

epitetracycline fraction until the column runs dry. Determine the absorbance of the 4-epitetracycline eluate as described in paragraph (b)(1)(v) of this section.

Calculate the 4-epitetracycline hydrochloride content of the 4-epitetracycline hydrochloride bulk powder as follows:

$$\text{Percent by weight 4-epitetracycline content} = \frac{A \times 25 \times 10 \times 50 \times 100}{a \times W \times 2 \times 2}$$

where:

A=Absorbance at 366 nanometers of the low-actinic 50-milliliter volumetric flask.

a=Previously established mean absorptivity of the tetracycline hydrochloride working standard eluates in liters/gram/centimeter with the calculation corrected for potency.

W=Weight of 4-epitetracycline hydrochloride bulk powder in milligrams.

The identity of the 4-epitetracycline hydrochloride is confirmed if the absorbance of the sample after column elution is such that the 4-epitetracycline hydrochloride content is greater than 70 percent by weight.

(2) *Total anhydrotetracycline and 4-epianhydrotetracycline content.* Proceed as directed in § 436.309 of this chapter.

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

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

[42 FR 59066, Nov. 15, 1977; 43 FR 3705, Jan. 27, 1978, as amended at 48 FR 51291, Nov. 8, 1983; 50 FR 19920, May 13, 1985]

§ 446.581d Tetracycline hydrochloride ointment.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Tetracycline hydrochloride ointment contains tetracycline hydrochloride in a suitable and harmless ointment base. Each gram contains 30 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 tetracycline hydrochloride that it is represented to contain. Its moisture content is not more than 1 percent. The tetracycline hydrochloride used conforms to the

standards prescribed by § 446.81(a)(1), except 4-epianhydrotetracycline content.

(2) *Labeling.* In addition to the labeling requirements prescribed by § 432.5(a)(3) of this chapter, each package shall bear on its label or labeling as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(a) The batch mark.

(b) The name and quantity of each active ingredient contained in the drug.

(ii) On the label of the immediate container or other labeling attached to or inserted within the package: Adequate directions under which the layperson can use the drug safely and efficaciously.

(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 and moisture.

(ii) Samples required:

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

(b) The batch: A minimum of six immediate containers.

(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 three more 20- to 25-milliliter quantities of 0.1N hydrochloric acid. Combine the acid 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 of the stock solution with sterile distilled water to the reference concentration of 0.24 microgram of tetracycline hydrochloride per milliliter (estimated).

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

[43 FR 11174, Mar. 17, 1978 as amended at 44 FR 30333, May 25, 1979. Redesignated at 45 FR 16472, Mar. 14, 1980, and amended at 50 FR 19920, May 13, 1985]

Subpart G—Vaginal Dosage Forms

§ 446.667 Oxytetracycline hydrochloride-polymyxin B sulfate vaginal tablets.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Oxytetracycline hydrochloride-polymyxin B sulfate vaginal tablets are tablets composed of oxytetracycline hydrochloride and polymyxin B sulfate with one or more suitable diluents, binders, lubricants, and preservatives. Each tablet contains oxytetracycline hydrochloride equivalent to 100 milligrams of oxytetracycline and polymyxin B sulfate equivalent to 100,000 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 120 percent of the number of units of polymyxin B that it is represented to contain. The loss on drying is not more than 3.0 percent. The oxytetracycline hydrochloride used conforms to the standards prescribed by § 446.67(a)(1). The polymyxin B sulfate used conforms to the standards prescribed by § 448.30(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, identity, and crystallinity.

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

(c) The batch for oxytetracycline content, polymyxin B content, and loss on drying.

(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: A minimum of 30 tablets.

(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 a representative number of tablets into a high-speed glass blender jar containing sufficient 0.1N 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. Remove an aliquot of the stock solution and further dilute 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: Grind a representative number of tablets into a fine powder and place this powder, accurately weighed, into a filter funnel with a solvent-resistant membrane filter of 1.0 micrometer porosity. Wash the powder with five 20-milliliter portions of acetone or until the yellow color has disappeared. Remove the filter and soak in 400 milliliters of 10 percent potassium phosphate buffer, pH 6.0 (solution 6), and blend. Quantitatively transfer to a 500-milliliter volumetric flask and adjust to volume with solution 6. Further dilute an aliquot with solution 6 to the reference concentration of 10 units of polymyxin B per milliliter (estimated).