

§ 455.204b

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

$A_s$ =Area of the aztreonam peak in the chromatogram of the working standard;

$P_s$ =Aztreonam activity in the working standard solution in micrograms per milliliter; and

$C_u$ =Milligrams of sample per milliliter of sample solution.

(2) Calculate the micrograms of arginine per milligram as follows:

$$\frac{\text{Micrograms of arginine}}{\text{per milligram}} = \frac{A_u \times P_s}{A_s \times C_u}$$

$$\frac{\text{Micrograms of aztreonam per milligram (corrected)}}{\text{Micrograms of aztreonam per milligram (uncorrected)} \times 1,000} = \frac{1,000 - [\text{Micrograms of arginine per milligram} + (\text{Percent moisture}) \times 10]}{1,000 - [\text{Micrograms of arginine per milligram} + (\text{Percent moisture}) \times 10]}$$

(b) *Content (milligrams of aztreonam per container)*. Calculate the aztreonam content of the container as follows:

$$\frac{\text{Milligrams of aztreonam}}{\text{per container}} = \frac{A_u \times P_s \times d}{A_s \times 1,000}$$

where:

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

$A_s$ =Area of the aztreonam peak in the chromatogram of the working standard;

$P_s$ =Aztreonam activity in the aztreonam working standard solution in micrograms per milliliter; and

$d$ =Dilution factor of the sample.

(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 50 milligrams of aztreonam 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 an aqueous solu-

where:

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

$A_s$ =Area of the arginine peak in the chromatogram of the working standard;

$P_s$ =Arginine activity in the working standard solution in micrograms per milliliter; and

$C_u$ =Milligrams of sample per milliliter of sample solution.

(3) Calculate the micrograms of aztreonam per milligram (corrected) as follows:

tion containing 100 milligrams of aztreonam per milliliter.

[52 FR 4615, Feb. 13, 1987; 52 FR 8550, Mar. 18, 1987. Redesignated at 54 FR 40385, Oct. 2, 1989, and amended at 54 FR 41824, Oct. 12, 1989; 55 FR 11585, Mar. 29, 1990]

**§ 455.204b Aztreonam injection.**

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Aztreonam injection is a frozen aqueous iso-osmotic solution of aztreonam and arginine. Each milliliter contains aztreonam equivalent to either 10 milligrams, 20 milligrams, or 40 milligrams. Its aztreonam 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 pH is not less than 4.5 and not more than 7.5. It passes the identity test. The aztreonam used conforms to the standards prescribed by §455.4(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 aztreonam used in making the batch for potency, moisture, residue on ignition, heavy metals, and identity.

(B) The batch for aztreonam potency, sterility, pyrogens, pH, and identity.

(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.* Thaw the sample as directed in the labeling. The sample solution used for testing must be at room temperature.

(1) *Potency.* Proceed as directed in §436.361 of this chapter, except in addition to the column described in paragraph (a)(4) of that section, use a 5- to 50-centimeter saturator column having an inside diameter of 2 to 4.6 millimeters and packed with approximately 37 micrometer silica, and use the resolution test solution to determine resolution in lieu of the working standard solution. Perform the assay at ambient temperature, using an ultraviolet detection system operating a wavelength of 206 nanometers, and a column packed with Chromegabond Diol (dihydroxypropane chemically bonded to porous silica), 5 to 10 micrometers or equivalent. Mobile phase, working standard solution, sample solution, resolution test solution, system suitability requirements, and calculations as follows:

(i) *Mobile phase.* Acetonitrile: 0.01M pH 2.0 ammonium phosphate (75:25). Transfer 1.15 grams of ammonium phosphate monobasic to a 1-liter volumetric flask. Add about 800 milliliters of distilled water and sonicate to aid dissolution. Adjust the solution to pH 2.0 with *o*-phosphoric acid, 85 percent. Dilute the solution to volume with distilled water and mix well. Transfer about 250 milliliters of this solution and 750 milliliters of acetonitrile to a suitable-sized container and mix well. Filter the mobile phase through a suitable glass fiber 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.* Transfer approximately 25 milligrams each of the aztreonam working standard and the arginine working standard, accurately weighed, to a 25-milliliter volumetric flask. Dissolve and dilute to volume with mobile phase (primary working standard solution). Further dilute with mobile phase to obtain a solution containing 0.2 milligram of aztreonam per milliliter.

(B) *Sample solution.* Using a suitable hypodermic needle and syringe, remove an accurately measured representative portion from each container and dilute with sufficient mobile phase to obtain a solution containing 0.2 milligram of aztreonam per milliliter (estimated).

(C) *Resolution test solution.* Dissolve 10 milligrams of open ring aztreonam, 2-[[[(2-amino-4-thiazoly)](1-carboxy-1-methylethoxy)imino]acetyl]amino]-3-(sulfoamino)-butanoic acid, in 10.0 milliliters of primary standard solution. Further dilute 5 milliliters of this solution to 25.0 milliliters with mobile phase.

(iii) *System suitability requirements—(A) Tailing factor.* The tailing factor (*T*) of the aztreonam peak is satisfactory if it is not more than 2 at 5 percent of peak height.

(B) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 1,000 theoretical plates.

(C) *Resolution.* The resolution (*R*) between the aztreonam peak and open ring aztreonam is satisfactory if it is not less than 2.0.

(D) *Coefficient of variation.* 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.

If the system suitability requirements have been met, then proceed as described in §436.361(b) of this chapter. Alternative chromatographic conditions are acceptable, provided reproducibility and resolution are comparable to the system. However, the

sample preparation described in paragraph (b)(1)(ii)(B) of this section should not be changed.

(iv) *Calculations*: Calculate the milligrams of aztreonam per milliliter of sample as follows:

$$\text{Milligrams of aztreonam per milliliter} = \frac{A_u \times P_s \times d}{A_s \times 1,000}$$

where:

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

$A_s$ =Area of the aztreonam peak in the chromatogram of the working standard;

$P_s$ =Aztreonam activity in the aztreonam working standard solution in micrograms per milliliter; and

$d$ =Dilution factor of the sample.

(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, except inject a sufficient volume of the undiluted solution to deliver 50 milligrams of aztreonam per kilogram.

(4) *pH*. Proceed as directed in § 436.202 of this chapter, using the undiluted solution.

(5) *Identity*. The high-performance liquid chromatogram of the sample is determined as directed in paragraph (b)(1) of this section compares qualitatively to that of the aztreonam working standard.

[54 FR 40385, Oct. 2, 1989]

**§ 455.210 Chloramphenicol injection.**

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity*. Chloramphenicol injection is chloramphenicol, with or without one or more suitable and harmless buffer substances, dissolved in one or more suitable and harmless solvents. Each milliliter contains 250 milligrams of chloramphenicol. Its potency is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of milligrams of chloramphenicol that it is represented to contain. It is sterile. It is nonpyrogenic. Its pH is not less than 4.7 and not more than 5.0. The chloramphenicol used conforms to

the standards prescribed by § 455.10a(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 chloramphenicol used in making the batch for potency, pH, specific rotation, melting range, absorptivity, and crystallinity.

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

(ii) Samples required:

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

(b) The batch:

(1) For all tests except sterility: A minimum of eight 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 § 436.106 of this chapter, preparing the sample for assay as follows: Dilute an accurately measured representative portion of the sample in sufficient distilled water to obtain a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with distilled water to the reference concentration of 2.5 micrograms of chloramphenicol 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, except add the contents of each container directly to the dry filter, thus eliminating the preliminary solubilization step.

(3) *Pyrogens*. Proceed as directed in § 436.32(a) of this chapter, using a solution containing 5 milligrams per milliliter.

(4)–(5) [Reserved]

(6) *pH*. Proceed as directed in § 436.202 of this chapter, using the undiluted drug.

[39 FR 19166, May 30, 1974, as amended at 45 FR 64568, Sept. 30, 1980; 48 FR 3961, Jan. 28, 1983; 48 FR 7440, Feb. 22, 1983; 50 FR 19921, May 13, 1985]