

solution with 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of cyclacillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in §436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in §436.205 of this chapter.

(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 solution containing 10 milligrams per milliliter.

(5) *Cyclacillin content.* Proceed as directed in §436.213 of this chapter, using both the titration procedures described in paragraph (e)(1) and (2) of that section. Calculate the percent cyclacillin content as follows:

(i) *Acid titration.*

$$\text{Percent cyclacillin content} = \frac{(A - B)(\text{normality of perchloric acid reagent})(341.4)(100)}{(\text{Weight of sample in milligrams})(100 - m)}$$

where:

A=Milliliters of lithium methoxide reagent used in titrating the sample;

B=Milliliters of lithium methoxide reagent used in titrating the blank;

m=Percent moisture content of the sample.

Calculate the difference between the potency and the cyclacillin content as follows:

$$\text{Difference} = \frac{\text{Potency in micrograms per milligram}}{10} - \text{percent cyclacillin content}$$

(ii) *Base titration.*

$$\text{Percent cyclacillin content} = \frac{(A - B)(\text{normality of perchloric acid reagent})(341.4)(100)(100)}{(\text{Weight of sample in milligrams})(100 - m)}$$

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.

Calculate the difference between the potency and the cyclacillin content as follows:

$$\text{Difference} = \frac{\text{Potency in micrograms per milligrams}}{10} - \text{percent cyclacillin content}$$

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

[46 FR 2981, Jan. 13, 1981; 46 FR 15880, Mar. 10, 1981, as amended at 50 FR 19918, May 13, 1985]

**§440.19 Dicloxacillin sodium monohydrate.**

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Dicloxacillin sodium monohydrate is the monohydrated sodium salt of 5-methyl-3-(2,6-dichlorophenyl)-4-isoxazolyl penicillin. It is so purified and dried that:

(i) Its potency is not less than 850 micrograms of dicloxacillin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not less than 3 percent nor more than 5 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 4.5 nor more than 7.5.

(v) Its organic chlorine content is not less than 13.0 percent nor more than 14.2 percent.

(vi) Its free chloride content is not more than 0.5 percent.

(vii) It is crystalline.

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

(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, organic chlorine content, free chloride content, crystallinity, and identity.

(ii) *Samples required:* 10 containers, each containing not less than 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 portion of the sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (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 5 micrograms of dicloxacillin per milliliter (estimated).

(ii) *Iodometric assay.* Proceed as directed in § 436.204 of this chapter.

(iii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter.

(2) [Reserved]

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

(4) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams per milliliter.

(5) *Organic chlorine content—(i) Reagents.* (a) *o*-Chlorobenzoic acid of known purity.

(b) 0.01*N* Silver nitrate solution. Store in brown glass reagent bottle. Standardize against an accurately weighed sample of 20 to 25 milligrams of *o*-chlorobenzoic acid using the procedure described in paragraph (b)(5)(ii) of this section.

$$\text{Normality } (N) = \frac{\text{Percent purity of the } o\text{-chlorobenzoic acid} \times \text{milligrams of } o\text{-chlorobenzoic acid}}{15,657 \times \text{milliliters of silver nitrate consumed}}$$

(c) 0.1*N* Sodium hydroxide solution.

(d) 1:1 Nitric acid solution: Mix 1 volume of concentrated nitric acid with 1 volume of distilled water.

(ii) *Total chlorine.* (Caution—The analyst should wear safety glasses and use a suitable shield between himself and the apparatus. The glassware must be scrupulously clean.) Accurately weigh 20 to 25 milligrams of the sample and place it on the center of a piece of halide-free filter paper measuring about 4 centimeters square (this is specially cut paper with a fuse strip attached to

the area that holds the sample), and fold the paper to enclose it. Place 10 milliliters of 0.1*N* sodium hydroxide into an oxygen combustion flask (Schoniger flask), and flush the air from the flask with a stream of rapidly flowing oxygen. Place the sample into the platinum sample holder and ignite the fuse strip by suitable means. If the strip is ignited outside the flask, immediately plunge the stopper into the flask, invert so that the sodium hydroxide solution makes a seal around

the stopper, and hold the stopper firmly in place. If the ignition is carried out in a closed system, the inversion of the flask may be omitted. After combustion is completed, shake the flask vigorously, add a small amount of distilled water to the collar to insure an air tight seal, and allow to stand for not less than 10 minutes with intermit-

tent shaking. Transfer to a suitable titration vessel, heat on a steam bath for 20 to 30 minutes, cool to room temperature, add 5 milliliters of nitric acid solution, and titrate potentiometrically with 0.01*N* silver nitrate, using one silver electrode and one silver/silver chloride electrode.

$$\text{Percent total chlorine} = \frac{N \times \text{milliliters of silver nitrate} \times 3545.7}{\text{Milligrams of sample}}$$

(iii) *Free chloride*. Accurately weigh 100 to 150 milligrams of sample directly into a titration flask, dissolve in 10 milliliters of 0.1*N* sodium hydroxide, and add about 20 milliliters of distilled water, heat this solution on the steam

bath 20 to 30 minutes. Cool to room temperature, add 5 milliliters of 1:1 nitric acid solution and titrate potentiometrically with 0.01*N* silver nitrate using one silver electrode and one silver/silver chloride electrode.

$$\text{Percent free chloride} = \frac{N \times \text{milliliters of silver nitrate} \times 3545.7}{\text{Milligrams of sample}}$$

(iv) *Organic chlorine*. Percent organic chlorine = Percent total chlorine – percent free chloride.

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

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

[39 FR 18976, May 30, 1974, as amended at 42 FR 59857, Nov. 22, 1977; 44 FR 10378, Feb. 20, 1979; 50 FR 19918, May 13, 1985]

**§ 440.19a Sterile dicloxacillin sodium monohydrate.**

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Sterile dicloxacillin sodium monohydrate is the monohydrated sodium salt of 5-methyl-3-(2,6-dichlorophenyl)-4-isoxazolyl penicillin. It is so purified and dried that:

(i) Its potency is not less than 850 micrograms of dicloxacillin per milligram. If it is packaged for dispensing, its potency is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of

milligrams of dicloxacillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not less than 3 percent and not more than 5 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams per milliliter or when reconstituted as directed in the labeling, if it is packaged for dispensing is not less than 4.5 nor more than 7.5.

(vii) Its organic chlorine content is not less than 13.0 percent and not more than 14.2 percent.

(viii) Its free chloride content is not more than 0.5 percent.

(ix) It is crystalline.

(x) It gives a positive identity test for dicloxacillin sodium monohydrate.

(2) *Labeling*. If this drug is packaged for dispensing, in addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled "sterile dicloxacillin sodium".