

glass blender jar with sufficient distilled water to obtain a stock solution of convenient concentration. Blend for 3 to 5 minutes. Further dilute an aliquot of the stock solution with 0.1M potassium phosphate buffer, pH 4.5 (solution 4) to the reference concentration of 10 micrograms of vancomycin per milliliter (estimated).

(2) *Moisture*. Proceed as directed in § 436.201 of this chapter, using the titration procedure described in paragraph (e)(1) of that section, except:

(i) Remove gelatin coating before grinding the capsules; and

(ii) Use solvent C in lieu of solvent A.

(3) *Dissolution*. Proceed as directed in § 436.215 of this chapter. The quantity *Q* (the amount of vancomycin dissolved) is 85 percent within 45 minutes.

[51 FR 22072, June 18, 1986, as amended at 55 FR 11585, Mar. 29, 1990]

§ 455.188 Rifabutin capsules.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity*. Rifabutin capsules are gelatin capsules containing rifabutin with a suitable and harmless filler and with or without binders, lubricants, and stabilizers. Each capsule contains rifabutin equivalent to 150 milligrams of rifabutin. Its rifabutin content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of rifabutin that it is represented to contain. Its content of the four major related substances detected by high-performance liquid chromatography (HPLC) is not more than 1.0 percent each. All other unknown related substances are not more than 0.5 percent. The total of all related substances is not more than 4.5 percent. It passes the dissolution test if the quantity (*Q*) dissolved is 75 percent at 45 minutes. It passes the identity test. The rifabutin used conforms to the standards prescribed by § 455.88(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 rifabutin used in making the batch for potency, related substances, moisture, *N*-isobutylpiperidone, and identity.

(B) The batch for content, related substances, dissolution, and identity.

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

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

(B) The batch: A minimum of 30 capsules.

(b) *Tests and methods of assay—(1) Rifabutin content*. Proceed as directed in § 455.88(b)(1), preparing the sample solution and calculating the rifabutin content as follows:

(i) *Preparation of sample solution*. Empty 20 capsules, collecting the contents quantitatively. Weigh the powder and determine the average capsule fill weight. Mix the powder and accurately weigh a portion containing the equivalent of about 25 milligrams of rifabutin into a 50-milliliter volumetric flask. Add 5 milliliters of acetonitrile. Dilute to volume with mobile phase and mix to yield a solution containing 0.5 milligram of rifabutin per milliliter (estimated). Filter through a suitable filter capable of removing particulate matter 0.5 micron in diameter prior to injection into the chromatographic system.

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

$$\text{Milligrams of rifabutin per capsule} = \frac{A_U \times C_S \times P_S \times W_a}{A_S \times C_U \times 1,000}$$

where:

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

A_S = Area of the rifabutin peak in the chromatogram of the rifabutin working standard;

C_S = Milligrams of rifabutin working standard per milliliter of standard solution;

C_U = Milligrams of sample per milliliter of sample solution;

P_S = Rifabutin activity in the rifabutin working standard solution in micrograms per milliliter; and

W_a = Average capsule fill weight in milligrams.

(2) *Related substances.* Proceed as directed in paragraph (b)(1) of this section for rifabutin content using the sample prepared as described in paragraph (b)(1)(i) of this section and calculating the amounts of related substances as follows.

(i) *Calculations.* Calculate the percentage of related substances as follows:

$$\text{Percent individual HPLC - related substance} = \frac{A_i \times 100}{A_t}$$

$$\text{Percent total HPLC - related substances} = \frac{A \times 100}{A_t}$$

where:

A_i = Area of the individual related substance peak;

A = The sum of areas of all peaks minus the area due to the rifabutin peak and solvent front peak; and

A_t = The sum of areas of all peaks in the chromatogram excluding the solvent peak.

(ii) [Reserved]

(3) *Dissolution test.* Proceed as directed in §436.215 of this chapter. The quantity (Q) (the amount of rifabutin activity dissolved) is 75 percent within 45 minutes.

(4) *Identity.* (i) The retention time of the rifabutin response in the HPLC procedure described in paragraph (b)(1) of this section as applied to the sample solution compares qualitatively to that of the rifabutin reference standard.

(ii) The identity of rifabutin capsules is also confirmed by the spectrophotometric identity test described in §436.370 of this chapter.

[59 FR 40808, Aug. 10, 1994]

Subpart C—Injectable Dosage Forms

§ 455.204 Aztreonam injectable dosage forms.

§ 455.204a Aztreonam for injection.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Aztreonam for injection is a dry mixture of aztreonam and arginine. Its potency is satisfactory if each mil-

ligram of aztreonam for injection contains not less than 900 micrograms and not more than 1,050 micrograms of aztreonam when corrected for arginine content and moisture content. Its aztreonam immediate container fill (content) is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of aztreonam that it is represented to contain. It is sterile. It is nonpyrogenic. Its moisture content is not more than 2.0 percent. Its pH in an aqueous solution containing 100 milligrams of aztreonam per milliliter is not less than 4.5 and not more than 7.5. The aztreonam used conforms to the standards prescribed by §455.4a(a)(1), except if the aztreonam for injection is manufactured by lyophilization, in which case the aztreonam need not be sterile.

(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 aztreonam used in making the batch for potency, sterility, pyrogens, moisture, residue on ignition, heavy metals, and identity. If the aztreonam for injection is made by lyophilization, the aztreonam need not be tested for sterility.

(b) The batch for aztreonam potency, aztreonam content, sterility, pyrogens, moisture, and pH.

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

(a) The aztreonam used in making the batch: 10 packages, each containing approximately 500 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 and content.* Determine both micrograms of aztreonam per milligram of sample and milligrams of aztreonam per container. Proceed as