

(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, pH, specific rotation, and identity.

(ii) Samples required:

(a) If the batch is packaged for re-packing or for use in the manufacture of another drug:

(1) For all tests except sterility: 9 packages, each containing approximately 500 milligrams, and 1 package containing approximately 5 grams.

(2) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 15 immediate containers, except if each contains less than 1.0 gram, a minimum of 24 immediate containers.

(2) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Sample preparation.* Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration; also if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents. Dilute with sufficient solution 1 to give a stock solution of convenient concentration.

(ii) *Assay procedure.* Use either of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(a) *Microbiological agar diffusion assay.* Proceed as directed in §436.105 of this chapter, diluting an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 micrograms of cefazolin per milliliter (estimated).

(b) *Hydroxylamine colorimetric assay.* Proceed as directed in §436.205 of this chapter, preparing the working standard solution as follows: Dissolve an ac-

curately weighed portion of approximately 30 milligrams of cefazolin working standard in 3 milliliters of 10 percent potassium phosphate buffer, pH 6.0 (solution 6), and further dilute with solution 1 to the final concentration.

(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 50 milligrams of cefazolin per milliliter.

(4) [Reserved]

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

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

(7) *Specific rotation.* Proceed as directed in §436.210 of this chapter, using a solution containing 50 milligrams of cefazolin per milliliter in 0.1M sodium bicarbonate and a polarimeter tube 1.0 decimeter in length. Calculate the specific rotation on an anhydrous basis.

(8) *Identity.* Using a 0.002 percent solution of the sample in 0.1M sodium bicarbonate solution and a suitable spectrophotometer, record the ultraviolet spectrum from 220 to 340 nanometers. The spectrum compares qualitatively to that of the cefazolin working standard similarly tested.

[39 FR 19040, May 30, 1974, as amended at 42 FR 18059, Apr. 5, 1977; 50 FR 19919, May 13, 1985]

#### §442.12 Cefoperazone sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Cefoperazone sodium is the sodium salt of (6*R*, 7*R*)-7-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-(*p*-hydroxyphenyl)acetamido]-3-[[1-(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. It is a white to off-white crystalline powder or a lyophilized powder. It is so purified and dried that:

(i) Its cefoperazone content is not less than 870 micrograms and not more than 1,015 micrograms of cefoperazone per milligram on an anhydrous basis.

(ii) Its moisture content is not more than 5.0 percent, except if it is the

lyophilized powder, its moisture content is not more than 2.0 percent.

(iii) The pH of an aqueous solution containing 250 milligrams per milliliter is not less than 4.5 and not more than 6.5.

(iv) It passes the identity test if the retention times of the sample and working standard agree within  $\pm 3.0$  percent.

(v) It is crystalline, except if it is the lyophilized powder.

(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 cefoperazone content, moisture, pH, identity, and crystallinity (if it is not the lyophilized powder).

(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) *Cefoperazone content.* Proceed as directed in § 436.338 of this chapter.

(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 250 milligrams per milliliter.

(4) *Identity.* From the high-performance liquid chromatograms of the sample and the cefoperazone working standard determined as directed in paragraph (b)(1) of this section, calculate the adjusted retention times of the cefoperazone in the sample and standard solutions as follows:

Adjusted retention time of cefoperazone =  $t - t_0$   
where:

$t$  = Retention time measured from point of injection into the chromatograph until the maximum of the cefoperazone sample or working standard peak appears on the chromatogram; and

$t_0$  = Retention time measured from point of injection into the chromatograph until the maximum of nonretarded solute appears in the chromatogram.

The sample and the cefoperazone working standard should have corresponding

adjusted cefoperazone retention times within  $\pm 3.0$  percent.

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

[51 FR 36688, Oct. 15, 1986, as amended at 55 FR 11583, Mar. 29, 1990]

#### § 442.12a Sterile cefoperazone sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile cefoperazone sodium is the sodium salt of (6*R*, 7*R*)-7-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-2-(*p*-hydroxyphenyl)acetamido]-3-[[1-(methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. It is a white to off-white crystalline powder or it may be a lyophilized powder. It is so purified and dried that:

(i) If the cefoperazone sodium is not packaged for dispensing, its cefoperazone content is not less than 870 micrograms and not more than 1,015 micrograms of cefoperazone per milligram on an anhydrous basis. If the cefoperazone sodium is packaged for dispensing, its cefoperazone content is not less than 870 micrograms and not more than 1,015 micrograms of cefoperazone per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of cefoperazone that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 5.0 percent, except if it is the lyophilized powder, its moisture content is not more than 2.0 percent.

(v) Its pH in an aqueous solution containing 250 milligrams per milliliter is not less than 4.5 and not more than 6.5.

(vi) It passes the identity test if the retention times of the sample and working standard agree within  $\pm 3$  percent.

(vii) It is crystalline, except if it is the lyophilized powder, it is not crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.