

(a) The tobramycin used in making the batch: 10 packages, each containing approximately 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*—(1) *Potency*. Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Dilute an accurately measured representative portion of the sample with sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with distilled water to the reference concentration of 2.5 micrograms of tobramycin 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) *pH*. Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

[46 FR 16681, Mar. 13, 1981; 46 FR 22359, Apr. 17, 1981. Redesignated at 47 FR 7827, Feb. 23, 1982, and amended at 50 FR 19919, May 13, 1985; 59 FR 8399, Feb. 22, 1994]

§ 444.380b Tobramycin ophthalmic ointment.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Tobramycin ophthalmic ointment contains, in each gram, 3.0 milligrams of tobramycin with a suitable preservative in a suitable and harmless ointment base. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of tobramycin that it is represented to contain. It is sterile. Its moisture content is not more than 1.0 percent. It passes the test for metal particles. The tobramycin used conforms to the standards prescribed by § 444.80(a)(1), except heavy metals.

(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 re-

quirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The tobramycin used in making the batch for potency, moisture, pH, identity, and residue on ignition.

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

(ii) Samples required:

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

(b) The batch:

(1) For all tests except sterility: A minimum of 20 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 distilled water, and shake well. Allow the layers to separate. Remove the distilled water layer and repeat the extraction procedure with each of three more 20- to 25-milliliter quantities of distilled water. Combine the extractives in a suitable volumetric flask and dilute to volume with distilled water. Further dilute an aliquot with distilled water to the reference concentration of 2.5 micrograms of tobramycin 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.

[47 FR 7827, Feb. 23, 1982; 47 FR 16320, Apr. 16, 1982, as amended at 50 FR 19919, May 13, 1985]

§ 444.380c Tobramycin-dexamethasone ophthalmic suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Tobramycin-dexamethasone ophthalmic suspension is an aqueous suspension containing, in each milliliter, 3.0 milligrams of tobramycin and

1.0 milligram of dexamethasone in a suitable and harmless aqueous vehicle. It contains suitable and harmless buffers, dispersants, preservatives, and tonicity agents. Its tobramycin potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of tobramycin that it is represented to contain. Its dexamethasone content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of dexamethasone that it is represented to contain. It is sterile. Its pH is not less than 5.0 and not more than 6.0. It passes the identity tests for tobramycin and dexamethasone. The tobramycin used conforms to the standards prescribed by § 444.80(a)(1), except heavy metals. The dexamethasone used conforms to the standards prescribed by the USP XXI.

(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 tobramycin used in making the batch for potency, moisture, pH, identity, and residue on ignition.

(B) The dexamethasone used in making the batch for all USP XXI specifications.

(C) The batch for tobramycin potency, dexamethasone content, sterility, pH, tobramycin identity, and dexamethasone identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The tobramycin 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) *Tobramycin potency.* Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Dilute an accurately measured representative portion of the sample with

sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with distilled water to the reference concentration of 2.5 micrograms of tobramycin per milliliter (estimated).

(2) *Dexamethasone content.* Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 254 nanometers, a column packed with microparticulate (3 to 10 micrometers in diameter) reversed phase packing material such as octadecyl hydrocarbon bonded silicas, a flow rate of 1.5 milliliters per minute, and an injection volume of 20 microliters. Mobile phase, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Mobile phase.* Mix acetonitrile:water (45:55). Filter the mobile phase through a suitable glass fiber filter or equivalent that is capable of removing particulate contamination to 1 micron in diameter. Degas the mobile phase just prior to its introduction into the chromatograph pumping system.

(ii) *Preparation of working standard and sample solutions*—(A) *Working standard solution.* Accurately weigh approximately 25 milligrams of the dexamethasone working standard into a 25-milliliter volumetric flask containing methanol. Shake until dissolved. Dilute to volume with methanol. Further dilute 4.0 milliliters of this solution to 100 milliliters with methanol to obtain a solution containing approximately 40 micrograms of dexamethasone per milliliter. Mix well.

(B) *Sample solutions.* Remove an accurately measured representative portion from each container. Dilute the solution thus obtained with sufficient methanol to obtain a solution containing 40 micrograms of dexamethasone per milliliter (estimated).

(iii) *System suitability requirements*—(A) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 1.6 at 10 percent of peak height in lieu of 5 percent of peak height.

(B) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory

if it is greater than 5,500 theoretical plates.

(C) *Resolution*. The resolution (R) between the peak for dexamethasone and its nearest eluting impurity is satisfactory if it is not less than 1.1.

(D) *Coefficient of variation*. The coefficient of variation (S_R in percent) of 5 replicate injections is satisfactory if it is not more than 2.0 percent. If the system suitability requirements have been met, then proceed as described in § 436.216(b) of this chapter. Alternate chromatographic conditions are acceptable provided reproducibility and resolution are comparable to the system. However, the sample preparation described in paragraph (b)(2)(ii)(B) of this section should not be changed.

(iv) *Calculations*. Calculate the dexamethasone content of the container as follows:

$$\frac{\text{Milligrams of dexamethasone per container}}{A_s \times 1,000} = \frac{A_u \times P_a \times d}{A_s \times 1,000}$$

where:

A_u =Area of the dexamethasone peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);

A_s =Area of the dexamethasone peak in the chromatogram of the dexamethasone working standard;

P_a =Dexamethasone content in the dexamethasone working standard solution in micrograms per milliliter; and

d =Dilution factor of the sample.

(3) *Sterility*. Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

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

(5) *Tobramycin identity*. Proceed as directed in § 436.318 of this chapter, except prepare the sample for assay as follows; decant 1 milliliter into a test tube. Add 100 milligrams of sodium sulfate to the test tube and shake until the sodium sulfate has been dispersed. Centrifuge to obtain a clear supernatant. Use the supernatant as the sample solution.

(6) *Dexamethasone identity*. The high-pressure liquid chromatogram of the sample determined as directed in paragraph (b)(2) of this section, compares

qualitatively to that of the dexamethasone working standard.

[54 FR 13879, Apr. 6, 1989, as amended at 59 FR 8399, Feb. 22, 1994]

§ 444.380d Tobramycin-dexamethasone ophthalmic ointment.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Tobramycin-dexamethasone ophthalmic ointment contains in each gram, tobramycin equivalent to 3.0 milligrams of tobramycin and 1.0 milligram of dexamethasone, with a suitable preservative in a suitable and harmless white petrolatum base. Its tobramycin potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of tobramycin that it is represented to contain. Its dexamethasone content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of dexamethasone that it is represented to contain. It is sterile. Its moisture content is not more than 1.0 percent. It passes the test for metal particles. It passes the identity tests for tobramycin and dexamethasone. The tobramycin used conforms to the standards prescribed by § 444.80(a)(1), except heavy metals. The dexamethasone used conforms to the standards prescribed by the U.S. Pharmacopeia XXII.

(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 tobramycin used in making the batch for potency, moisture, pH, identity, and residue on ignition.

(B) The dexamethasone used in making the batch for all U.S. Pharmacopeia XXII specifications.

(C) The batch for tobramycin potency, dexamethasone content, sterility, moisture, metal particles, tobramycin identity, and dexamethasone identity.

(ii) Samples, if required by the Center for Drug Evaluation and Research: