Vancomycin Injection

Type of Posting	Revision Bulletin
Posting Date	28–Feb–2019
Official Date	01–Mar–2019
Expert Committee	Biologics Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Biologics Monographs 4 Expert Committee has revised the Vancomycin Injection monograph. The purpose of the revision is to accommodate FDA-approved drug products.

- The *Definition* is revised to accommodate products with different formulations.
- The requirements associated with thawing Injection for the preparation of solutions are revised in the *Assay* and test for the *Composition of Vancomycin* to accommodate products with different formulations.
- The acceptance criteria for the *pH* test are revised to accommodate products stored either at room temperature or maintained in a frozen state.
- The acceptance criteria for the *Particulate Matter in Injections* test are revised to accommodate small-volume injections and large-volume injections.
- *Packaging and Storage* and *Labeling* are revised to accommodate products with different formulations.

The Vancomycin Injection Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Ying Han, Associate Science and Standards Liaison to the Biologics Monographs 4 Expert Committee (301-692-3294 or ying.han@usp.org).

Vancomycin Injection

Change to read:

DEFINITION

Vancomycin Injection is a sterile ▲ (RB 1-Mar-2019) solution of Vancomycin Hydrochloride in Water for Injection. It contains NLT 90.0% and NMT 115.0% of the labeled amount of vancomycin ($C_{66}H_{75}Cl_2N_9O_{24}$). It contains ▲one or more suitable excipients.▲ (RB 1-Mar-2019)

IDENTIFICATION

- **A.** The retention time of the main vancomycin peak of the *Sample stock solution*, obtained as directed in *Composition of Vancomycin*, corresponds to that of a similarly prepared solution of USP Vancomycin Hydrochloride RS.

ASSAY

Change to read:

- **ANTIBIOTICS—MICROBIAL ASSAYS** ⟨81⟩

Sample solution: Allow a container of Injection to thaw, ▲if applicable,▲ (RB 1-Mar-2019) and mix the solution. Dilute a portion of this solution with Buffer B.4 to yield a test dilution having a concentration assumed to be equal to that of the median dose of the standard.

Analysis: Proceed as directed for vancomycin in the chapter.

Acceptance criteria: 90.0%–115.0%

SPECIFIC TESTS

Change to read:

- **COMPOSITION OF VANCOMYCIN**

Buffer: Triethylamine and water (1:500). Adjust with phosphoric acid to a pH of 3.2.

Solution A: Acetonitrile, tetrahydrofuran, and *Buffer* (7:1:92)

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, ▲if applicable,▲ (RB 1-Mar-2019) 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, ▲if applicable,▲ (RB 1-Mar-2019) 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

Change to read:

- **pH** ⟨791⟩**:** ▲4.5–5.5 for products stored at room temperature; 3.0–5.0 for products maintained in a frozen state▲ (RB 1-Mar-2019)
- **BACTERIAL ENDOTOXINS TEST** ⟨85⟩**:** NMT 0.33 USP Endotoxin Units/mg of vancomycin

Change to read:

- **PARTICULATE MATTER IN INJECTIONS** ⟨788⟩**:** Meets the requirements for small-volume injections ▲or large-volume injections, whichever is applicable▲ (RB 1-Mar-2019)
- **STERILITY TESTS** ⟨71⟩**,** *Test for Sterility of the Product to Be Examined, Membrane Filtration***:** Meets the requirements, except use water instead of diluting *Fluid A*
- **OTHER REQUIREMENTS:** Meets the requirements in *Injections and Implanted Drug Products* ⟨1⟩

ADDITIONAL REQUIREMENTS

Change to read:

- **PACKAGING AND STORAGE:** Preserve as described in *Packaging and Storage Requirements* ⟨659⟩*, Injection Packaging*. ▲Store as directed by product label.▲ (RB 1-Mar-2019)

Change to read:

- **LABELING:** It meets the requirements in *Labeling* ⟨7⟩*, Labels and Labeling for Injectable Products*. ▲For the product stored in a frozen state,▲ (RB 1-Mar-2019) 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 Vancomycin Hydrochloride RS