CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213895Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213895
Assessment # 3

Drug Product Name	Vancomycin Injection
Dosage Form	Solution
Strength	5 g/100 mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Xellia Pharmaceuticals ApS
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCDT 0018 (SD-18) (*NDA resubmission*)	February 26, 2021	
eCDT 0019	March 21, 2021	Drug Product
eCDT 0023	July 23, 2021	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katherine Windsor	Paresma Patel
Drug Product	George Lunn	Thomas Oliver
Manufacturing	Golam Kibria	James Norman
Microbiology	Dustin Thomas	Yan Zheng
Labeling	N/A	N/A
Biopharmaceutics	N/A	N/A
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Dorota Matecka	

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QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
31868	II	Xellia Pharmaceuticals ApS	Vancomycin	Adequate	10/20/2020*	Review by Donglei Yu*
	Other	Refer to OPQ Assessments # 1 and # 2				

**This is the only update to the table from OPQ Assessments # 1 and # 2*

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
ANDA	60180	Vancomycin Hydrochloride for Injection
NDA	211962	Vancomycin Injection
IND	129733	Vancomycin Injection

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology (P/T)	Adequate	*Refer to the P/T review by Dr. Madisa Macon*		
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, vancomycin injection. All manufacturing and testing facilities are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment (OPMA) on April 21, 2021. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Vancomycin is a glycopeptide antibiotic derived from fermentation of Amycolatopsis orientalis. The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis.

The proposed drug product is a new intravenous formulation of vancomycin, to be used for the treatment of the same indications as for the listed drug (LD), Vancocin® Hydrochloride (Vancomycin Hydrochloride for Injection, USP) approved under ANDA 60180. This 505(b)(2) NDA relies on FDA's previous finding of safety and effectiveness of the LD; however, since Vancocin® Hydrochloride was discontinued, the Applicant used Vancomycin hydrochloride for Injection, USP, approved under ANDA 062663 and listed in the Orange Book as the Reference Standard (RS) for the in vivo BE study and the in vitro bridging.

The proposed drug product, vancomycin injection, is a light yellow or light brown solution supplied in a 100 mL clear glass bottle with a rubber stopper; it will be available in a single strength pharmacy bulk package (5 g/100 mL; 50 mg/mL). The proposed labeling describes both intravenous and oral administration. For intravenous administration, further dilution is required with 5% Dextrose, 5% Dextrose Injection and 0.9% Sodium Chloride Injection, Lactated Ringer's Injection, 5% Dextrose and Lactated Ringer's Injection, or 0.9% Sodium Chloride Injection. The product may alternatively be taken orally, undiluted or diluted with 1 oz of water.

Proposed Indication(s) including Intended Patient Population	*Intravenous administration/indications*: • Septicemia • Infective Endocarditis • Skin and Skin Structure Infections • Bone Infections • Lower Respiratory Tract Infections *Oral administration/indications*: • Clostridium Difficile-associated diarrhea • Enterocolitis caused by Staphylococcus aureus (including methicillin-resistant strains. The product is indicated in adult and pediatric patients.
Duration of Treatment	Up to 10 days
Maximum Daily Dose	2 g
Alternative Methods of Administration	Intravenous or oral administration

B. Quality Assessment Overview

This NDA, originally submitted on September 20, 2019, was recommended for Complete Response (CR) by the OPQ Review Team in the first review cycle due to the lack of leachable information for the container closure system proposed for the commercial drug product (refer to the OPQ Reviews # 1 and # 2 dated January 10, 2020 and March 9, 202, respectively). This deficiency was included in the CR Letter, which was issued on March 20, 2020. There were no other Product Quality deficiencies noted in the first review cycle. The current NDA resubmission addresses the deficiency listed in the CR letter and provides the leachable information, including the qualification data. In addition, several relatively minor CMC updates have been provided in the resubmission (as described below).

Drug Substance: Adequate

The chemistry, manufacturing and controls (CMC) information for vancomycin drug substance has been provided via a reference to DMF Type II 31868, which was found acceptable in the first NDA review cycle. A few updates have been made to the vancomycin drug substance by the DMF holder since the original NDA submission. That includes extension of the retest period (based on the udated stability results) to (b) (4) months for vancomycin wet base drug substance stored at (b) (4) °C. The status of the DMF continues to be adequate (based on the most recent DMF

review dated October 20, 2020).The drug product manufacturer established a retest period of (b) (4) months for the drug substance. *Refer to the Drug Substance Review, below*.

Drug Product: Adequate

The majority of the drug product information was found adequate in the first NDA review cycle. However, the leachable testing results and qualification data for the proposed container closure system were not provided. Therefore, the NDA was recommended for Complete Response. The leachable testing information was provided in the current NDA resubmission and found adequate by the Drug Product Reviewer. Also, qualification data, which were reviewed by the Pharmacology/Toxicology Reviewer for this NDA, were found acceptable (refer to the P/T review). In addition, 24-month long-term stability results for the primary stability batches were included in the NDA resubmission. Overall stability information provided in the NDA supports the proposed shelf life of 24 months for the drug product to be stored at 15°C-25°C, and protected from light. *For details, refer to the Drug Product Review, below*.

Labeling: Adequate

The labeling review was included in the OPQ Review # 1. Several revisions were recommended in the CMC related sections of the package insert, the carton labeling, and the container label. That includes a prominent placement of the following statement: “For Oral Use, see prescribing information” in the container label and carton labeling. These recommended labeling revisions have been accepted by the Applicant. The labeling is being currently finalized by the NDA review team.

Manufacturing: Adequate

The drug product manufacturing process and facilities were found adequate in the previous NDA OPQ assessment (refer to the OPQ Review # 1, dated January 10, 2020). The only changes to the facilities in the current NDA resubmission involve: 1) inclusion of an additional testing site by the drug substance supplier, and 2) change of the drug product manufacturing facility owner (from Xellia (b) (4)); however, the location of the facility has not changed. According to the OPMA review of the current resubmission, all associated facilities are considered adequate to support this NDA, and overall “Approve” recommendation was entered into Panorama by OPMA on April 21, 2021. *For further details refer to the Manufacturing Integrated Assesssment, below*.

Biopharmaceutics: Adequate

The Biopharmaceutics information was found adequate in the previous review cycle (refer to the OPQ Review # 1 dated January 10, 2020).

Microbiology: Adequate

The Product Quality Microbiology information was found adequate in the previous review cycle (refer to the OPQ Review # 1 dated January 10, 2020). No significant product quality microbiology changes have been proposed in the current NDA resubmission; the updated stability data (24-month) have been found acceptable from the microbiology perspective (*refer to the Microbiology Review, below*).

C. Risk Assessment

The risk table below has been replicated from the OPQ Assessment # 1 (dated January 10, 2020); the only update made to the table includes the extractable/leachable assessment (now changed to: Acceptable).

From Initial Risk Identification			**Review Assessment**		
From Initial Risk Identification	**Review Assessment**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	Formulation Manufacturing Process	H		Acceptable	
Endotoxin/ pyrogen	Formulation Manufacturing Process	M		Acceptable	
Assay /Stability	Formulation Manufacturing Raw Materials	L		Acceptable	
Extractables/ Leachables	Formulation Container Closure System	M		Acceptable	
Particulate matter	Formulation Manufacturing Process	M		Acceptable	

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CHAPTER VII: MICROBIOLOGY
IQA NDA Assessment Guide Reference

Product Information	
NDA Number	213895
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Vancomycin Injection, 5 g/100 mL (50 mg/mL)
Route of Administration	Intravenous or Oral
Applicant Name	Xellia Pharmaceuticals ApS
Therapeutic Classification/ OND Division	CDER/OGD
Manufacturing Site	Xellia Pharmaceuticals USA, LLC 8900 Capital Boulevard Raleigh, NC, USA 27616
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
NDA 213895 0018 (18)	**02/26/2021**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The submission is in the eCTD format. The submission is a resubmission in response to a CR sent 03/20/2020.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed):

Supporting Documents: N/A

The applicant submitted this amendment as a resubmission in response to a CR dated 03/20/2020. Drug product specifications were adjusted in this submission, however, microbiology related parameters are unchanged. The applicant proposes an increase in the expiration date (b) (4) to 24 months and stability data is reviewed below. No other microbiology related changes to the drug product are proposed.

P.8 Stability

P. 8.1 Stability Summary and Conclusion
(3.2.P.8.1 Stability Summary)

Proposed Expiry: 24 months when store at 15-25°C.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment
(3.2.P.8.2 Postapproval Stability Protocol)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	USP <85>	(b) (4)
Sterility	USP <71>	Sterile

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25 ± 2°C/60% ± 5% RH Inverted and Upright orientation. The shelf life will be confirmed from stability studies performed on the exhibit batches.

Test	Time (Months)								
	0	3	6	9	12	15	18	Shelf Life -1 Month	Shelf Life
Bacterial Endotoxins	X	X	X	X	X	X	X	X	X
Sterility	X	X	X	X	X	X	X	X	X

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Reviewer's Assessment: ***Adequate***

P.8.3 Stability Data
(3.2.P.8.3 Stability Data – Exhibit Batches 5g)

The applicant provided stability data for three exhibit lots 2981017, 2984251, and 2983354 at 25 ± 2°C/60% ± 5% RH in the inverted and upright orientation. The applicant also performed an accelerated study at 40±2°C/75% ± 5% RH, but does not contain microbiology testing and is not reviewed.

Long term stability testing schedule:

Test	Time (Months)													
	0	12	13	14	15	16	17	18	19	20	21	22	23	24
Bacterial Endotoxins	R	I	-	-	-	-	-	-	-	-	-	-	-	U/I
Sterility	R	I	-	-	-	-	-	-	-	-	-	-	-	U/I

R- Release Testing
U-Upright Orientation
I-Inverted Orientation

Long term stability acceptance criteria:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	USP <85>	(b) (4)
Sterility	USP <71>	Sterile

The initial and 24 month time points are shown to meet acceptance criteria for long term storage studies on lots # 2981017, 2984251, and 2983354 in the inverted orientation.

Long term stability testing meets acceptance criteria up to the 24 month time point.

Reviewer's Assessment: *Adequate*

Long term stability testing adequately validates the proposed 24 month expiration date.

A Appendices N/A

Reviewer's Assessment: *Adequate*

R Regional Information

Executed Batch Records

Executed lot #s: 2983346, 2980989, and 2983354

The batch records confirm that validated (b) (4) manufacturing processes were used for the manufacture of the exhibit batches. The intended Master Batch Record is provided.

Reviewer's Assessment: *Adequate*

Comparability Protocols - No CP was included in the application.

Reviewer's Assessment: N/A

The following deficiencies are considered: N/A

Primary Microbiology Assessor: Dustin Thomas, Ph.D. 04/09/2021

Secondary Microbiology Assessor: Yan Zheng, Ph.D. 04/09/2021

Yan Zheng

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Dustin Thomas

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA # 213895
Assessment # 2

Drug Product Name	Vancomycin Injection
Dosage Form	Injection solution
Strength	5 g/100 mL
Route of Administration	Injection (IV)
Rx/OTC Dispensed	Rx
Applicant	Xellia
US agent, if applicable	Edward Eichmann

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0007	11/29/2019	Quality
eCTD 0010	12/16/2019	Quality
eCTD 0013	01/23/2020	Quality

QUALITY ASSESSMENT TEAM- Refer to Review #1
RELATED/SUPPORTING DOCUMENTS – Refer to Review #1

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

This NDA, as amended, has **not** provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for a **complete response** by the Office of Pharmaceutical Quality (OPQ) at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on January 2, 2020. However, the drug product review found the NDA inadequate. Therefore, this NDA is recommended for a CR from a CMC perspective.

An information request was sent on October 28, 2019 requesting results from a leachables study. The applicant responded on December 16, 2019

that the leachables data would not be available until the end of March 2020. The following information request was sent on December 19, 2019:

We acknowledge your December 16, 2019 response that you plan to submit the screening leachables study at the end of March 2020, but we are not able to guarantee that we will be able to review any information received after January 21, 2020 as specified in our Information Request of December 9, 2019. This may be considered an approvability issue for your application.

As of March 9, 2020, the leachables study has not been received. Therefore, this NDA is recommended for a Complete Response from a CMC perspective.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Refer to Review #1.

B. Quality Assessment Overview

Drug Substance: Adequate

Refer to review #1.

Drug Product: Inadequate

This product is a sterile liquid vancomycin injection in a glass vial with a rubber stopper and aluminum overseal. Various diluents have been shown by testing to be physically and chemically compatible with the vancomycin solution.

The container-closure system is a 100 mL glass vial with a rubber stopper and aluminum overseal. Extractables testing has been carried out and no compounds of concern have been identified; however, leachables testing data are not provided. The applicant indicates that they have contracted for a study of leachables from product near the end of shelf life. This information has not been submitted to the NDA as of March 9, 2020. For this reason, this NDA is not recommended for approval at the present time.

This NDA is recommended for a Complete Response from a Drug Product perspective. For additional details, refer to the review by George Lunn.

Labeling: Adequate

Refer to Review #1.

Manufacturing: Adequate

Refer to Review #1.

Biopharmaceutics: Adequate

Refer to review #1.

Microbiology (if applicable): Adequate

Refer to review #1.

C. Risk Assessment- Refer to Review #1

D. List of Deficiencies for Complete Response

1. Drug Product Deficiency

The leachables data was requested by January 21, 2020; however, the results from the leachables studies have not been received. Qualify all applicable leachables for the proposed vancomycin drug product. The acceptability of the proposed stopper cannot be determined until the identity safety profile of the leachables is considered acceptable from a nonclinical perspective.

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George Lunn

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Erika Englund

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