

area (sum of both epimers) to the internal standard peak response in the working standard solution;

P_s = Cefpodoxime proxetil activity of the 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) *Isomer ratio.* Using the procedure described in paragraph (b)(1) of this section, calculate the ratio of the R-epimer (Ab) to the sum of the S-epimer and R-epimer (Aa and Ab), by the equation

$$\text{Isomer Ratio} = \text{Ab}/(\text{Aa} + \text{Ab})$$

where:

Aa = Area of the early eluting S-epimer peak; and

Ab = Area of the late eluting R-epimer peak.

(3) *Moisture.* Proceed as directed in § 436.201 of this chapter, except use 30 milliliters of solvent C instead of 20 milliliters of solvent A.

(4) *Identity.* Proceed as directed in § 436.211 of this chapter, using the mineral oil mull prepared as described in paragraph (b)(2) of that section.

[60 FR 58231, Nov. 27, 1995]

§ 442.55 Ceftriaxone sodium.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Ceftriaxone sodium is the 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, [6R-[6 α , 7 β (Z)]]-. It is so purified and dried that:

(i) Its ceftriaxone potency is not less than 795 micrograms of ceftriaxone per milligram on an anhydrous free acid basis.

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

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

(iv) It is crystalline.

(v) 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, moisture, pH, crystallinity, 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) Ceftriaxone potency.* Proceed as directed in § 442.55a(b)(1) of this chapter, except prepare the sample solution and calculate the micrograms of ceftriaxone free acid per milligram as follows:

(i) *Preparation of sample solution.* Dissolve an accurately weighed portion of the sample with sufficient water to obtain a concentration of 180 micrograms of ceftriaxone activity per milliliter. Prepare the sample solution just prior to its introduction into the chromatograph.

(ii) *Calculation.* Calculate the micrograms of ceftriaxone anhydrous free acid per milligram as follows:

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

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.

(2) *Moisture.* Proceed as directed in § 436.201 of this chapter.

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

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

(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.