

contains cefuroxime sodium equivalent to 15 or 30 milligrams of cefuroxime per milliliter. Its cefuroxime content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of cefuroxime that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 5.0 and not more than 7.5. It passes the identity test. The cefuroxime sodium used conforms to the standards prescribed by § 442.18(a)(1).

(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 cefuroxime sodium used in making the batch for potency, moisture, pH, and identity.

(B) The batch for cefuroxime content, sterility, pyrogens, pH, and identity.

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

(A) The cefuroxime sodium used in making the batch: 10 packages, each containing 1 gram.

(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*—Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) *Cefuroxime content.* Proceed as directed in § 436.343 of this chapter, except prepare the sample solution and calculate the cefuroxime content as follows:

(i) *Preparation of sample solution.* Remove an accurately measured representative portion from each container immediately after thawing and reaching room temperature and dilute with water to obtain a solution containing 50 micrograms of cefuroxime per milliliter (estimated). Prepare the sample solution just prior to its introduction in the chromatograph.

(ii) *Calculation.* Calculate the milligrams of cefuroxime per milliliter of sample as follows:

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

where:

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

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

P_s =Cefuroxime activity in the cefuroxime 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) this chapter, except inject a sufficient volume of the undiluted solution to deliver 50 milligrams of cefuroxime per kilogram.

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

(5) *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 cefuroxime working standard.

[54 FR 40654, Oct. 3, 1989]

§ 442.220 Sterile cefonicid sodium.

The requirements for certification and the tests and methods of assay for sterile cefonicid sodium packaged for dispensing are described in § 442.20a.

[49 FR 34349, Aug. 30, 1984]

§ 442.222 Cefmenoxime hydrochloride for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cefmenoxime hydrochloride for injection is a dry mixture of cefmenoxime hydrochloride and sodium carbonate. Each milligram of cefmenoxime hydrochloride for injection contains not less than 869 and not more than 1,015 micrograms of cefmenoxime on an anhydrous and sodium carbonate-free basis. Its

cefmenoxime content is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of cefmenoxime that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 1.5 percent. Its pH in an aqueous solution containing 100 milligrams per milliliter is not less than 6.4 and not more than 7.9. The cefmenoxime hydrochloride used conforms to the standards prescribed by § 442.22a(1) of this chapter.

(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 cefmenoxime hydrochloride used in making the batch for cefmenoxime content, moisture, identity, and crystallinity.

(B) The batch for cefmenoxime content, sterility, pyrogens, loss on drying, pH, and sodium carbonate content.

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

(A) The cefmenoxime hydrochloride used in making the batch: 10 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) *Cefmenoxime content.* Proceed as directed in § 436.363 of this chapter, using ambient temperature, 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 to exceed 2.0 milliliters per minute, and a known injection volume between 10 and 20 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents*—(A) *0.1M Phosphate buffer solution, pH 6.8.* Dissolve 6.4 grams of

monobasic potassium phosphate and 18.9 grams of dibasic sodium phosphate in 750 milliliters of water. Adjust the pH to 6.8 with 1*N* sodium hydroxide and dilute to 1,000 milliliters.

(B) *Internal standard solution.* Dissolve and dilute 0.15 gram of phthalimide in methanol to 100 milliliters.

(C) *Mobile phase.* Mix water:acetonitrile:glacial acetic acid (50:10:1). 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) *Preparation of working standard and sample solutions*—(A) *Working standard solution.* Dissolve approximately 50 milligrams of the cefmenoxime working standard, accurately weighed, in 10 milliliters of 0.1*M* phosphate buffer solution, pH 6.8 and dilute to 50 milliliters with mobile phase. Transfer 4.0 milliliters of this solution to a 50-milliliter volumetric flask, add 20 milliliters of internal standard solution and dilute to volume with mobile phase to obtain a solution containing 80 micrograms of cefmenoxime per milliliter.

(B) *Sample solutions.* Determine both micrograms of cefmenoxime per milligram of the sample and milligrams of cefmenoxime per container. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(ii)(B) (1) and (2) of this section.

(1) *Micrograms of cefmenoxime per milligram.* Dissolve the accurately weighed dry contents of a sample with sufficient distilled water to obtain a solution containing 1 milligram of cefmenoxime per milliliter (estimated). Transfer 4.0 milliliters of this solution to a 50-milliliter volumetric flask, add 20 milliliters of internal standard solution and dilute to volume with mobile phase to obtain a solution containing 80 micrograms of cefmenoxime per milliliter (estimated).

(2) *Milligrams of cefmenoxime 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. Dilute the solution thus obtained with sufficient distilled water to obtain a solution containing 1 milligram of cefmenoxime per milliliter (estimated). Transfer 4.0 milliliters of this solution to a 50-milliliter volumetric flask, add 20 milliliters of internal standard solution and dilute to volume with mobile phase to obtain a solution containing 80 micrograms of cefmenoxime per milliliter (estimated).

(iii) *System suitability requirements*—(A) *Tailing factor*. The tailing factor (*T*) for the cefmenoxime peak is satisfactory if it is not more than 1.6 at 5 percent of peak height.

(B) *Efficiency of the column*. The efficiency of the column (*n*) is satisfactory if it is greater than 1,200 theoretical plates for the cefmenoxime peak.

(C) *Resolution*. The resolution (*R*) between the peak for cefmenoxime and phthalimide is satisfactory if it is not less than 2.3.

(D) *Coefficient of variation*. The coefficient of variation (*S_r* in percent) of 5 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 § 436.363(b) of this chapter.

(iv) *Calculations*—(A) *Micrograms per milligram*. Calculate the micrograms of cefmenoxime per milligram as follows:

$$\text{Micrograms of cefmenoxime per milligram} = \frac{T3R_u \times P_3 \times 100 \times d}{R_s \times C_u (100 - L - S)}$$

where:

R_u=Area of the cefmenoxime peak in the chromatogram of the sample/Area of internal standard peak;

R_s=Area of the cefmenoxime peak in the chromatogram of the cefmenoxime working standard/Area of internal standard peak;

P₃=Cefmenoxime activity in the cefmenoxime working standard solution in micrograms per milliliter;

C_u=Milligrams of sample per milliliter of sample solution;

d=Dilution factor of the sample;

L=Percent loss on drying (determined as directed in paragraph (b)(4) of this section); and

S=Percent sodium carbonate (determined as directed in paragraph (b)(6) of this section).

(B) *Milligrams of cefmenoxime per vial*. Calculate the cefmenoxime content of the vial as follows:

$$\text{Milligrams of cefmenoxime per vial} = \frac{R_u \times P_s \times d}{R_s \times 1,000}$$

where:

R_u=Area of the cefmenoxime peak in the chromatogram of the sample/Area of internal standard peak;

R_s=Area of the cefmenoxime peak in the chromatogram of the cefmenoxime working standard/Area of internal standard peak;

P_s=Cefmenoxime activity in the cefmenoxime 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 60 milligrams of cefmenoxime per milliliter.

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

(5) *pH*. Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 100 milligrams per milliliter.

(6) *Sodium carbonate content*. Proceed as directed in § 436.364 of this chapter.

[53 FR 13403, Apr. 25, 1988; 53 FR 19369, May 27, 1988]

§ 442.223 Sterile cephaloridine.

The requirements for certification and the tests and methods of assay for sterile cephaloridine packaged for dispensing are described in § 442.23a.

[39 FR 19040, May 30, 1974, as amended at 55 FR 11583, Mar. 29, 1990]

§ 442.225 Cephalothin sodium injectable dosage forms.

§ 442.225a Sterile sodium cephalothin.

The requirements for certification and the tests and methods of assay for sterile sodium cephalothin packaged for dispensing are described in § 442.25a.

[39 FR 19040, May 30, 1974. Redesignated at 40 FR 11351, Mar. 11, 1975]