

**§ 446.81a Sterile tetracycline hydrochloride.**

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Tetracycline hydrochloride is [4S - (4 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ ,6 $\beta$ , 12 $\alpha$ )] - 4 - dimethylamino) - 1,4,4a,5,5a,6,11,12a - octahydro - 3,6,10,12,12a - pentahydroxy - 6 - methyl - 1,11 - dioxo - 2 - naphthacene - carboxamide monohydrochloride. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms of tetracycline hydrochloride per milligram. If it is packaged for dispensing, its content is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of tetracycline hydrochloride that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) It contains no depressor substances.

(vi) Its loss on drying is not more than 2 percent.

(vii) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 1.8 and not more than 2.8.

(viii) When calculated on the anhydrous basis, its absorptivity at 380 nanometers relative to that of the tetracycline hydrochloride working standard similarly treated is 100 $\pm$ 4 percent.

(ix) Its 4-epianhydrotetracycline content is not more than 2.0 percent.

(x) It is crystalline.

(xi) It passes the identity test for tetracycline.

(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 the batch for potency, sterility, pyrogens, depressor substances, loss on drying, pH, absorptivity, 4-epianhydrotetracycline content, crystallinity, and identity.

(ii) Samples required:

(a) If the batch is packaged for repackaging or for use in the manufacture of another drug:

(1) For all tests except sterility: 10 packages, each containing approximately 300 milligrams.

(2) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

(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 § 436.106 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 0.1N hydrochloric acid to obtain a stock solution containing 1,000 micrograms of tetracycline hydrochloride per milliliter (estimated); also, if it is packaged for dispensing, 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 the sample thus obtained with sufficient 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) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section, except use diluting fluid D in lieu of diluting fluid A.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a [solution containing 5.0 milligrams of tetracycline] hydrochloride per milliliter.

(4) [Reserved]

(5) *Depressor substances.* Proceed as directed in § 436.35 of this chapter.

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

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

(8) *Absorptivity*. Dissolve approximately 40 milligrams of the sample, accurately weighed, in approximately 150 milliliters of distilled water by mixing thoroughly. Dilute to 250 milliliters with distilled water and mix thoroughly. Transfer a 10.0-milliliter aliquot of this solution to a 100-milliliter volumetric flask, add approximately 75 milliliters of distilled water and 5.0

milliliters of 5*N* NaOH, dilute to volume with water, and mix thoroughly. Treat a sample of the tetracycline hydrochloride working standard in the same manner. Exactly 6 minutes after the addition of the NaOH, determine the absorbance of each solution at 380 nanometers, using a suitable spectrophotometer and distilled water as the blank. Determine the percent absorptivity of the sample relative to the absorptivity of the standard using the following calculation:

$$\text{Percent relative absorptivity} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times \frac{\text{Milligrams of standard}}{\text{Milligrams of sample}} \times \frac{\text{Potency of standard in micrograms per milligram}}{10} \times \frac{10}{100 - m}$$

where: *m* = Percent moisture in the sample.

(9) *4-Epianhydrotetracycline*. Proceed as directed in § 436.309 of this chapter.

(10) *Crystallinity*. Proceed as directed in § 436.203(a) of this chapter.

(11) *Identity*. Proceed as directed in § 436.308 of this chapter.

[43 FR 11160, Mar. 17, 1978; 43 FR 34456, Aug. 4, 1978, as amended at 44 FR 31636, June 1, 1979; 46 FR 60568, Dec. 11, 1981; 50 FR 19920, May 13, 1985]

#### § 446.82 Tetracycline phosphate complex.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Tetracycline phosphate complex is [4S-(4 $\alpha$ ,4 $\alpha$ ,5 $\alpha$ ,6 $\beta$ , 12 $\alpha$ )] - 4 - (dimethylamino) - 1,4,4a,5,5a,6,11,12a - octahydro - 3,6,10,12,12a - pentahydroxy - 6 - methyl - 1,11 - dioxo - 2 - naphthacenicarboxamide phosphate complex. It is so purified and dried that:

(i) Its potency is not less than 750 micrograms per milligram on the anhydrous basis.

(ii) [Reserved]

(iii) Its moisture content is not more than 9 percent.

(iv) Its pH in an aqueous suspension containing 10 milligrams per milliliter is not less than 2.0 and not more than 4.0.

(v) When calculated on the anhydrous basis, its absorptivity at 380 nanometers relative to that of the tet-

racycline hydrochloride working standard similarly treated is 82.0 $\pm$ 4.9 percent.

(vi) Its 4-epianhydrotetracycline content is not more than 2.0 percent.

(vii) It passes the identity test, showing a presence of phosphate, a content of not more than 0.2 percent chloride, and a content of not more than 1 percent tetracycline base.

(viii) It is crystalline.

(2) *Labeling*. In addition to the requirements of § 432.5 of this chapter, each such package shall bear on its label or labeling the statement "For use only in the manufacture of non-parenteral drugs".

(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 the batch for potency, moisture, pH, absorptivity, 4-epianhydro tetracycline content, identity, and crystallinity.

(ii) Samples required: 10 packages, each containing approximately 60 milligrams.

(b) *Tests and methods of assay—(1) Potency*. Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 0.1*N* hydrochloric acid to obtain a concentration of 1,000 micrograms of tetracycline hydrochloride per milliliter (estimated). Further dilute an aliquot of