Dicloxacillin Sodium

Type of Posting	Revision Bulletin
Posting Date	29–Jul–2016; updated 26–Aug–2016*
Official Date	01–Aug–2016
Expert Committee	Chemical Medicines Monographs 1
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Dicloxacillin Sodium Monograph. The purpose of this revision is to update the organic impurity limits to reflect FDA-approved acceptance criteria.

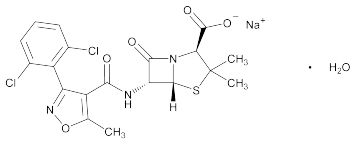
The Dicloxacillin Sodium Revision Bulletin supersedes the currently official Dicloxacillin Sodium monograph. The Revision Bulletin will be incorporated in the *USP 40–NF 35*.

Should you have any questions, please contact Slavica Shane, Scientific Liaison (301-230-3384 or sis@usp.org.)

**The Revision Bulletin Notice was corrected on July 29, 2016 to specify that, "The purpose of this revision is to update the organic impurity limits." Previously the notice had inaccurately stated that the purpose of the revision was to widen the organic impurity limits.*

Dicloxacillin Sodium

Change to read:



$C_{19}H_{16}Cl_2N_3NaO_5S \cdot H_2O$ 510.32
4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, monohydrate, [2*S*-(2α,5α,6β)]-;
Monosodium (2*S*,5*R*,6*R*)-6-[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate monohydrate [13412-64-1].
Anhydrous
$C_{19}H_{16}Cl_2N_3NaO_5S$ •492.30• (RB 1-Aug-2016)
[343-55-5].

DEFINITION
Dicloxacillin Sodium contains the equivalent of NLT 850 µg/mg of dicloxacillin ($C_{19}H_{17}Cl_2N_3O_5S$).

IDENTIFICATION
• **A. INFRARED ABSORPTION** ⟨197K⟩

Add the following:

▲• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲*USP39*

Change to read:

• ▲**C.**▲*USP39* **IDENTIFICATION TESTS—GENERAL** ⟨191⟩, *Sodium*
Analysis: Ignite about 100 mg. Proceed as directed in the chapter using a solution (1 in 20) of the residue in acetic acid.
Acceptance criteria: Meets the requirements

ASSAY

Change to read:

• **PROCEDURE**
▲Protect solutions containing dicloxacillin from light.
Solution A: 1.18 g/L of sodium 1-hexanesulfonate monohydrate and 0.8 mL/L of ammonium hydroxide in water; adjusted with phosphoric acid to a pH of 2.9–3.1
Solution B: Acetonitrile
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	45	55
2	45	55
2.5	35	65
5	35	65

Return to the original conditions and re-equilibrate the system.

Diluent: Acetonitrile and water (50:50)
System suitability stock solution: 0.1 mg/mL of USP Dicloxacillin Related Compound D RS in *Diluent*. Sonicate as needed to dissolve.
System suitability solution: 0.001 mg/mL of USP Dicloxacillin Related Compound D RS from the *System suitability stock solution* and 0.1 mg/mL of USP Dicloxacillin Sodium RS in *Diluent*. Store this solution at 4°.
Standard solution: 0.1 mg/mL of USP Dicloxacillin Sodium RS in *Diluent*. Sonicate as needed to dissolve. Store this solution at 4°.
Sample solution: 0.1 mg/mL of Dicloxacillin Sodium in *Diluent*. Sonicate as needed to dissolve. Store this solution at 4°.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Temperatures
Autosampler: 4°
Column: 40°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for dicloxacillin and dicloxacillin related compound D are about 1.0 and 1.1, respectively.]
Suitability requirements
Resolution: NLT 1.5 between dicloxacillin and dicloxacillin related compound D, *System suitability solution*
Tailing factor: 0.8–1.5, *Standard solution*
Relative standard deviation: NMT 0.73%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the quantity, in µg/mg, of dicloxacillin ($C_{19}H_{17}Cl_2N_3O_5S$) in the portion of Dicloxacillin Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Dicloxacillin Sodium RS in the *Standard solution* (mg/mL)
C_U = concentration of Dicloxacillin Sodium in the *Sample solution* (mg/mL)
P = potency of dicloxacillin in USP Dicloxacillin Sodium RS (µg/mg)
Acceptance criteria: NLT 850 µg/mg▲*USP39*

IMPURITIES

Change to read:

▲• **ORGANIC IMPURITIES**
Protect solutions containing dicloxacillin from light.
Solution A, Solution B, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	70	30
10	70	30

Table 2 *(Continued)*

Time (min)	Solution A (%)	Solution B (%)
30	50	50
35	35	65
45	25	75

Return to the original conditions and re-equilibrate the system.

System suitability stock solution: 0.1 mg/mL of USP Dicloxacillin Related Compound D RS in *Diluent*

System suitability solution: 0.01 mg/mL of USP Dicloxacillin Related Compound D RS from the *System suitability stock solution* and 1 mg/mL of USP Dicloxacillin Sodium RS in *Diluent*. Store this solution at 4°.

Standard solution: 0.01 mg/mL of USP Dicloxacillin Sodium RS in *Diluent*. Sonicate as needed to dissolve. Store this solution at 4°.

Sample solution: 1 mg/mL of Dicloxacillin Sodium in *Diluent*. Sonicate as needed to dissolve. Store this solution at 4°.

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between dicloxacillin related compound D and dicloxacillin, *System suitability solution*

Tailing factor: 0.8–1.5, *Standard solution*

Relative standard deviation: NMT 2.5%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Dicloxacillin Sodium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times (F_1/F_2) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Dicloxacillin Sodium RS in the *Standard solution* (mg/mL)

C_U = concentration of Dicloxacillin Sodium in the *Sample solution* (mg/mL)

P = potency of dicloxacillin in USP Dicloxacillin Sodium RS (µg/mg)

F_1 = conversion factor, 0.001 mg/µg

F_2 = relative response factor (see *Table 3*)

Acceptance criteria

●**Individual impurities:** NMT 1.0%

Total impurities: NMT 5.0%

See *Table 3* for relative retention times and relative response factors.● (RB 1-Aug-2016) The reporting threshold is 0.05%.

●**Table 3**

Name	Relative Retention Time	Relative Response Factor
Amoxicillin related compound A[a]	0.07	0.20
	0.23	
Dicloxacillin penicilloic acid[b,c]	0.25	1.0
Dicloxacillin glycine analog[d]	0.38	1.0
Dicloxacillin *N*-acetyl penicilloic acid[e]	0.43	1.0
	0.61	
Dicloxacillin penilloic acid[b,f]	0.69	0.75
Dicloxacillin related compound D[g]	0.90	1.4
Dicloxacillin	1.0	—
Dicloxacillin penicillamide[h]	1.3	1.0

[a] 6-Aminopenicillanic acid; (2*S*,5*R*,6*R*)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

[b] The system resolves two isomers.

[c] (4*S*)-2-{Carboxy[3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxamido]methyl}-5,5-dimethylthiazolidine-4-carboxylic acid.

[d] [3-(2,6-Dichlorophenyl)-5-methylisoxazole-4-carbonyl]glycine.

[e] (2*R*,4*S*)-3-Acetyl-2-{(*R*)-carboxy[3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carboxamido]methyl}-5,5-dimethylthiazolidine-4-carboxylic acid.

[f] (4*S*)-2-{[3-(2,6-Dichlorophenyl)-5-methylisoxazole-4-carboxamido]methyl}-5,5-dimethylthiazolidine-4-carboxylic acid.

[g] 3-(2,6-Dichlorophenyl)-5-methylisoxazole-4-carboxylic acid.

[h] (2*S*,5*R*,6*R*)-6-{(2*S*,5*R*,6*R*)-6-[3-(2,6-Dichlorophenyl)-5-methylisoxazole-4-carboxamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamido}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

● (RB 1-Aug-2016)▲*USP39*

• **DIMETHYLANILINE** ⟨**223**⟩**:** Meets the requirements

SPECIFIC TESTS

• **CRYSTALLINITY** ⟨**695**⟩**:** Meets the requirements

• **pH** ⟨**791**⟩

Sample solution: 10 mg/mL in water

Acceptance criteria: 4.5–7.5

• **WATER DETERMINATION** ⟨**921**⟩**,** *Method I***:** 3.0%–5.0%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers.

Change to read:

• **USP REFERENCE STANDARDS** ⟨**11**⟩

USP Dicloxacillin Sodium RS

▲USP Dicloxacillin Related Compound D RS

3-(2,6-Dichlorophenyl)-5-methylisoxazole-4-carboxylic acid.

$C_{11}H_7Cl_2NO_3$ 272.08▲*USP39*