

for isomer A if it is greater than 3,000 theoretical plates.

(C) *Resolution.* The resolution (R) between isomer A and isomer B of cefuroxime axetil is satisfactory if it is not less than 1.5 and the resolution (R) between isomer A and the delta-2 isomers of cefuroxime axetil is satisfactory if it is not less than 1.5.

(D) *Coefficient of variation.* The coefficient of variation (S_R in percent) of five replicate injections is satisfactory if it is not more than 2.0 percent. If the system suitability requirements have been met, then proceed as described in § 436.216(b) of this chapter. Alternate chromatographic conditions are acceptable provided reproducibility and resolution are recomparable to the system. However, the sample preparation described in paragraph (b)(1)(ii)(B) of this section should not be changed.

(iv) *Calculations*—(A) Calculate the micrograms of cefuroxime per milligram of sample as follows:

$$\frac{\text{Micrograms of cefuroxime per milligram}}{= \frac{R_u \times P_s \times 100}{R_s \times C_u \times (100 - m)}}$$

where:

R_u = Sum of the peak height of the cefuroxime axetil sample isomer A and isomer B peaks/Peak height of the internal standard;

R_s = Sum of the peak heights of the cefuroxime axetil working standard isomer A and isomer B peaks/Peak height of the internal standard;

P_s = Cefuroxime activity in the cefuroxime axetil working standard solution in micrograms per milliliter;

C_u = Milligrams of sample per milliliter of sample solution; and

m = Percent moisture content of the sample.

(B) Calculate the ratio of isomer A to total isomer content as follows:

$$\text{Ratio of isomer A to isomer content} = \frac{\text{Peak height of isomer A peak}}{\text{Peak height of isomer A peak} + \text{Peak height of isomer B peak}}$$

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter, using the titration procedure described in paragraph (e)(1) of that section.

(3) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter, except that the particles do not reveal the phenomena of birefringence and extinction positions on revolving the microscope stage.

(4) *Identity.* Proceed as directed in § 436.211 of this chapter, using the mineral oil mull prepared as described in paragraph (b)(2) of that section.

[52 FR 42432, Nov. 5, 1987; 52 FR 43966, Nov. 17, 1987; 52 FR 45528, Nov. 30, 1987, as amended at 54 FR 47351, Nov. 14, 1989; 55 FR 11583, Mar. 29, 1990]

§ 442.20a Sterile cefonicid sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile cefonicid sodium is a white to off-white lyophilized powder. It is so purified and dried that:

(i) If the cefonicid sodium is not packaged for dispensing, its cefonicid

content is not less than 832 micrograms and not more than 970 micrograms of cefonicid per milligram on an anhydrous basis. If the cefonicid sodium is packaged for dispensing, its cefonicid content is not less than 832 micrograms and not more than 970 micrograms of cefonicid per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefonicid that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 5.0 percent.

(v) Its pH in an aqueous solution containing 50 milligrams per milliliter is not less than 3.5 and not more than 6.5.

(vi) The specific rotation in a methanol solution containing 10 milligrams of cefonicid sodium per milliliter at 25° C is $-42^{\circ} \pm 5^{\circ}$.

(vii) It passes the identity test.

(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 cefonicid content, sterility, pyrogens, moisture, pH, specific rotation, and identity.

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

(a) If the batch is packaged for repackaging or for use as an ingredient in the manufacture of another drug:

(1) For all tests except sterility: 10 packages, each containing at least 500 milligrams.

(2) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

(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) Cefonicid content.* Proceed as directed in § 436.350 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 254 nanometers, and a column packed with octadecyl silane bonded silica ranging from 3 to 30 micrometers in particle size. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents—(a) 0.2M Ammonium phosphate solution.* Transfer 23.0 grams of ammonium dihydrogen phosphate to a 1-liter volumetric flask. Dissolve and dilute to volume with distilled water. Mix well.

(b) *Mobile phase.* Mix 0.2M ammonium phosphate solution: methyl alcohol: distilled water (1:2.5:16.5). Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) *Working standard and sample solutions—(a) Preparation of working standard solution.* Prepare the working

standard solution fresh before injection by dissolving an accurately weighed portion of the cefonicid working standard with sufficient mobile phase as described in paragraph (b)(1)(i)(b) of this section to obtain a solution containing approximately 20 micrograms of cefonicid per milliliter.

(b) *Preparation of sample solutions—(1) Product not packaged for dispensing (micrograms of cefonicid per milligram).*

Dissolve an accurately weighed portion of the sample with sufficient mobile phase as described in paragraph (b)(1)(i)(b) of this section to obtain a concentration of approximately 20 micrograms of cefonicid per milliliter.

(2) *Product packaged for dispensing.* Determine both micrograms of cefonicid per milligram of the sample and milligrams of cefonicid per container. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(i)(b)(2) (i) and (ii) of this section.

(i) *Micrograms of cefonicid per milligram.* Dissolve an accurately weighed portion of the sample with sufficient mobile phase as described in paragraph (b)(1)(i)(b) of this section to obtain a concentration of approximately 20 micrograms of cefonicid per milliliter.

(ii) *Milligrams of cefonicid per container.* Reconstitute the sample as directed in the labeling. Then, 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. Further dilute an aliquot of the solution thus obtained with sufficient mobile phase to obtain a concentration of approximately 20 micrograms of cefonicid per milliliter.

(iii) *System suitability requirements—(a) Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 1.3 at 5 percent of peak height.

(b) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 1,500 theoretical plates.

(c) *Resolution factor.* Prepare a resolution solution containing desacetyl cefonicid by heating a 200-microgram-

per-milliliter solution of cefonicid working standard in mobile phase described in paragraph (b)(1)(i)(b) of this section, on a steam bath for 30 minutes. Inject a known volume between 10 and 20 microliters of the desacetyl cefonicid containing solution in the same manner as described for the standard solution. The resolution factor (*R*) between cefonicid and desacetyl cefonicid is satisfactory if it is not less than 1.1.

(d) *Coefficient of variation.* The coefficient of variation (*S_R* in percent) of five replicate injections is satisfactory if it is not more than 2.0 percent.

If the system suitability parameters have been met, then proceed as described in § 436.350(b) of this chapter.

(iv) *Calculations—(a)* Calculate the micrograms of cefonicid per milligram of sample as follows:

$$\text{Micrograms of cefonicid per milligram} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - m)}$$

where:

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

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

P_s=Cefonicid activity in the cefonicid working standard solution in micrograms per milliliter;

C_u=Milligrams of sample per milliliter of sample solution; and

m=Percent moisture content of the sample.

(b) Calculate the cefonicid content of the container as follows:

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

where:

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

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

P_s=Cefonicid activity in the cefonicid 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 meth-

od described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 50 milligrams of cefonicid per milliliter.

(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 50 milligrams per milliliter.

(6) *Specific rotation.* Dissolve and dilute an accurately weighed sample with sufficient methanol to obtain a concentration of approximately 10 milligrams of cefonicid sodium per milliliter. Proceed as directed in § 436.210 of this chapter, using a 1.0-decimeter polarimeter tube. Calculate the specific rotation on an anhydrous basis.

(7) *Identity.* The high-performance liquid chromatogram of the sample, determined as directed in paragraph (b)(1) of this section, compares qualitatively to that of the cefonicid working standard.

[49 FR 34348, Aug. 30, 1984; 49 FR 44460, Nov. 7, 1984, as amended at 54 FR 41824, Oct. 12, 1989; 55 FR 11583, Mar. 29, 1990]

§ 442.21 Cephaloglycin dihydrate.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Cephaloglycin dihydrate is the dihydrate form of 7-(D-α-aminophenylacetamido) cephalosporanic acid. It is a white to off-white powder. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms of cephaloglycin per milligram on an anhydrous basis.

(ii) [Reserved]

(iii) Its moisture is not less than 8.2 and not more than 12 percent.

(iv) Its pH in an aqueous suspension containing 50 milligrams per milliliter is not less than 3.0 and not more than 5.5.

(v) Its cephaloglycin content is not less than 95 and not more than 104 percent on an anhydrous basis.

(vi) It gives a positive identity test for cephaloglycin dihydrate.

(vii) It is crystalline.

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