Solution B: Acetonitrile, tetrahydrofuran, and *Buffer* (29:1:70)

Mobile phase: See *Table 1*. Make adjustments if necessary, changing the acetonitrile proportion in *Solution A* to obtain a retention time of 7.5–10.5 min for the main vancomycin peak.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
12	100	0
20	0	100
22	0	100
23	100	0
30	100	0

System suitability solution: Allow a container of Injection to thaw, and mix the solution. Dilute a portion of the Injection with water to obtain a solution containing 0.5 mg/mL of vancomycin. Heat at 65° for 24 h, and allow to cool.

Sample stock solution: Allow a container of Injection to thaw, and mix the solution.

Sample solution: Equivalent to 0.4 mg/mL of vancomycin hydrochloride from the *Sample stock solution* in *Solution A*

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 2 mL/min

Injection size: 20 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

[NOTE—The elution order is compound 1, vancomycin B, and compound 2. Compound 2 elutes 3–6 min after the start of the period, when the percentage of *Solution B* is increasing from 0% to 100%.]

Resolution: NLT 3.0 between compound 1 and vancomycin B

Column efficiency: NLT 1500 theoretical plates for the vancomycin B peak

Analysis

Samples: *Sample stock solution* and *Sample solution*

Where baseline separation is not achieved, peak areas are defined by vertical lines extended from the valleys between peaks to the baseline. The main component peak may include a fronting shoulder, which is attributed to monodechlorovancomycin. This shoulder should not be integrated separately.

Correct any peak observed in the chromatograms from *Sample stock solution* and *Sample solution* by subtracting the area response of any peak observed in the chromatogram of *Solution A* at the corresponding retention time.

Calculate the percentage of vancomycin B in the portion of Injection taken:

$$\text{Result} = \{(D \times r_B)/[(D \times r_B) + r_A]\} \times 100$$

D = dilution factor, *Sample stock solution* to *Sample solution*

r_B = corrected peak area response of the main peak from the *Sample solution*

r_A = sum of the corrected peak area responses of all the peaks, other than the main peak, from the *Sample stock solution*

Calculate the percentage of any individual peak, other than the main peak, in the portion of Injection taken:

$$\text{Result} = \{r_i/[(D \times r_B) + r_A]\} \times 100$$

r_i = corrected peak area response of any individual peak, other than the main peak, from the *Sample stock solution*

D = dilution factor, *Sample stock solution* to *Sample solution*

r_B = corrected peak area response of the main peak from the *Sample solution*

r_A = sum of the corrected peak area responses of all the peaks, other than the main peak, from the *Sample stock solution*

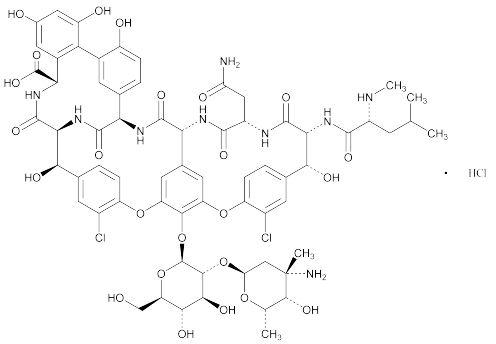
Acceptance criteria: NLT 88% of vancomycin B; NMT 4% of any individual peak other than the main peak

- **pH** ⟨**791**⟩**:** 3.0–5.0
- **BACTERIAL ENDOTOXINS TEST** ⟨**85**⟩**:** NMT 0.33 USP Endotoxin Unit/mg of vancomycin
- **PARTICULATE MATTER IN INJECTIONS** ⟨**788**⟩**:** Meets the requirements for small-volume injections
- **STERILITY TESTS** ⟨**71**⟩**:** Meets the requirements when tested as directed in *Test for Sterility of the Product to Be Examined, Membrane Filtration*, except use water instead of *Diluting Fluid A*
- **OTHER REQUIREMENTS:** Meets the requirements in *Injections and Implanted Drug Products* ⟨1⟩

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve as described in *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging*. Maintain in a frozen state.
- **LABELING:** It meets the requirements in *Labeling* ⟨7⟩*, Labels and Labeling for Injectable Products*. The label states that it is to be thawed just before use, describes conditions for proper storage of the resultant solution, and directs that the solution is not to be refrozen.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Endotoxin RS
  USP Vancomycin Hydrochloride RS

Vancomycin Hydrochloride



$C_{66}H_{75}Cl_2N_9O_{24} \cdot HCl$ 1485.71

Vancomycin, monohydrochloride;
Vancomycin monohydrochloride;
(S_a)-(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-44-[[2-*O*-(3-Amino-2,3,6-trideoxy-3-C-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]oxy]-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(methylamino)]valeramido]-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*]

USP Monographs

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[10,2,16]benzoxadiazacyclotetracosine-26-carboxylic acid, monohydrochloride;
[3*S*-[3*R**,6*S**(*S**),7*S**,22*S**,23*R**,26*R**,36*S**,38a*S**]]-3-(2-Amino-2-oxoethyl)-44-[[2-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]oxy]-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[[4-methyl-2-(methylamino)-1-oxopentyl]amino]-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36-(iminomethano)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]oxadiazacyclohexadecino[4,5-*m*][10,2,16]-benzoxadiazacyclotetracosine-26-carboxylic acid, monohydrochloride [1404-93-9].

DEFINITION

Vancomycin Hydrochloride is the hydrochloride salt of a kind of vancomycin, a substance produced by the growth of *Streptomyces orientalis* (Fam. Streptomycetaceae), or a mixture of two or more such salts. It has a potency equivalent to NLT 900 µg/mg of vancomycin, calculated on the anhydrous basis.

IDENTIFICATION

- **INFRARED ABSORPTION** ⟨197K⟩

ASSAY

- **PROCEDURE:** Proceed with Vancomycin Hydrochloride as directed under *Antibiotics—Microbial Assays* ⟨81⟩.
  Acceptance criteria: NLT 900 µg/mg on the anhydrous basis

IMPURITIES

Inorganic Impurities

Delete the following:

- **HEAVY METALS,** *Method II* ⟨231⟩**:** NMT 30 ppm (Official 1-Jan-2018)

Organic Impurities

- **PROCEDURE: LIMIT OF MONODECHLOROVANCOMYCIN**
  [NOTE—The *System suitability solution*, *Standard solution*, and *Sample solution* should be refrigerated immediately after preparation and during analysis. The solutions are stable for 4 days when refrigerated.]
  Mobile phase: Dissolve 2.2 g of 1-heptanesulfonic acid sodium salt in about 500 mL of water, add 125 mL of acetonitrile and 10 mL of acetic acid, and dilute with water to 1 L.
  Rinse solution: 10% acetonitrile in water. [NOTE—Use to rinse needle and column.]
  System suitability solution: Equivalent to 1 mg/mL of vancomycin B from USP Vancomycin B with Monodechlorovancomycin RS in water
  Standard solution: Equivalent to 50 µg/mL of vancomycin B, from *System suitability solution*
  Sample solution: 1 mg/mL of Vancomycin Hydrochloride in water
  Blank: Water
  Chromatographic system
  (See *Chromatography* ⟨621⟩*, System Suitability*.)
  Mode: LC
  Detector: UV 280 nm
  Column: 4.6 mm × 25 cm; packing L1
  Column temperature: 60°
  Autosampler temperature: 5°
  Flow rate: 1.5 mL/min
  Injection volume: 50 µL
  [NOTE—This procedure is sensitive to temperature changes. Sufficient tubing should be placed in the column oven to ensure that the samples have reached 60° before separation.]
  System suitability
  Samples: *System suitability solution*, *Standard solution*, *Sample solution*, and *Blank*
  [NOTE—*Blank* and *Standard solution* run times are about 90 min. *System suitability solution* and *Sample solution* run times are about 120 min.]
  [NOTE—The relative retention times for vancomycin B and monodechlorovancomycin are 1.0 and 1.1, respectively.]
  Suitability requirements
  Selectivity: The chromatogram for the *Blank* does not contain peaks that interfere with vancomycin B or monodechlorovancomycin.
  Retention times: ±3.0% between monodechlorovancomycin in the *Sample solution* and the mean of the monodechlorovancomycin peaks in the *Standard solution*
  Resolution: NLT 1.5 between vancomycin B and monodechlorovancomycin, *System suitability solution*
  Relative standard deviation: NMT 2.0%, *Standard solution*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of monodechlorovancomycin in the portion of Vancomycin Hydrochloride taken:

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

r_U = peak area of monodechlorovancomycin in the *Sample solution*
r_S = average peak area of the vancomycin B peak in the *Standard solution*
C_S = concentration of USP Vancomycin B with Monodechlorovancomycin RS in the *Standard solution* (mg/mL)
C_U = concentration of Vancomycin Hydrochloride in the *Sample solution* (mg/mL)
P = potency of vancomycin B in USP Vancomycin B with Monodechlorovancomycin RS (mg/mg)

Acceptance criteria: NMT 4.7% of monodechlorovancomycin is found.

SPECIFIC TESTS

- **STERILITY TESTS** ⟨71⟩**:** Where the label states that Vancomycin Hydrochloride is sterile, it meets the requirements when tested as directed for *Test for Sterility of the Product to Be Examined, Membrane Filtration*, except to dissolve the specimen in water, instead of in *Fluid A*.
- **BACTERIAL ENDOTOXINS TEST** ⟨85⟩**:** Where the label states that Vancomycin Hydrochloride is sterile or must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 0.33 USP Endotoxin Unit/mg of vancomycin.
- **pH** ⟨791⟩**:** 2.5–4.5, 50 mg/mL in water
- **WATER DETERMINATION,** *Method I* ⟨921⟩**:** NMT 5.0%
- **COMPOSITION OF VANCOMYCIN**
  Solution A: Triethylamine and water (1:500). Adjust with phosphoric acid to a pH of 3.2.
  Solution B: Acetonitrile, tetrahydrofuran, and *Solution A* (7:1:92)
  Solution C: Acetonitrile, tetrahydrofuran, and *Solution A* (29:1:70)
  Mobile phase: See the gradient table below. [NOTE—Make adjustments, if necessary, changing the acetonitrile proportion in *Solution B* to obtain a retention time of 7.5–10.5 min for the main vancomycin peak.]

Time (min)	Solution B (%)	Solution C (%)
0	100	0
12	100	0
20	0	100
22	0	100
23	100	0
30	100	0

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System suitability solution: 0.5 mg/mL of USP Vancomycin Hydrochloride RS in water. Heat at 65° for 48 h, and allow to cool.
Sample solution 1: 10 mg/mL of Vancomycin Hydrochloride in *Solution B*
Sample solution 2: 0.4 mg/mL of Vancomycin Hydrochloride, from *Sample solution 1* in *Solution B*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 2 mL/min
Injection size: 20 µL
System suitability
Sample: *System suitability solution*
[NOTE—The elution order is compound 1, vancomycin B, and compound 2. Compound 2 elutes 3–6 min after the start of the period when the percentage of *Solution C* increases from 0%–100%.]
Suitability requirements
Resolution: NLT 3.0 between compound 1 and vancomycin B
Column efficiency: NLT 1500 theoretical plates, calculated from the vancomycin B peak
Analysis
Samples: *Sample solution 1* and *Sample solution 2*
[NOTE—Where baseline separation is not achieved, peak areas are defined by vertical lines extended from the valleys between the peaks to the baseline. The main component peak may include a fronting shoulder, which is attributed to monodechlorovancomycin. This shoulder should not be integrated separately.]
[NOTE—Correct any peak observed in the chromatograms obtained from *Sample solution 1* and *Sample solution 2* by subtracting the area response of any peak observed in the chromatogram of *Solution B* at the corresponding retention time.]
Measure the area responses for all of the peaks. Calculate the percentage of vancomycin B in the portion of Vancomycin Hydrochloride taken:

$$\text{Result} = [(D \times r_B)/((D \times r_B) + r_A)] \times 100$$

D = dilution factor, *Sample solution 1* to *Sample solution 2*, 25
r_B = corrected area response of the main peak of *Sample solution 2*
r_A = sum of the corrected area responses of all the peaks, other than the main peak, from *Sample solution 1*

Calculate the percentage of each other peak in the portion of Vancomycin Hydrochloride taken:

$$\text{Result} = \{r_I/[(D \times r_B) + r_A]\} \times 100$$

r_I = corrected area response of any individual peak, other than the main peak of *Sample solution 1*
D = dilution factor, *Sample solution 1* to *Sample solution 2*, 25
r_B = corrected area response of the main peak of *Sample solution 2*
r_A = sum of the corrected area responses of all the peaks, other than the main peak from *Sample solution 1*

Acceptance criteria: NLT 85.0% of vancomycin B; NMT 5.0% of any peak other than the main peak

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **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 Endotoxin RS
  USP Vancomycin Hydrochloride RS
  USP Vancomycin B with Monodechlorovancomycin RS

Vancomycin Hydrochloride Capsules

DEFINITION
Vancomycin Hydrochloride Capsules contain the equivalent of NLT 90.0% and NMT 115.0% of the labeled amount of vancomycin ($C_{66}H_{75}Cl_2N_9O_{24}$).

IDENTIFICATION
- **INFRARED ABSORPTION** ⟨**197K**⟩
  Sample: Disperse the contents of 1 Capsule in about 20 mL of chloroform. Pass the liquid through a suitable filter. Rinse the filter and residue with chloroform. Dry the residue in a vacuum at 60° for 1 h.

ASSAY

Change to read:

- **ANTIBIOTICS—MICROBIAL ASSAYS** ⟨**81**⟩
  Analysis: Proceed as directed, using NLT 5 Capsules blended at high speed in a glass blender jar for 3–5 min with a sufficient volume of •*Buffer B.4*• (CN 1-May-2017) to yield a stock solution having a convenient concentration of vancomycin. Dilute a volume of this stock solution with •*Buffer B.4*• (CN 1-May-2017) to obtain a *Test Dilution* having a concentration assumed to be equal to the median dose level of the Standard.
  Acceptance criteria: 90.0%–115.0%

PERFORMANCE TESTS
- **DISSOLUTION** ⟨**711**⟩
  Medium: Water; 900 mL
  Apparatus 1: 100 rpm
  Time: 45 min
  Sample solution: Sample per *Dissolution* ⟨711⟩
  Analysis: Determine the amount of vancomycin dissolved by assaying a filtered portion of the *Sample solution* as directed for vancomycin under *Antibiotics—Microbial Assays* ⟨81⟩.
  Tolerances: NLT 85% (Q) of the labeled amount of vancomycin is dissolved.
- **UNIFORMITY OF DOSAGE UNITS** ⟨**905**⟩**:** Meet the requirements

SPECIFIC TESTS
- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** NMT 8.0%

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Vancomycin Hydrochloride RS

Vancomycin Hydrochloride for Injection

DEFINITION
Vancomycin Hydrochloride for Injection is a sterile dry mixture of Vancomycin Hydrochloride and may contain a suitable stabilizing agent. It contains NLT 90.0% and NMT 115.0% of the labeled amount of vancomycin.

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