

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209481Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality (OPQ) Review

NDA 209481 (Resubmission)

Review # 2

Submissions reviewed: SDN#9 (dated 10/10/2017 – NDA Resubmission)
SDN#11 (dated 11/13/2017)
SDN#13 (dated 3/6/2018)
SDN#15 (dated 3/29/2018)
SDN#17 (dated 3/29/2018 – Major Amendment)
SDN#18 (dated 4/12/2018)

OND Division: Division of Anti-Infective Products (DAIP)

Product Name: Vancomycin Hydrochloride for Injection, 250 mg/vial; 750 mg/vial; 1.25 g/vial; 1.50 g/vial

Applicant: Mylan Pharmaceuticals Limited

Recommendation:

This NDA is recommended for Approval from the Product Quality perspective.

Executive Summary:

NDA 209481, originally submitted on July 20, 2016, was recommended for Complete Response (CR) by the OPQ Review Team due to the unacceptable status of the drug substance and drug product manufacturing facilities (refer to the OPQ Review # 1 dated May 18, 2017 in Panorama). The CR letter dated May 19, 2017 also included one non-CR, product quality related, comment (b) (4). Based on a review of the application and inspectional documents, the manufacturing facilities have been now found acceptable to support this NDA by the Facilities Reviewer (see Attachment I). In addition, the drug product stability update has been found acceptable to further support the originally proposed expiration dating of 24 months (see Attachment II). Also, per the FDA request, the Applicant provided information to address the elemental impurities issue, which was found acceptable by the Drug Product and the Drug Substance Reviewers (refer to Attachments III and IV, respectively). During the labeling review, additional chemical and microbiological in-use stability information was requested by the FDA, to support the proposed storage time and condition statements for the reconstituted and further diluted solutions of vancomycin (using the reconstitution and dilution agents listed in the proposed package insert). These data were provided in the March 29, 2018 amendment, which was considered a major amendment and extended the PDUFA goal date for this resubmission by three months (i.e., from April 10, 2018 to July 10, 2018). The in-use stability data were reviewed and found acceptable to support the storage statements in the labeling by both Drug Product and Microbiology Reviewers (refer to Attachments V and VI, respectively). (b) (4)

Based on the above assessments and the overall manufacturing inspection recommendation of “Approve” entered by the Office of Process and Facilities into Panorama on February 16, 2018, this NDA can now be recommended for approval.

Attachments

Attachment I (Facilities - Dr. Jonathan Swoboda)

Attachment II and III (Drug Product - Dr. George Lunn)

Attachment IV (Drug Substance - Dr. Haripada Sarker)

Attachment V (Labeling - Dr. George Lunn)

Attachment VI (Microbiology - Dr. Wendy Tan)

Attachment VII (Updated Final Risk Table)

This NDA is recommended for Approval from the Product Quality perspective.

On behalf of the OPQ Review Team

Dorota Matecka, ATL for NDA 209481

Dorota M.
Matecka -S

Doc #011 prepared by Dorota M. Matecka, S.
DN # US # U.S. Government au 095 au FDA
au Project # 2048 15000000 100 11 1300132091
au Dorota M. Matecka, S.
Date 2016/04/23 17:06:40/09

40 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Attachment V

NDA 209481 Vancomycin Hydrochloride for Injection, USP 250 mg, 750 mg, 1.25 g, 1.5 g Mylan

Review of Common Technical Document-Quality (Ctd-Q) Module 1 Labeling & Package Insert

- **Package Insert as amended by OND through 5/30/18**
- **Vial Labels and Cartons as amended through the Amendment of 4/12/18**

1. Package Insert

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

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

Vancomycin Hydrochloride for Injection is a sterile lyophilized powder for injection in single-dose vials containing vancomycin hydrochloride, USP equivalent to 250 mg, 750 mg, 1.25 g, or 1.5 g of vancomycin base.

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	No proprietary name; Vancomycin Hydrochloride for Injection	Adequate
Dosage form, route of administration	for injection, for intravenous use	Adequate
Controlled drug substance symbol (if applicable)	NA	Adequate
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths and salt equivalency statement	Vancomycin Hydrochloride for Injection is a sterile lyophilized powder for injection in single-dose vials containing vancomycin hydrochloride, USP equivalent to 250 mg, 750 mg, 1.25 g, or 1.5 g of vancomycin base	Adequate

(b) “Full Prescribing Information” Section

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

2.5 Preparation of Vancomycin Hydrochloride for Injection for Intravenous Administration and Storage Instructions

Vancomycin Hydrochloride for Injection must be reconstituted and further diluted.

Reconstitution of the Lyophilized Powder and further dilution

At the time of use, reconstitute the vials of Vancomycin Hydrochloride for Injection (lyophilized powder) with Sterile Water for Injection to a concentration of 50 mg of vancomycin/mL then further dilute with an infusion solution to a final concentration of 5 mg/mL (see Table 1 for the appropriate volumes). Discard any reconstituted solution remaining in the vial.

Table 1 Volume of Sterile Water for Injection to be Added for Reconstitution and Volume of Infusion Solution to be Used for Further Dilution

<u>Vancomycin Strength per Vial</u>	<u>Volume of Sterile Water for Injection for reconstitution^a</u>	<u>Volume of infusion solution^b to further dilute to a final concentration of 5 mg/mL</u>
250mg	5 mL	50 mL
750mg	15 mL	150 mL
1.25 g	25 mL	250 mL
1.5 g	30 mL	300 mL

^aAfter reconstitution, the vials may be stored in a refrigerator for 14 days without significant loss of potency. [A]

^b Use an infusion solution from the list of the compatible infusion solutions below [see Dosage and Administration (2.6)].

The desired dose diluted in this manner should be administered by intermittent IV infusion over a period of 60 minutes or greater.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

Discard reconstituted and diluted solutions 14 days after initial reconstitution. [A]

2.6 Compatibility with Intravenous Fluids

The following diluents are physically and chemically compatible with 5 g/L vancomycin hydrochloride-:

5% Dextrose Injection, USP [B]

5% Dextrose Injection and 0.9% Sodium Chloride Injection, USP [B]

Lactated Ringer's Injection, USP [B]

Lactated Ringer's and 5% Dextrose Injection, USP [B]

0.9% Sodium Chloride Injection, USP [B]

Storage of Diluted Solutions:

Solutions that are diluted with 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP may be stored in a refrigerator for 14 days without significant loss of potency. [C]

Solutions that are diluted with the following infusion fluids may be stored in a refrigerator for 96 hours: [D]

5% Dextrose Injection and 0.9% Sodium Chloride Injection, USP

Lactated Ringer's Injection, USP

Lactated Ringer's and 5 % Dextrose Injection, USP

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	Adequate, as amended. Letters in red refer to the sources of the supporting data. See below.

- A. Solutions in water were shown to be stable on a CMC basis (P.8.3) and a microbiological basis (Amendment of 3/29/18) for 14 days.
- B. An in-use study was carried out (Table 3.2.P.2/49). Solutions (50 mg/mL) were prepared with water, allowed to stand at 2-8°C for 96 h, then further diluted with various diluents

and allowed to stand at room temperature for 90 min. These other diluents are saline, 5% dextrose, 5% dextrose and saline, Lactated Ringer's, and Lactated Ringer's and 5% dextrose. These solutions were then tested for appearance, assay (biological), purity by HPLC, impurities, pH, and particulates. No significant changes were observed.

- C. Solutions in 5% dextrose and saline were shown to be stable on a CMC basis (Amendment of 3/23/18) and a microbiological basis (Amendment of 3/29/18) for 14 days.
- D. Solutions in Ringer's, Ringer's/dextrose, and dextrose/saline were shown to be stable for 96 hours on a CMC basis (Amendment of 4/12/18) and for 96 hours on a microbiological basis (Amendment of 3/29/18).

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

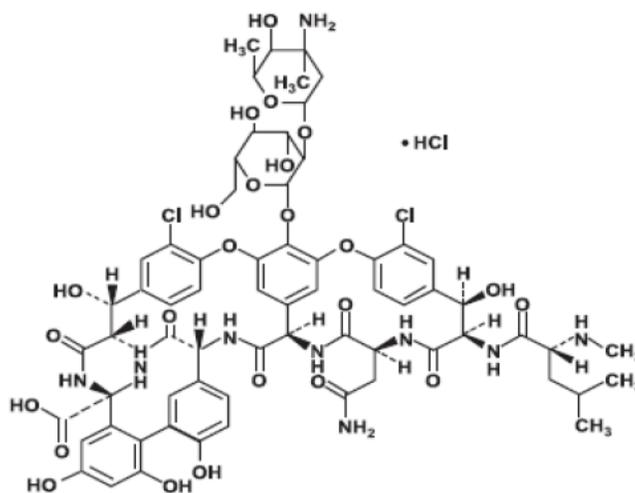
Vancomycin Hydrochloride for Injection, USP is a sterile lyophilized powder for injection supplied as an off-white to light tan colored powder or plug in single-dose vials containing vancomycin hydrochloride, USP equivalent to 250 mg, 750 mg, 1.25 g, or 1.5 g of vancomycin base.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	for Injection	Adequate
Strengths: in metric system and salt equivalency statement	vancomycin hydrochloride, USP equivalent to 250 mg, 750 mg, 1.25 g, or 1.5 g of vancomycin base.	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.	off-white to light tan colored lyophilized powder or plug in single dose vials	Adequate

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

Vancomycin Hydrochloride for Injection, USP, contains the hydrochloride salt of vancomycin, a tricyclic glycopeptide antibacterial derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). The chemical name for vancomycin hydrochloride, USP is (Sa)-(3S, 6R, 7R, 22R, 23S, 26S, 36R, 38aR)-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-[(2R)-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*] [10, 2, 16]- benzoxadiazacyclotetracosine-26-carboxylic acid, monohydrochloride. The molecular formula is $C_{66}H_{75}Cl_2N_9O_{24} \cdot HCl$ and the molecular weight is 1,485.71. Vancomycin hydrochloride, USP has the following structural formula:



Vancomycin Hydrochloride for Injection, USP is a sterile lyophilized powder for injection. Vancomycin Hydrochloride for Injection, USP is supplied in single-dose vials, containing 256 mg, 769 mg, 1.28 g, or 1.54 g of vancomycin hydrochloride, USP equivalent to 250 mg, 750 mg, 1.25 g, or 1.5 g of vancomycin base. The lyophilized powder is reconstituted with Sterile Water for Injection and subsequently diluted prior to intravenous administration [see *Dosage and Administration* (2.5)].

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	No proprietary name; Vancomycin Hydrochloride for Injection, USP	Adequate
Dosage form and route of administration	intravenous administration	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	vancomycin hydrochloride, USP equivalent to 250 mg, 750 mg, 1.25 g, or 1.5 g of vancomycin base	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	None	Adequate
Statement of being sterile (if applicable)	Present	Adequate
Pharmacological/ therapeutic class	tricyclic glycopeptide antibacterial	Adequate
Chemical name, structural formula, molecular weight	Present	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa, solubility, or pH)	None	Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

How Supplied:

Vancomycin Hydrochloride for Injection, USP is a sterile lyophilized powder for injection supplied as an off-white to light tan colored powder or plug in single-dose flip top vials that contain vancomycin hydrochloride, USP equivalent to 250 mg, 750 mg, 1.25 g, or 1.5 g of vancomycin base. They are available as follows:

NDC No. 67457-822-99: Vancomycin Hydrochloride for Injection, USP equivalent to 250 mg vancomycin in a 5 mL flip top vial with an ash gray seal, in packages of 10 vials.

NDC No. 67457-705-75: Vancomycin Hydrochloride for Injection, USP equivalent to 750 mg vancomycin in a 20 mL flip top vial with an ash gray seal, in packages of 10 vials.

NDC No. 67457-823-99: Vancomycin Hydrochloride for Injection, USP equivalent to 1.25 g vancomycin in a 30 mL flip top vial with an ash gray seal, in packages of 10 vials.

NDC No. 67457-824-99: Vancomycin Hydrochloride for Injection, USP equivalent to 1.5 g vancomycin in a 30 mL flip top vial with a golden brown seal, in packages of 10 vials.

Storage:

Prior to reconstitution, store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	250 mg, 750 mg, 1.25 g, 1.5 g	Adequate
Available units (e.g., bottles of 100 tablets). Include child-resistant closure, induction seal, coil, and desiccant as appropriate.	single-dose flip top vials that contain vancomycin hydrochloride equivalent to 250 mg, 750 mg, 1.25 g, or 1.5 g of vancomycin base	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number. Include "functional score", if present.	<p>NDC No. 67457-822 (b) (4) - Vancomycin Hydrochloride for Injection, USP equivalent to 250 mg vancomycin in a 5 mL flip top vial with an ash gray seal, in packages of 10 vials.</p> <p>NDC No. 67457-705-75 - Vancomycin Hydrochloride for Injection, USP equivalent to 750 mg vancomycin in a 20 mL flip top vial with an ash gray seal in packages of 10 vials.</p> <p>NDC No. 67457-823 (b) (4) - Vancomycin Hydrochloride for Injection, USP equivalent to 1.25 g vancomycin in a 30 mL flip top vial with an ash gray seal, in packages of 10 vials.</p> <p>NDC No. 67457-824 (b) (4) - Vancomycin Hydrochloride for Injection, USP equivalent to 1.5 g vancomycin in a 30 mL flip top vial, with an golden brown seal, in packages of 10 vials.</p>	Adequate
Special handling (e.g., protect from light, do not freeze)	None	Adequate
Storage conditions	Prior to reconstitution, store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]	Adequate

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: Mylan Institutional LLC Rockford, IL 61103 U.S.A. Manufactured by: Mylan Laboratories Limited Bangalore, India	Adequate

2. Container and Carton Labeling

1) Immediate Container Label



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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	No proprietary name; Vancomycin Hydrochloride for Injection, USP	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4)) and salt equivalency statement (space permitting)	Example: 250 mg*/vial *Each vial contains: Vancomycin hydrochloride equivalent to 250 mg vancomycin	Adequate
Route of administration (21.CFR 201.100(b)(3))	For intravenous use	Adequate
Net contents* (21 CFR 201.51(a))	250 mg, 750 mg, 1.25 g, 1.5 g	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) (21CFR 201.100(b)(5)**	None	
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)	Prior to reconstitution, store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]	Recommend: Prior to reconstitution, store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature] Because of lack of space it is acceptable to omit excursions statement.
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21CFR 207.35(b)(3)	NDC 67457-822 (b) (4) NDC 67457-705 NDC 67457-823 NDC 67457-824	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Present	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Mylan Institutional LLC, Rockford, IL 61103, USA	Adequate

Others	<p>Important – Read insert for precautions and directions before use. Usual Adult dosage: (b) (4)</p> <p>. See package insert. (b) (4) contents with 5 mL Sterile Water for Injection. (b) (4)</p> <p>Lyophilized. (b) (4)</p>	<p>Suggestions:</p> <p>Important – Read insert for precautions and directions before use. (b) (4)</p> <p>Reconstitute (b) (4) contents with (b) (4) mL Sterile Water for Injection. (b) (4)</p> <p>(b) (4)</p> <p>Lyophilized. (b) (4)</p> <p>. Usual Adult dosage: (b) (4)</p> <p>-See package insert.</p>
--------	--	---

2) Carton Labeling

The carton labels are as follows. According to the Amendment of 2/16/18 the vials are packaged in cartons of 10.



(b) (4)

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

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))	No proprietary name; Vancomycin Hydrochloride for Injection, USP	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(d)(2)) and salt equivalency statement	Example: 250 mg*/vial *Each vial contains: (b) (4) Vancomycin hydrochloride, USP equivalent to 250 mg vancomycin	Adequate
Net contents (21 CFR 201.51(a))	250 mg, 750 mg, 1.25 g, 1.5 g	Adequate
Lot number per 21 CFR 201.18	Lot number per 21 CFR 201.18	Present
Expiration date per 21 CFR 201.17	Expiration date per 21 CFR 201.17	Present
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	None	
Sterility Information (if applicable)	Sterile powder	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Present	Adequate
Storage Conditions	Prior to reconstitution, store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]	Recommend: Prior to reconstitution, store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature] Because of lack of space it is acceptable to omit excursions
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 67457-822- (b) (4) NDC 67457-705- (b) (4) NDC 67457-823- (b) (4) NDC 67457-824- (b) (4)	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Present	Adequate
Name of manufacturer/distributor	Mylan Institutional LLC, Rockford, IL 61103, USA	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Important – Read insert for precautions and directions before use. Usual Adult dosage: (b) (4) (b) (4) See package insert (b) (4)	Suggestions: Important – Read insert for precautions

	(b) (4) contents with 5 mL Sterile Water for Injection. After reconstitution, may be stored in a refrigerator for (b) (4) without significant loss of potency. (b) (4) Lyophilized. (b) (4)	and directions before use. Usual Adult dosage: (b) (4) - See package insert (b) (4) Reconstitute (b) (4) contents with (b) (4) mL Sterile Water for Injection. After reconstitution, may be stored in a refrigerator for (b) (4) without significant loss of potency. (b) (4) Lyophilized. (b) (4)
"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 use	Adequate

Conclusions: As currently amended the Package Insert is acceptable to CMC. Suggestions have previously been conveyed to the clinical division by amending the label in SharePoint.

The vial labels and cartons are generally acceptable to CMC. It is recommended that the storage statement be changed as follows. "Prior to reconstitution, store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]". Because of lack of space it is acceptable to omit excursions

It is suggested that changes to other wording on the vial labels and cartons be made as follows. "Important – Read insert for precautions and directions before use. (b) (4). Reconstitute (b) (4) contents with (b) (4) mL Sterile Water for Injection. (b) (4) Lyophilized. (b) (4) Usual Adult dosage: (b) (4) (b) (4) - See package insert."

These suggestions were conveyed to the clinical Division.

George Lunn, Ph.D.

Balajee Shanmugam, Ph.D.



George
Lunn

Digitally signed by George Lunn

Date: 6/04/2018 09:20:33AM

GUID: 508da72000029f40833369b0a181e8b3



Balajee
Shanmugam

Digitally signed by Balajee Shanmugam

Date: 6/04/2018 10:04:19AM

GUID: 50758d5000003c1b1962e036ea11002c

Attachment VI

MICROBIOLOGY

Product Background

NDA: 209481 S/N 0017 & 0018

Drug Product Name / Strength: Vancomycin Hydrochloride for Injection, USP;
250mg; 750 mg; 1.250 g; and 1.5 g per vial

Route of Administration: Intravenous

Applicant Name: Mylan Laboratories Limited
Opp. To IIM, Bilekahalli, Bannerghatta Road, Bangalore, Karnataka,
India 560076

Manufacturing Site: Mylan Laboratories Limited, Plot No 14, Sipcot II, Krishnagiri Road,
Hosur, Tamil Nadu, India 635109 (250mg, 750 mg, and 1500 mg)

Mylan Laboratories Limited (Speciality formulation Facility) No: 19
A, Plot No: 284 B/1, Bommasandra-Jigani Link Road, Industrial
Area, Anekal Taluk, Bangalore, Karnataka 560105, India (1250 mg)

Method of Sterilization: (b) (4)

Review Recommendation: Adequate

Theme (ANDA only): Product sterility assurance

Justification (ANDA only): N/A

Review Summary:

- The submission is **recommended** for approval on the basis of sterility assurance.
- The product is (b) (4). There are currently no deficiencies identified based on the information submitted.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
3/29/2017	3/29/2017	N/A	4/4/2017
4/12/2018	4/12/2018	N/A	4/16/2018

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
07/20/2016	1	04/08/2017

Highlight Key Outstanding Issues from Last Cycle: None

Remarks: None

Concise Description Outstanding Issues Remaining: Post-reconstitution and dilution storage studies are deficient.

Supporting Documents: None

List Number of Comparability Protocols (ANDA only): N/A

(b) (4)

Attachment VII

ATTACHMENT I: Final Risk Assessment

From Initial Risk Identification			Review Assessment		
From Initial Risk Identification	Review Assessment	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
		H, M, or L		Acceptable or Not Acceptable	
Assay /Stability	Formulation Raw materials Process parameters Scale/equipment Site	M		Acceptable	
Extractables and leachables	Formulation Container closure	M	Acceptable studies have been carried out	Acceptable	Re-evaluate if the stopper is changed
Endotoxins	Formulation Raw materials Process parameters Scale/equipment Site	M	Controlled in drug product specification	Acceptable	
Sterility	Formulation Raw materials Process parameters Scale/equipment Site	H	Controlled in drug product specification	Acceptable	
Particulate matter	Formulation Raw materials Process parameters	M	Controlled in drug product specification by USP <788>	Acceptable	Re-evaluate if changes in the formulation, process or container are proposed
Facilities	cGMP issues identified at DS and DP facilities	H	<i>Adequate results of inspectional history of facilities</i>	Acceptable	

Recommendation: *Complete Response*

NDA 209481

Review # 1

Drug Name/Dosage Form	Vancomycin Hydrochloride for Injection
Strength	250 mg/vial; 750 mg/vial; 1.25 g/vial; 1.50 g/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Mylan Laboratories Limited
US agent, if applicable	Mylan Pharmaceuticals Inc. Anil Sachdeva, Senior Director, Regulatory Affairs anil.sachdeva@mylan.com (Secure Email verified)

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	July 20, 2016	All
Amendment (eCTD 002)	October 25, 2016	Drug Product
Amendment (eCTD 004)	November 4, 2016	Drug Product
Amendment (eCTD 005)	January 18, 2017	Microbiology, Process
Amendment (eCTD 006)	February 28, 2017	Microbiology
Amendment (eCTD 007)	March 22, 2017	Microbiology, Drug Product
Amendment (eCTD 008)	May 4, 2017	Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Haripada Sarker	Benjamin Stevens
Drug Product	George Lunn	Dorota Matecka
Process	Nancy Waites	David Dean Anderson
Microbiology	Wendy Tan	Nandini Bhattacharya
Facilities	Jonathan Swoboda	Christina Capacci-Daniel
Biopharmaceutics	Yang Zhao	Elsbeth Chikhale
Regulatory Business Process Manager	Luz Rivera	N/A
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Environmental Assessment*	George Lunn	Dorota Matecka
Application Technical Lead	Dorota Matecka	N/A

*EA addressed in DP Chapter

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	April 3, 2017 (DARRTS)	Review by Haripada Sarker

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
preIND	118864	Preliminary Responses dated August 8, 2013 in DARRTS (<i>preIND meeting cancelled</i>)

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

This NDA has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, vancomycin hydrochloride for injection. Significant cGMP deficiencies were identified at the drug substance and drug product manufacturing sites and the overall recommendation of “Withhold” for manufacturing facilities has been entered in Panorama on May 17, 2017. Therefore, this NDA is recommended for Complete Response (CR) from the Product Quality perspective.

II. Summary of Quality Assessments

A. Product Overview

Vancomycin is a tricyclic glycopeptide antibacterial indicated for the treatment of the following infections:

[Redacted] (b) (4)

- Septicemia
- Bone infections
- Lower respiratory tract infections
- Skin and skin structure infections

[Redacted] (b) (4)

This 505(b)(2) NDA provides for several new strengths (i.e., a total vial content) of injectable formulation of vancomycin hydrochloride [Redacted] (b) (4). The listed drug for this 505(b)(2) NDA is Vancomycin for Injection (500 mg/vial, 1 g/vial, 5 g/vial, and 10 g/vial) approved under ANDA 62663 held by Fresenius Kabi. The drug products strengths proposed via this NDA include the following: 250 mg/vial, 750 mg/vial, 1.25 g/vial, and 1.50 g/vial. No other changes have been proposed in the formulation of the current drug product.

Proposed Indication(s) including Intended Patient Population	As listed above (adults and pediatric patients)
Duration of Treatment	Intravenous indications: Adults with normal renal function: 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours Pediatric patients with normal renal function: 10 mg/kg per dose given every 6 hours.

Maximum Daily Dose	As above (see the package insert for details)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Vancomycin hydrochloride is a white or almost white amorphous powder freely soluble in water, slightly soluble in alcohol, insoluble in ether and in chloroform.

The chemistry manufacturing and controls information for vancomycin hydrochloride drug substance has been provided via a reference to DMF Type II (b) (4) held by (b) (4). (b) (4) DMF (b) (4) has been previously found adequate in support of several ANDAs. The most recent review of the latest DMF amendment conducted in support of the current NDA also found it to be acceptable (review dated April 3, 2017, in DARRTS). The retest period established by the drug substance manufacturer for vancomycin hydrochloride stored between (b) (4) for is (b) (4) months. However, the drug product manufacturer has assigned a retest period of (b) (4) months for vancomycin hydrochloride drug substance (to be stored between (b) (4)).

The drug product, vancomycin for injection, which consists of vancomycin hydrochloride lyophilized in a glass vial with a rubber stopper and aluminum overseal is supplied in the following strengths: 250 mg/vial, 750 mg/vial, 1.25 g/vial, and 1.50 g/vial. The drug product formulation (b) (4). Each vial is reconstituted with water for injection to yield a 50 mg/mL solution. (b) (4)

The drug product specification includes tests and acceptance criteria for appearance, identity, pH, osmolality, particulate matter, assay and impurities by HPLC, heavy metals, (b) (4), reconstitution time, and appearance of reconstituted solution, sterility, bacterial endotoxin and content uniformity. During the NDA review additional information and clarifications were provided regarding the drug product impurity profile and its comparison with the listed drug. In addition, clarifications regarding the analytical procedures, specifically the HPLC method used for the detection of impurities were also requested. The batch analyses for three batches of each vial presentation were provided and found acceptable with no out of specification results and no obvious differences. The proposed container closure system for the finished drug product, i.e., (b) (4) glass tubular vials with 20 mm necks and all stoppers (b) (4) has been found suitable for the proposed use. In response to the FDA question, the Applicant clarified that the 1.25 g and 1.5 g presentations (each supplied in a 30 mL vial) have different colored overseals so that each presentation can be distinguished either by vial size (5, 20, or 30 mL) or, for the two 30 mL vial size presentations, by overseal color (ash grey or golden brown). At least 12 months of long term and 6 months of accelerated stability data were provided for three representative batches of each drug product strength. Based on the overall stability information provided in the NDA, the proposed 24-month expiration dating for the drug

product to be stored at room temperature has been found acceptable. In addition, the in-use stability studies were conducted for the drug product supporting the proposed storage time and conditions for the reconstituted and further diluted solutions to be used for intravenous infusion. (b) (4)

The manufacturing process consists of (b) (4)

During the review several comments were conveyed to the Applicant and additional information was requested regarding the proposed manufacturing process, (b) (4)

. In addition, in response to the FDA recommendations, the acceptance criteria for (b) (4)

Additionally, master batch records were updated to address several FDA comments regarding the (b) (4)

Based on the overall information provided in the initial NDA submission and subsequent amendments, the proposed drug product manufacturing process has been found acceptable.

From the product quality microbiology perspective, additional information was requested by the FDA regarding the following: container closure integrity, floor plans and manufacturing flow, (b) (4)

bacterial endotoxin method validation, and several other issues and areas. Consequently, the product quality microbiology information provided in the initial NDA submission and subsequent amendments was found acceptable.

The biopharmaceutics review focused on the review of the request submitted by the Applicant to waive the requirement to conduct bioavailability/bioequivalence studies for all proposed drug product strengths. Based on the information provided in the NDA, the biowaiver request has been granted for the proposed drug product (b) (4)

The vancomycin hydrochloride drug substance is manufactured by (b) (4) and the drug product is manufactured by Mylan Laboratories Limited, India. Due to the unacceptable status of the both drug substance and drug product sites, the overall recommendation for this NDA entered into Panorama by the Office of Process and Facilities on May 17, 2017 is "Withhold".

Consequently, due to unresolved issues related to the proposed manufacturing facilities, this NDA is currently not recommended for approval from the Product Quality perspective.

The following CR comment should be included in the CR letter for this NDA:

During a recent inspection of the [REDACTED] (b) (4) and Mylan Laboratories Ltd. (FEI 3008255419) manufacturing facilities for this NDA, our field investigator observed objectionable conditions at the facilities and conveyed that information to the representative of the facilities at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

In addition, the following non-CR comment will be included in the letter [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

- B. Special Product Quality Labeling Recommendations (NDA only)
N/A
- C. Final Risk Assessment (see Attachment I)

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Process

CHAPTER IV: Microbiology

CHAPTER V: Biopharmaceutics

CHAPTER VI: Facilities

ATTACHMENT I: Risk Assessment

188 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

MICROBIOLOGY

Product Background

NDA: 209481

Drug Product Name / Strength: Vancomycin Hydrochloride for Injection, USP;
250mg; 750 mg; 1.250 g; and 1.5 g per vial

Route of Administration: Intravenous (b) (4)

Applicant Name: Mylan Laboratories Limited
Opp. To IIM, Bilekahalli, Bannerghatta Road, Bangalore, Karnataka,
India 560076

US Agent: Mylan Pharmaceuticals Inc.,
781 Chestnut Ridge Road, Morgantown, WV 26505

Representative: Anil Sachdeva, Senior Director, Regulatory Affairs

Tel: 304-554-4884

Fax: 732-249-0225

Manufacturing Site: Mylan Laboratories Limited, Plot No 14, Sipcot II, Krishnagiri Road,
Hosur, Tamil Nadu, India 635109 (250mg, 750 mg, and 1500 mg)

Mylan Laboratories Limited (Speciality formulation Facility) No: 19
A, Plot No: 284 B/1, Bommasandra-Jigani Link Road, Industrial
Area, Anekal Taluk, Bangalore, Karnataka 560105, India (1250 mg)

Method of Sterilization: (b) (4)

Review Summary:

List Submissions being reviewed (table):

Submit	Received	Review Request	Assigned to Reviewer
07/20/2016	07/20/2016	N/A	08/05/2016
10/25/2016	10/25/2016	N/A	11/14/2016
10/28/2016	10/28/2016	N/A	11/14/2016
01/18/2017	01/18/2017	N/A	01/23/2017
02/28/2017	02/28/2017	N/A	03/01/2017
03/22/2017	03/22/2017	N/A	03//27/2017

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description of Outstanding Issues Remaining: None

Review Recommendation: Adequate

BIOPHARMACEUTICS

NDA: 209481

Drug Product Name / Strength: Vancomycin Hydrochloride Injection USP/250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.50 g/vial

Route of Administration: Intravenous infusion (b) (4)

Applicant Name: Mylan Laboratories Ltd.

Product Background:

Mylan Laboratories Ltd. submits NDA 209481 for Vancomycin Hydrochloride Injection USP 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.50 g/vial under 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act. The listed drug products, Vancomycin Hydrochloride for Injection, USP, 500 mg/vial, 1 g/vial, 5 g/vial, and 10 g/vial, manufactured by Fresenius Kabi were approved by FDA on March 17, 1987, July 31, 1987, June 3, 1988, and November 28, 1997 under ANDA 062663 [ANDA 062663 Vancomycin Hydrochloride for Injection, USP, 750 mg/vial was approved by FDA on August 17, 2016 (see the Orange Book)]. (b) (4)

Vancomycin hydrochloride for intravenous use is indicated for: (b) (4)

(b) (4) treatment of (b) (4) septicemia, bone infections, lower respiratory tract infections, skin and skin structure infections. The usual daily intravenous dose of Vancomycin Hydrochloride Injection in adults with normal renal function is 2 g divided either as 500 mg every 6 hours or 1 g every 12 hours. The usual intravenous dosage of vancomycin in pediatric patients with normal renal function is 10 mg/kg per dose given every 6 hours.

(b) (4)

Review Summary:

Submission: Mylan Laboratories Ltd. submitted NDA 209481 for Vancomycin Hydrochloride Injection USP 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.50 g/vial under 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act.

Reviewer's Assessment: Both the listed and proposed drug products are formulated as a lyophilized powder. For intravenous administration, both products are reconstituted with sterile water and further diluted in a suitable solution for infusion. (b) (4)

The proposed drug product is qualitatively the same as the listed drug product, and the concentration of vancomycin upon reconstitution and dilution for intravenous infusion (b) (4) is the same for the proposed drug product and the listed drug product. However, the amount of drug per vial is different, and therefore the strength (amount of vancomycin HCl lyophilized powder per vial) is different.

Based on the provided information, the request to waive the requirement to conduct Bioavailability/Bioequivalence studies for NDA 209481, Vancomycin Hydrochloride Injection USP/250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.50 g/vial is granted.

Recommendation: From the Biopharmaceutics perspective, NDA 209481 for Vancomycin Hydrochloride Injection USP 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.50 g/vial is recommended for **APPROVAL**.

List of Submissions being reviewed: The original NDA 209481, submitted on July 20, 2016 is being reviewed, including the modules 2.3, 2.5, 2.7, 3.2.P.

Highlight Key Outstanding Issues from Last Cycle: None. This is the first review cycle.

Concise Description of Outstanding Issues: None.

BCS Designation

Solubility: It is reported by the Applicant that vancomycin is freely soluble in water.

Table 1. Solubility of vancomycin in different pH aqueous solutions (Page 23, Module 3.2.P.2).

Buffer (pH)	Solubility (mg/mL)
Aqueous media (pH 1)	140
Aqueous media (pH 3)	196
Aqueous media (pH 4)	2.9
Aqueous media (pH 5)	9.5
Aqueous media (pH 7.5)	17.5

Permeability: No data for the permeability of vancomycin were provided in this NDA.

Biowaiver Request

The Applicant requests a biowaiver for all proposed strengths of Vancomycin Hydrochloride Injection USP (250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.50 g/vial).

Administration of the proposed Vancomycin Hydrochloride Injection

The proposed Vancomycin Hydrochloride for Injection, USP is supplied as an off-white to light tan colored lyophilized powder in vials containing the amount of vancomycin hydrochloride equivalent to 250 mg, 750 mg, 1.25 g, or 1.5 g of vancomycin base.

For intravenous administration, after being reconstituted with sterile water to a concentration of 50 mg of vancomycin/mL, the reconstituted solution should be further diluted in a suitable infusion solution before intravenous administration. Based on the proposed labeling information, reconstituted solutions of vancomycin 250 mg/5 mL, 750 mg/15 mL, 1.25 g/25 mL, and 1.5 g/30 mL must be further diluted in respectively at least 50 mL, 150 mL, 250 mL, and 300 mL of a suitable infusion solution. It is recommended to dilute solutions of vancomycin to a final concentration of 5 mg/mL or less. The desired dose diluted in this manner should be administered by intermittent intravenous infusion over a period of at least 60 minutes.

(b) (4)

Comparison of composition and routes of administration between the proposed drug product and the list drug

Both the proposed drug product and the listed drug product are formulated as a lyophilized powder for injection. They have qualitatively the same composition and both contain the same active and inactive ingredients (Table 2). The only difference between the proposed drug product and the listed drug product is the amount of the lyophilized powder in the vials.

Both the proposed drug product and the listed drug product can be intravenously administered. (b) (4)

For intravenous administration, upon reconstitution with sterile water, both products achieve the same concentration of 50 mg/mL and achieve comparable pH values (b) (4) and osmolality after reconstitution (Table 2). Based on the labeling information, both products are further diluted in a suitable infusion solution and infused at the same rate (no more than 10 mg/min recommended) and same drug concentration (no more than 5 mg/mL recommended).

(b) (4)

Table 2. Side by side comparison table for the proposed drug product versus the listed drug.

Parameters	Reference listed drug	Proposed drug product
Drug name	Vancomycin hydrochloride for Injection, USP	Vancomycin hydrochloride for Injection USP
Active Ingredients	Vancomycin hydrochloride	Vancomycin hydrochloride
Inactive Ingredients	(b) (4)	
Route of administration	Intravenous	Intravenous
Dosage form	Lyophilized powder	Lyophilized powder
Strength	500 mg/vial, 1 g/vial, 5 g/vial, 10 g/vial	250 mg/vial, 750 mg/vial, 1.25 g/vial, 1.50 g/vial
Description	Off white lyophilized plug filled in (b) (4) vial plugged with stopper and aluminum seal	Off white to light tan colored lyophilized plug or powder filled in vial plugged with stopper and aluminum seal
pH	2.5-4.5	(b) (4)
Osmolality	(b) (4)	
Drug concentration	50 mg/mL (when reconstituted with Sterile water for injection)	50 mg/mL (when reconstituted with Sterile water for injection)

(b) (4)

Reviewer’s Overall Assessment:

Biowaiver for parenteral solution:

According to 21 CFR 320.22(b)(1), for certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. The Agency can waive the requirement for the submission of in vivo evidence measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product’s in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

- (i) the drug product is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) the drug product contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

For intravenous administration, based on the information provided in NDA 209481, the proposed Vancomycin Hydrochloride Injection USP 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.50 g/vial meets the above requirement for granting the biowaiver request, because:

(i) the proposed product is a lyophilized powder to be reconstituted and further diluted in a solution for intravenous infusion.

(ii) the proposed drug product is qualitatively the same as the listed drug. Though the amount of the active ingredient in each vial is different from the listed drug, the final concentration in the reconstituted (50 mg/mL) or further diluted solution (≤ 5 mg/mL) is the same due to the use of different volumes of the reconstitution water or diluted liquid.

(iii) the pH and osmolality of the proposed reconstituted product are comparable to that of the listed drug.

(b) (4)

Therefore, the biowaiver submitted in NDA 209481, which waives the requirement to submit in vivo bioavailability/bioequivalence study for the proposed Vancomycin Hydrochloride Injection USP/250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.50 g/vial is granted.

Reviewer's Recommendations:

From a Biopharmaceutics perspective, NDA 209481 for the proposed Vancomycin Hydrochloride Injection USP 250 mg/vial, 750 mg/vial, 1.25 g/vial and 1.50 g/vial is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date:

Yang Zhao, Ph.D.
Biopharmaceutics Primary Reviewer
Division of Biopharmaceutics
Office of New Drug Products, OPQ
02/15/2017

Secondary Reviewer Name and Date:

I concur with Dr. Zhao's assessment and Approval recommendation.

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Team Lead
Division of Biopharmaceutics
Office of New Drug Products, OPQ
02/27/2017



Yang
Zhao

Digitally signed by Yang Zhao
Date: 2/27/2017 11:26:26PM
GUID: 56f958740001a1f9707b4476d760e12f



Elsbeth
Chikhale

Digitally signed by Elsbeth Chikhale
Date: 2/28/2017 07:19:44AM
GUID: 50743ccc000031928b54eba1769a5df9

11 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

ATTACHMENT I: Final Risk Assessment

From Initial Risk Identification			Review Assessment		
From Initial Risk Identification	Review Assessment	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
		H, M, or L		Acceptable or Not Acceptable	
Assay /Stability	Formulation Raw materials Process parameters Scale/equipment Site	M		Acceptable	
Extractables and leachables	Formulation Container closure	M	Acceptable studies have been carried out	Acceptable	Re-evaluate if the stopper is changed
Endotoxins	Formulation Raw materials Process parameters Scale/equipment Site	M	Controlled in drug product specification	Acceptable	
Sterility	Formulation Raw materials Process parameters Scale/equipment Site	H	Controlled in drug product specification	Acceptable	
Particulate matter	Formulation Raw materials Process parameters	M	Controlled in drug product specification by USP <788>	Acceptable	Re-evaluate if changes in the formulation, process or container are proposed
Facilities	Significant cGMP deficiencies identified at the DS site	H		Not acceptable	

This NDA is recommended for Complete Response from the Product Quality perspective.

Dorota M.
Matecka -S

 Digital signed by Dorota M. Matecka -S
DN: cn=US, o=US Government, ou=FDA,
ou=People,
ou=2342, 1.3.6.1.5.5.3.1.1.1=1300123201, cn=Dorota
M. Matecka -S
Date: 2017.05.18 16:32:35 -0400

Dorota Matecka, Ph.D. ATL for NDA 209481 on behalf of OPQ Team

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELISSA V CHHANGTE
07/18/2018