

§ 442.50a

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(5) *Cephalexin content.* Proceed as directed in § 436.337 of this chapter.

(6) *Identity.* Proceed as directed in § 436.211 of this chapter, using the 1 percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

(7) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

[47 FR 11856, Mar. 19, 1982, as amended at 49 FR 47485, Dec. 5, 1984; 50 FR 19919, May 13, 1985]

**§ 442.50a Sterile ceforanide.**

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Ceforanide is 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[2-(amino-methyl)phenyl]acetyl]amino]-3-[[[1-(carboxymethyl)-1*H*-tetrazol-5-yl]-thio]methyl]-8-oxo-, (6*R*-*trans*)-. It is a white to off-white powder. It is so purified and dried that:

(i) Its ceforanide content is not less than 900 micrograms and not more than 1,050 micrograms of ceforanide per milligram.

(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 suspension containing 50 milligrams per milliliter is not less than 2.5 and not more than 4.5.

(vi) 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 ceforanide content, sterility, pyrogens, moisture, pH, and identity.

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

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

(b) For sterility testing: One package containing approximately 6 grams of a composite sample.

(b) *Tests and methods of assay—(1) Ceforanide content.* Proceed as directed in § 436.348 of this chapter, preparing

the sample and calculating the ceforanide content as follows:

(i) *Preparation of sample solution.* Prepare a solution containing 1.0 milligram per milliliter in mobile phase. Inject each sample within 5 minutes after dissolution.

(ii) *Calculations.* Calculate the micrograms of ceforanide per milligram of sample as follows:

$$\frac{\text{Micrograms of ceforanide}}{\text{per milligram}} = \frac{A_u \times P_s}{A_s \times C_u}$$

where:

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

$A_s$  = Area of the ceforanide peak in the chromatogram of the ceforanide working standard;

$P_s$  = Ceforanide activity in the ceforanide working standard solution in micrograms per milliliter; and

$C_u$  = Milligrams of sample per milliliter of sample solution.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except:

(i) In paragraph (e)(1)(i)(a) of that section, use diluting fluid G in lieu of diluting fluid A; and

(ii) In lieu of three 100-milliliter quantities of diluting fluid A in paragraph (e)(2) of that section, filter three 100-milliliter quantities of diluting fluid D followed by a 100-milliliter quantity of diluting fluid A.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, except suspend 1 gram of sterile ceforanide in 12.5 milliliters of pyrogen-free water (diluent 1). Add 320 milligrams of pyrogen-free *L*-lysine base, shake to dissolve the mixture. If the mixture is not dissolved, add an amount of *L*-lysine necessary to obtain a solution. The test sample should contain not more than a total of 340 milligrams of *L*-lysine. Dilute the resulting solution to 20 milliliters. Use a test dose of 1 milliliter of the 50 milligrams per milliliter test solution per kilogram of rabbit weight.

(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 suspension containing 50 milligrams per milliliter.

(6) *Identity*. Proceed as directed in § 436.211 of this chapter, using the sample preparation as described in paragraph (b)(2) of that section.

[49 FR 25847, June 25, 1984; 49 FR 40006, Oct. 12, 1984, as amended at 55 FR 11583, Mar. 29, 1990]

#### § 442.52 Cefotetan.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Cefotetan is (6*R*,7*S*)-4-[[2-carboxy-7-methoxy-3-[[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-7-yl]-carbamoyl]-1,3-dithietane- $\Delta^2,\alpha$ -malonic acid. It is so purified and dried that:

(i) Its potency is not less than 950 micrograms and not more than 1,030 micrograms of cefotetan activity per milligram on the anhydrous basis.

(ii) Its moisture content is not more than 2.5 percent.

(iii) 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, 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, 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 0.1*M* 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 solution*. 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.

(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.