

percent potassium bromide disc prepared as described in paragraph (b)(1) of that section.

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

[39 FR 19040, May 30, 1974, as amended at 50 FR 19919, May 13, 1985; 52 FR 35912, Sept. 24, 1987]

**§ 442.28 Cephalexin hydrochloride monohydrate.**

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Cephalexin hydrochloride monohydrate is the hydrochloride salt of 7-(*D*-alpha-amino-alpha-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid monohydrate. It is so purified and dried that:

(i) Its potency is not less than 800 micrograms and not more than 880 micrograms of cephalexin per milligram on an “as is” basis.

(ii) Its moisture content is not less than 3.0 nor more than 6.5 percent.

(iii) The pH of an aqueous solution containing 10 milligrams per milliliter is not less than 1.5 nor more than 3.0.

(iv) It gives a positive identity test.

(v) 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 cephalexin potency, moisture, pH, identity, and crystallinity.

(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) Cephalexin potency*. Proceed as directed in § 442.40(b)(1)(ii), except that “cephalexin” is substituted at each occurrence of “cephradine”.

(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 10 milligrams per milliliter.

(4) *Identity*. Proceed as directed in § 436.367 of this chapter.

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

[54 FR 48860, Nov. 28, 1989]

**§ 442.29a Sterile cephalosporin sodium.**

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Sterile cephalosporin sodium is the sodium salt of 7-[ $\alpha$ (4-pyridylthio)-acetamido]-cephalosporanic acid. It is a white to off-white powder. It is so purified and dried that:

(i) Its potency is not less than 855 micrograms and not more than 1,000 micrograms of cephalosporin sodium per milligram on an “as is” basis. If it is packaged for dispensing, its content is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of cephalosporin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 2.0 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams of cephalosporin per milliliter is not less than 6.5 and not more than 8.5.

(vii) Its cephalosporin content is not less than 92 percent and not more than 105 percent on an anhydrous basis.

(viii) It gives a positive identity test for sodium cephalosporin.

(ix) 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, pH, cephalosporin content, identity, and crystallinity.

(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 14 immediate containers, except if each contains less than 1 gram, a minimum of 19 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*. Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in §436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 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 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 solution 1 to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 1.0 microgram of cephapirin per milliliter (estimated).

(ii) *Iodometric assay*. Proceed as directed in §436.204 of this chapter. In addition 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 distilled water to the prescribed concentration.

(iii) *Hydroxylamine colorimetric assay*. Proceed as directed in §436.205 of this chapter. In addition, 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 distilled water to the prescribed 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 100 milligrams of cephapirin 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 10 milligrams per milliliter.

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

$$\text{Percent cephapirin content} = \frac{(A - B) (\text{normality of perchloric acid reagent}) (222.7) (100) (100)}{(\text{Weight of sample in milligrams}) (100 - m)}$$

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.

(8) *Identity*. Proceed as directed in §436.211 of this chapter, using a 1.0 percent potassium bromide disc prepared

as directed in paragraph (b)(1) of that section.

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

[39 FR 19040, May 30, 1974, as amended at 40 FR 23725, June 2, 1975; 50 FR 19919, May 13, 1985]

#### § 442.40 Cephhradine.

(a) *Requirements of certification—(1) Standards of identity, strength, quality, and purity*. Cephhradine is (6*R*, 7*R*)-7-[(*R*)-2-amino-2-(1,4-cyclohexadien-1-yl)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms and not more than 1,050 micrograms of cephradine per milligram on an anhydrous basis.

(ii) [Reserved]

(iii) Its moisture content is not more than 6.0 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 3.5 and not more than 6.0.

(v) Its cephalixin content is not more than 5 percent on an anhydrous basis.

(vi) It passes the identity test.

(vii) 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, moisture, pH, cephalixin content, identity, and crystallinity.

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

(b) *Tests and methods of assay—(1) Potency*. Use any of the following methods; however, the results obtained from the microbiological agar diffusion assay shall be conclusive.

(i) *Microbiological agar diffusion assay*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution containing 1.0 milligram of cephradine per milliliter (estimated). Further dilute

an aliquot of the stock solution with solution 1 to the reference concentration of 10 micrograms of cephradine per milliliter (estimated).

(ii) *Hydroxylamine colorimetric assay for cephradine—(a) Typical equipment*. Use automated equipment capable of performing the following functions: Introduction of sample into reaction vessels, addition of reagents to the samples to form reaction mixtures, incubation of the reaction mixtures, colorimetric determination of the reaction product at 480 nanometers using a 1-centimeter tubular flow cuvette, and documentation of the results with a strip chart recorder. A suitable system is the Auto Analyzer II equipment consisting of a Solid or Liquid Sampler II, a twenty channel Pump III, a colorimeter equipped with a 1-centimeter tubular flow cuvette and light filters producing incident light at 480 nanometers, and a strip chart recorder with scale expander.

(b) *Reagents—(1) Hydroxylamine hydrochloride solution*. Dissolve 20 grams of hydroxylamine hydrochloride and 5 milliliters of emulsifying stock solution (prepared to contain 100 milligrams of polyoxyethylene fatty alcohol ether, such as Brij-35 or equivalent, per 100 milliliters distilled water) in sufficient distilled water to make 1 liter.

(2) *Buffer*. Dissolve 173 grams of sodium hydroxide and 20.6 grams of sodium acetate in sufficient distilled water to make 1 liter. Dilute 75 milliliters of this solution with distilled water to 500 milliliters.

(3) *3.3*N* Sulfuric acid*. Dilute 91 milliliters of concentrated sulfuric acid to 1 liter with distilled water.

(4) *Ferric nitrate solution*. Dissolve 300 grams of ferric nitrate nonahydrate (9H<sub>2</sub>O) in a mixture of 2.8 milliliters of concentrated sulfuric acid and sufficient distilled water to make 1 liter.

(c) *Preparation of working standard solutions*. Dissolve and dilute an accurately weighed portion of the cephradine working standard in sufficient distilled water to obtain a concentration of 1 milligram of cephradine per milliliter.

(d) *Preparation of sample solutions*. Dissolve an accurately weighed portion of the sample in distilled water and