

(a) The nystatin used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of 36 pastilles.

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Place a representative number of pastilles into a high-speed glass blender jar containing 100 milliliters of sterile distilled water. Blend for 18 to 20 minutes. Add 400 milliliters of dimethylformamide and continue blending for an additional 10 minutes. Remove an aliquot and add sufficient 80 percent dimethylformamide so that upon final dilution with 10 percent potassium phosphate buffer, pH 6.0 (solution 6), to the reference concentration of 20 units of nystatin per milliliter, the concentration of dimethylformamide will be 4 percent.

(2) *pH*. Dissolve 1 pastille in 100 milliliters of distilled water at 37 °C, cool, and proceed as directed in § 436.202 of this chapter.

(3) *Disintegration time*. Proceed as directed in § 436.212 of this chapter, using the method described in paragraph (e)(4) of that section.

[52 FR 4617, Feb. 13, 1987; 52 FR 7741, Mar. 12, 1987, as amended at 55 FR 11584, Mar. 29, 1990]

Subpart C—Injectable Dosage Forms

§ 449.204 Amphotericin B for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Amphotericin B for injection is a dry mixture containing in each immediate container 50 milligrams of amphotericin B, 41 milligrams of sodium desoxycholate, and suitable buffering substances. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of amphotericin B that it is represented to contain. It is sterile. It is nonpyrogenic. Its loss on drying is not more than 8.0 percent. Its pH in an aqueous solution containing 10 milligrams of amphotericin B per milliliter is not less than 7.2 and not more than 8.0. The amphotericin B used conforms

to the standards prescribed by § 449.4a(a)(1).

(2) *Labeling*. In addition to the labeling requirements prescribed by § 432.5 of this chapter, each package shall bear on its label and labeling the following statement: “For intravenous infusion in hospitals only”.

(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:

(a) The amphotericin B used in making the batch for potency, amphotericin A content, loss on drying, pH, residue on ignition, and identity.

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

(ii) Samples required:

(a) Amphotericin B used in making the batch: 10 packages, each containing approximately equal portions of not less than 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*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute as directed in the labeling. Then using a suitable syringe and hypodermic needle, remove all of the withdrawable contents if the container 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 sufficient dimethylsulfoxide to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with dimethylsulfoxide to a concentration of 20 micrograms of amphotericin B per milliliter (estimated). Remove an aliquot of this solution and dilute with 0.2M potassium phosphate buffer, pH 10.5 (solution 10), to the reference concentration of 1.0 microgram of amphotericin B 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, except use 50 milligrams in lieu of 300 milligrams.

(3) [Reserved]

(4) *Pyrogens*. Proceed as directed in § 436.32(e) of this chapter, using a solution containing 2 milligrams of amphotericin B per milliliter, except in lieu of paragraph (a)(3), if no rabbit shows an individual rise in temperature of 1.1° C. or more above its respective control temperature, and if the sum of the three temperature rises does not exceed 3° C., the sample meets the requirements for absence of pyrogen. If one or two rabbits show a temperature rise of 1.1° C. or more, or if the sum of temperature rises exceeds 3° C., repeat the test using five other rabbits. If not more than three of the eight rabbits show a temperature rise of 1.1° C. or more, and if the sum of the temperature rises does not exceed 8° C. the sample meets the requirements for absence of pyrogens.

(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 an aqueous solution containing 10 milligrams of amphotericin B per milliliter.

[39 FR 19134, May 30, 1974, as amended at 45 FR 16472, Mar. 14, 1980; 50 FR 19920, May 13, 1985]

Subpart D—Ophthalmic Dosage Forms

§ 449.340 Natamycin ophthalmic suspension.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Natamycin ophthalmic suspension contains natamycin with one or more suitable and harmless preservatives in a suitable and harmless aqueous vehicle. Each milliliter contains 50 milligrams of natamycin. Its potency is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of natamycin that it is represented to contain. It is sterile. Its pH is not less than 5.0 and not more than 7.5. The natamycin used conforms to the standards prescribed by § 449.40(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 natamycin used in making the batch for potency, moisture, pH, identity, and crystallinity.

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

(ii) Samples required:

(a) The natamycin used in making the batch: 10 packages, each containing not less than 500 milligrams.

(b) The batch:

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

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

(b) *Tests and methods of assay*. Dilute solutions of natamycin are very sensitive to light and should be kept in the dark as much as possible or substantial decomposition will take place.

(1) *Potency*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dilute an accurately measured representative portion of the sample with sufficient dimethylsulfoxide to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with dimethylsulfoxide to a concentration of 100 micrograms of natamycin per milliliter (estimated). Further dilute an aliquot with 0.2M potassium phosphate buffer, pH 10.5 (solution 10), to the reference concentration of 5.0 micrograms of natamycin per milliliter (estimated).

(2) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(2) of that section, except use 0.25 milliliter of sample in lieu of 1.0 milliliter.

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

[43 FR 55384, Nov. 28, 1978, as amended at 48 FR 51293, Nov. 8, 1983]