

analysis, add 10 milliliters of 0.9 percent saline solution and 1 milliliter of 0.1 percent bicarbonate solution. Add phosphate buffer, 0.001M, and shake until dissolved. Sonicate, if necessary, but for no longer than 1 minute. Dilute to volume with phosphate buffer, 0.001M, to obtain a solution containing approximately 500 micrograms of imipenem per milliliter. Mix well and inject immediately.

(b) *Sample solution.* Dissolve an accurately weighed portion (approximately 25 milligrams) of the sample with 10 milliliters of 0.9 percent saline solution and 1 milliliter of 0.1 percent bicarbonate solution in a 50-milliliter volumetric flask. Dilute the sample solution to volume with phosphate buffer, 0.001M, to obtain a solution containing 500 micrograms of imipenem per milliliter (estimated).

(iii) *System suitability requirements—*

(a) *Tailing factor.* The tailing factor (*T*) is satisfactory if it is not more than 1.5 at 10 percent of peak height in lieu of 5 percent of peak height.

(b) *Efficiency of the column.* The efficiency of the column (*n*) is satisfactory if it is greater than 600 theoretical plates for a 30-centimeter column.

(c) *Resolution.* The resolution (*R*) between the peaks for thienamycin and imipenem is satisfactory if it is not less than 2.0.

(d) *Coefficient of variation (relative standard deviation).* The coefficient of variation (*S_R* 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 § 436.216(b) of this chapter. Alternate 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 micrograms of imipenem per milligram of sample as follows:

$$\frac{\text{Micrograms of imipenem per milligram}}{\text{milligram}} = \frac{A_u \times P_s \times 100}{A_s \times C_u \times (100 - L)}$$

where:

A_u=Area of the imipenem peak in the chromatogram of the sample (at a retention

time equal to that observed for the standard);

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

P_s=Anhydrous imipenem activity in the imipenem working standard solution in micrograms per milliliter;

C_u=Milligrams of sample per milliliter of sample solution; and

L=Percent loss on drying 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(a) of this chapter, using a solution containing 5.0 milligrams of imipenem per milliliter, except inject 10 milliliters per kilogram of rabbit weight.

(4) *Loss on drying.* Proceed as directed in § 436.200(i) of this chapter.

(5) *Specific rotation.* Dilute an accurately weighed sample with sufficient pH 7.0 phosphate buffer to give a concentration of approximately 5.0 milligrams of imipenem per milliliter. Proceed as directed in § 436.210 of this chapter, using a 1.0-decimeter polarimeter tube. To prepare the pH 7.0 phosphate buffer, transfer 5 grams of monobasic potassium phosphate and 11 grams of dibasic potassium phosphate to a 1.0-liter volumetric flask. Dissolve and dilute to volume with distilled water.

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

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

[51 FR 11573, Apr. 4, 1986; 51 FR 16517, May 5, 1986, as amended at 55 FR 11582, Mar. 29, 1990; 59 FR 8133, Feb. 18, 1994]

Subpart B—[Reserved]

Subpart C—Injectable Dosage Forms

§ 441.220 Imipenem monohydrate-cilastatin sodium injectable dosage forms.

§ 441.220a Sterile imipenem monohydrate-cilastatin sodium.

(a) *Requirements for certification—(1) Standards of identity, strength, quality, and purity.* Imipenem monohydrate-