

**§ 446.121 Doxycycline monohydrate oral dosage forms.****§ 446.121a Doxycycline monohydrate for oral suspension.**

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Doxycycline monohydrate for oral suspension is doxycycline monohydrate with one or more suitable and harmless buffer substances, preservatives, diluents, colorings, and flavorings. Its moisture content is not more than 3 percent. It passes the identity test for the presence of the doxycycline moiety. When prepared as directed in the labeling, each milliliter contains the equivalent of 5 milligrams of doxycycline and its pH is not less than 5.0 and not more than 6.5. Its potency is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of doxycycline that it is represented to contain. The doxycycline monohydrate used conforms to the standards prescribed by § 446.21(a)(1).

(2) *Labeling.* In addition to the labeling requirements of § 432.5 of this chapter, this drug shall be labeled “doxycycline for oral suspension”.

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

(i) Results of tests and assays on:

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

(b) The batch for potency, moisture, pH, and identity.

(ii) Samples required:

(a) The doxycycline monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of six immediate containers.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.106 of this chapter, preparing the sample for assay as follows: Reconstitute the sample as directed in the labeling. Transfer an accurately measured representative portion of the well-shaken suspension to an appropriate-sized volumetric flask and dilute to volume with 0.1*N* hydrochloric acid to obtain a stock so-

lution of convenient concentration containing not less than 150 micrograms of doxycycline per milliliter (estimated). 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) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(3) *pH.* Reconstitute as directed in the labeling and proceed as directed in § 436.202 of this chapter, using the undiluted sample.

(4) *Identity.* Proceed as directed in § 436.308 of this chapter, except prepare the standard and sample solutions as follows: Dissolve precise amounts of the doxycycline monohydrate for oral suspension 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 11163, Mar. 17, 1978; 50 FR 19920, May 13, 1985. Redesignated at 55 FR 6637, Feb. 26, 1990]

**§ 446.121b Doxycycline monohydrate capsules.**

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Doxycycline monohydrate capsules are composed of doxycycline monohydrate and one or more suitable and harmless lubricants and diluents enclosed in a gelatin capsule. Each capsule contains doxycycline monohydrate equivalent to 100 milligrams of doxycycline. 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. The moisture content is not more than 5.5 percent. It passes the dissolution test. It passes the identity test. The doxycycline monohydrate used conforms to the standards prescribed by § 446.21.

(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 doxycycline monohydrate used in making the batch for potency, moisture, pH, doxycycline content, identity, and crystallinity.

(B) The batch for potency, moisture, dissolution, and identity.

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

(A) The doxycycline monohydrate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(B) The batch: A minimum of 100 capsules.

(b) *Tests and methods of assay—(1) Doxycycline potency.* Proceed as directed in § 436.216 of this chapter, using ambient temperature, an ultraviolet detection system operating at a wavelength of 280 nanometers, a 4.6-millimeter X 3-centimeter guard column containing 5- to 10-micrometer diameter octyl silane chemically bonded to totally porous microsilica particles, a 3.9-millimeter X 30-centimeter analytical column packed with octadecyl silane chemically bonded to porous silica or ceramic microparticles, 5 to 10 micrometers in diameter, a flow rate of 1.5 milliliters per minute, and a 10-microliter loop injector. Reagents, working standard and sample solutions, system suitability requirements, and calculations are as follows:

(i) *Reagents—(A) 0.1M sodium phosphate buffer.* Prepare a solution containing 13.8 grams of monobasic sodium phosphate per liter of distilled water.

(B) *Mobile phase.* Mix 450 milliliters of 0.1M monobasic sodium phosphate and 550 milliliters of methanol. Add 3 milliliters of *N,N*-dimethyl-*n*-octylamine. Adjust the pH to 8.0 with 5N sodium hydroxide. Filter the mobile phase through a suitable glass 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, sample, and resolution test solutions—(A) Working standard solution.* Dissolve an accurately weighed portion of the doxycycline hyclate working standard in sufficient 0.1N hydrochloric acid to obtain a known concentration of about 1,000 micrograms of doxycycline per milliliter. Further dilute with distilled water to a concentration of 40 micrograms of doxycycline activity per milliliter. Filter through a membrane filter of 0.5 micron or finer porosity.

(B) *Sample solution.* Remove, as completely as possible, the contents of a representative number of capsules. Mix the combined contents and transfer an accurately weighed portion of the powder, equivalent to about 100 milligrams of doxycycline, to a 100-milliliter volumetric flask. Add 20 milliliters of 0.1N hydrochloric acid and sonicate for 5 minutes. Dilute to mark with 0.1N hydrochloric acid. Further quantitatively dilute an aliquot of this solution with distilled water to a concentration of 40 micrograms of doxycycline activity per milliliter (estimated). Filter through a membrane filter of 0.5 micron or finer porosity. Content uniformity analyses may be obtained from sample solutions prepared as above except that the contents of one capsule are quantitatively transferred to the 100-milliliter volumetric flask.

(C) *Resolution test solution.* Dissolve 50 milligrams of doxycycline in 25 milliliters of distilled water. Pipet 5 milliliters of this solution into a 25-milliliter volumetric flask and heat on a steam bath for 60 minutes. Transfer the contents of the flask to a small beaker and evaporate to dryness. Dissolve the residue in distilled water, transfer to a 25-milliliter volumetric flask, dilute to mark with distilled water, mix, and filter through Whatman No. 1 filter paper. Use this solution to determine the resolution factor.

(iii) *System suitability requirements—(A) Asymmetry factor.* Calculate the asymmetry factor ( $A_s$ ), measured at a point 5 percent of the peak height from the baseline, as follows:

$$A_s = \frac{a+b}{2a}$$

where:

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*a*=Horizontal distance from point of ascent to a point of a maximum peak height; and  
*b*=Horizontal distance from the point of maximum peak height to point of descent.

The asymmetry factor (*A<sub>s</sub>*) is satisfactory if it is not less than 1.4 and not more than 2.0

(B) *Efficiency of the column.* From the number of theoretical plates (*n*) calculated as described in §436.216(c)(2) of this chapter calculate the reduced plate height (*h<sub>r</sub>*) as follows:

$$h_r = \frac{(L)(10,000)}{(n)(d_p)}$$

where:

*L*=Length of the column in centimeters;  
*n*=number of theoretical plates; and  
*d<sub>p</sub>*=Average diameter of the particles in analytical column packing in micrometers.

The absolute efficiency (*h<sub>a</sub>*) is satisfactory if it is not more than 37.5 for the doxycycline peak.

(C) The resolution (*R*) between peaks for doxycycline and epi-doxycycline is satisfactory if it is not less than 1.5.

(D) *Coefficient of variation (relative standard deviation).* The coefficient of variation (*S<sub>R</sub>* in percent) of 5 replicate injections is satisfactory if it is not more than 2.0 percent.

(E) *Capacity factor (k').* Calculate the capacity factor (*k'*) for doxycycline as follows:

$$k' = \frac{t_r - t_o}{t_o}$$

where:

*t<sub>r</sub>*=Retention time of doxycycline in minutes; and  
*t<sub>o</sub>*=Column dead time in minutes, which is estimated from the following equation:

$$t_o = \frac{(3.1416)(D^2)(L)(0.75)}{4F}$$

where:

*D*=Column diameter in centimeters;  
*L*=Column length in centimeters;  
 0.75=Average total column porosity; and  
*F*=Flow rate in milliliters per minute.

The capacity factor (*k'*) for doxycycline is satisfactory if it is not less than 1.5 and not more than 2.5. 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 described. However, the sample preparation described in paragraph (b)(1)(ii)(B) of this section should not be changed.

(iv) *Calculations.* Calculate the doxycycline content as follows:

$$\text{Milligrams of doxycycline per capsule} = \frac{A_u \times P_s \times d}{A_s \times 1,000 \times n}$$

where:

*A<sub>u</sub>*=Area of the doxycycline peak in the chromatogram of the sample (at a retention time equal to that observed for the standard);  
*A<sub>s</sub>*=Area of the doxycycline peak in the chromatogram of the working standard;  
*P<sub>s</sub>*=Doxycycline activity in the doxycycline working standard solution in micrograms per milliliter;  
*d*=Dilution factor of the sample; and  
*n*=Number of capsules in the sample assayed.

(2) *Moisture.* Proceed as directed in §436.201 of this chapter.

(3) *Dissolution.* Proceed as directed in §436.215 of this chapter. The quantity *Q* (the amount of doxycycline dissolved) is 85 percent at 60 minutes.

(4) *Identity.* The high-pressure liquid chromatogram of the sample determined in paragraph (b)(1) of this section compares qualitatively to that of the doxycycline working standard.

[55 FR 6637, Feb. 26, 1990]

**§ 446.150 Methacycline hydrochloride oral dosage forms.**

**§ 446.150a Methacycline hydrochloride capsules.**

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Methacycline hydrochloride capsules are composed of methacycline hydrochloride and one or more suitable and harmless lubricants and diluents enclosed in a gelatin capsule. Each capsule contains methacycline hydrochloride equivalent to either 70 milligrams of methacycline, 140 milligrams of methacycline, or 280 milligrams of methacycline. Its potency is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of methacycline that