

(b) *Tests and methods of assay*—(1) *Potency*. Proceed as directed in §436.106 of this chapter, preparing the sample for assay as follows: Place an accurately measured, representative portion of the sample into a high-speed glass blender jar containing 1.0 milliliter of polysorbate 80 and sufficient 0.1*N* hydrochloric acid to obtain a stock solution of convenient concentration containing not less than 150 micrograms of oxytetracycline per milliliter (estimated). Blend for 3 to 5 minutes. Further dilute an aliquot with sterile distilled water to the reference concentration of 0.24 microgram of oxytetracycline 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 the sample in lieu of 1.0 milliliter.

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

[43 FR 11169, Mar. 17, 1978, as amended at 50 FR 19920, May 13, 1985]

§446.367e Oxytetracycline hydrochloride-polymyxin B sulfate ophthalmic ointment.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Oxytetracycline hydrochloride-polymyxin B sulfate ophthalmic ointment is oxytetracycline hydrochloride and polymyxin B sulfate in a suitable and harmless ointment base. Each gram contains oxytetracycline hydrochloride equivalent to 5 milligrams of oxytetracycline and polymyxin B sulfate equivalent to 10,000 units of polymyxin B. Its oxytetracycline content is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of oxytetracycline that it is represented to contain. Its polymyxin B content is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of units of polymyxin B that it is represented to contain. It is sterile. Its moisture content is not more than 1 percent. It passes the test for metal particles. The oxytetracycline hydrochloride used conforms to the standards prescribed by §446.67a (a)(1). The polymyxin B sulfate used conforms to the standards prescribed by §448.30a(a)(1) of this chapter.

(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 oxytetracycline hydrochloride used in making the batch for potency, loss on drying, pH, absorptivity, crystallinity, and identity.

(b) The polymyxin B sulfate used in making the batch for potency, pH, loss on drying, residue on ignition, and identity.

(c) The batch for oxytetracycline content, polymyxin B content, sterility, moisture, and metal particles.

(ii) Samples required:

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

(b) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(c) The batch:

(1) For all tests except sterility: A minimum of 16 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*—(i) *Oxytetracycline content*. Proceed as directed in §436.106 of this chapter, preparing the sample for assay as follows: Place an accurately weighed representative portion of the sample into a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Shake the ointment and ether until homogeneous. Add 20 to 25 milliliters of 0.1*N* hydrochloric acid and shake well. Allow the layers to separate. Remove the acid layer and repeat the extraction procedure with each of three more 20- to 25-milliliter quantities of 0.1*N* hydrochloric acid. Combine the acid extractives in a suitable volumetric flask and dilute to volume with 0.1*N* hydrochloric acid to obtain a stock solution of convenient concentration containing not less than 150 micrograms of oxytetracycline per milliliter (estimated). Further dilute an aliquot of the stock solution with sterile distilled water to the reference

concentration of 0.24 microgram of oxytetracycline per milliliter (estimated).

(ii) *Polymyxin B content.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Weigh accurately 0.5 to 1 gram of the ointment and place into a 15-milliliter centrifuge tube. Add 10 milliliters of peroxide-free ether. Stir until contents are homogeneous and centrifuge for 10 minutes at 3,000 revolutions per minute. Decant the supernatant ether. Repeat washing and centrifugation steps once more. Add 10 milliliters of acetone, stir until contents are homogeneous, and centrifuge for 10 minutes at 3,000 revolutions per minute. Decant the supernatant acetone. Repeat acetone wash and centrifugation once more. Continue acetone washings until the yellow color in the residue disappears. Add 3 to 4 drops of polysorbate 80 to the residue and mix well. Gently wash the residue into a 100-milliliter volumetric flask with 10 percent potassium phosphate buffer, pH 6.0 (solution 6), and further dilute with solution 6 to the reference concentration of 10 units of polymyxin B per milliliter (estimated).

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(3) of that section.

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

(4) *Metal particles.* Proceed as directed in § 436.206 of this chapter.

[43 FR 11170, Mar. 17, 1978; 43 FR 34457, Aug. 4, 1978, as amended at 50 FR 19920, May 13, 1985]

§ 446.381 Tetracycline hydrochloride ophthalmic dosage forms.

§ 446.381a Tetracycline hydrochloride ophthalmic ointment.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Tetracycline hydrochloride ophthalmic ointment contains tetracycline hydrochloride in a suitable and harmless ointment base. Each gram contains 10 milligrams of tetracycline hydrochloride. Its potency is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of tetra-

cycline hydrochloride that it is represented to contain. It is sterile. Its moisture content is not more than 0.5 percent. It passes the test for metal particles. The tetracycline hydrochloride used conforms to the standards prescribed by § 446.81a(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 tetracycline hydrochloride used in making the batch for potency, loss on drying, pH, absorptivity, crystallinity, and identity.

(b) The batch for potency, sterility, moisture, and metal particles.

(ii) Samples required:

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

(b) The batch:

(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.* Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Place an accurately weighed representative portion of the sample into a separatory funnel containing approximately 50 milliliters of peroxide-free ether. Shake the sample and ether until homogeneous. Add 20 to 25 milliliters of 0.1N hydrochloric acid and shake well. Allow the layers to separate. Remove the acid layer and repeat the extraction procedure with each of 3 more 20- to 25-milliliter quantities of 0.1N hydrochloric acid. Combine the extractives in a suitable volumetric flask and fill to volume with 0.1N hydrochloric acid to obtain a stock solution of convenient concentration containing not less than 150 micrograms of tetracycline hydrochloride per milliliter (estimated). Further dilute an aliquot with sterile distilled water to the reference concentration of 0.24 micrograms of tetracycline hydrochloride per milliliter (estimated).