Table 2 *(Continued)*

Name	Relative Retention Time	Relative Response Factor	Reporting Threshold (% Cefdinir)	Acceptance Criteria, NMT (%)
7*S*-Cefdinir[f]	1.18	1.1	0.05	0.2
Cefdinir lactone[j]	1.23	1.2	0.05	0.8
Cefdinir related compound B[k]	1.28	1.1	0.05	0.2
Cefdinir isoxazole analog[l]	1.37	1.4	0.05	0.5
Cefdinir impurity 2[e]	1.44	1.0	0.05	0.2
Cefdinir glyoxalic analog[m]	1.49	1.0	0.05	0.2
E-Cefdinir[n]	1.51	1.1	0.05	1.2
Cefdinir decarboxy open ring lactone a[o,p]	1.62	1.3	0.05	1.1
Cefdinir decarboxy open ring lactone b[o,p]	1.64	1.3	0.05	
Cefdinir impurity 3[e]	1.82	1.0	0.05	0.2
Individual unidentified impurities	—	1.0	0.05	0.2
Total impurities	—	—	—	6.2

[a] *N*-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetyl]glycine.
[b] (*Z*)-2-(2-Aminothiazol-4-yl)-*N*-(2,2-dihydroxyethyl)-2-(hydroxyimino)acetamide.
[c] (6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-5,8-dioxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[d] (*R*,*Z*)-2-{(*R*)-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido](carboxy)methyl}-5-ethylidene-5,6-dihydro-2*H*-1,3-thiazine-4-carboxylic acid.
[e] (6*R*,7*R*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[f] Cefdinir impurity 1, cefdinir impurity 2, and cefdinir impurity 3 are unidentified impurities.
[g] Cefdinir related compound A is a mixture of 4 isomers labeled cefdinir open ring lactones a, b, c, and d. The sum of the values is reported; the limit for the sum of the 4 isomers is 3.3%.
[h] 2(*R*)-2-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-2-[(2*RS*,5*RS*)-5-methyl-7-oxo-2,4,5,7-tetrahydro-1*H*-furo[3,4-*d*][1,3]thiazin-2-yl]acetic acid.
[i] (6*R*,7*S*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[j] (*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)-*N*-((3*RS*,5a*R*,6*R*)-3-methyl-1,7-dioxo-1,3,4,5*a*,6,7-hexahydroazeto[2,1-*b*]furo[3,4-*d*][1,3]thiazin-6-yl)acetamide.
[k] (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[l] (6*R*,7*R*)-7-(4-Hydroxyisoxazole-3-carboxamido)-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[m] (6*R*,7*R*)-7-[2-(2-Aminothiazol-4-yl)-2-oxoacetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[n] (6*R*,7*R*)-7-[(*E*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.
[o] Cefdinir decarboxy open ring lactone is a mixture of 2 isomers labeled cefdinir decarboxy open ring lactone a and b. The sum of the values is reported; the limit for the sum of the 2 isomers is 1.1%.
[p] (*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)-*N*-{[(2*RS*,5*RS*)-5-methyl-7-oxo-2,4,5,7-tetrahydro-1*H*-furo[3,4-*d*][1,3]thiazin-2-yl]methyl}acetamide.

▲*USP35*

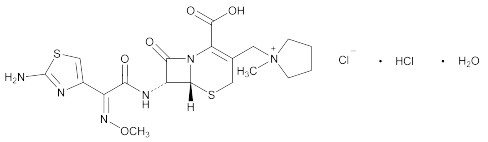
SPECIFIC TESTS
- **pH** ⟨**791**⟩**:** 3.5–4.5

Delete the following:

▲• **Loss on Drying** ⟨**731**⟩**:** Dry about 1 g over phosphorous pentoxide in a vacuum not exceeding 5 mm of mer cury at 70° for 4–4.5 h: it loses NMT 1.0% of its weight. ▲*USP35*

ADDITIONAL REQUIREMENTS
- **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at controlled room temperature.
- **Labeling:** The label specifies the directions for the constitution of the powder and states the equivalent amount of $C_{14}H_{13}N_5O_5S_2$ in a given volume of Cefdinir for Oral Suspension after constitution.
- **USP Reference Standards** ⟨**11**⟩
  USP Cefdinir RS
  USP Cefdinir Related Compound A RS
  (2*R*)-2-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(hydroxyimino)acetamido]-2-[(2*RS*,5*RS*)-5-methyl-7-oxo-2,4,5,7-tetrahydro-1*H*-furo[3,4-*d*][1,3]thiazin-2-yl]acetic acid
  (three other stereoisomers are also present in this RS).
  $C_{14}H_{15}N_5O_6S_2$ 413.43
  USP Cefdinir Related Compound B RS
  (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)acetamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo](4.2.0)]oct-2-ene-2-carboxylic acid.
  $C_{14}H_{13}N_4O_4S_2$ 365.41

Cefepime Hydrochloride



$C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$ 571.50
Pyrrolidinium, 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-methyl-, chloride, monohydrochloride, monohydrate, [6*R*-[6α,7β(*Z*)]]-.
1-[[(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methylpyrrolidinium chloride, 7 [2-(*Z*)-(*O*-methyloxime), monohydrochloride, monohydrate [123171-59-5].

» Cefepime Hydrochloride contains the equivalent of not less than 825 µg and not more than 911 µg of cefepime ($C_{19}H_{24}N_6O_5S_2$) per mg, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight, light-resistant containers, and store at controlled room temperature.

Labeling—Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

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

Identification, *Infrared Absorption* ⟨197M⟩**.**

Test specimen—Proceed as directed in the chapter, but do not dry.

Crystallinity ⟨695⟩**:** meets the requirements.

Bacterial endotoxins ⟨85⟩**—**Where the label states that Cefepime Hydrochloride is sterile or that it must be subjected to further processing during the preparation of injectable dosage forms, it contains not more than 0.04 USP Endotoxin Unit per mg of cefepime hydrochloride.

Water, *Method I* ⟨921⟩**:** between 3.0% and 4.5%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Limit of *N*-methylpyrrolidine—

Mobile phase—Prepare a filtered and degassed mixture of 0.01 N nitric acid and acetonitrile (100:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Column rinse solution—Transfer 5.0 mL of nitric acid to a 1-L volumetric flask. Dilute with water to volume, and mix. Transfer this solution to an appropriate flask, add 1 L of acetonitrile, and mix.

Standard solution—Transfer about 0.16 mL of *N*-methylpyrrolidine, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Transfer 4.0 mL of this solution to a 100-mL volumetric flask, dilute with 0.01 N nitric acid to volume, and mix. This solution contains about 0.05 mg of *N*-methylpyrrolidine per mL.

Test solution—Transfer about 100 mg of Cefepime Hydrochloride, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with 0.01 N nitric acid to volume, and mix. [NOTE—This solution may be kept up to 6 hours if maintained at 5°; otherwise, use this solution within 30 minutes.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a conductivity detector and a 4.6-mm × 5-cm column that contains 5- µm packing L52. It is recommended that a 4.6-mm × 5-cm guard column containing packing L17 be placed between the pump and the injector. The flow rate is about 1 mL per minute. The typical background conductance is about 3500 µS. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention time of *N*-methylpyrrolidine is not less than 8 minutes, and the relative standard deviation for replicate injections is not more than 5.0%.

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 percentage of *N*-methylpyrrolidine in the portion of Cefepime Hydrochloride taken by the formula:

$$1000(C/W)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of *N*-methylpyrrolidine in the *Standard solution; W* is the quantity, in mg, of Cefepime Hydrochloride taken to prepare the *Test solution;* 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 0.3% is found. [NOTE—Cefepime from the *Test solution* elutes as a broad peak at about 55 minutes. To minimize equilibration time at the start of the next day, it is recommended that the detector be turned on the night before and that *Mobile phase* be pumped through the system overnight at a flow rate of 0.2 mL per minute. After every *Test solution* injection, it is recommended that the chromatograph be flushed with *Column rinse solution* for 30 minutes at a flow rate of 1 mL per minute to remove cefepime from the column; and that the system then be switched back to *Mobile phase* at a flow rate of 1 mL per minute for reequilibration.]

Related compounds—

Potassium phosphate solution—Dissolve 0.68 g of monobasic potassium phosphate in 1000 mL of water.

Solution A—Prepare a mixture of *Potassium phosphate solution* and acetonitrile (9:1). Adjust with potassium hydroxide or phosphoric acid to a pH of 5.0, filter, and degas.

Solution B—Prepare a mixture of *Potassium phosphate solution* and acetonitrile (1:1). Adjust with potassium hydroxide or phosphoric acid to a pH of 5.0, filter, and degas.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Prepare a solution of USP Cefepime Hydrochloride System Suitability RS in *Solution A* containing about 1.4 mg per mL.

Test solution—Transfer about 70 mg of Cefepime Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Solution A* to volume, sonicate, and mix. [NOTE—Inject this solution immediately, or store in a refrigerator and inject within 12 hours.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5- µm packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–10	100	0	isocratic
10–30	100→50	0→50	linear gradient
30–35	50	50	isocratic
35–36	50→100	50→0	linear gradient

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cefepime and cefepime related compound A is not less than 5 and between cefepime related compound A and cefepime related compound B is not less than 10. Chromatograph the *Test solution,* and record the peak responses as directed for *Procedure:* the capacity factor, *k′,* is more than 0.6; the column efficiency is not less than 4000 theoretical plates; and the tailing factor is not more than 1.5. [NOTE—For the purpose of identification, the relative retention times are about 1.0 for cefepime, 2.7 for cefepime related compound A, and about 4.3 for cefepime related compound B.]

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Cefepime Hydrochloride 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 for all the peaks: not more than 0.3% of cefepime related compound A is found; not more than 0.2% of cefepime related compound B is found; and not more than 0.1% of any other impurity is found.

Other requirements—Where the label states that Cefepime Hydrochloride is sterile, it meets the requirements for *Sterility* under *Cefepime for Injection.*

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-