

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

[43 FR 11165, Mar. 17, 1978, as amended at 44 FR 48189, Aug. 17, 1979; 47 FR 32938, July 30, 1982; 48 FR 51293, Nov. 8, 1983; 49 FR 37058, Sept. 21, 1984; 50 FR 19920, May 13, 1985]

§ 446.181e Tetracycline hydrochloride capsules.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Tetracycline hydrochloride capsules are composed of tetracycline hydrochloride with or without one or more suitable and harmless buffer substances, preservatives, diluents, binders, lubricants, colorings, and flavorings enclosed in a gelatin capsule. Each capsule contains 50, 100, 125, 250, or 500 milligrams of tetracycline hydrochloride. Its potency is satisfactory if it is 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 loss on drying is not more than 4 percent. Its 4-epianhydrotetracycline content is not more than 3.0 percent. It passes the dissolution test. The tetracycline hydrochloride used conforms to the standards prescribed by § 446.81(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 tetracycline hydrochloride used in making the batch for potency, loss on drying, pH, absorptivity, 4-epianhydrotetracycline content, crystallinity, and identity.

(b) The batch for potency, loss on drying, 4-epianhydrotetracycline content, and dissolution.

(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 30 capsules.

(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 a representative

number of capsules into a high-speed glass blender jar containing sufficient 0.1*N* hydrochloric acid to obtain a stock solution of convenient concentration containing not less than 150 micrograms of tetracycline hydrochloride 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 tetracycline hydrochloride per milliliter (estimated).

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

(3) *4-Epianhydrotetracycline.* Proceed as directed in § 436.309 of this chapter.

(4) *Dissolution.* Proceed as directed in § 436.215 of this chapter except in lieu of paragraph (a) of that section, a distance of 4.5±0.5 centimeters should be maintained between the lower edge of the stirring blade and the lowest inner surface of the vessel during the test. The quantity *Q* (the amount of tetracycline hydrochloride dissolved), except for the 500-milligram capsule, is 60 percent within 30 minutes and 85 percent within 60 minutes. For the 500-milligram capsule, the quantity *Q* is 50 percent within 30 minutes, 70 percent within 60 minutes, and 85 percent within 90 minutes.

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§ 446.182 Tetracycline phosphate complex capsules.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Tetracycline phosphate complex capsules contain tetracycline phosphate complex with or without one or more buffer substances, preservatives, diluents, binders, lubricants, colorings, and flavorings enclosed in a gelatin capsule. Each capsule contains tetracycline phosphate complex equivalent to 50, 100, 125, 250, or 500 milligrams of tetracycline hydrochloride. Its potency is satisfactory if it contains the equivalent of 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 loss on drying is not more than 9.0 percent. Its 4-

epianhydrotetracycline content is not more than 3.0 percent. The tetracycline phosphate complex used conforms to the standards prescribed by § 446.82 (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 tetracycline phosphate complex used in making the batch for potency, moisture, pH, absorptivity, 4-epianhydrotetracycline content, identity, and crystallinity.

(b) The batch for potency, loss on drying, and 4-epianhydrotetracycline content.

(ii) Samples required:

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

(b) The batch: A minimum of 30 capsules.

(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 a representative number of capsules into a high-speed glass blender jar containing sufficient 0.1*N* hydrochloric acid to obtain a stock solution of convenient concentration containing not less than 150 micrograms of tetracycline hydrochloride 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 tetracycline per milliliter (estimated).

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

(3) *4-Epianhydrotetracycline.* Proceed as directed in § 436.309 of this chapter.

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Subpart C—Injectable Dosage Forms

§ 446.220 Doxycycline hyclate for injection.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality,*

and purity. Doxycycline hyclate for injection is a dry mixture of doxycycline hyclate and a buffer substance. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of doxycycline that it is represented to contain. It is sterile. It is nonpyrogenic. It contains no depressor substances. Its loss on drying is not more than 2.0 percent. Its pH when reconstituted as directed in the labeling is not less than 1.8 and not more than 3.3. It passes the identity test for the presence of the doxycycline moiety. The doxycycline hyclate used conforms to the standards prescribed by § 446.20a(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this subchapter.

(3) *Requests for certification: samples.* In addition to complying with the requirements of § 431.1 of this subchapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The doxycycline hyclate used in making the batch for potency, moisture, pH, doxycycline content, identity, and crystallinity.

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

(ii) Samples required:

(a) The doxycycline hyclate used in making the batch: 10 packages, each containing approximately 300 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 subchapter, preparing the sample for assay as follows: Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe, remove all of the withdrawable contents from each container 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 solution thus obtained with sufficient 0.1*N* hydrochloric