Vancomycin Injection

Type of Posting	Notice of Intent to Revise
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Expert Committee	Biologics Monographs 4

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Biologics Monographs 4 Expert Committee intends to revise the Vancomycin Injection monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes the following changes to accommodate products formulated with vancomycin free base, along with vancomycin hydrochloride:

- The *Definition* is revised to include vancomycin free base
- The *Sample solution* in the *Composition of Vancomycin* test is revised to include concentration of vancomycin free base
- The test for *pH* is revised to include acceptance criteria for products formulated with vancomycin and stored at room temperature
- The *Labeling* statement is revised to indicate whether the product contains Vancomycin or Vancomycin Hydrochloride

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

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

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Vancomycin Injection

Change to read:

DEFINITION

Vancomycin Injection is a sterile solution of ▲Vancomycin or▲ (TBD) 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.

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

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

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

Sample solution: Equivalent to 0.4 mg/mL of ▲vancomycin or▲ (TBD) 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⟩**:** ▲For products formulated with vancomycin hydrochloride,▲ (TBD) 4.5–5.5 for products stored at room temperature; 3.0–5.0 for products maintained in a frozen state; ▲3.9–5.5 for products formulated with vancomycin and stored at room temperature▲ (TBD)
- **Bacterial Endotoxins Test** ⟨85⟩**:** NMT 0.33 USP Endotoxin Units/mg of vancomycin
- **Particulate Matter in Injections** ⟨788⟩**:** Meets the requirements for small-volume injections or large-volume injections, whichever is applicable
- **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

- **Packaging and Storage:** Preserve as described in *Packaging and Storage Requirements* ⟨659⟩, *Injection Packaging*. Store as directed by product label.

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, 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. ▲The label states whether the product contains Vancomycin or Vancomycin Hydrochloride.▲ (TBD)
- **USP Reference Standards** ⟨11⟩
  USP Vancomycin Hydrochloride RS

Page Information:

Not Applicable

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