

working standard in the same manner. Determine the percent relative absorp-

tivity of the sample using the following calculation:

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

where: m = percent moisture in the sample.

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

(7) *Identity*. Proceed as directed in § 446.16(b)(7). The value yielded by calculation ranges between 0.97 and 1.17.

[39 FR 19076, May 30, 1974, as amended at 43 FR 11155, Mar. 17, 1978; 43 FR 34456, Aug. 4, 1978; 46 FR 16683, Mar. 13, 1981; 50 FR 19920, May 13, 1985]

§ 446.16 Demeclocycline hydrochloride.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Demeclocycline hydrochloride is [4S - (4 α 4 α ,5 α ,6 β ,12 α)] - 7 - chloro - 4 - (dimethylamino) - 1,4,4a,5,5a,6,11,12a - octahydro-3,6,10,12,12a - pentahydroxy - 1,11 - dioxo - 2 - naphthacenicarboxamide monohydrochloride. It is so purified and dried that:

(i) Its potency is not less than 900 micrograms per milligram on the anhydrous basis.

(ii) [Reserved]

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

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 2 and not more than 3.

(v) When calculated on the anhydrous basis, its absorptivity at 380 nanometers relative to that of the demeclocycline hydrochloride standard is 100 \pm 4.2 percent.

(vi) It is crystalline.

(vii) It passes the identity test.

(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, loss on drying, pH, absorptivity, crystallinity, and identity.

(ii) Samples required: 10 packages, each containing approximately 250 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 0.1N hydrochloric acid to obtain a concentration of 1,000 micrograms of demeclocycline hydrochloride per milliliter (estimated). Further dilute an aliquot of the stock solution with sterile distilled water to the reference concentration of 0.100 microgram of demeclocycline hydrochloride per milliliter (estimated).

(2) [Reserved]

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

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

(5) *Absorptivity*. Determine the percent absorptivity of the sample relative to that of the standard in the following manner: Dissolve an accurately weighed portion of approximately 40 milligrams of the sample in 2 milliliters of 0.1N HCl, dilute to exactly 250 milliliters with distilled water, and mix thoroughly. Transfer a 10 milliliter aliquot of this solution to a 100-milliliter volumetric flask. Add about 75 milliliters of distilled water and 5 milliliters of 5N NaOH, dilute to volume with distilled water, and mix thoroughly. Exactly 6 minutes after the addition of the NaOH, determine the absorbance of the solution at a wavelength of 380 nanometers, using a suitable spectrophotometer and distilled water as the blank. Treat a portion of

the working standard in the same manner. Determine the percent relative ab-

sorptivity of the sample using the following calculation:

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

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

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

(7) *Identity*. Accurately weigh 40 milligrams of the sample and place into a 200-milliliter volumetric flask. Add 100 milliliters of 0.1*N* HCl and place on a shaker until the sample is dissolved. Dilute to volume with 0.1*N* HCl and mix well. Transfer a 5-milliliter aliquot of the solution to each of two 50-milliliter volumetric flasks. To one flask add 10 milliliters of 6*N* HCl and to the

other add 10 milliliters of 3*N* HCl. Place the acid-treated flasks into a boiling water bath for 20 minutes. Remove the flasks and place in a cold water bath. When cool, dilute to volume with water and mix well. Treat a portion of the standard in the same manner. Using a suitable spectrophotometer, place the 6*N* HCl-treated sample into the reference cell and read against the 3*N* HCl-treated sample at a wavelength of 368 nanometers. Reverse the order of the cells in the cell holder and read at a wavelength of 430 nanometers.

$$\frac{(A_{368} + A_{430} \text{ sample}) (\text{milligrams of standard per milliliter}) (100)}{(A_{368} + A_{430} \text{ standard}) (\text{milligrams of sample per milliliter}) (100 - m)} = 0.9 \text{ to } 1.1$$

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

[39 FR 19076, May 30, 1974, as amended at 43 FR 11155, Mar. 17, 1978; 43 FR 34456, Aug. 4, 1978; 50 FR 19920, May 13, 1985]

§ 446.20 Doxycycline hyclate.

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

- (i) Its potency is not less than 800 nor more than 920 micrograms of doxycycline per milligram on an “as is” basis.
- (ii) [Reserved]
- (iii) Its moisture content is not less than 1.4 nor more than 2.75 percent.

(iv) Its pH in an aqueous solution containing 10 milligrams per milliliter is not less than 2.0 nor more than 3.0.

(v) It contains not less than 82 nor more than 90 percent doxycycline on an “as is” basis.

(vi) It gives a positive identity test for doxycycline hyclate.

(vii) It is crystalline.

(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, moisture, pH, doxycycline content, identity, and crystallinity.
- (ii) Samples required: 10 packages, each containing approximately 300 milligrams.