

(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) *Ceftriaxone content.* Proceed as directed in §442.55a(b)(1) of this chapter, except prepare the sample solution and calculate the ceftriaxone content as follows:

(i) *Preparation of sample solution.* Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container immediately after thawing and reaching room temperature and dilute with mobile phase to obtain a solution containing 180 micrograms of ceftriaxone per milliliter (estimated). Prepare the sample solution just prior to its introduction into the chromatograph.

(ii) *Calculation.* Calculate the milligrams of ceftriaxone anhydrous free acid per milliliter of sample as follows:

$$\frac{\text{Milligrams of ceftriaxone anhydrous free acid per milliliter}}{\text{per milliliter}} = \frac{A_u \times P_s \times d}{A_s \times 1,000}$$

where:

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

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

P_s =Ceftriaxone activity in the ceftriaxone working standard solution in micrograms of anhydrous free acid 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(a) of this chapter, except inject a sufficient volume of the undiluted solution to deliver 40 milligrams of ceftriaxone per kilogram.

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

(5) *Identify.* 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 ceftriaxone working standard.

[52 FR 44860, Nov. 23, 1987, as amended at 55 FR 11583, Mar. 29, 1990]

§ 442.258 Cefotiam dihydrochloride for injection.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Cefotiam dehydrochloride for injection is a dry mixture of cefotiam dihydrochloride and sodium carbonate. Its cefotiam potency is satisfactory if each milligram of cefotiam dihydrochloride for injection contains not less than 790 micrograms and not more than 925 micrograms of cefotiam on an anhydrous basis, when corrected for sodium carbonate content. Its cefotiam content is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefotiam that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 6.0 percent. The pH of an aqueous solution containing 100 milligrams per milliliter is not less than 5.7 and not more than 7.2. The cefotiam dihydrochloride used conforms to the standards prescribed by §442.58a(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 cefotiam dihydrochloride used in making the batch for potency, moisture, identity, and crystallinity.

(B) The batch for cefotiam potency, cefotiam 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 cefotiam dihydrochloride 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) *Cefotiam potency and content*. Determine both micrograms of cefotiam per milligram of sample and milligrams of cefotiam per container. Proceed as directed in § 442.58a(b)(1), preparing the sample solutions and calculating the potency and content as follows:

(i) *Preparation of sample solutions*. Use separate containers for preparation of each sample solution as described in paragraphs (b)(1)(i) (A) and (B) of this section.

(A) *Cefotiam potency (micrograms of cefotiam per milligram)*. Dissolve an accurately weighed sample with sufficient distilled water to obtain a solution containing approximately 1,000 micrograms of cefotiam per milliliter. Further dilute this solution with mobile phase to obtain a solution containing 50 micrograms of cefotiam activity per milliliter (estimated).

(B) *Cefotiam content (milligrams of cefotiam per vial)*. 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 1,000 micrograms of cefotiam activity per milliliter (estimated). Further dilute this solution with mobile phase to obtain a solution containing 50 micrograms of cefotiam activity per milliliter (estimated).

(ii) *Calculations*—(A) *Cefotiam potency (micrograms per milligram)*. Calculate the micrograms of cefotiam per milligram as follows:

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

where:

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

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

P_s =Cefotiam activity in the cefotiam work-

ing standard solution in micrograms per milliliter;

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

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) *Cefotiam content (milligrams of cefotiam per vial)*. Calculate the cefotiam content of the vial as follows:

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

where:

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

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

P_s =Cefotiam activity in the cefotiam 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(g) of this chapter, using a solution containing 40 milligrams of cefotiam 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 § 436.357 of this chapter.

[54 FR 20786, May 15, 1989]

§ 442.260 Cefpiramide sodium for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Cefpiramide sodium for injection is a dry mixture of cefpiramide and sodium benzoate. It contains other buffers and preservatives. Its cefpiramide potency is satisfactory if each milligram of cefpiramide sodium for injection contains not less than 754 micrograms and not more than 924