

(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) *Cefotetan potency.* Proceed as directed in §442.52(b)(1), except prepare the sample solution and calculate the cefotetan content as follows:

(i) *Preparation of sample solution.* Using a suitable hypodermic needle and syringe, remove an accurately measured portion from each container immediately after thawing and reaching room temperature and dilute with mobile phase to obtain a solution containing 200 micrograms of cefotetan per milliliter (estimated). Prepare the sample solution just prior to its introduction into the chromatograph.

(ii) *Calculation.* Calculate the milligrams of cefotetan per milliliter 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.

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

(3) *Bacterial endotoxins.* Proceed as directed in the U.S. Pharmacopeia bacterial endotoxins test.

(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 quali-

tatively to that of the cefotetan working standard.

[59 FR 26941, May 25, 1994]

§ 442.255 Ceftriaxone injectable dosage forms.

§ 442.255a Sterile ceftriaxone sodium.

The requirements for certification and the tests and methods of assay for sterile ceftriaxone sodium packaged for dispensing as described in §442.55a.

[50 FR 10001, Mar. 13, 1985. Redesignated at 52 FR 44860, Nov. 23, 1987]

§ 442.255b Ceftriaxone sodium injection.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Ceftriaxone sodium injection is a frozen aqueous iso-osmotic solution of ceftriaxone sodium which may contain one or more suitable and harmless buffer substances. Each milliliter contains ceftriaxone sodium equivalent to 10, 20, or 40 milligrams of ceftriaxone per milliliter. Its ceftriaxone content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of ceftriaxone that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 6.0 and not more than 8.0. It passes the identity test. The ceftriaxone sodium used conforms to the standards prescribed by §442.55(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 ceftriaxone sodium used in making the batch for potency, moisture, pH, crystallinity, and identity.

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

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

(A) The ceftriaxone sodium used in making the batch: 10 packages, each containing 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.* 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.