

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211962Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

**NDA 211962
Review 1**

Drug Name/Dosage Form	Vancomycin Injection
Strength	500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL, 2 g/400 mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Xelia Pharmaceuticals ApS
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>New NDA</i>	<i>05/23/2018</i>	<i>All</i>
<i>Quality Amendment</i>	<i>08/03/2018</i>	<i>Drug Product/Quality Micro</i>
<i>Quality Amendment</i>	<i>08/24/2018</i>	<i>Quality Micro</i>
<i>Quality Amendment</i>	<i>09/06/2018</i>	<i>Drug Product/Process</i>
<i>Quality Amendment</i>	<i>09/24/2018</i>	<i>Drug Product</i>
<i>Quality Amendment</i>	<i>09/25/2018</i>	<i>Drug Product/Quality Micro</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance/Drug Master File	Katherine Windsor	Suong Tran
Drug Product/Labeling	George Lunn	Balajee Shanmugam
Process/Facility	Ruan Xiumei	Steven Frisbee
Quality Micro	Helen Ngai	Jess Wells
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Yushi Feng	
Laboratory (OTR)	N/A	
ORA Lead	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
31868	Type II	See DS review				
Various	Type III	See DP review				

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	131664	IND for this NDA

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA is recommended for APPROVAL from the product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

Vancomycin is a tricyclic glycopeptide derived from *Amycolatopsis orientalis* (previously *Nocardia orientalis*). The drug product, vancomycin injection for intravenous infusion, in presentations of single-dose containers of 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL, and 2 g/400 mL, is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (beta-lactam resistant) staphylococci, including staphylococcal endocarditis.

Proposed Indication(s) including Intended Patient Population	Treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (beta-lactam resistant) staphylococci, including staphylococcal endocarditis.
Duration of Treatment	Not specified
Maximum Daily Dose	2 g divided either as 500 mg every 6 hours or 1 g every 12 hours
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

Vancomycin, a glycopeptide antibiotic derived from *Amycolatopsis orientalis*, was first approved in the US in 1958. There are USP monographs for vancomycin and vancomycin hydrochloride.

The applicant cross-referenced the CMC information for vancomycin wet base drug substance to DMF 31868. DMF 31868 was reviewed by Katherine Windsor, Ph.D. (final signature 28-SEP-2018) and was found adequate to support NDA 211962. Specified and unspecified impurities are controlled at or below the limits in the vancomycin and vancomycin hydrochloride USP monographs.

Stability data from the DMF holder support the applicant's proposed retest period of (b) (4) months for vancomycin wet base drug substance manufactured at Xellia and stored at (b) (4) °C.

For additional details, see the Drug Substance review below.

Drug Product:

FOIA Warning: Section contains information concerning another application.

This product is a ready to use vancomycin injection. Flexible bags contain 500 mg, 1 g, 1.5 g, or 2 g vancomycin in 5 mg/mL solution. Excipients N-acetyl-D-alanine (NADA), L-lysine, and PEG 400 are (b) (4). The RLD is considered to be Baxter's Vancomycin Injection, USP which is premixed and stored frozen (NDA 50671). While the Baxter product degrades rapidly at room temperature and this product is reasonably stable at room temperature the same degradants are formed when they degrade. Overfills of (b) (4) - (b) (4)% are used to ensure that the labeled amount of drug product can be delivered. The overfill amounts have been justified. For elemental impurities a satisfactory risk assessment and testing of 8 batches have been carried out.

NADA is a non-compendial and a novel excipient. A satisfactory specification that includes tests for (b) (4) is provided for NADA. Generally, the specification is conventional and could be applied to a drug substance. Pharm/Tox have found the proposed NADA impurity limits to be acceptable. The analytical methods are described at a reasonable level of detail and have been validated. Satisfactory Certificates of Analysis are provided for two batches. More information is found in a DMF that has been reviewed and found to be adequate.

A reasonable drug product specification with tests for appearance, identity, pH, extractable volume, particulates, bioassay, impurities, endotoxins, container integrity, osmolarity, weight loss, and sterility is provided. The analytical methods are described in reasonable detail and have been validated. A justification of the specification is provided. Generally, the tests and limits are conventional and comply with USP and are aligned with ICH recommendations. The impurities specifications appear to be generally in line with previous experience of vancomycin products and also with the various USP specifications with the largest impurity being \leq (b) (4)% and total impurities being \leq (b) (4)%. Unspecified impurities are \leq (b) (4)%. The degradants are the same as those found for the Baxter product (stored frozen) but largely different from those typically found with the lyophilized vancomycin products. Satisfactory batch analyses are provided for 8 batches.

The drug product is packaged in IV bags made of (b) (4) with a filling port and a twist-off access port. The container-closure system is made from components that comply with the 21 CFR regulations and USP chapters <661>, <87>, and <88>. Extractables and leachables testing has been carried out and no compounds of concern have been identified. This container-closure system has been previously used for 4 approved ANDAs.

Sixteen months of stability data obtained at 25°C/40% RH are provided for 8 batches. In addition, 12 months of data obtained at 30°C/65% RH and 6 months obtained at 40°C/< 25% RH are provided for these same batches. There are no significant changes in pH, color of solution, delivered volume, osmolarity, particulates, endotoxins, container integrity, weight loss, and sterility. The general trends are to lower purity and bioassay values and higher impurities with time and temperature. The product is reasonably stable at 25°C/40% RH for up to 16 months with an overwrap. The product fails after 12 months at 30°C/65% RH and after 3 months at 40°C/< 25% RH. Based on satisfactory data from 8 batches stored at 25°C/40% RH for 16 months the proposed expiration dating period of 16 months when stored below 25°C is acceptable. Given the pronounced trends towards lower purity and higher impurities the applicant has committed to making future expiration extensions by means of a CBE-30 Supplement rather than an Annual Report.

For additional details, see the Drug Product review below.

Process:

(b) (4)



A drug product (DP) comparability protocol (CP) has been submitted in the original NDA and the proposed future process changes include:

(b) (4)



(b) (4)



For additional details, see the Process review below.

Facilities:

Following a review of the application, inspectional documents and pre-approval inspection results, there are no significant, outstanding manufacturing or facility risks

that prevent approval of this application. All listed facilities for NDA 211962 are found to be acceptable for their proposed manufacturing and testing operations.

A Drug Substance Comparability Protocol (CP) was submitted for Xellia Pharmaceuticals, (b) (4)

The acceptability of the CP was reviewed by the Agency and deemed acceptable.

(b) (4)

For additional details, see the Facilities review below.

Quality Micro:

(b) (4)

Data from microbial ingress and bag integrity tests demonstrated adequate container closure and package integrity that the container closure system is capable of maintaining a barrier against microbial ingress.

The manufacturing process is suitable to support the manufacture of a (b) (4) drug product. The buildings and facilities are suitable to support the manufacture of a (b) (4) drug product. The environmental monitoring (b) (4) is suitable to manufacture a (b) (4) drug product. The (b) (4) studies are suitable to manufacture a (b) (4) drug product.

(b) (4)

(b) (4)

The Drug Product Specifications include Bacterial Endotoxins Testing and Sterility Testing per USP requirements. The BET method has been adequately validated and the maximum potential endotoxins exposure is less than or equal to the USP <85> recommended hourly amount for drug administered on a body mass (per kg) basis. The sterility test method has been adequately validated as per USP <71>. The microbiological test methods, acceptance criteria and frequencies in the stability protocol are suitable for a parenteral drug product.

The DP comparability protocol

(b) (4)

For additional details, see the Quality Micro review below.

Biopharmaceutics:

This 505(b)(2) NDA for Vancomycin Injection, 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL, and 2 g/400 mL in transparent single-dose containers, relies for approval on FDA's findings of safety and effectiveness of the Listed Drug (LD), Vancomycin Injection USP in GALAXY plastic single dose container, 500 mg/100 mL, 750 mg/150 mL, and 1 g/200 mL [NDA 050671, Baxter Healthcare Corp].

The Biopharmaceutics review evaluates information and data supporting the Applicant's biowaiver request.

Because the formulation of the proposed to-be-marketed parenteral drug product (DP) is not qualitatively and quantitatively (Q1/Q2) the same as that of the LD, due to the presence of (b) (4) N-acetyl-D-alanine 1.36% (w/v) and L-lysine hydrochloride 1.26% (w/v) and (b) (4) polyethylene glycol 400, 1.8% (v/v)), the biowaiver request per 21 CFR § 320.22(b)(1) is not feasible. However, a scientific bridge can be established between the proposed DP and the LD, based on 21 CFR 320.24(b)(6).

Based on the side-by-side comparison of drug product formulation, physicochemical properties, in vitro antimicrobial activity and in vivo animal studies between the proposed and LD products, as well as information available in the labeling of the LD, the proposed DP and the LD are the same in terms of indication, dosage form, dosage and administration route, concentration and infusion volume and rate. The proposed and LD products are both sterile, non-pyrogenic, and colorless solutions with comparable pH and osmolality. The addition of polyethylene glycol 400 (b) (4) and N-acetyl-D-alanine and L-lysine hydrochloride (b) (4) to the formulation of the proposed DP, is not anticipated to alter the PK, efficacy and safety of vancomycin in human subjects.

Overall, per 21 CFR 320.24(b)(6), the Applicant's proposed drug product has been adequately bridged to the LD; therefore, an in-vivo bioavailability study, comparing the LD to the proposed drug product, is not needed.

For additional details, see the Biopharmaceutics review below.

Environmental Assessment:

The applicant claims a categorical exclusion from the requirement to prepare an Environmental Assessment. The claim is reasonable.

For additional details, see the Drug Product review below.

C. Special Product Quality Labeling Recommendations (NDA only)

Recommendations have been conveyed to the OND PM for consideration as the labeling is finalized. See the OPQ Labeling review below.

D. Final Risk Assessment (see Attachment)



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Feng

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MEMO

From: George Lunn, Ph.D.

To: Balajee Shanmugam, Ph.D.

Date: October 22, 2018

Subject: NDA 211962 Vancomycin Injection from Xellia:
Review of Common Technical Document-Quality
(Ctd-Q) Module 1 Labeling & Package Insert

Summary

The CMC-related aspects of the package insert, container labels, overpouch labels, and cartons were reviewed. The recommendations for the package insert, as described below, were used to annotate the amended package insert maintained by OND. The recommendations for the container labels, overpouch labels, and cartons were communicated to the applicant in the FDA communication of 9/19/18 and accepted in the Amendment of 9/24/18 within the exception of the addition of ‘(b) (4)’. The applicant provided data to show (b) (4) the product produced no deleterious effects on the quality of the product. Therefore omitting ‘(b) (4)’ is acceptable.

Review Notes

Notes on terminology: The USP vancomycin drug products are currently vancomycin injection, vancomycin hydrochloride for injection, vancomycin hydrochloride for oral solution, and vancomycin hydrochloride capsules. Vancomycin injection is clearly the Baxter product that is stored frozen. Given that the manufacturing process involves (b) (4) it could be argued that the name should be “vancomycin hydrochloride injection”. On the other hand following the principle of avoiding confusion it could also be argued that “vancomycin injection” is reasonable, particularly given that being the hydrochloride is not essential to the function of the product. The name will not be further addressed in this review. Sections where “vancomycin injection” is accepted as a name are indicated by *.

Initially the container was termed an ‘(b) (4),’ but this was later changed to “flexible bag”. Also the term “outlet port” is used to describe the tube with a membrane that is punctured to access the solution. I believe that clinical is on board with these terms.

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

-----DOSAGE FORMS AND STRENGTHS-----



Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	VANCOMYCIN Injection	*
Dosage form, route of administration	Injection	Adequate
Controlled drug substance symbol (if applicable)	NA	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths and salt equivalency statement:	(b) (4)	Single-dose flexible bags containing 500 mg vancomycin in 100 mL, 1 g vancomycin in 200 mL, 1.5 g vancomycin in 300 mL, and 2 g vancomycin in 400 mL [if the name contains hydrochloride then “as the hydrochloride” should be added to each name]

(b) “Full Prescribing Information” Section

#2: Section 2 Dosage and Administration (21 CFR 201.57(c)(12))

2.1 Important Administration (b) (4)

VANCOMYCIN Injection in transparent single-dose (b) (4) intended for intravenous use only. (b) (4) orally.

An infusion rate of 10 mg/min or less is associated with fewer infusion-related events [see *Warnings and Precautions* (b) (4)]. Infusion related events may occur, however, at any rate or concentration.

Drug additives should not be made to this solution.

(b) (4) Directions for use of Vancomycin Injection

Vancomycin Injection, in transparent single-dose (b) (4) is for intravenous administration only. Vancomycin Injection is room temperature stable, ready-to-use drug product.

Preparation for Intravenous Administration:

1. Remove the (b) (4) from aluminum overpouch.
2. Check for minute leaks by squeezing the bag firmly. If leaks are detected, discard solution because sterility may be impaired.
3. Do not add supplemental medication.
4. Visually inspect the (b) (4). If the outlet port protector is damaged, detached, or not present, discard (b) (4) as solution path sterility may be impaired. If after visual inspection the solution is cloudy or if an insoluble precipitate is noted or if any seals are not intact, the (b) (4) should be discarded.
5. The solution in (b) (4) remains chemically stable for 28 days after removal from aluminum overpouch at room temperature (up to 25°C/77°F).
6. Suspend the (b) (4) from eyelet support.
7. Remove protector from outlet port at bottom of (b) (4).
8. Attach administration set. Refer to complete directions accompanying set.
9. Use sterile equipment.

(b) (4) Do not use (b) (4) in series connections. Such use could result in an embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Item	Information Provided in NDA	Reviewer's Assessment
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	See above	Generally adequate. the container closure system is described as (b) (4) and (b) (4). This should be changed to "flexible bag".

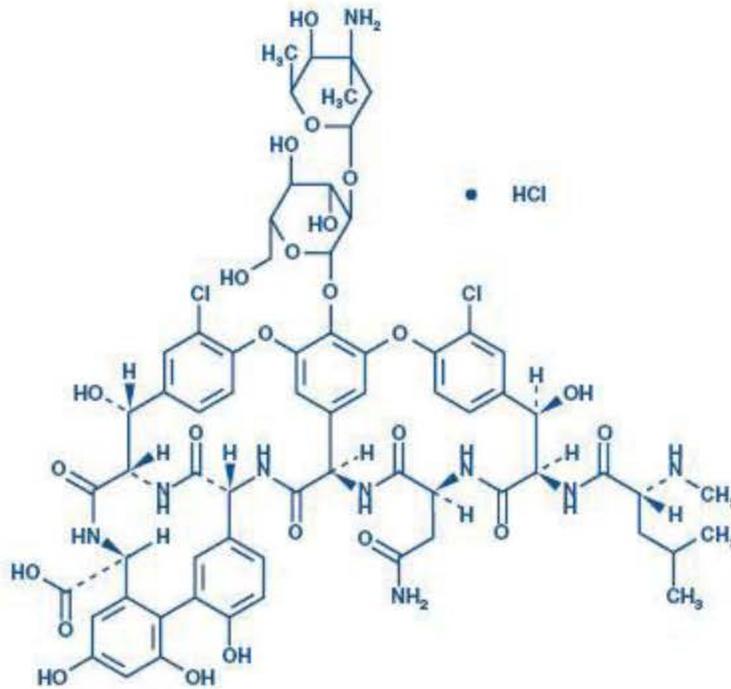
3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Injection	Adequate
Strengths: in metric system and salt equivalency statement	500 mg, 1 g, 1.5 g and 2 g	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. Include "functional score", if present.	(b) (4)	Suggest: Vancomycin Injection (b) (4) a ready to use clear, colorless to light brown solution in single-dose flexible bags containing 500 mg, 1 g, 1.5 g, and 2 g vancomycin in 100 mL, 200 mL, 300 mL, and 400 mL of liquid. The flexible bags (b) (4) are supplied in sealed aluminum overpouches.

#11: Description (21CFR 201.57(c)(12))

Vancomycin Injection, in (b) (4) single-dose (b) (4) vancomycin as Vancomycin Hydrochloride. It is a tricyclic glycopeptide (b) (4) drug derived from *Amiclatopsis orientalis* (formerly *Nocardia orientalis*). The molecular formula is $C_{66}H_{75}Cl_2N_9O_{24} \cdot HCl$ and the molecular weight is 1,485.71. Vancomycin hydrochloride has the following structural formula:



Vancomycin Injection, in (b) (4) single-dose (b) (4) sterile, nonpyrogenic premixed 100 mL, 200 mL, 300 mL or 400 mL solution containing 500 mg, 1 g, 1.5 g or 2 g Vancomycin, respectively, as Vancomycin hydrochloride. Each 100 mL of solution contains (b) (4) 1.8 mL polyethylene glycol, 1.36 g N-acetyl-D-alanine, 1.26 g L-lysine hydrochloride (monochloride) in water for injection, (b) (4). (b) (4) hydrochloric acid and (b) (4) sodium hydroxide (b) (4) 4.5 to 5.5 for pH and 350 to 475 mOsmol/L for osmolarity.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Vancomycin Injection	Adequate*
Dosage form and route of administration	sterile, nonpyrogenic premixed 100 mL, 200 mL, 300 mL or 400 mL solution	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	containing 500 mg, 1 g, 1.5 g or 2 g Vancomycin, respectively, as Vancomycin hydrochloride.	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Each 100 mL of solution contains (b) (4) 1.8 mL polyethylene glycol, 1.36 g N-acetyl-D-alanine, 1.26 g L-lysine hydrochloride (monochloride) in water for injection, (b) (4).	Adequate. Delete (b) (4)
Statement of being sterile (if applicable)	Present	Adequate
Pharmacological/ therapeutic class	It is a tricyclic glycopeptide (b) (4) drug derived from <i>Amycolatopsis orientalis</i> (formerly <i>Nocardia orientalis</i>).	Adequate
Chemical name, structural formula, molecular weight	Structural formula and molecular weight are present. Chemical name not present.	Chemical name should be added. Otherwise adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa, solubility, or pH)	(b) (4)	Change to: Hydrochloric acid and sodium hydroxide are used for pH adjustment. The pH is 4.5 to 5.5 and the osmolarity is 350 to 475 mOsmol/L. Delete statement about (b) (4).

	(b) (4)	Delete the entire paragraph (b) (4) . Change the term (b) (4) " to "flexible bag" in this section.
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#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

(b) (4)

(b) (4)

16.2 Storage

Store below 25°C (77°F), in original package. Product should be used within 28 days of removal from aluminum overpouch.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	500 mg/100 mL etc.	Adequate
Available units (e.g., bottles of 100 tablets). Include child-resistant closure, induction seal, coil, and desiccant as appropriate.	(b) (4)	Suggest: Vancomycin Injection is supplied as a ready to use clear, colorless to light brown solution in single-dose flexible bags containing 500 mg, 1 g, 1.5 g, and 2 g vancomycin in 100 mL, 200 mL, 300 mL, and 400 mL of liquid. The flexible bags (b) (4) are supplied in sealed aluminum overpouches. The bags are supplied in the following packages: [See example below]
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Include "functional score", if present.	(b) (4)	See above
Special handling (e.g., protect from light, do not freeze)	Product should be used within 28 days of removal from aluminum overpouch.	Adequate. Applicant provided data to show that the product can be (b) (4). Therefore the label does not need to state (b) (4)". Amendment of 9/24/18.
Storage conditions	Store below 25°C (77°F), in original package.	Adequate

Proposed by applicant

(b) (4)

Suggested by FDA

NDC number	Packaging configuration
70594-041-02	Carton of six 500 mg/100 mL bags
70594-041-03	Carton of twelve 500 mg/100 mL bags
70594-042-02	Carton of six 1 g/200 mL bags
70594-042-03	Carton of twelve 1 g/200 mL bags
70594-043-02	Carton of six x 1.5 g/300 mL bags
70594-044-02	Carton of six x 2 g/400 mL bags

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured for: Xellia Pharmaceuticals USA, LLC Raleigh, NC 27616	Adequate

2. Container and Carton Labeling

1) Immediate Container Label and Overwrap Label

[The overwrap labels contain the same information as the immediate container labels. The only changes between the various dosage strengths are the obvious changes required for dosage strength and NDC code. The 500 mg immediate container label is shown below. For the larger sizes "100 mL contains:" is changed to "Each 100 mL contains:" The overwraps have a colored background stripe between the two horizontal lines of the product title (yellow for 500 mg, red for 1 g, blue for 1.5 g, and green for 2 g.)

Example of immediate container label:

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Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Vancomycin Injection	Adequate*
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)) and salt equivalency statement (space permitting)	500 mg per 100 mL (5 mg/mL) [and so forth]	Adequate
Route of administration 21. CFR 201.100(b)(3))	For intravenous infusion only.	Adequate
Net contents* (21 CFR 201.51(a))	500 mg per 100 mL [and so forth]	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	1.8 ml Polyethylene Glycol 400, (b) (4); 1.36 g N-Acetyl-D-Alanine and 1.26 g L-Lysine Hydrochloride, (b) (4) in Water for Injection, (b) (4). pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.	Adequate. Remove capitalization and (b) (4)
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Present	Adequate
Storage (not required)	Store below 25°C (77°F), in original package. Use within 28 days of removal from aluminum overpouch.	Adequate. Applicant provided data to show that the product can be (b) (4). Therefore the label does not need to state "(b) (4)". Amendment of 9/24/18.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC 70594-041-01 [and so forth]	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Present	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Xellia Pharmaceuticals USA, LLC Raleigh, NC 27616	Adequate
Others	Single-Dose (b) (4) Sterile, Nonpyrogenic	Adequate

	Ready To Use Dosage: See prescribing information. Cautions: Do not add supplementary medication or additives. Discard unused portion.	
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2) Carton Labeling

There are a number of variants in the cartons but they all adhere to the basic layout shown below.



The following variants are found:

- The NDC number changes as appropriate
- The dose changes as appropriate
- The highlight color changes as appropriate (yellow for 500 mg, red for 1 g, blue for 1.5 g, and green for 2 g). This is the same code that is used for the overwrap.
- Depending on the size of the carton it states “(b) (4)” or “(b) (4)”. The latter statement only applies to the 500 mg and 1 g cartons.
- There are variant cartons (b) (4). The variation appears to be in (b) (4) and the wording and colors are the same. As is the case (b) (4) has a carton of 6 for all strengths and cartons of 12 for 500 mg and 1 g only.

The wording for the front panel (defined as the lower left panel with the space entitled “varnish free – label”) for the 500 mg size is as follows.



The carton will also have (presumably in the varnish-free area):

Notes: Each panel except the bottom contains the wording:

The “back” panel also contains “Rx Only” but this is not on the side panels.

The “top” panel has this wording, Rx Only, and “**Caution:** Do not add supplementary medication or additives.”

Comments: Generally the carton has the information that you would expect and the wording matches that on the flexible bag and on the overpouch. However, the words “sterile” and “Discard unused portion” are not used and “**Caution:** Do not add supplementary medication or additives” is found only on the top of the carton.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Vancomycin Injection There is no proprietary name.	Adequate*
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2)) and salt equivalency statement	500 mg per 100 mL (5 mg/mL) [and so forth] Each 100 mL contains: Vancomycin Hydrochloride equivalent to 500 mg vancomycin	Adequate
Net contents (21 CFR 201.51(a))	500 mg per 100 mL; 1 g per 200 mL [and so forth]	Adequate
Lot number per 21 CFR 201.18	Present	Adequate
Expiration date per 21 CFR 201.17	Present	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	1.8 ml Polyethylene Glycol 400, (b) (4); 1.36 g N-Acetyl-D-Alanine and 1.26 g L-Lysine Hydrochloride, (b) (4) in Water for Injection, (b) (4). pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.	Adequate. Remove capitalization and (b) (4)
Sterility Information (if applicable)	This is a sterile product but "sterile" is not present on the carton.	Add the words "sterile" and "Discard unused portion" to (b) (4).
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Present on front and back panels but not on side panels.	Add to side panels
Storage Conditions	Store below 25°C (77°F), in original package. Use within 28 days of removal from aluminum overpouch.	Adequate. Note that the second statement is only on the front panel. Applicant provided data to show that the product can be (b) (4). Therefore the label does not need to state (b) (4). Amendment of 9/24/18.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Present	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Present (in fact there are three!)	Adequate
Name of manufacturer/distributor	Manufactured for: Xellia Pharmaceuticals USA, LLC	Adequate (on front panel only)

	Raleigh, NC 27616	
"See package insert for dosage information" (21CFR 201.55)	Dosage: (b) (4)	On front panel only. Suggest: Dosage: See package insert for prescribing information
"Keep out of reach of children" (optional for Rx, required for OTC)	Not present	Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	For intravenous infusion only	Adequate, on all panels.
Additional information	Ready to use [all panels] Infuse over at least 60 minutes [front panel only] Caution: Do not add supplementary medication or additives [top panel only]	Generally adequate. Add Caution to front panel.

3. Container and Carton Labeling Information Request

The following Information Request was sent to the applicant on 9/19/18 and accepted in the Amendment of 9/24/18 within the exception of the addition of '(b) (4)'. The applicant provided data to show that (b) (4) produced no deleterious effects on the quality of the product. Therefore omitting '(b) (4)' is acceptable.

We have the following comments concerning the container labels, the overwrap labels, and the cartons.

1) Immediate Container Label and Overwrap Label

We note that the overwrap labels contain the same information as the immediate container labels. The only changes between the various dosage strengths are the obvious changes required for dosage strength and NDC code. The overwraps have a colored background stripe between the two horizontal lines of the product title (yellow for 500 mg, red for 1 g, blue for 1.5 g, and green for 2 g. The following comments use the 500 mg per 100 mL size as an example but they apply to all sizes, as appropriate.

Immediate container label:

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

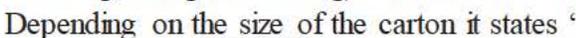
2) Carton Labeling

The following comments use the 500 mg per 100 mL size as an example but they apply to all sizes, as appropriate.

We note that there are a number of variants in the cartons but they all adhere to the basic layout shown below.



The following variants are found:

- The NDC number changes as appropriate
- The dose changes as appropriate
- The highlight color changes as appropriate (yellow for 500 mg, red for 1 g, blue for 1.5 g, and green for 2 g). This is the same code that is used for the overwrap.
- Depending on the size of the carton it states “ (b) (4)” or “ (b) (4)”. The latter statement only applies to the 500 mg and 1 g cartons.
- There are variant cartons for  (b) (4) but the text appears to be the same.

Text for annotation:

Front Panel: Wording for the front panel (defined as the lower left panel with the space entitled “varnish free – label”) for the 500 mg size for annotation.



(b) (4)

* Otherwise this statement is only on the top panel

Other Panels:

(b) (4)

Side Panels:

In addition please add “Rx Only” to the side panels.



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Balajee
Shanmugam

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MICROBIOLOGY[IQA Review Guide Reference](#)**Product Background:** 505(b)(2)**NDA:** 211962**Drug Product Name / Strength:** Vancomycin Injection**Route of Administration:** Injection (intravenous)**Applicant Name:** Xellia Pharmaceuticals ApS**Manufacturing Site:** (b) (4)**Method of Sterilization:** (b) (4)**Review Recommendation:** Adequate**Theme (ANDA only):** N/A**Justification (ANDA only):** N/A**Review Summary:** The submission is **recommended** for approval on the basis of sterility assurance.**List Submissions Being Reviewed:**

Submit	Received	Review Request	Assigned to Reviewer
5/23/2018	5/23/2018	N/A	5/30/2018
8/24/2018	8/24/2018	N/A	8/24/2018

Highlight Key Outstanding Issues from Last Cycle: N/A**Remarks:** eCTD/ Global submit review. Priority/ fast track designation was requested. The 74 day letter due date is 8/5/2018, mid-cycle meeting is 8/29/2018, action date is 11/23/2018. A microbiology IR letter was issued on 8/5/2018; response received 8/24/2018.**Concise Description Outstanding Issues Remaining:** none.**Supporting Documents:**

(b) (4)

List Number of Comparability Protocols (ANDA only): Provided; CP reviewed on pages 32-35.

Filename: N211962MR01.docx

The NDA applicant requested and was granted fast track/ priority review request. The application was received on 5/23/2018, 74 day letter due date is 8/5/2018, mid-cycle meeting is 8/29/2018, action date is 11/23/2018.

P.1 Description of the Composition of the Drug Product

- Description of drug product – The drug product is a ready to use product, clear, colorless to light brown solution without visible particles supplied as 5 mg/ mL concentration, as four different strengths (500 mg/ 100 mL bag, 1 g/ 200 mL bag, 1.5 g 300 mL bag, 2 g/ 400 mL bag).
- Drug product composition –

Ingredient	Quantity per unit				Function
	500 mg / 100 mL (5 mg/ mL)	1 g / 200 mL (5 mg/ mL)	1.5 g / 300 mL (5 mg/ mL)	2 g / 400 mL (5 g / mL)	
Vancomycin (b) (4) *	0.5 g	1.0 g	1.5 g	2.0 g	API
N-acetyl-D-alanine	1.36 g	(b) (4)			(b) (4)
L-lysine hydrochloride (monochloride)	1.26 g	2.52 g	3.78 g	5.04 g	
Polyethylene glycol 400	1.8 mL	3.6 mL	5.4 mL	7.2 mL	
Hydrochloric acid	q.s.	q.s.	q.s.	q.s.	pH adjusting agent
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	pH adjusting agent
(b) (4)	q.s. 100 mL	q.s. 200 mL	q.s. 300 mL	q.s. 400 mL	(b) (4)

* An overfill of (b) (4)% is employed for manufacture of Vancomycin Injection, 500 mg/ 100 mL, 1 g/ 200 mL, 1.5 g/ 300 mL and 2g/ 400 mL to ensure administration of labelled amount of active (for more details on set Overfill, please refer to Section 3.2.P.2.2 within 3.2.P.2. Pharmaceutical Development).

Commercial batch size: (b) (4) L

Maximum proposed commercial batch size: (b) (4)

- Description of container closure system – The drug product is (b) (4) with two connector tubes (b) (4)

(b) (4). One tube contains a twist off port (b) (4).

Configuration	Component	Description	Manufacturer
100- 400 mL bags	Bag	(b) (4) 100, 200, 300, 400 mL bags. (b) (4)	(b) (4)
	Connector tubing	Tubing port is composed of (b) (4)	
	Port	Twist off port	

(b) (4)

Reviewer's Assessment: Acceptable. The drug product description, composition and container closure system are appropriate for the subject drug product.

P.2 Pharmaceutical Development

(b) (4)

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Jesse
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BIOPHARMACEUTICS

NDA: 211962

Submission Type: 505(b)(2) Type 5-New Formulation

Drug Product Name/Strength: Vancomycin Injection, 500 mg/100 mL, 1 g/ 200 mL, 1.5 g/300 mL, and 2 g/400 mL

Dosage Form: Injection, solution

Route of Administration: Intravenous (IV)

Applicant Name: Xelia Pharmaceuticals APS

Intended Use: Vancomycin Injection is a glycopeptide antibacterial indicated in adult and pediatric patients ((b) (4) and older) for the treatment of septicemia, infective endocarditis, skin and skin structure infections, bone infections, and lower respiratory tract infections.

Listed Drug (LD): Vancomycin Injection USP (Vancomycin hydrochloride in the GALAXY plastic container), 500 mg/100 mL, 750 mg/150 mL and 1 g/200 mL [NDA 050671, Baxter Healthcare Corp, approved on April 29, 1993 (500 mg/100 mL and 1 g/200 mL) and December 20, 2010 (750 mg/150 mL)].

REVIEW SUMMARY

This 505(b)(2) NDA, for Vancomycin Injection, 500 mg/100 mL, 1 g/ 200 mL, 1.5 g/300 mL, and 2 g/400 mL in transparent single-dose container, relies for approval on FDA's findings of safety and effectiveness of the Listed Drug (LD), Vancomycin Injection USP in GALAXY plastic single dose container, 500 mg/100 mL, 750 mg/150 mL, and 1 g/200 mL [NDA 050671, Baxter Healthcare Corp].

The Biopharmaceutics review evaluates information and data supporting the Applicant's biowaiver request.

Because the formulation of the proposed to-be-marketed parenteral drug product (DP) is not qualitatively and quantitatively (Q1/Q2) the same as that of the LD, due to the presence of (b) (4) N-acetyl-D-alanine 1.36% (w/v) and L-lysine hydrochloride 1.26% (w/v) and (b) (4) (b) (4) polyethylene glycol 400, 1.8% (v/v)), the biowaiver request per 21 CFR § 320.22(b)(1) is not feasible. However, a scientific bridge can be established between the proposed DP and the LD, based on 21 CFR 320.24(b)(6).

Based on the side-by-side comparison of drug product formulation, physicochemical properties, in vitro antimicrobial activity and in vivo animal studies between the proposed and LD products, as well as information available in the labeling of the LD, the proposed DP and the LD are the same in terms of indication, dosage form, dosage and administration route, concentration and infusion volume and rate. The proposed and LD products are both sterile, non-pyrogenic, and



**QUALITY ASSESSMENT
Biopharmaceutics**



colorless solutions with comparable pH and osmolality. The addition of polyethylene glycol 400 (b) (4) and N-acetyl-D-alanine and L-lysine hydrochloride (b) (4) to the formulation of the proposed DP, is not anticipated to alter the PK, efficacy and safety of vancomycin in human subjects.

Overall, per 21 CFR 320.24(b)(6), the Applicant's proposed drug product has been adequately bridged to the LD; therefore, an in-vivo bioavailability study, comparing the LD to the proposed drug product, is not needed.

RECOMMENDATION: ADEQUATE

From the Biopharmaceutics perspective NDA 211962 for Vancomycin Injection, 500 mg/100 mL, 1 g/ 200 mL, 1.5 g/300 mL, and 2 g/400 mL, is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Qi Zhang, PhD
Division of Biopharmaceutics
Office of New Drug Products, OPQ

10/22/2018

Secondary Biopharmaceutics Reviewer Name and Date:

Elsbeth Chikhale, PhD
Division of Biopharmaceutics
Office of New Drug Products, OPQ

10/22/2018

BIOPHARMACEUTICS ASSESSMENT

List of Submissions Being Reviewed:

eCTD # (SND #)	Received date	Document
0000 (1)	2/14/2018	Original submission

Biowaiver Request:

This 505(b)(2) NDA relies for approval on FDA’s findings of safety and effectiveness of the Listed Drug (LD), Vancomycin Injection, USP supplied as frozen, iso-osmotic, sterile, nonpyrogenic premixed solution in either 5% Dextrose or 0.9% Sodium Chloride in a single dose GALAXY® plastic container (PL 2040) (NDA 050671 approved in 1993, Baxter Healthcare Corporation).

Unlike the LD, the proposed drug product (DP) is supplied as ready-to-use (RTU) solution stored at room temperature (to be stored below 25°C), and is formulated to contain (b) (4) N-acetyl-D-alanine (NADA) and L-lysine hydrochloride) and (b) (4) polyethylene glycol 400 (PEG 400)). (Table 1)

Table 1: Comparison of qualitative and quantitative composition of the proposed Vancomycin Injection, 500 mg/100 mL and the LD, 500 mg/100 mL.

Name of ingredient	Quantity	
	Applicant's formulation (500 mg/100 mL)	Reference product (500 mg/100 mL)
Vancomycin	500 mg (b) (4)	500 mg (as Vancomycin Hydrochloride)
N-acetyl-D-alanine	1.36 g	NA
L-lysine Hydrochloride (Monochloride)	1.26 g	NA
Polyethylene glycol 400	1.8 ml	NA
Hydrochloric acid ¹	q.s.	q.s.
Sodium hydroxide ¹	q.s.	q.s.
Water for Injection or 0.9% NaCl / 5% Dextrose	q.s. 100 mL (WFI)	q.s. 100 mL (0.9% NaCl / 5% Dextrose)

NA – Not Applicable

¹ Used for pH adjustment

Per the approved (listed drug NDA 050671) and proposed (NDA 211962) labels, both products contain vancomycin HCl equivalent to 500 mg vancomycin per 100 mL. Therefore, the concentration of vancomycin is the same in both drug products.

For a parenteral injection product, under 21 CFR 320.22(b)(1), bioequivalence of the drug product may be self-evident when both Q1/Q2 requirements are met, namely when the test product

contains the same active and inactive ingredients in the same concentration as the LD. The proposed DP does not meet the Q1/Q2 criteria for a waiver of the requirement to submit evidence of in vivo bioavailability or bioequivalence under 21 CFR 320.22(b)(1), because the formulation of the proposed injectable product is Q1/Q2 different from the LD in terms of the inactive ingredients. Each 100 mL solution of LD contains approximately 5 g of dextrose hydrous, USP or 0.9 g of sodium chloride, USP, whereas each 100 mL solution of the proposed injection contains approximately 1.8 mL PEG 400, 1.36 g NADA, 1.26 g L-lysine hydrochloride (monochloride) in water for injection, USP. (Tables 1 and 2)

Table 2: Formulation of the proposed Vancomycin Injection, 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL.

Name of ingredient	Quantity per unit					Function	Reference to Standard
	500 mg/100 mL	1 g/200 mL	1.5 g/300 mL	2 g/400 mL	Percentage		
Vancomycin (b) (4) (b) (4)	0.5 g	1.0 g	1.5 g	2.0 g	0.5 % (w/V)	Active substance	In house
N-acetyl-D-alanine	1.36 g	(b) (4)			1.36 % (w/V)	(b) (4)	In house
L-lysine Hydrochloride (Monochloride)	1.26 g	2.52 g	3.78 g	5.04 g	1.26 % (w/V)		USP
Polyethylene glycol 400	1.8 mL	3.6 mL	5.4 mL	7.2 mL	1.8% (V/V)		NF
Hydrochloric acid	q.s. ¹	q.s. ¹	q.s. ¹	q.s. ¹	q.s.	pH adjusting agent	NF
Sodium hydroxide	q.s. ²	q.s. ²	q.s. ²	q.s. ²	q.s.	pH adjusting agent	NF + In house
Water for Injection	q.s. 100 mL	q.s. 200 mL	q.s. 300 mL	q.s. 400 mL	NA	(b) (4)	USP

(b) (4)

NA – Not Applicable

*An overfill of (b) (4)% is employed for manufacture of Vancomycin Injection, 500 mg/100 mL, 1 g/200 mL, 1.5 g/300 mL and 2 g/400 mL to ensure administration of labelled amount of active (for more details on set Overfill please refer to Section 3.2.P.2.2 within 3.2.P.2 Pharmaceutical Development).

(b) (4)

(b) (4)

The Applicant’s request for a waiver of BA/BE studies was discussed at the PIND meeting on Nov 15, 2016 and Pre-NDA meeting on Jan 29, 2018. FDA notified the Applicant that their biowaiver request per 21 CFR § 320.22(b)(1) is not feasible. However, the “bridge” between the proposed drug product and the LD could be based on 21 CFR 320.24(b)(6). For this purpose, the Applicant

had provided the side-by-side comparison information/data for the differences between the proposed DP and the LD including the qualitative/quantitative compositions, the physiochemical characteristics such as pH and osmolality, in vitro microbial activity and animal PK and safety studies (Section 2.7.1).

Information to Support Bridging:

Indication

The indication for which the Applicant seeks approval for this NDA submission is (b) (4)

Strength

The proposed DP contains the same active drug substance (refer the Drug Product Review for the final determination of the API sameness) in the same concentration per mL of drug product as the LD (i.e. 5 mg of vancomycin per mL) and in the same total quantity per unit as the LD (vancomycin 500 mg/100 mL, and 1 g/200 mL), while the two additional strengths proposed for vancomycin injection, 1.5 g/300 mL and 2 g/400 mL, are proportionally similar in composition compared to the 500 mg and 1 g strengths (Table 2).

Dosage and Administration

- Per Section 2 (Dosage and Administration) and Section 11 (Description) of the proposed labeling, the proposed DP and the LD are same in terms of dosage and administration route (injection solution for IV infusion). The drug concentration (5 mg/mL), dose and infusion rate (e.g., daily dose is 2 g divided 500 mg every 6 hours for adult, 10 mg/kg per dose every 6 hours in pediatric patients, and administer each dose at no more than 10 mg/min or over a period of at least 60 minutes) are the same.
- The maximum daily dose for adults is 2 g vancomycin in 400 mL infusion solution which contains 7.2 mL PEG 400, 5.04 g L-lysine hydrochloride, and (b) (4) g NADA.

Presence of Polyethylene Glycol 400 (b) (4)

- Polyethylene glycol 400 (PEG 400) is listed in the FDA Inactive Ingredient (IIG) Database. Per the IIG database, the maximum level of PEG 400 is 75.58% (w/v) for IV administration (Busulfan Injection, 6 mg/mL, ANDA 202259, approved on 12/22/2015]. The maximum daily dose of 37.2 ml of busulfan injection (9.3 mL busulfan injection every six hours per labelling of ANDA 202259) for adults (e.g., 70 kg patient) delivers 24.924 mL PEG 400, which is about 3.5 times of the amount of PEG 400 (7.5 mL) delivered by the proposed DP. Refer to the Non-Clinical Review for the determination of the safety of the presence of PEG 400.
- As requested by FDA (Response to pre-IND questions), to demonstrate the absence of embryo-fetal toxic effects of PEG 400, the Applicant conducted a safety assessment of PEG

400 in a novel embryo-fetal development study in rabbits [Study No DG90YB]. Refer to the Non-Clinical Review for the determination of the adequacy of the study.

Presence of N-Acetyl-D-Alanine (NADA) and L-Lysine Hydrochloride (b) (4)

- N-acetyl-D-alanine (NADA) is a novel excipient and is not listed in the IIG Database. The Applicant conducted GLP compliant nonclinical toxicology studies to demonstrate the safety of NADA, and per the Applicant the excipient was found to be safe for use in the amount present in the proposed finished drug products. Refer to the Drug Substance Review and Non-Clinical Review for the final determination of the adequacy of the safety studies for NADA.
- To support the lysine hydrochloride content in the proposed DP, the Applicant provided two listed parenteral nutrition drugs, Kabiven® and Perkabiven® [NDA 200656, Fresenius Kabi, approved on 08/25/2014], which contain 263 mg/100 mL and 187 mg/100 mL lysine (added as the hydrochloride salt), respectively. Per the Applicant, the maximum daily intake of lysine for these two products (based on 60 kg body weight) is about 6 g (Kabiven) and 4.5 g (Perkabiven), which is equivalent to 7.5 g and 5.6 g of lysine hydrochloride. Those amounts are more than the amount of lysine (5.04 g) that patients received from the proposed DP in adults. Refer to the Non-Clinical Review for the determination of the safety of the presence of lysine.
- To support the safe use of lysine for pediatric patients, the Applicant provided one listed drug, TrophAmine 10% (B. Braun Inc., NDA 019018) indicated for intravenous nutritional support of infants that contains 820 mg/100 mL lysine acetate. Per the Applicant, the maximum daily intake of lysine received from TrophAmine (based on 4.4 kg body weight) is about 1 g. The maximum daily intake of lysine in the proposed DP is 443 mg per day, which is less than the amount of lysine that patients receive from TrophAmine. Refer to the Non-Clinical Review for the determination of the safety of the presence of lysine in pediatric patients.

Absence of Dextrose or NaCl

The absence of dextrose or NaCl is not expected to change the vancomycin drug distribution of the proposed drug product.

Comparative Physicochemical Properties

- The pH (5.0-5.2 [measured] and (b) (4) [proposed acceptance range]) and osmolality (402-417 [measured] and (b) (4) mOsmol/L [proposed acceptance range]) of the proposed DP are different from the pH (3.8-3.9 [measured] and (b) (4) [approved acceptance range]) and osmolality (276-292 [measured] and (b) (4) mOsmol/L [approved acceptance range]) of the LD product, based on the COA data generated from eight (8) registration lots of the proposed DP, and three (3) LD product lots.
- Per the Applicant, the pH of its formulation of approximately (b) (4) is favorable as it is associated with a lower risk of phlebitis development than the pH of the LD, and it is in line with the Infusion Nurses Society (INS) recommendation for preferable pH range of 5 to 9 for drugs intended for peripheral vein administration.

- The osmolality of the proposed DP is below the threshold of approximately 500 mOsmol/L for peripheral use as recommended in the literature. In addition, a number of marketed drug products approved for IV infusion use, including antibiotics have higher osmolality than the proposed DP.
- Note that per the respective package inserts, the storage condition for the proposed DP [$\leq 25^{\circ}\text{C}$] is different for the LD [$\leq -20^{\circ}\text{C}$]. Refer to the Drug Product Review for the adequacy of the physicochemical stability of the proposed DP.

In conclusion, both the proposed and the LD products are sterile, non-pyrogenic and colorless solutions, and the difference in pH and osmolality attributes between the proposed and LD product is not a concern when considering the safety of the proposed DP.

Table 3: Mean toxicokinetic parameters of vancomycin after dosing the proposed Vancomycin Injection RTU and the LD[RLD] to dogs for 13-weeks

Group	Dose level	Day	Sex	AUC _{0-Tmax} (hr* $\mu\text{g}/\text{mL}$)	AUC _{INF} (hr* $\mu\text{g}/\text{mL}$)	Tmax (hr)	Cmax ($\mu\text{g}/\text{m}$)	t1/2 (hr)	Vz (mL/kg)	Cl (mL/hr/kg)
Xellia Vancomycin Injection RTU	75-100 mg/kg	1	Female	242.49 \pm 10.396	247.51 \pm 10.876	1.0 \pm 0.0	122.65 \pm 4.410	1.69 \pm 0.031	996.09 \pm 40.188	408.78 \pm 18.044
			Male	235.82 \pm 12.623	240.99 \pm 13.028	1.0 \pm 0.0	123.46 \pm 4.888	1.70 \pm 0.037	1031.51 \pm 57.488	422.15 \pm 22.251
		45	Female	226.77 \pm 17.965	#	1.01 \pm 0.012	111.51 \pm 9.453	1.56 \pm 0.063	752.26 \pm 52.417	336.17 \pm 25.520
			Male	231.93 \pm 16.554	#	1.02 \pm 0.015	110.56 \pm 8.493	1.64 \pm 0.068	779.50 \pm 77.744	327.73 \pm 26.385
		91	Female	379.26 \pm 4.658	#	1.0 \pm 0.0	159.03 \pm 8.283	5.12 \pm 0.458	1881.44 \pm 152.113	255.48 \pm 3.944
			Male	362.31 \pm 13.387	#	1.04 \pm 0.042	145.72 \pm 10.791	4.87 \pm 0.569	1871.73 \pm 197.951	269.10 \pm 11.341
RLD	75-100 mg/kg	1	Female	333.56 \pm 63.115	339.14 \pm 62.858	1.0 \pm 0.0	136.87 \pm 8.401	1.91 \pm 0.250	852.38 \pm 50.525	334.09 \pm 36.729
			Male	280.38 \pm 10.370	286.56 \pm 10.518	1.0 \pm 0.0	129.44 \pm 4.327	1.85 \pm 0.195	928.28 \pm 80.195	351.61 \pm 11.980
		45	Female	250.34 \pm 12.183	#	1.02 \pm 0.015	120.78 \pm 6.999	1.87 \pm 0.285	795.53 \pm 110.076	298.48 \pm 15.149
			Male	261.11 \pm 13.910	#	0.95 \pm 0.077	118.38 \pm 6.644	2.01 \pm 0.334	806.32 \pm 98.739	285.89 \pm 14.634
		91	Female	377.85 \pm 29.249	#	1.01 \pm 0.014	159.41 \pm 5.698	4.57 \pm 0.674	1664.87 \pm 206.438	263.82 \pm 19.317
			Male	429.29 \pm 40.709	#	1.05 \pm 0.036	158.39 \pm 7.416	4.33 \pm 0.602	1380.15 \pm 116.787	241.35 \pm 27.820

In Vitro Antimicrobial Activity

- The in vitro antimicrobial activity of the proposed drug product was found to be equivalent to that of the LD. In addition, the proposed drug product formulation does not influence the activity of vancomycin, because the placebo control (liquid solution containing all the excipients in the same amounts as in the proposed Vancomycin Injection, but without the active pharmaceutical ingredient, vancomycin) had no inhibitory effect on the *in vitro* antimicrobial activity.

Animal Studies

- A 13-week GLP general toxicology study in the dog with 75/100 mg/kg/day of the proposed Vancomycin Injection RTU or the LD demonstrate that the PK/TK parameters are similar (Table 3) and safety profiles are comparable between the proposed and the LD products, suggesting that the proposed formulation has no impact on overall exposure to vancomycin, and would not pose additional safety concern. Refer to the Non-Clinical Review for further details.

Reviewer's Assessment: ADEQUATE

The scientific bridge to the LD was established pursuant to 21 CFR 320.24(b)(6), based on the side-by-side comparison of the formulation, physicochemical properties, the in vitro antimicrobial activity and in vivo animal studies between the proposed and listed products, as well as information available in the labeling of the LD; therefore, an in-vivo bioavailability study, comparing the LD to the proposed drug product, is not needed.

From the Biopharmaceutics perspective, NDA 211962 for Vancomycin Injection, 500 mg/100 mL, 1 g/ 200 mL, 1.5 g/300 mL, and 2 g/400 mL, is **ADEQUATE** and recommended for **APPROVAL**.

Refer to the Drug Substance and Drug Product Reviews for additional CMC information. Refer to the Non-Clinical Reviews for additional animal PK and safety information. Refer to the FDA recommended labeling to ensure safe and effective use of the proposed drug product.



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Chikhale

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations/ Comments
Assay, stability (impurities/degradation products)		L		Acc	
Appearance (color, turbidity)		L		Acc	
Extractables and Leachables		M	Extractables and leachables testing has been carried out and no compounds of concern have been identified. This container-closure system has been previously used for 4 approved ANDAs.	Acc	
Endotoxins		M	The Drug Product Specifications include Bacterial Endotoxins Testing per USP <85>. The BET method has been adequately validated and the maximum potential endotoxins exposure is less than or equal to the USP requirements recommended hourly amount for drug administered on a body mass (per kg) basis.	Acc	
Sterility		H	The Drug Product Specifications include Sterility Testing per USP <71>. The test method has been adequately validated per USP. DP is provided in single-dose containers.	Acc	
Particulate Matter		M	Controlled in the Drug Product Specifications per USP <788>. Batch analysis and stability data are well within specification limits.	Acc	



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