15 minutes. If necessary, ultrasonicate until the solution becomes completely clear. Dilute with ethanol to obtain a solution containing 1 milligram of cyclosporine activity per milliliter.

(b) *Preparation of sample solution.* 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 concentration of cyclosporine in a given volume of the resultant preparation, remove an

accurately measured portion from each container. Dilute with ethanol to obtain a stock solution of 1 milligram of cyclosporine activity per milliliter (estimated).

(ii) *Calculations.* Calculate the cyclosporine content of the vial as follows:

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

where:

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

A_s =Area of the cyclosporine peak in the chromatogram of the cyclosporine working standard;

P_s =Cyclosporine activity in the cyclosporine 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)(2) of that section.

(3) *Bacterial endotoxins.* Proceed as directed in the United States Pharmacopeia XX bacterial endotoxins test.

[49 FR 22633, May 31, 1984, as amended at 55 FR 11584, Mar. 29, 1990]

§ 448.230 Sterile polymyxin B sulfate.

The requirements for certification and the tests and methods of assay for sterile polymyxin B sulfate packaged for dispensing are described in § 448.30a.

[44 FR 10379, Feb. 20, 1979]

Subpart D—Ophthalmic Dosage Forms

§ 448.310 Bacitracin ophthalmic dosage forms.

§ 448.310a [Reserved]

§ 448.310b Bacitracin-neomycin sulfate-polymyxin B sulfate ophthalmic ointment.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Bacitracin-neomycin sulfate-polymyxin B sulfate ophthalmic ointment contains bacitracin, neomycin sulfate, and polymyxin B sulfate in a suitable and harmless ointment base.

Each gram contains 500 units of bacitracin, 3.5 milligrams of neomycin, and 10,000 units of polymyxin B. Its bacitracin content is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of units of bacitracin that it is represented to contain. Its neomycin content is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of neomycin that it is represented to contain. Its polymyxin B content is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of units of polymyxin B that it is represented to contain. It is sterile. Its moisture content is not more than 0.5 percent. It passes the test for metal particles. The bacitracin used conforms to the standards prescribed by § 448.10a(a)(1), except pyrogens, residue on ignition, and heavy metals. The neomycin sulfate used conforms to the standards prescribed by § 444.42a(a)(1) of this chapter, except pyrogens. The polymyxin B sulfate used conforms to the standards prescribed by § 448.30a(a)(1), except pyrogens, residue on ignition, and heavy metals.

(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 bacitracin used in making the batch for potency, loss on drying, pH, and identity.

(b) The neomycin sulfate used in making the batch for potency, loss on drying, pH, and identity.

(c) The polymyxin B sulfate used in making the batch for potency, loss on drying, pH, and identity.

(d) The batch for bacitracin content, neomycin content, polymyxin B content, sterility, moisture, and metal particles.

(ii) Samples required:

(a) The bacitracin used in making the batch: 10 packages, each containing approximately 1.0 gram.

(b) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 1.0 gram.