

(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, moisture, pH, cephaloglycin content, identity, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 500 milligrams.

(b) *Tests and methods of assay—(1) Potency.* Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed portion of the sample in sufficient sterile distilled water to give a stock solution of 100 micrograms of cephaloglycin per milliliter (esti-

mated). Further dilute an aliquot of the stock solution with 0.1M potassium phosphate buffer, pH 4.5 (solution 4), to the reference concentration of 10 micrograms of cephaloglycin per milliliter (estimated).

(2) [Reserved]

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

(4) *pH.* Proceed as directed in §436.202 of this chapter, using an aqueous suspension containing 50 milligrams per milliliter.

(5) *Cephaloglycin content.* Proceed as directed in §436.213 of this chapter, using the titration procedure described in paragraph (e)(2) of that section. Calculate the cephaloglycin content as follows:

$$\text{Percent cephaloglycin content} = \frac{(A - B) (\text{normality of perchloric acid reagent}) (405.4) (100) (100)}{(\text{Weight of sample in milligrams}) (100 - m)}$$

where:

A=Milliliters of perchloric acid reagent used in titrating the sample;

B=Milliliters of perchloric acid reagent used in titrating the blank;

m=Percent moisture content of the sample.

(6) *Identity.* Proceed as directed in §436.211 of this chapter, using the 0.5-percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

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

[39 FR 19040, May 30, 1974, as amended at 50 FR 19919, May 13, 1985]

**§442.22a Sterile cefmenoxime hydrochloride.**

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

(i) Its cefmenoxime content is not less than 869 and not more than 1,015

micrograms of cefmenoxime per milligram on an anhydrous basis.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 1.5 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 cefmenoxime content, 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: 1 package containing approximately 6 grams of a composite sample.

(b) *Tests and methods of assay—(1) Cefmenoxime content.* Proceed as directed in §436.363 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 between 10 and 20 microliters. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents*—(A) *0.1M Phosphate buffer solution, pH 6.8*. Dissolve 6.4 grams of monobasic potassium phosphate and 18.9 grams of dibasic sodium phosphate in 750 milliliters of water. Adjust the pH to 6.8 with 1N sodium hydroxide and dilute to 1,000 milliliters.

(B) *Internal standard solution*. Dissolve and dilute 0.15 gram of phthalimide in methanol to 100 milliliters.

(C) *Mobile phase*. Mix water:acetonitrile:glacial acetic acid (50:10:1). 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 and sample solutions*—(A) *Working standard solution*. Dissolve approximately 50 milligrams of the cefmenoxime working standard, accurately weighed, in 10 milliliters of 0.1M phosphate buffer solution, pH 6.8 and dilute to 50 milliliters with mobile phase. Transfer 4.0 milliliters of this solution to a 50-milliliter volumetric flask, add 20 milliliters of internal standard solution and dilute to volume with mobile phase to obtain a solution containing 80 micrograms of cefmenoxime per milliliter.

(B) *Sample solution*. Dissolve approximately 50 milligrams of cefmenoxime sample, accurately weighed, in 10 milliliters of 0.1M phosphate buffer solution, pH 6.8. Dilute to 50 milliliters with mobile phase. Transfer 4.0 milliliters of this solution to a 50-milliliter volumetric flask, add 20 milliliters of internal standard solution and dilute to volume with mobile phase.

(iii) *System suitability requirements*—(A) *Tailing factor*. The tailing factor (*T*) for the cefmenoxime peak is satisfac-

tory if it is not more than 1.6 at 5 percent of peak height.

(B) *Efficiency of the column*. The efficiency of the column (*n*) is satisfactory if it is greater than 1,200 theoretical plates for the cefmenoxime peak.

(C) *Resolution*. The resolution (*R*) between the peak for cefmenoxime and phthalimide is satisfactory if it is not less than 2.3.

(D) *Coefficient of variation*. The coefficient of variation (*S<sub>R</sub>* in percent) of 5 replicate injections is satisfactory if it is not more than 2.0 percent. If the system suitability requirements have been met, then proceed as described in § 436.363(b) of this chapter.

(iv) *Calculations*. Calculate the micrograms of cefmenoxime per milligram of sample as follows:

$$\frac{\text{Micrograms of cefmenoxime per milligram}}{=} = \frac{R_u \times P_s \times 100}{R_s \times C_u \times (100 - m)}$$

where:

*R<sub>u</sub>*=Area of cefmenoxime peak in the chromatogram of the sample/Area of internal standard peak;

*R<sub>s</sub>*=Area of the cefmenoxime peak in the chromatogram of the cefmenoxime working standard/Area of internal standard peak;

*P<sub>s</sub>*=Cefmenoxime activity in the cefmenoxime working standard solution in micrograms per milliliter;

*C<sub>u</sub>*=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, except in lieu of diluting fluid A use diluting fluid H.

(3) *Pyrogens*. Proceed as directed in § 436.32(i) of this chapter, using a solution containing 60 milligrams per milliliter.

(4) *Moisture*. Proceed as directed in § 436.201 of this chapter, using the sample preparation described in paragraph (d)(4) of that section and the titration procedure described in paragraph (e)(3) of that section, except:

(i) In lieu of 3 milliliters of anhydrous methanol solution, inject 20 milliliters of a formamide:methanol solution (2:1) into the container and shake to dissolve the contents (prior to use in preparation of the formamide:methanol solution, dry 500

grams of formamide over 20 grams of anhydrous sodium sulfate for 24 hours);

(ii) Rinse the syringe, needle, and immediate container with two separate 5-milliliter portions of anhydrous methanol, in lieu of one 3-milliliter portion of anhydrous methanol; and

(iii) In § 436.201(e)(3) of this chapter, add a sufficient volume of the formamide:methanol solution (2:1) to cover the electrodes in the dry titrating vessel, in lieu of 20 milliliters of solvent A before starting the titration.

(5) *Identity*. Using a 0.0025-percent solution of the sample in 0.1M phosphate buffer, pH 6.8 and a suitable spectrophotometer, record the ultraviolet absorption spectrum from 220 to 310 nanometers. The spectrum compares qualitatively to that of the cefmenoxime working standard similarly tested.

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

[53 FR 13402, Apr. 25, 1988; 53 FR 19368, May 27, 1988]

#### § 442.23a Sterile cephaloridine.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Cephaloridine is 7-[ $\alpha$ -(2-thienyl)-acetamido]-3-(1-pyridyl-methyl)-3-cephem-4-carboxylic acid betaine. It is a white to off-white powder. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms of cephaloridine per milligram. If it is packaged for dispensing, its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cephaloridine that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its loss on drying is not more than 2.5 percent.

(vi) Its pH in an aqueous solution is not less than 3.5 and not more than 6.

(vii) The specific rotation in an aqueous solution containing 10 milligrams of cephaloridine per milliliter at 25° C. is +48°±4°.

(viii) It is crystalline.

(ix) The ultraviolet absorption spectrum between the wavelengths of 220 and 310 nanometers compares qualitatively to that of the cephaloridine

working standard. The ratio of the absorbance of the maximum at the wavelength of 240 nanometers to that of the shoulder at 255 nanometers is not less than 1.05 and not more than 1.17.

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

(3) *Requests for certification; samples*. In addition to 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, loss on drying, pH, specific rotation, crystallinity, and identity.

(ii) Samples of the batch:

(a) If the batch is packaged for repackaging or for use as an ingredient in the manufacture of another drug:

(1) For all tests except sterility: 10 packages, each containing at least 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 13 immediate containers of the batch.

(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), for the microbiological agar diffusion assay, distilled water for the iodometric assay or hydroxylamine colorimetric assay, 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 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 with either solution 1 or distilled water as specified above to give a stock solution of convenient concentration.