

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".

(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, organic chlorine content, free chloride content, crystallinity, 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: 10 packages, each containing approximately 500 milligrams.

(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.

(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) *Sample preparation.* Dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), for the microbiological agar diffusion assay and the hydroxylamine colorimetric assay or in distilled water for the iodometric assay, to give a stock solution of convenient concentration; and 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.

(ii) *Assay procedures.* Use any 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 5 micrograms of dicloxacillin per milliliter (estimated).

(b) *Iodometric assay.* Proceed as directed in §436.204 of this subchapter.

(c) *Hydroxylamine colorimetric assay.* Proceed as directed in §436.205 of this subchapter.

(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(a) of this chapter, using a solution containing 20 milligrams of dicloxacillin 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 subchapter, using an aqueous solution containing 10 milligrams per milliliter (or using a solution reconstituted as directed in the labeling if it is packaged for dispensing).

(7) *Organic chlorine content.* Proceed as directed in §440.19(b)(5).

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

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

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#### § 440.25 Hetacillin.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Hetacillin is 6-(2,2-Dimethyl-5-oxo-4-phenyl-1-imidazolidinyl)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. It occurs as a fine, white to off-white powder. It is so purified and dried that:

(i) Its potency is not less than 810 micrograms of ampicillin per milligram.

(ii) [Reserved]

(iii) Its moisture content is not more than 1.0 percent.