

labeling, its pH is not less than 6.0 and not more than 9.0. The erythromycin stearate used conforms to the standards prescribed by § 452.35(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 erythromycin stearate used in making the batch for potency, moisture, pH, residue on ignition, identity, and crystallinity.

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

(ii) Samples required:

(a) The erythromycin stearate used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch: A minimum of 6 immediate containers.

(b) *Tests and methods of assay—(1) Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Reconstitute as directed in the labeling. Place an accurately measured representative portion of the suspension into a high-speed glass blender jar with sufficient methyl alcohol to give a concentration of 1.0 milligram of erythromycin base per milliliter (estimated). Blend for 3 to 5 minutes. Further dilute with 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

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

(3) *pH.* Proceed as directed in § 436.202 of this chapter, using the suspension obtained when the drug is reconstituted as directed in the labeling.

[40 FR 49083, Oct. 21, 1975, as amended at 41 FR 24884, June 21, 1976; 50 FR 19921, May 13, 1985]

§ 452.150 Clarithromycin oral dosage forms.

§ 452.150a Clarithromycin tablets.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Clarithromycin tablets are composed of clarithromycin and one or

more suitable and harmless diluents, binders, lubricants, colorings, and flavorings. Each tablet contains 250 milligrams or 500 milligrams of clarithromycin activity. Its clarithromycin content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of clarithromycin that it is represented to contain. The loss on drying is not more than 6.0 percent. It passes the dissolution test. It passes the identity test. The clarithromycin used conforms to the standards prescribed by § 452.50(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 clarithromycin used in making the batch for potency, moisture, pH, residue on ignition, heavy metals, specific rotation, identity, and crystallinity.

(B) The batch for content, loss on drying, dissolution, and identity.

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

(A) The clarithromycin used in making the batch: 10 packages, each containing approximately 500 milligrams.

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

(b) *Tests and methods of assay—(1) Clarithromycin content.* Proceed as directed in § 452.50(b)(1), preparing the sample solution and calculating the clarithromycin content as follows:

(i) *Preparation of sample solution.* Grind and composite five whole tablets in a glass mortar and pestle and quantitatively transfer the powder to a 500-milliliter volumetric flask with 50 milliliters of distilled water and shake mechanically until the tablets are well dispersed (approximately 5 to 10 minutes). Add 300 milliliters of methanol and shake mechanically for 30 minutes. Dilute with methanol to volume and mix. Allow the excipients to settle. Quantitatively transfer and dilute a convenient aliquot of the supernatant with mobile phase (described in § 452.50(b)(1)(i)) to obtain a solution

containing 125 micrograms of clarithromycin per milliliter (estimated). Filter through a suitable filter capable of removing particulate matter 0.5 micron in diameter.

(ii) *Calculations.* Calculate the clarithromycin content as follows:

$$\frac{\text{Milligrams of clarithromycin per tablet}}{A_s \times 1,000 \times n} = \frac{A_U \times P_s \times d}{A_s \times 1,000 \times n}$$

where:

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

A_s = Area of the clarithromycin peak in the chromatogram of the clarithromycin working standard;

P_s = Clarithromycin activity in the clarithromycin working standard solution in micrograms per milliliter;

d = Dilution factor of the sample; and

n = Number of tablets in the sample.

(2) *Loss on drying.* Proceed as directed in § 436.200(c) of this chapter, using a sample weight of 1 to 2 grams.

(3) *Dissolution.* Proceed as directed in § 436.215 of this chapter. The quantity Q (the amount of clarithromycin dissolved) is 80 percent at 30 minutes.

(4) *Identity.* Using the high-performance liquid chromatographic procedure described in paragraph (b)(1) of this section, the retention time for the peak of the active ingredient must be within 2 percent of the retention time for the peak of the corresponding reference standard.

[58 FR 26654, May 4, 1993. Redesignated at 61 FR 34726, July 3, 1996]

§ 452.150b Clarithromycin granules for oral suspension.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Clarithromycin granules for oral suspension is a dry mixture containing clarithromycin-coated particles, suitable and harmless dispersing agents, diluents, preservatives, and flavorings. It contains the equivalent of 25 or 50 milligrams of clarithromycin activity per milliliter of the reconstituted suspension. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of clarithromycin that it is represented

to contain. Its loss on drying is not more than 2.0 percent. When constituted as directed in the labeling, its pH is not less than 4.0 nor more than 5.4. The clarithromycin used conforms to the standards prescribed by § 452.50(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 clarithromycin used in making the batch for potency, moisture, pH, residue on ignition, heavy metals, specific rotation, identity, and crystallinity.

(B) The batch for content, loss on drying, pH, and identity.

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

(A) The clarithromycin used in making the batch: 10 packages, each containing approximately 500 milligrams.

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

(b) *Tests and methods of assay—(1) Clarithromycin content.* Proceed as directed in § 452.50(b)(1), except use a known injection volume between 10 and 60 microliters. Also, prepare the mobile phase, working standard solution, and sample solution, and use system suitability requirements and calculation as follows:

(i) *Mobile phase.* Add 600 milliliters of methanol and 400 milliliters of 0.067M potassium phosphate, monobasic, to a suitable container, mix well, and adjust the pH to 3.5 with phosphoric acid. Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter. Degas the mobile phase just before its introduction into the chromatographic system.

(ii) *Preparation of standard solution.* Dissolve an accurately weighed portion of the clarithromycin working standard in sufficient methanol to obtain a solution having a known concentration of approximately 2.1 milligrams per milliliter of clarithromycin. Quantitatively transfer and dilute an aliquot of this solution with mobile phase and mix to obtain a solution of known