

(5) *Identity*. Proceed as directed in § 436.211 of this chapter, using a potassium bromide disc containing 1.3 milligrams of ceftriaxone sodium in 300 milligrams of potassium bromide, prepared as described in paragraph (b)(1) of that section.

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

§ 442.55a Sterile ceftriaxone sodium.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Ceftriaxone sodium is 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[2-amino-4-thiazolyl(methoxyimino)acetyl]amino]-8-oxo-3-[[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-, disodium salt, [6*R*-[6 α ,7 β (*Z*)]]. It is so purified and dried that:

(i) If the ceftriaxone sodium is not packaged for dispensing, its ceftriaxone potency is not less than 795 micrograms of ceftriaxone per milligram on an anhydrous free acid basis. If the ceftriaxone sodium is packaged for dispensing, its ceftriaxone potency is not less than 776 micrograms of ceftriaxone per milligram on an anhydrous free acid basis and also, each container contains not less than 90 percent and not more than 115 percent of the number of milligrams of ceftriaxone that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not less than 8 percent and not more than 11 percent.

(v) Its pH in an aqueous solution containing the equivalent of 100.0 milligrams per milliliter is not less than 6.0 and not more than 8.0.

(vi) It is crystalline.

(vii) It gives a positive identity test for ceftriaxone.

(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 ceftriaxone potency, and if packaged for dispensing, potency and container content, sterility, pyrogens,

moisture, pH, crystallinity, 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 manufacturing use:

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

(2) For sterility testing: 20 packages, each containing equal portions of 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) Ceftriaxone potency and container content*. Proceed as directed in § 436.354 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 270 nonometers (or 254 nanometers fixed mercury source), and a column packed with a five-micron octadecyl reverse phase packing or equivalent; and also, using the following system suitability requirements, reagents, working standard, test and sample solutions, and calculations:

(i) *System suitability requirements—(a) Capacity factor*. The capacity factor (*k*) for the ceftriaxone peak is satisfactory if it is not less than 2 and not more than 5.

(b) *Resolution*. The resolution (*R*) between the peak for ceftriaxone E-isomer and ceftriaxone is satisfactory if it is not less than 3.0.

(c) *Asymmetry factor*. The asymmetry factor (*A_s*) is satisfactory if it is not more than 1.6 at 10 percent of the peak height.

(d) *Efficiency of the column*. The efficiency of the column (*h_r*) is satisfactory if it is less than 20 (equivalent to a value of 1,500 or greater theoretical plates when using a 15-centimeter column with 5-micrometer-size particles).

(e) *Coefficient of variation*. The coefficient of variation (*S_R* in percent) of five replicate injections is satisfactory if it is less than 2.0 percent.

If the system suitability parameters have been met, then proceed as described in § 436.354(b) of this chapter.

(ii) *Reagents*—(a) *pH 7.0 phosphate buffer*. Dissolve 13.6 grams of dibasic potassium phosphate and 4.0 grams of monobasic potassium phosphate in sufficient water to make 1,000 milliliters. Adjust to pH 7.0 ±0.1 with 18*N* phosphoric acid or 10*N* potassium hydroxide.

(b) *pH 5.0 citrate buffer*. Dissolve 25.8 grams of sodium citrate in 500 milliliters of water. Adjust the pH to 5.0±0.1 with 20 percent aqueous citric acid, and dilute to 1,000 milliliters with water.

(c) *Mobile phase*. Dissolve 4.0 grams of tetraheptylammonium bromide with 500 milliliters of acetonitrile. Add 440 milliliters of water, 55 milliliters of pH 7.0 phosphate buffer, and 5 milliliters of pH 5.0 citrate buffer. Mix and dilute 800 milliliters of this solution with 200 milliliters of distilled water. Filter the mobile phase through a suitable glass fiber filter or equivalent which is capable of removing particulate contamination greater than 0.5 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph.

(iii) *Working standard and sample solutions*—(a) *Preparation of working standard solution*. Dissolve an accurately weighed portion of the ceftriaxone working standard with sufficient water to obtain a solution containing approximately 180 micrograms of ceftriaxone activity per milliliter. Prepare the working standard solution just prior to its introduction into the chromatograph.

(b) *Preparation of test solution*. Dissolve together accurately weighed portions of the ceftriaxone working standard and the ceftriaxone sodium E-isomer reference standard with sufficient water to obtain a solution containing approximately 160 micrograms of ceftriaxone activity per milliliter of each standard. Prepare the test solution just prior to its introduction into the chromatograph.

(c) *Preparation of sample solution*. Prepare the sample solution just prior to its introduction into the chromatograph.

(1) *Product not packaged for dispensing (micrograms of ceftriaxone anhydrous free*

acid per milligram). Dissolve an accurately weighed portion of the sample with sufficient water to obtain a concentration of 180 micrograms of ceftriaxone activity per milliliter.

(2) *Product packaged for dispensing*. Determine both potency (micrograms of ceftriaxone anhydrous free acid per milligram of the sample) and container content (milligrams of anhydrous free acid ceftriaxone per container). Use separate containers for preparation of each sample solution as described in paragraph (b)(1)(iii)(b)(2) (i) and (ii) of this section.

(i) *Micrograms of ceftriaxone anhydrous free acid per milligram*. Dissolve an accurately weighed portion of the sample with sufficient water to obtain a concentration of approximately 180 micrograms of ceftriaxone activity per milliliter.

(ii) *Milligrams of ceftriaxone 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 potency contained in a given volume of the resulting preparation, remove an accurately measured representative portion from each container. Dilute the aliquot of the solution thus obtained with sufficient water to obtain a concentration of approximately 180 micrograms of ceftriaxone activity per milliliter.

(iv) *Calculations*. (a) Calculate the micrograms of ceftriaxone anhydrous free acid per milligram as follows:

$$\begin{array}{l} \text{Micrograms of} \\ \text{ceftriaxone anhydrous} \\ \text{free acid per milligram} \end{array} = \frac{A_u \times P_s}{A_s \times C_u}$$

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

C_u =Milligrams of sample per milliliter of sample solution.

(b) Calculate the ceftriaxone anhydrous free acid content of the container as follows:

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

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(h) of this chapter, using a solution containing 20 milligrams of ceftriaxone 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 per milliliter.

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

(7) *Identity*. Proceed as directed in § 436.211 of this chapter, using a potassium bromide disc containing 1.3 milligrams of ceftriaxone sodium in 300 milligrams of potassium bromide, prepared as described in paragraph (b)(1) of that section.

[50 FR 9999, Mar. 13, 1985; 50 FR 11690, Mar. 25, 1985; 50 FR 18243, Apr. 30, 1985, as amended at 55 FR 11583, Mar. 29, 1990]

§ 442.58a Sterile cefotiam dihydrochloride.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Cefotiam dihydrochloride is 5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[(2-amino-4-thiazolyl)acetyl]-amino-3[[[1-[2-(dimethylamino)ethyl]-1H-tetrazol-5-yl]-thio]methyl]-8-oxo-, dihydrochloride, (6*R*-trans)-. It is so purified and dried that:

(i) Its potency is not less than 790 and not more than 925 micrograms of cefotiam per milligram on an anhydrous basis.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 7.0 percent.

(v) It passes the identity test.

(vi) It is crystalline.

(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, identity, and crystallinity.

(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) Potency*. Proceed as directed in § 436.216 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 of between 10 and 20 microliters. Mobile phase, working standard and sample solutions, resolution test solution, system suitability requirements, and calculations are as follows:

(i) *Mobile phase*. Dissolve 13.1 grams of ammonium sulfate in 850 milliliters of water. Adjust the pH to 6.5 with dilute aqueous ammonia. Add 150 milliliters of acetonitrile. 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, sample, and resolution test solutions—(A)*