

§ 442.225b Cephalothin sodium injection.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Cephalothin sodium injection is a frozen aqueous solution of cephalothin sodium with one or more suitable and harmless buffer substances. It may contain sodium chloride or dextrose. Each milliliter contains cephalothin sodium equivalent to 20 milligrams, 40 milligrams, or 100 milligrams of cephalothin. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cephalothin that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 6.0 and not more than 8.5. The cephalothin sodium used conforms to the standards prescribed by § 442.25a(a)(1).

(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:

(a) The cephalothin sodium used in making the batch for potency, loss on drying, pH, specific rotation, identity, and crystallinity.

(b) The batch for potency, sterility, pyrogens, and pH.

(ii) Samples required:

(a) The cephalothin sodium used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 immediate containers.

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

(b) *Tests and methods of assay.* Thaw the ampoule contents as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) *Potency.* Use either 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: Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with 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 1.0 microgram of cephalothin per milliliter (estimated).

(ii) *Hydroxylamine colorimetric assay.* Proceed as directed in § 436.205 of this chapter, preparing the sample as follows: Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with distilled water to give a stock solution of convenient concentration. Further 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 50 milligrams of cephalothin per milliliter.

(4) [Reserved]

(5) *pH.* Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

[40 FR 11351, Mar. 11, 1975, as amended at 49 FR 13493, Apr. 5, 1984; 50 FR 19919, May 13, 1985]

§ 442.225c Cephalothin sodium for injection.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Cephalothin sodium for injection is a dry mixture of cephalothin sodium with one or more suitable and harmless buffer substances. The cephalothin sodium may be isolated in the manufacture of cephalothin sodium for injection. Its cephalothin content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of cephalothin that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 1.5 percent. When reconstituted as directed in the labeling, its pH is not less than 6.0 and not more than

8.5. If isolated, the cephalothin sodium used conforms to the standards prescribed by § 442.25a(a)(1). If the cephalothin sodium is not isolated: The potency of the dry mixture is not less than 850 micrograms of cephalothin per milligram on an anhydrous basis when corrected for sodium bicarbonate; the specific rotation of the dry mixture in an aqueous solution containing 50 milligrams of cephalothin per milliliter at 25° C is $+129^\circ \pm 5^\circ$; and the dry mixture gives a positive identity test.

(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:

(a) If isolated, the cephalothin sodium used in making the batch for potency, loss on drying, pH, specific rotation, identity, and crystallinity.

(b) The batch for potency, sterility, pyrogens, loss on drying, and pH. In addition, if the cephalothin sodium is not isolated, results of tests and assays on the dry mixture for potency, specific rotation, and identity.

(ii) Samples required:

(a) For all tests except sterility: A minimum of 10 immediate containers, unless the cephalothin sodium is not isolated, a minimum of 15 immediate containers.

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

(b) *Tests and methods of assay—(1) Content; potency—(i) Sample preparation.* 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 1 percent potassium phosphate buffer, pH 6.0 (solution 1), for the microbiological agar diffusion assay or distilled water for the hydroxylamine colorimetric assay to obtain a stock solution of convenient concentration. In addition, if

the cephalothin sodium is not isolated, dissolve an accurately weighed sample in sufficient 1 percent potassium phosphate buffer, pH 6.0 (solution 1), for the microbiological agar diffusion assay or distilled water for the hydroxylamine colorimetric assay to obtain a stock solution of convenient concentration. Correct the potency, micrograms of cephalothin per milligram, for sodium bicarbonate content determined as described in paragraph (b)(7) of this section.

(ii) *Assay procedures.* Use either of the following methods; however, the results obtained from the hydroxylamine colorimetric 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 microgram of cephalothin per milliliter (estimated).

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

(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 cephalothin per milliliter.

(4) [Reserved]

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using the drug reconstituted as directed in the labeling.

(7) *Specific rotation.* Dissolve and dilute an accurately weighed portion of the dry mixture with sufficient distilled water to give a concentration of approximately 50 milligrams per milliliter. Proceed as directed in § 436.210 of this chapter, using a 1.0-decimeter polarimeter tube. Calculate the specific rotation on an anhydrous basis and correct for sodium bicarbonate content. Determine the sodium bicarbonate content as follows: Dissolve an accurately weighed portion of the dry mixture, approximately 1.0 gram, with approximately 50 milliliters of distilled water. Titrate with 0.1N sulfuric acid.

Determine the end-point potentiometrically using a glass calomel combination electrode. Each milliliter of 0.1*N* sulfuric acid is equivalent to 8.401 milligrams of sodium bicarbonate.

(8) *Identity*. Using a 0.0025-percent solution of the sample in water and a suitable spectrophotometer, record the ultraviolet absorption spectrum from 220 to 310 nanometers. The spectrum compares qualitatively to that of the working standard similarly tested.

[40 FR 5355, Feb. 5, 1975, as amended at 46 FR 38503, July 28, 1981; 48 FR 51293, Nov. 8, 1983; 49 FR 5097, Feb. 10, 1984; 50 FR 19919, May 13, 1985]

§ 442.229 Sterile cephalixin sodium.

The requirements for certification and the tests and methods of assay for sterile cephalixin sodium packaged for dispensing are described in § 442.29a.

§ 442.240 Cephadrine injectable dosage forms.

§ 442.240a Cephadrine for injection.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Cephadrine for injection is a dry mixture of cephadrine and one or more suitable and harmless solubilizing and buffering agents. Its potency is satisfactory if it contains not less than 90 percent and not more than 115 percent of the number of milligrams of cephadrine that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 5.0 percent. Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 8.0 and not more than 9.6. The cephadrine used conforms to the standards prescribed by § 442.40a(a)(1).

(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:

(a) The sterile cephadrine used in making the batch for potency, moisture, pH, cephalixin content, identity, and crystallinity.

(b) The batch for potency, sterility, pyrogens, loss on drying, and pH.

(ii) Samples required:

(a) The cephadrine used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch:

(1) For all tests except sterility: A minimum of 10 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 either 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: Reconstitute the sample as directed in the labeling for intramuscular use. 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. Further dilute an aliquot of this solution with solution 1 to the reference concentration of 10.0 micrograms of cephadrine per milliliter (estimated).

(ii) *Hydroxylamine colorimetric assay*. Proceed as directed in § 442.40(b)(1)(ii), preparing the sample as follows: Reconstitute the sample as directed in the labeling for intramuscular use. 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. Further dilute an aliquot of this solution with distilled water to 1 milligram of cephadrine per milliliter (estimated).

(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 80 milligrams of cephadrine per milliliter.

(4) [Reserved]