

(C) *Resolution.* The resolution (*R*) between the peak for cefotetan and its tautomer is satisfactory if it is not less than 2.0.

(D) *Coefficient of variation.* The coefficient of variation (*S_v* 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 comparable system suitability requirements are met. However, the sample preparation described in paragraph (b)(1)(ii)(B) of this section should not be changed.

(iv) *Calculation.* Calculate the micrograms of cefotetan per milligram of sample as follows:

$$\frac{\text{Micrograms of cefotetan per milligram}}{=} = \frac{A_U \times P_S \times V_f \times 1,000}{A_S \times V_s}$$

where:

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

A_S = Area of the cefotetan peak in the chromatogram of the cefotetan working standard;

P_S = Cefotetan activity in the cefotetan working standard solution in micrograms per milliliter;

V_f = Volume of flask used to dilute standard; and

V_s = Volume of sample diluted.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *Identity.* Proceed as directed in § 436.211 of this chapter using the potassium bromide discs prepared as described in § 436.211(b)(1) of this chapter or the mineral oil mull prepared as described in § 436.211(b)(2) of this chapter.

[59 FR 26940, May 25, 1994, as amended at 60 FR 33712, June 29, 1995]

§ 442.53a Sterile cefotetan disodium.

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

(i) If the cefotetan disodium is not packaged for dispensing, its potency is not less than 830 micrograms and not more than 970 micrograms of cefotetan

per milligram on the anhydrous basis. If the cefotetan disodium is packaged for dispensing, its potency is not less than 830 micrograms and not more than 970 micrograms of cefotetan per milligram on the anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefotetan that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 1.5 percent.

(v) Its pH in an aqueous solution containing 100 milligrams of cefotetan disodium per milliliter is not less than 4.0 and not more than 6.5.

(vi) It gives a positive identity test for cefotetan.

(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 potency, sterility, pyrogens, moisture, pH, 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 in the manufacture of another drug:

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

(2) For sterility testing: 20 packages, each containing 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) Potency.* Proceed as directed in § 436.216 of this chapter, except use the resolution test solution to determine resolution in lieu of the working standard solution. Perform the assay at ambient temperature, using an ultraviolet detection system operating at a wavelength of 254 nanometers, a column

packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silicas, a flow rate not exceeding 2.0 milliliters per minute, and a known injection volume of between 10 and 20 microliters. Reagents, working standard solution, sample solution, resolution test solution, system suitability requirements, and calculations are as follows:

(i) *Reagents—(a) Diluting solution.* Mix water:methanol:acetonitrile (90:5:5).

(b) *Mobile phase.* Mix 0.1M phosphoric acid:glacial acetic acid:methanol:acetonitrile (1700:100:105:105). Filter through a suitable filter capable of removing particulate matter greater than 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(ii) *Preparation of working standard, sample, and resolution test solutions—(a) Working standard solution.* Accurately weigh approximately 50 milligrams of the cefotetan working standard into a 250-milliliter volumetric flask containing 12.5 milliliters of methanol. Swirl the flask for several minutes, then add 12.5 milliliters of acetonitrile. Swirl the flask until the cefotetan is dissolved. Dilute to volume with water to obtain a solution containing approximately 200 micrograms of cefotetan per milliliter. Mix well. Protect the working standard solution from light.

(b) *Sample solutions—(1) Product not packaged for dispensing (micrograms of cefotetan per milligram).* Dissolve an accurately weighed portion of the sample with sufficient diluting solution described in paragraph (b)(1)(i)(a) of this section, to obtain a concentration of approximately 200 micrograms of cefotetan per milliliter.

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

(i) *Micrograms of cefotetan per milligram.* Dissolve an accurately weighed portion of the sample with sufficient diluting solution described in paragraph (b)(1)(i)(a) of this section, to ob-

tain a concentration of approximately 200 micrograms of cefotetan per milliliter.

(ii) *Milligrams of cefotetan 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 diluting solution described in paragraph (b)(1)(i)(a) of this section, to obtain a concentration of approximately 200 micrograms of cefotetan per milliliter.

(c) *Resolution test solution.* Place 10 milliliters of the working standard solution in a stoppered flask containing a few milligrams of magnesium carbonate. Close the flask and sonicate for 10 minutes. If the solution is not slightly turbid, add more magnesium carbonate and repeat sonication. Filter the turbid solution through a 0.5-micron filter and use within 2 hours. As this solution stands, the tautomer concentration increases.

(iii) *System suitability requirements—(a) Tailing factor.* The tailing factor (T) is satisfactory if it is not more than 1.3 at 10 percent of peak height in lieu of 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.* The resolution (R) between the peak for cefotetan and its tautomer is satisfactory if it is not less than 2.0.

(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 comparable system suitability requirements are met. 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 cefotetan per milligram of sample as follows:

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

where:

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

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

P_s =Cefotetan activity in the cefotetan 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 cefotetan content of the container as follows:

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

where:

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

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

P_s =Cefotetan activity in the cefotetan 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)(1) of that section.

(3) *Pyrogens*. Proceed as directed in § 436.32(b) of this chapter, using a solution containing 50 milligrams of cefotetan 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 100 milligrams of cefotetan disodium per milliliter.

(6) *Identity*. The high-performance liquid chromatogram of the sample determined as directed in paragraph (b)(1) of this section, compares quali-

tatively to that of the cefotetan working standard.

[51 FR 20263, June 4, 1986, as amended at 52 FR 35912, Sept. 24, 1987; 55 FR 11583, Mar. 29, 1990]

§ 442.54 Cefpodoxime proxetil.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Cefpodoxime proxetil is (±)-1-hydroxyethyl(+)-(6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate,7²-(*Z*)-(O-methyloxime), isopropyl carbonate (ester). It is so purified and dried that:

(i) Its potency is not less than 690 micrograms and not more than 804 micrograms of cefpodoxime activity per milligram, on an anhydrous basis.

(ii) The ratio of its R-epimer to total cefpodoxime is not less than 0.5 and not more than 0.6.

(iii) Its moisture content is not more than 3 percent.

(iv) It gives a positive 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 cefpodoxime potency, isomer ratio, moisture, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed in § 436.216 of this chapter, using a suitable thermostatted column heating mechanism to maintain a column temperature of 40 °C, an ultraviolet detection system operating at a wavelength of 254 nanometers, a 15 centimeter X 4.6 millimeter (i.d.) column packed with microparticulate (5 micrometers in diameter) reversed phase packing material such as octadecyl silane bonded to silicas, a flow rate of 0.8 milliliter per minute, and a known injection volume of 2 microliters. The retention time for