

is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of colistin that it is represented to contain. The loss on drying is not more than 3.0 percent. The pH of the reconstituted suspension is not less than 5.0 and not more than 6.0. The colistin sulfate used conforms to the standards prescribed by § 448.21(a)(1).

(2) *Labeling.* It shall be labeled as prescribed in § 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 colistin sulfate used in making the batch for potency, loss on drying, pH, and identity.

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

(ii) Samples required:

(a) The colistin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

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

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute the suspension as directed in the label. Remove an accurately measured representative portion of the reconstituted suspension with a hypodermic needle and syringe and dilute with 10 percent potassium phosphate buffer, pH 6.0 (solution 6), to the reference concentration of 1.0 microgram of colistin per milliliter (estimated).

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

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

[39 FR 19115, May 30, 1974, as amended at 50 FR 19920, May 13, 1985]

#### § 448.123 Cyclosporine oral dosage forms.

##### § 448.123a Cyclosporine oral solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cyclosporine oral solution contains, in each milliliter, 100 milligrams of cyclosporine in a suitable and

harmless alcohol-vegetable oil solution. 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. The cyclosporine used conforms to the standards prescribed by § 448.23, except 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 cyclosporine used in making the batch for cyclosporine content, loss on drying, and identity.

(b) The batch for cyclosporine content.

(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: A minimum of five immediate containers.

(b) *Tests and methods of assay; 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) and (2) 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)].

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

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

(i) *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.

(ii) *Preparation of sample solution.* Place an accurately measured representative volume of the cyclosporine oral solution into a volumetric flask. Add sufficient ethanol to obtain a concentration of 1 milligram of cyclosporine activity per milliliter (estimated).

(2) *Calculations.* Calculate the cyclosporine content 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 of the cyclosporine working standard solution in micrograms per milliliter; and

$d$ =Dilution factor of the sample.

[49 FR 22633, May 31, 1984, as amended at 55 FR 11584, Mar. 29, 1990. Redesignated at 55 FR 19873, May 14, 1990]

#### § 448.123b Cyclosporine capsules.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Cyclosporine capsules are composed of cyclosporine in a suitable and harmless alcohol-vegetable oil solution enclosed by a soft gelatin capsule. 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. The capsules shall disintegrate within 30 minutes. The cyclosporine used conforms to the standards prescribed by § 448.23, except 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 cyclosporine used in making the batch for cyclosporine content, loss on drying, and identity.

(B) The batch for cyclosporine content and disintegration time.

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

(A) The cyclosporine used in making the batch: Six packages, each containing approximately 500 milligrams.

(B) The batch: A minimum of 36 capsules.

(b) *Test 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) (A) and (B) and (b)(1)(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) *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) *Sample solution.* Cut open a representative number of capsules with a sharp blade and quantitatively transfer the capsule contents to a volumetric flask. Add sufficient ethanol to obtain a concentration of 1 milligram of cyclosporine activity per milliliter (estimated).

(ii) *Calculations.* Calculate the cyclosporine content in milligrams per capsule as follows:

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

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;