Assay—

Mobile phase—Dissolve 5.76 g of sodium 1-pentanesulfonate in 2000 mL of water. Adjust with glacial acetic acid to a pH of 3.4, and then with potassium hydroxide TS to a pH of 4.0. Prepare a filtered and degassed mixture of this solution and acetonitrile (94:6). Make adjustments if necessar y (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Cefepime Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 1.4 mg per mL.

Assay preparation—Transfer about 70 mg of Cefepime Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 1500 theoretical plates; the tailing factor is not more than 1.7; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of cefepime ($C_{19}H_{24}N_6O_5S_2$) in each mg of Cefepime Hydrochloride taken by the formula:

$$50(CP/W)(r_U/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Cefepime Hydrochloride RS in the *Standard preparation; P* is the content, in µg per mg, of cefepime in USP Cefepime Hydrochloride RS; *W* is the weight, in mg, of Cefepime Hydrochloride taken to prepare the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Cefepime for Injection

» Cefepime for Injection is a sterile mixture of Cefepime Hydrochloride and Arginine. It contains the equivalent of not less than 90.0 per cent and not more than 115.0 per cent of the labeled amount of cefepime ($C_{19}H_{24}N_6O_5S_2$).

Packaging and storage—Preserve in tight, light-resistant *Containers for Sterile Solids* as described under *Injections* ⟨1⟩, and store in a refrigerator or at controlled room temperature. Store reconstituted powder in a refrigerator for no more than 7 days.

Labeling—Label it to indicate that it is to be diluted with a suitable parenteral vehicle prior to intravenous infusion.

USP Reference standards ⟨11⟩**—**
USP Cefepime Hydrochloride RS
USP Cefepime Hydrochloride System Suitability RS
This is a mixture of cefepime hydrochloride related compound A ([6 *R*-[6α,7β(*E*)]]-1-[[7-[[(2-amino-4-thiazolyl) (methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, monohydrochloride, monohydrate; ($C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$ ◊ 571.50); cefepime related compound B [6 *R-trans*]-7-[[[2-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-4-thiazolyl](methoxyimino)acetyl]amino]-3-(1-methylpyrrolidinium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, inner salt; ($C_{25}H_{29}N_9O_7S_3$ ◊ 663.75); and cefepime hydrochloride.
USP Endotoxin RS

Constituted solution—At the time of use, it meets the requirements for *Constituted Solutions* under *Injections* ⟨1⟩.

Identification—

A: *Thin-layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Prepare a solution having a concentration of about 40 mg of Cefepime for Injection per mL.

Standard solution: 20 mg of arginine per mL.

Developing solvent system: a mixture of *n*-propyl alcohol, water, and ammonium hydroxide (7:5:4).

Procedure—Proceed as directed in the chapter, except to spray the plate with ninhydrin TS. Arginine appears as a dark red spot. The intensity and the R_F value of the spot in the chromatogram of the *Test solution* correspond to those in the chromatogram of the *Standard solution.*

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Bacterial endotoxins ⟨85⟩**—**It contains not more than 0.06 USP Endotoxin Unit per mg of cefepime.

Sterility ⟨71⟩: meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined.*

Uniformity of dosage units ⟨905⟩: meets the requirements.

pH ⟨791⟩: between 4.0 and 6.0, in a solution containing about 100 mg of cefepime per mL.

Water, *Method I* ⟨921⟩: not more than 4.0%.

Limit of *N*-methylpyrrolidine—

Mobile phase, *Standard solution*, and *Chromatographic system*—Prepare as directed in the test for *Limit of N-methylpyrrolidine* under *Cefepime Hydrochloride*.

Test solution—Constitute one container of Cefepime for Injection with the volume of water specified in the labeling. Dilute an accurately measured volume of this solution with 0.05 N nitric acid to obtain a solution having a concentration of about 10 mg of cefepime per mL. [NOTE—Inject this solution immediately.]

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses for *N*-methylpyrrolidine. Calculate the per centage of *N*-methylpyrrolidine in the portion of Cefepime for Injection taken by the formula:

$$100(C/D)(r_U / r_S)$$

in which *C* is the concentration, in mg per mL, of *N*-methylpyrrolidine in the *Standard solution; D* is the concentration, in mg per mL, of cefepime in the *Test solution* based on the labeled quantity in the container and the extent of dilution; and r_U and r_S are the *N*-methylpyrrolidine peak responses obtained from the *Test solution* and the *Standard solution*, respectively: not more than 1.0% is found.

Related compounds—

Potassium phosphate solution, *Solution A*, *Solution B*, *Mobile phase*, *System suitability solution*, and *Chromatographic system*—Proceed as directed in the test for *Related compounds* under *Cefepime Hydrochloride*.

Test solution—Constitute one container of Cefepime for Injection with a volume of *Solution A* equivalent to the volume of solvent specified in the labeling, and shake to dissolve. T ransfer the constituted solution to a volumetric flask, and dilute with *Solution A* to obtain a solution having a concentration of about 2 mg of cefepime per mL. [NOTE—Inject this solution immediately, or store in a refrigerator and inject within 12 hours.]

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the per centage of each impu-

rity in the portion of Cefepime for Injection taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity; and r_s is the sum of the responses of all the peaks: not more than 0.5% each of cefepime related compound A and cefepime related compound B is found; and not more than 0.5% of any other impurity is found.

Other requirements—It meets the requirements for *Labeling* under *Injections* ⟨1⟩.

Assay—

Mobile phase, *Standard preparation*, and *Chromatographic system*—Proceed as directed in the *Assay* under *Cefepime Hydrochloride*.

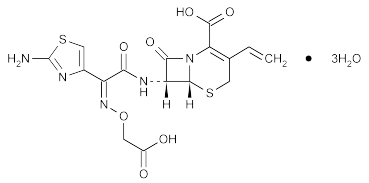
Assay preparation—Constitute one container of Cefepime for Injection with the volume of water specified in the labeling. Using a suitable hypodermic needle and syringe, withdraw the entire contents of the vial, and quantitatively dilute with *Mobile phase* to obtain a solution having a concentration of about 1 mg of cefepime per mL.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of cefepime ($C_{19}H_{24}N_6O_5S_2$) in the container of Cefepime for Injection taken by the formula:

$$0.001CD(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Cefepime Hydrochloride RS in the *Standard preparation; D* is the dilution factor used to prepare the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Cefixime



$C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$ 507.50

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)[(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-, trihydrate, [6*R*-[6α,7β(*Z*)]]-.

(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7 ²-(*Z*)-[*O*-(carboxymethyl)oxime]trihydrate [79350-37-1].

Anhydrous 453.46

» Cefixime contains the equivalent of not less than 950 µg and not more than 1030 µg of Cefixime ($C_{16}H_{15}N_5O_7S_2$) per mg, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.

Labeling—Label to indicate that it is the trihydrate form. Where the quantity of Cefixime is indicated in the labeling of any preparation containing Cefixime, this shall be understood to be in terms of anhydrous cefixime ($C_{16}H_{15}N_5O_7S_2$).

USP Reference standards ⟨11⟩**—**
USP Cefixime RS

Identification, *Infrared Absorption* ⟨197K⟩**—**Prepare the test specimen as follows. Dissolve about 5 mg of it by trituration in 2 mL of methanol and evaporate with the aid of gentle heat to dryness.

Specific rotation ⟨781S⟩: between −75° and −88°.

Test solution: 10 mg per mL, in sodium bicarbonate solution (2 in 100).

Crystallinity ⟨695⟩: meets the requirements.

pH ⟨791⟩: between 2.6 and 4.1, in a solution containing the equivalent of 0.7 mg of cefixime per mL.

Water, *Method I* ⟨921⟩: between 9.0% and 12.0%.

Chromatographic purity—

Tetrabutylammonium hydroxide solution, *Mobile phase*, *Monobasic potassium phosphate solution*, *pH 7.0 Phosphate Buffer*, *Resolution solution*, and *Chromatographic system*—Proceed as directed in the *Assay*.

Standard solution—Use the *Standard preparation* prepared as directed in the *Assay*.

Test solution—Use the *Assay preparation*.

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak areas. Calculate the per centage of each impurity in the portion of Cefixime taken by the formula:

$$0.1P(r_i / r_s)$$

in which P is the potency, in µg per mg, of cefixime calculated in the *Assay;* r_i is the peak area for each impurity; and r_s is the cefixime peak area: not more than 1.0% of any individual impurity is found; and not more than 2.0% of total impurities is found.

Assay—

Tetrabutylammonium hydroxide solution—Dilute 25 mL of 0.4 M tetrabutylammonium hydroxide solution with water to obtain 1000 mL of solution, and adjust with 1.5 M phosphoric acid to a pH of 6.5.

Mobile phase—Prepare a suitable filtered and degassed mixture of *Tetrabutylammonium hydroxide solution* and acetonitrile (3:1). Make adjustments if necessar y (see *System Suitability* under *Chromatography* ⟨621⟩).

Monobasic potassium phosphate solution—Dissolve 6.8 g of monobasic potassium phosphate in water to make 500 mL of solution.

pH 7.0 Phosphate Buffer—Dissolve 7.1 g of anhydrous dibasic sodium phosphate in water to make 500 mL of solution. Adjust a volume of this solution with a sufficient volume of *Monobasic potassium phosphate solution* to a pH of 7.0.

Resolution solution—Dissolve USP Cefixime RS in water to obtain a solution having a concentration of about 1 mg per mL. Heat this solution at 95 ° in an oil bath for 45 minutes, cool, and use promptly.

Standard preparation—Dissolve an accurately weighed quantity of USP Cefixime RS in *pH 7.0 Phosphate buffer* to obtain a solution having a known concentration of about 0.2 mg of cefixime ($C_{16}H_{15}N_5O_7S_2$) per mL. Use this solution promptly.

Assay preparation—Transfer about 110 mg of Cefixime, accurately weighed, to a 100-mL volumetric flask, dilute with *pH 7.0 Phosphate buffer* to volume, and mix. T ransfer 10.0 mL of this solution to a 50-mL volumetric flask, dilute with *pH 7.0 Phosphate buffer* to volume, and mix. Use this solution promptly.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 12.5-cm column containing 4- µm packing L1. The flow rate is adjusted so that the retention time of cefixime is about 10 minutes. The column is maintained at a constant temperature of about 40 °. Chromatograph the *Resolution solution,* and record the peak areas as directed for *Procedure:* the relative retention times are about 0.9 for cefixime (*E*)-isomer and 1.0 for cefixime; and the resolution, *R,* between cefixime and cefixime (*E*)-isomer is not less than 2.0. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Pro-*