World Health Organization

CEFIDEROCOL SULFATE TOSILATE

(CEFIDEROCOLI SULFAS TOSILATUM)

Draft proposal for inclusion in *The International Pharmacopoeia*

(09 December 2025)

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For any technical questions, you may contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to **Ms Sinéad Jones** (jonessi@who.int, nsp@who.int).
Comments should be submitted through the online platform on or by **09 February 2026**. Please note that only comments received by this deadline will be considered for the preparation of this document.
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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/24.967

CEFIDEROCOL SULFATE TOSILATE
(CEFIDEROCOLI SULFAS TOSILATUM)

Description	Date
Drafting of the monograph by the Secretariat based on information received from manufacturers and found in the public domain.	July 2024
Draft monograph sent out for public consultation.	July to August 2025
Presentation to the 58th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2025
Draft monograph sent out for public consultation	December 2025 to February 2026
Further follow-up action as required.	

*[**Note from the Secretariat.** The monograph on Cefiderocol sulfate tosilate is proposed for inclusion in* The International Pharmacopoeia*.*

Being one of the first public standards, the monographs on Cefiderocol sulfate tosilate and Cefiderocol powder for concentrate for solution for infusion are expected to play an important role in ensuring access to safe, effective and quality-assured essential medicines. Manufacturers, regulatory authorities, procurement agencies and other stakeholders are therefore invited to provide their feedback on the proposed specifications and analytical procedures.

The draft monograph is based on information and samples received from a manufacturer, found in the public domain and on laboratory investigations.

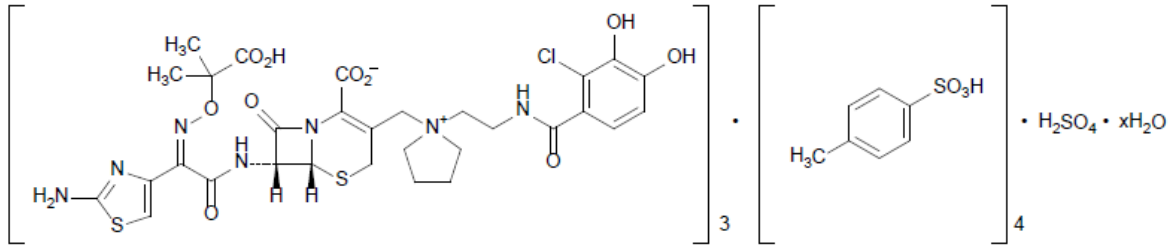
Draft monographs are subject to change.]

CEFIDEROCOL SULFATE TOSILATE

Molecular formula. $3C_{30}H_{34}ClN_7O_{10}S_2 \cdot 4C_7H_8O_3S \cdot H_2SO_4 \cdot xH_2O$

Relative molecular mass. 3043.50 (anhydrous cefiderocol sulfate tosilate), 752.21 (cefiderocol base)

Graphic formula.



Chemical names. Tris[(6*R*,7*R*)-7-[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetamido]-3-({1-[2-(2-chloro-3,4-dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate] tetrakis(4-methylbenzenesulfonate) monosulfate hydrate (*IUPAC*).

CAS Registry Number. 2009350-94-9 (anhydrous substance), 2135543-94-9 (hydrate)

Description. A white to slightly yellow powder.

Solubility. It is freely soluble in methanol R, slightly soluble in water R and dehydrated ethanol R and practically insoluble in acetonitrile R.

Category. Antibacterial (reserve group antibiotic).

Storage. Cefiderocol sulfate tosilate should be kept in tightly closed containers, protected from light and below -15 °C.

Additional information. Cefiderocol sulfate tosylate is a mixed salt of cefidericol base and two acids, namely 4-toluene sulfonic acid and sulfuric acid. The nominal molar ratio of cefiderocol base to 4-toluene sulfonic acid to sulfuric acid in the salt is 3:4:1, but the substance may contain an excess of sulfuric acid.

Cefiderocol sulfate tosylate is hygroscopic, sensitive to hydrolysis and may show polymorphism.

Requirements

Manufacture. The production method is validated to demonstrate that genotoxic impurities of 4-toluenesulfonic acid are adequately controlled in the final product.

Definition. Cefiderocol sulfate tosilate contains not less than 96.0 % and not more than 104.0 % of $3C_{30}H_{34}ClN_7O_{10}S_2 \cdot 4C_7H_8O_3S \cdot H_2SO_4$, calculated with reference to the anhydrous substance.**Identity tests**

- Either tests A and F, or tests B and F, or any two of tests C, D and E together with test F, may be applied.

A. Carry out the test as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from cefiderocol sulfate tosilate RS or with the reference spectrum of cefiderocol sulfate tosilate.

If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and cefiderocol sulfate tosilate RS in a small amount of methanol R. Evaporate to dryness and record new spectra using the residues. The infrared absorption spectrum is concordant with the spectrum obtained from cefiderocol sulfate tosilate RS.

B. Carry out the test as described under *1.14.1 Chromatography,* High-performance liquid chromatography, using the conditions given under “Assay” but using, as

the detector, a diode array detector to record the UV spectra of the peaks due to cefiderocol and 4-toluenesulfonic acid in each chromatogram in the range of 210 nm to 350 nm and injecting 10 µL of solutions (1) and (2). The retention times and the UV spectra of the peaks due to cefiderocol and 4-toluenesulfonic acid in the chromatogram obtained with solution (1) correspond to the retention times and the UV spectra of the peaks due to cefiderocol and 4-toluenensulfonic acid in the chromatogram obtained with solution (2).

C. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions and solutions given under "Assay".

The retention times of the peaks due to cefiderocol and 4-toluenesulfonic acid in the chromatogram obtained with solution (1) correspond to the retention times of the peaks due to cefiderocol and 4-toluenesulfonic acid in the chromatogram obtained with solution (2).

D. The absorption spectrum (*1.6*) of a 0.01 mg per mL solution of the test substance in methanol R, when observed between 210 nm and 350 nm, corresponds to the spectrum of cefiderocol sulfate tosilate RS, recorded using the same conditions.

E. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R7 as the coating substance and a freshly prepared mixture of 1 volume of methanol R and 2 volumes of water R as the mobile phase.

Apply separately to the plate 10 µL of each of the following four solutions in methanol R. For solution (A), use a solution containing 1.0 mg of the test substance per mL. For solution (B), use a solution containing 20.0 mg of the test substance per mL. For solution (C), use a solution containing 1.0 mg of cefiderocol sulfate tosilate RS per mL. For solution (D), use a solution containing 4.5 mg of 4-toluenesulfonic acid R per mL. After removing the plate from the chromatographic chamber, allow it to dry in air, and examine the

chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with the spot due to cefiderocol in the chromatogram obtained with solution (C). The spot with an R_F value of about 0.83 obtained with solution (B) corresponds in position, appearance and intensity with the spot due to 4-toluenesulfonic acid in the chromatogram obtained with solution (D).

F. A 5 mg/mL solution of the test substance yields reaction A described under 2.1 General identification tests as characteristic of sulfate.

Sulfate. 3.5 % to 5.0 % calculated with reference to the anhydrous substance. Dissolve 0.250 g of the test substance in 100 mL of distilled water R and adjust the solution to pH 11 using concentrated ammonia R. Add 10.0 mL of barium chloride (0.1 mol/L) VS and about 0.5 mg of phthalein purple R. Titrate with disodium edetate (0.1 mol/L) VS, adding 50 mL of ethanol (~750 g/L) TS when the colour of the solution begins to change and continue the titration until the violet-blue colour disappears. 1 mL of 0.1 M barium chloride is equivalent to 9.606 mg of SO_4.

Water. Determine as described under *2.11 Micro determination of water by the Karl Fischer method.* Spread the test substance evenly on a petri dish and let its water content equilibrate for 3 hours under controlled temperature and humidity conditions (see also under "Assay"). Then determine the water content using 60.0 mg of the equilibrated test substance: it is not less than 110 mg/g and not more than 150 mg/g.

Sulfated ash (*2.3*, Method B)**.** Not more than 1.0 mg/g, determined on 1 to 2 g.

Heavy metals. Use 1.000 g for the preparation of the test solution as described under *2.2.3 Limit test for heavy metals*, Procedure 3. Determine the heavy metals content according to Method B; not more than 20 µg/g.

Related substances. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless-steel column (2.1 mm x 15 cm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (1.6 µm).[1]

Prepare a 0.2% trifluoroacetic acid solution by diluting 2.0 mL of trifluoroacetic acid R to 1000.0 mL with water R.

Use the following conditions for gradient elution:

- mobile phase A: a mixture of 0.2% trifluoroacetic acid solution and acetonitrile R (97:3 *V*/*V*);
- mobile phase B: acetonitrile R.

Time (minutes)	**Mobile phase A** (% *V*/*V*)	**Mobile phase B** (% *V*/*V*)	**Comments**
0–0.5	100	0	Isocratic
0.5–4.0	100 to 89	0 to 11	Linear gradient
4.0–9.0	89	11	Isocratic
9.0–30.0	89 to 62	11 to 38	Linear gradient
30.0–31.0	62 to 100	38 to 0	Return to initial composition
31.0–40.0	100	0	Re-equilibration

Operate with a flow rate of 0.3 mL per minute. Maintain the column temperature at 35°C and the autosampler at 5°C. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 261 nm.

Prepare the following solutions:

[1] A Waters CORTECS UPLC T3 has been found suitable.

- *Sodium dihydrogen phosphate solution (0.05 mol/L)*: dissolve 7.80 g of sodium dihydrogen phosphate dihydrate R in water R to dilute to 1000 mL with the same solvent.
- *Disodium hydrogen phosphate solution (0.05 mol/L)*: dissolve 7.098 g of anhydrous disodium hydrogen phosphate R in water R and dilute to 1000 mL with the same solvent.
- *Phosphate buffer solution (5 mmol/L)*: prepare a mixture of water R, sodium dihydrogen phosphate solution (0.05 mol/L), and disodium hydrogen phosphate solution (0.05 mol/L) (18:1:1 *V*/*V*/*V*).

Use as a diluent a mixture of phosphate buffer solution (5 mmol/L) and acetonitrile R (9:1 *V*/*V*).

For solution (1), transfer 40 mg of the test substance into a 25 mL volumetric flask, dissolve in diluent and dilute to volume with the same diluent.

For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL with diluent.

For solution (3), dilute 3.0 mL of solution (2) to 100.0 mL with the diluent.

For solution (4), transfer 32 mg of cefiderocol sulfate tosilate RS into a 20 mL volumetric flask, dissolve in diluent and dilute to volume with the same diluent. Heat the obtained solution at 50 °C for 20 minutes and cool to room temperature.

Inject 2 µL each of solutions (1), (2), (3) and (4).

Use the chromatogram obtained with solution (4) to identify the peaks due to 4-toluenesulonic acid, and the impurities A, B, C, E and G.

In the chromatogram obtained with solution (1), the impurities are eluted, if present, at the following relative retentions with reference to cefiderocol (retention time about 10 minutes): 4-toluenesulfonic acid about 0.40; impurity A about 0.45; impurity B about 0.61; impurity C about 0.76; impurity F about 0.83, impurity D about 1.23, impurity E

about 1.28, and impurity G about 1.83.The test is not valid unless, in this chromatogram obtained with solution (4), the resolution between the peaks due to 4-toluenesulfonic acid and impurity A is at least 1.5. Also, the test is not valid unless, in the chromatogram obtained with solution (3), the peak due to cefiderocol is obtained with a signal-to-noise ratio of at least 20.In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied with a correction factor of 2.4, is not greater than 0.1 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (0.10 %);
- the area of any peaks corresponding to impurities C or E are not greater than 0.1 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (0.10 %);
- the area of any peak corresponding to impurity B, when multiplied with a correction factor of 0.72, is not greater than 0.05 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (0.05 %);
- the area of any peak corresponding to impurity G, when multiplied with a correction factor of 1.6, is not greater than 0.05 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (0.05 %);
- the area of any other impurity peak is not greater than 0.05 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (0.05 %).
- The sum of the areas of all impurity peaks, including the corrected areas of any peaks corresponding to impurities A, B and G, is not greater than the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (1.0 %). Disregard all peaks with an area of less than the area of the peak due to cefiderocol in the chromatogram obtained with solution (3) (0.03 %) and any peak due to 4-toluenesulfonic acid.

Assay. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless-steel column (4.6 mm x 10 cm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (3 µm).[2]

Prepare a 0.1% trifluoroacetic acid solution by diluting 1.0 mL of trifluoroacetic acid R to 1000.0 mL with water R.

As the mobile phase, use a mixture of 0.1% trifluoroacetic acid solution and acetonitrile (86:14 *V*/*V*).

Operate with a flow rate of 1.0 mL per minute. Maintain the column temperature at 35°C and the autosampler at 5°C. Use an ultraviolet spectrophotometer set at a wavelength of 261 nm.

Prepare the following solutions:

- *Sodium dihydrogen phosphate solution (0.05 mol/L)*: dissolve 7.80 g of sodium dihydrogen phosphate dihydrate R in water R and dilute to 1000 mL with the same solvent.
- *Disodium hydrogen phosphate solution (0.05 mol/L)*: dissolve 7.098 g of anhydrous disodium hydrogen phosphate R in water R and dilute to 1000 mL with the same solvent.
- *Phosphate buffer solution (5 mmol/L)*: prepare a mixture of water R, sodium dihydrogen phosphate solution (0.05 mol/L), and disodium hydrogen phosphate solution (0.05 mol/L) (18:1:1 *V*/*V*/*V*).

Use as a diluent a mixture of phosphate buffer solution (5 mmol/L) and acetonitrile R (9:1 *V*/*V*).

[2] Unison UK-C18 column has been found suitable.

For solution (1), spread the test substance evenly on a petri dish and let its water content equilibrate for 3 hours under the same temperature and humidity conditions used for the determination of its water content, as described under "Water". Then transfer 40.0 mg of the equilibrated test substance into a 25 mL volumetric flask, dissolve in diluent and dilute to volume with the same diluent. Dilute 5.0 mL to 50.0 mL with the diluent.

For solution (2), transfer 40.0 mg of cefiderocol sulfate tosilate RS into a 25 mL volumetric flask, dissolve in diluent and dilute to volume with the same diluent. Dilute 5.0 mL to 50.0 mL with the diluent.

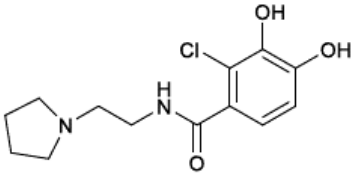
Inject 10 µL each of solutions (1) and (2) and record the chromatograms for 20 minutes. In the chromatograms obtained, the substances are eluted in the order: 4-toluenesulfonic acid, cefiderocol.

Measure the areas of the peaks corresponding to cefiderocol obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of $3C_{30}H_{34}ClN_7O_{10}S_2 \cdot 4C_7H_8O_3S \cdot H_2SO_4$ in the sample using the declared content of cefiderocol ($C_{30}H_{34}ClN_7O_{10}S_2$) in cefiderocol sulfate tosilate RS. Each mg of $C_{30}H_{34}ClN_7O_{10}S_2$ corresponds to 1.349 mg of $3C_{30}H_{34}ClN_7O_{10}S_2 \cdot 4C_7H_8O_3S \cdot H_2SO_4$.

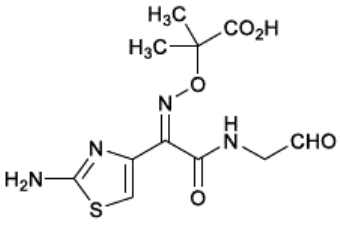
Bacterial endotoxins. If intended for use in the manufacture of a parenteral dosage form without a further appropriate procedure for the removal of bacterial endotoxins, carry out the test as described under *3.4 Test for bacterial endotoxins*; contains not more than 0.054 IU of endotoxin per mg of the test substance.

Sterility. If intended for use in the manufacture of either a parenteral or other sterile dosage form without a further appropriate sterilization procedure, complies with *3.2 Test for sterility*.

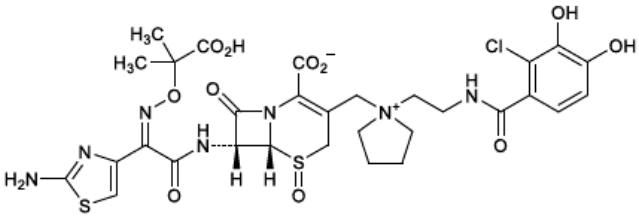
Impurities



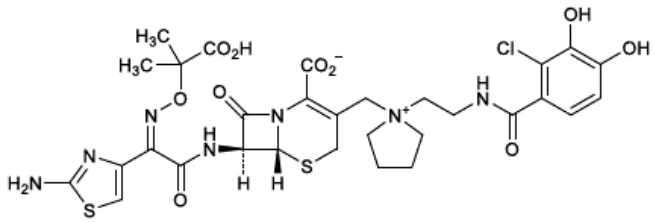
A. 2-Chloro-3,4-dihydroxy-*N*-[2-(pyrrolidin-1-yl)ethyl]benzamide (degradation product)



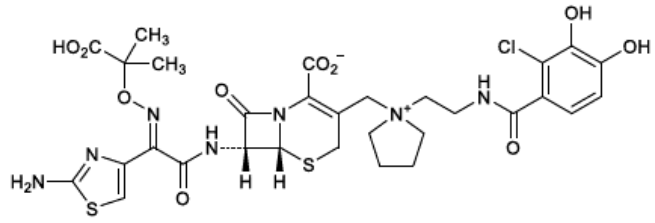
B. 2-{[(*Z*)-{1-(2-Amino-1,3-thiazol-4-yl)-2-oxo-2-[(2-oxoethyl)amino]ethylidene}amino]oxy}-2-methylpropanoic acid (degradation product)



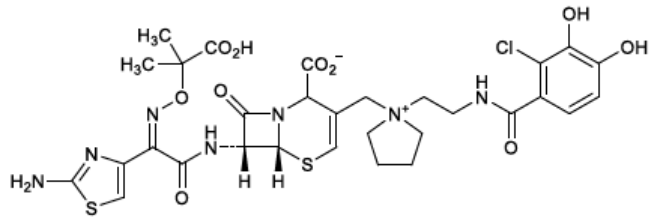
C. (6*R*,7*R*)-7-[(2*Z*)-2-(2-Amino-1,3-thiazol-4-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetamido]-3-({1-[2-(2-chloro-3,4-dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl}methyl)-5,8-dioxo-5λ4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (process related impurity and degradation product)



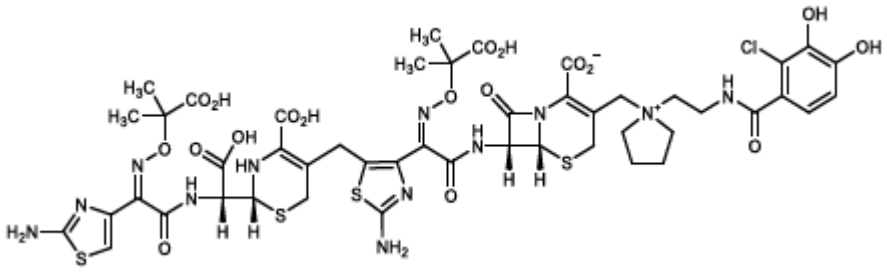
D. (6*R*,7*S*)-7-[(2*Z*)-2-(2-Amino-1,3-thiazol-4-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetamido]-3-({1-[2-(2-chloro-3,4-dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (process related impurity, degradation product)



E. (6*R*,7*R*)-7-[(2*E*)-2-(2-Amino-1,3-thiazol-4-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetamido]-3-({1-[2-(2-chloro-3,4-dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (process related impurity, degradation product)



F. *[chemical name to be added at a later stage]* (process related impurity and degradation product)



G. (6*R*,7*R*)-7-[(2*Z*)-2-(2-Amino-5-{[(2*R*)-2-{(*R*)-[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetamido](carboxy)methyl}-4-carboxy-3,6-dihydro-2*H*-1,3-thiazin-5-yl]methyl}-1,3-thiazol-4-yl)-2-{[(2-carboxypropan-2-yl)oxy]imino}acetamido]-3-({1-[2-(2-chloro-3,4-dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (degradation product)

***

Reference substances to be established.

Cefiderocol sulfate tosilate RS

- New International Chemical Reference Substance to be established.

Reagents to be revised.

4-Toluenesulfonic acid R

4-Methylbenzenesulfonic acid, $C_7H_8O_3S$, H_2O.

Content: minimum 87.0 % of $C_7H_8O_3S$.

Description: White or almost white, crystalline powder or crystals, freely soluble in water, soluble in Ethanol (~750 g/L) TS.

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