

acid salt of erythromycin or a mixture of two or more such salts. It is freely soluble in water, alcohol, and methyl alcohol. It is slightly soluble in acetone and chloroform, but is practically insoluble in ether. It is so purified and dried that:

(i) It contains not less than 600 micrograms of erythromycin per milligram, calculated on an anhydrous basis. If it is packaged for dispensing, its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of erythromycin that it is represented to contain.

(ii) It is sterile.

(iii) [Reserved]

(iv) It is nonpyrogenic.

(v) Its moisture content is not more than 5.0 percent.

(vi) Its pH in an aqueous solution containing 25 milligrams per milliliter is not less than 6.0 nor more than 8.0.

(vii) It gives a positive identity test for erythromycin gluceptate.

(2) [Reserved]

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

(4) *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 the batch for potency, sterility, pyrogens, moisture, pH, and identity.

(ii) Samples required:

(a) If the batch is packaged for repackaging or for use as an ingredient in the manufacture of another drug:

(1) For all tests except sterility: 10 packages, each containing not less than 300 milligrams.

(2) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 12 immediate containers of the batch.

(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 § 436.105 of this chapter, preparing the sample for assay as follows: If the batch is pack-

aged for repackaging or for use in manufacturing another drug, dissolve an accurately weighed sample in sufficient methyl alcohol to give a concentration of 10 milligrams of erythromycin base per milliliter (estimated). Dilute this solution further with sufficient 0.1M potassium phosphate buffer, pH 8.0 (solution 3), to give a stock solution containing 1.0 milligram of erythromycin base per milliliter (estimated). If it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents 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 with solution 3 to give a stock solution of convenient concentration. Further dilute the stock solution with solution 3 to the reference concentration of 1.0 microgram of erythromycin base per milliliter (estimated).

(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 30 milligrams of erythromycin per milliliter.

(4) [Reserved]

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

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using a concentration of 25 milligrams per milliliter.

(7) *Identity.* Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(2) of that section.

[39 FR 19149, May 30, 1974, as amended at 46 FR 16685, Mar. 13, 1981; 50 FR 19920, 19921, May 13, 1985]

§ 452.32a Sterile erythromycin lactobionate.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Erythromycin lactobionate is the white to off-white powder of the lactobionate salt of erythromycin or a mixture of two or more such salts. It is so purified and dried that:

(i) If the erythromycin lactobionate is not packaged for dispensing, its erythromycin potency is not less than 525 micrograms of erythromycin per milligram on an anhydrous basis. If the erythromycin lactobionate is packaged for dispensing, its erythromycin potency is not less than 525 micrograms of erythromycin per milligram on an anhydrous basis and also, each container contains not less than 90 percent and not more than 120 percent of the number of milligrams of erythromycin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) Its moisture content is not more than 5.0 percent.

(v) Its pH is not less than 6.5 and not more than 7.5.

(vi) Its residue on ignition is not more than 2.0 percent.

(vii) Its heavy metals content is not more than 50 parts per million.

(viii) 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 the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, residue on ignition, heavy metals, and identity.

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

(a) If the batch is packaged for re-packing or for use as an ingredient in the manufacture of another drug:

(1) For all tests except sterility: A minimum of 12 immediate containers.

(2) For sterility testing: 20 packages, each containing equal portions of approximately 300 milligrams.

(b) If the batch is packaged for dispensing:

(1) For all tests except sterility: A minimum of 12 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 § 436.105 of this chapter, preparing the sample for assay as follows:

(i) *Product not packaged for dispensing (micrograms of erythromycin per milligram).* Dissolve an accurately weighed sample with sufficient methyl alcohol to obtain a concentration of 10 milligrams of erythromycin base per milliliter (estimated). Further dilute an aliquot of this solution 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).

(ii) *Product packaged for dispensing.* Determine both micrograms of erythromycin per milligram of sample and milligrams of erythromycin per container. Use separate containers for preparation of each sample solution as described in paragraph (b)(1)(ii)(a) and (b) of this section.

(a) *Micrograms of erythromycin per milligram.* Dissolve an accurately weighed sample with sufficient methyl alcohol to obtain a concentration of 10 milligrams of erythromycin base per milliliter (estimated). Further dilute an aliquot of this solution 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).

(b) *Milligrams of erythromycin per container.* Reconstitute the sample as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all of the withdrawable contents 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 an aliquot of the solution thus obtained with sterile distilled water to obtain a concentration of 10 milligrams of erythromycin base per milliliter (estimated). Further dilute an aliquot of this solution 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) *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 30 milligrams of erythromycin per milliliter.

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

(5) *pH*. Proceed as directed in § 436.202 of this chapter, using a concentration of 50 milligrams of erythromycin per milliliter.

(6) *Residue on ignition*. Proceed as directed in § 436.207(a) of this chapter.

(7) *Heavy metals*. Proceed as directed in § 436.208 of this chapter.

(8) *Identity*. Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(3) of that section.

[51 FR 35215, Oct. 2, 1986, as amended at 55 FR 11584, Mar. 29, 1990]

§ 452.35 Erythromycin stearate.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Erythromycin stearate is the odorless, white or slightly yellow powder of the stearic acid salt of erythromycin. It is practically insoluble in water but is soluble in alcohol, methyl alcohol, chloroform, and ether. It is so purified and dried that:

(i) It contains not less than 550 micrograms of erythromycin per milligram, calculated on an anhydrous basis.

(ii) [Reserved]

(iii) Its moisture content is not more than 4.0 percent.

(iv) Its pH is not less than 6.0 and not more than 11.0.

(v) Its residue on ignition is not more than 1.0 percent.

(vi) It gives positive identity tests for erythromycin stearate.

(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 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 residue on ignition, identity, and crystallinity.

(ii) Samples required: A minimum of 10 containers, each consisting of 500 milligrams.

(b) *Tests and methods of assay—(1) Potency*. Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient methyl alcohol to give a concentration of 1 milligram of erythromycin base per milliliter (estimated). 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) [Reserved]

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

(4) *pH*. Proceed as directed in § 436.202 of this chapter, using a 1 percent slurry of erythromycin stearate in water.

(5) *Residue on ignition*. Proceed as directed in § 436.207(a) of this chapter.

(6) *Identity*. Proceed as directed in § 436.211 of this chapter, using the sample preparation method described in paragraph (b)(2) of that section.

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

[39 FR 19149, May 30, 1974, as amended at 50 FR 19920, 19921, May 13, 1985]

§ 452.50 Clarithromycin.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Clarithromycin is 6-O-methylerythromycin A. It is so purified and dried that:

(i) Its potency is not less than 960 micrograms of clarithromycin activity per milligram, on an anhydrous basis.

(ii) Its moisture content is not more than 2.0 percent.

(iii) The pH of a 0.2 percent (weight per volume) slurry in aqueous methanol (95:5) is not less than 7.5 and not more than 10.0.

(iv) Its residue on ignition is not more than 0.3 percent.

(v) Its heavy metals content is not more than 20 parts per million.

(vi) Its specific rotation in chloroform containing 10 milligrams of clarithromycin per milliliter at 20 °C is between -89° and -95°, calculated on an anhydrous basis.

(vii) It gives a positive identity test.

(viii) It is crystalline.

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