

acid to give a stock solution of convenient concentration (containing not less than 150 micrograms of doxycycline in acid). Further dilute an aliquot of the stock solution with sterile distilled water to the reference concentration of 0.100 microgram of doxycycline per milliliter (estimated).

(2) *Sterility*. Proceed as directed in §436.20 of this subchapter, 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(a) of this subchapter, using a solution containing 7.5 milligrams of doxycycline per milliliter.

(4) [Reserved]

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

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

(7) *pH*. Proceed as directed in §436.202 of this subchapter, using the drug reconstituted as directed in the labeling.

(8) *Identity*. Proceed as directed in §436.308 of this subchapter, except prepare the standard and sample solutions as follows: Dissolve precise amounts of the doxycycline hyclate for injection and of the doxycycline working standard in methanol and further dilute each solution to a concentration of 1 milligram of doxycycline per milliliter. Prepare the sample-standard mixed solution by mixing equal volumes of the final concentration of the sample and standard solutions. The sample and standard must each produce a major, yellow fluorescent spot with the same  $R_f$  value and the sample-standard mixed solution must show no separation of major spots.

[39 FR 19076, May 30, 1974, as amended at 43 FR 11166, Mar. 17, 1978; 43 FR 34457, Aug. 4, 1978; 46 FR 60568, Dec. 11, 1981; 50 FR 19920, May 13, 1985]

#### § 446.260 Sterile minocycline hydrochloride.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Sterile minocycline hydrochloride is a lyophilized powder of minocycline hydrochloride. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of minocycline that it is represented to

contain. It is sterile. It is nonpyrogenic. It contains no depressor substance. Its moisture content is not more than 3.0 percent. Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 2.0 and not more than 3.5. The minocycline hydrochloride used conforms to the standards prescribed by §446.60(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 minocycline hydrochloride used in making the batch for potency, moisture, pH, epi-minocycline content, identity, crystallinity, residue on ignition, and absorptivity.

(b) The batch for potency, sterility, pyrogens, depressor substances, moisture, and pH.

(ii) Samples required:

(a) The minocycline 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 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 §446.60(b)(1) of this part, except prepare the sample solution and calculate the minocycline potency as follows:

(i) *Sample solution*. Reconstitute as directed in the labeling. Using a suitable hypodermic needle and syringe, remove the withdrawable contents from each container represented as a single-dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, withdraw an accurately measured representation portion from each container. Dilute the sample thus obtained with sufficient mobile phase (described in §446.60(b)(1)(i)(c) of this part) to give a stock solution of convenient concentration. Filter the stock solution. Further dilute an aliquot of this stock solution with mobile phase to obtain a solution containing 500 micrograms of

minocycline activity per milliliter (estimated). Use this solution within 3 hours of preparation.

(ii) *Calculations*—(a) Calculate the minocycline content of the single-dose vial as follows:

$$\text{Milligrams of minocycline per single-dose vial} = \frac{A_u \times P_s \times d}{A_s \times 1,000}$$

where:

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

$A_s$ = Area of the minocycline peak in the chromatogram of the minocycline working standard;

$P_s$ = Minocycline activity in the minocycline working standard solution in micrograms per milliliter; and

$d$ = Dilution factor of the sample.

(b) Calculate the minocycline content of the multiple-dose vial as follows:

$$\text{Milligrams of minocycline per multiple-dose vial} = \frac{A_u \times P_s \times d}{A_s \times 1,000 \times n}$$

where:

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

$A_s$ = Area of the minocycline peak in the chromatogram of the minocycline working standard;

$P_s$ = Minocycline activity in the minocycline working standard solution in micrograms per milliliter;

$d$ = Dilution factor of the sample.

$n$ = Volume of sample solution assayed.

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

(3) *Pyrogens*. Proceed as directed in § 436.32(b) of this chapter, using a solution containing 5 milligrams per milliliter.

(4) [Reserved]

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

(6) *Moisture*. Proceed as directed in § 436.201 of this chapter, using the sample preparation described in paragraph (d)(4) of that section.

(7) *pH*. Proceed as directed in § 436.202 of this chapter, using an aqueous solu-

tion containing 10 milligrams of minocycline per milliliter.

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**§ 446.265 Oxytetracycline injection.**

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Oxytetracycline injection is a solution of oxytetracycline with or without one or more suitable and harmless buffer substances, anesthetics, preservatives, antioxidants, complexing agents, and solvents. Each milliliter contains 50 milligrams or 125 milligrams of oxytetracycline. Its potency 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. It is sterile. It is nonpyrogenic. It contains no depressor substances. Its pH is not less than 8.0 and not more than 9.0. The oxytetracycline used conforms to the standards prescribed by § 446.65a(a)(1), except sterility, pyrogens, and depressor substances.

(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 used in making the batch for potency, moisture, pH, absorptivity, identity, and crystallinity.

(b) The batch for potency, sterility, pyrogens, depressor substances, and pH.

(ii) Samples required:

(a) The oxytetracycline used in making the batch: 10 packages, each containing approximately 300 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) *Potency*. Proceed as directed in § 436.106 of this chapter, preparing the sample for