

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209463Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN
SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 13, 2017
From: Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 209463

Subject: Final Recommendation for NDA 209463

At the time when the CMC Review #1 was completed on May 09, 2017, it had noted the following pending issues:

- The label/labeling issues were not resolved.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

On June 12, 2017, the applicant submitted revised labels and labeling. The CMC sections of the submitted labels and labeling were reviewed by Dr. Caroline Strasinger, and found them acceptable (**Attachment -1**) from the CMC perspective.

Recommendation:

This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
June 13, 2017

Hitesh N.
Shroff -S

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Shroff -S
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Attachment 1:

Labeling:

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: 12-JUN-17

From: Caroline Strasinger, Ph.D.
Drug Product Reviewer
Branch V Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: Labeling Review #1 of NDA 209463

Subject: Finalized Label/labeling of CMC Sections

At the time when Labeling Review of this application was completed (05/04/2017), this NDA was not recommended for approval due to unresolved CMC label/labeling issues. On 06/12/2017, the applicant has submitted revised labels and labeling which satisfactorily addressed all CMC label/labeling issues (see the **Attachment**).

Recommendation:

The previously noted CMC label/labeling issues have been satisfactorily resolved, and therefore, this application is now recommended for **approval** from the label/labeling perspective.

Caroline Strasinger, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP

Attachment:

1. PI

Reviewer Comment: The Applicant has concurred with all recommendations to the label noted in the previous labeling review dated 04-MAY-2017. In the first labeling review, deficiencies were noted in Section 3 Dosage Forms and Strength, and Section 11 Description. The Applicant provided the revised label on 12-JUN-2017; all Quality related sections of the label have been provided below for completeness of the review.

a. Highlights of Prescribing Information - **ADEQUATE**

Product Title

PANTOPRAZOLE SODIUM for injection, for intravenous use

Initial U.S. Approval: 2000

Dosage Forms and Strength

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

For Injection: 40 mg pantoprazole lyophilized powder in single-dose vial for reconstitution (3)

b. FULL PRESCRIBING INFORMATION

#3 Dosage Forms and Strength – **ADEQUATE**

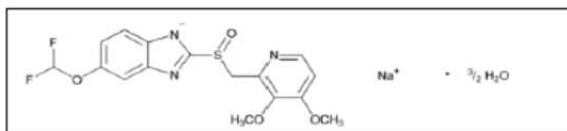
3 DOSAGE AND STRENGTHS

For Injection: 40 mg pantoprazole white to off-white lyophilized powder in a single-dose vial for reconstitution.

#11 Description - **ADEQUATE**

11 DESCRIPTION

The active ingredient in Pantoprazole Sodium for Injection, a PPI, is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S \cdot 1.5 H_2O$, with a molecular weight of 432.37. The structural formula is:



Pantoprazole sodium is a white to off-white crystalline powder and is racemic. Pantoprazole sodium is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane. The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. The reconstituted solution of Pantoprazole Sodium for Injection is in the pH range 9.5 to 11.5.

Pantoprazole Sodium for Injection is supplied for intravenous administration as a sterile lyophilized powder in a single-dose clear glass vial fitted with a rubber stopper and crimp seal. Each vial contains 40 mg pantoprazole (equivalent to 45.1 mg of pantoprazole sodium), and sodium hydroxide to adjust pH.

#16 How Supplied/Storage and Handling - ADEQUATE

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Pantoprazole Sodium for Injection is supplied in a single-dose vial as a white to off-white sterile lyophilized powder for reconstitution containing 40 mg of pantoprazole .

Pantoprazole Sodium for Injection is available as follows:

NDC Number	Strength	Package
0143-9284-01	40 mg pantoprazole	Single vial
0143-9284-10	40 mg pantoprazole	Package of 10 vials

Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° – 30°C (59° – 86°F) [see USP Controlled Room Temperature].

Protect from light.

2. Labels - ADEQUATE

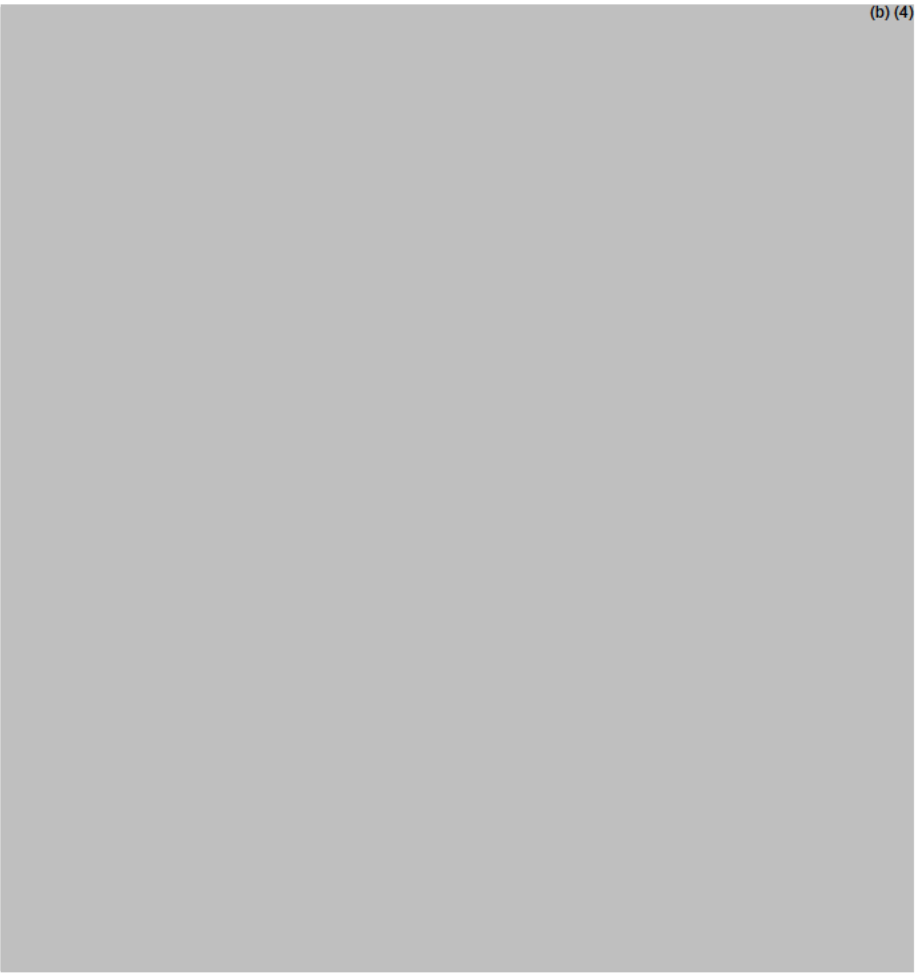
Reviewer Comment: On 10-MAY-2017 the applicant responded to previous comments contending space constraints prevented them from incorporating the requested formatting. After further evaluation and comparisons to similar labels, the FDA maintained the previous recommendation for formatting of the equivalency statement and the inclusion of the word Sterile on the primary display panel of both the container and carton. This was communicated to the Applicant on 07-JUN-2017. The Applicant agreed to the carton/container recommendations on 12-JUN-2017. The updated and final carton and container appear below.

a. Container labels



b. Carton labels

(b) (4)





Caroline
Strasinger

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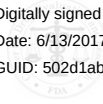
Moo Jhong
Rhee

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Hitesh
Shroff

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Recommendation: As of this review this 505 (b)(2) NDA is *not* ready for Approval in its present form per 21 CFR 314.125(b)(6)

**NDA 209463
Review 1**

Drug Name/Dosage Form	Pantoprazole sodium for injection
Strength	40 mg Pantoprazole
Route of Administration	Injection for intravenous use
Rx/OTC Dispensed	Rx
Applicant	Exela Pharma Sciences, LLC, Lenoir NC, USA
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	6/02/2016	OPQ
Amendment	12/9/2016	OPF/DMA
Amendment	11/11/2016	ONDP
Amendment	1/13/2017	ONDP, OPF
Amendment	2/24/2017	OPF/DMA
Amendment	2/27/2017	OPF/DMA
Amendment	3/14/2017	ONDP
Amendment	3/17/2017	ONDP
Amendment	3/23/2017	OPF/DMA
Amendment	3/24/2017	ONDP
Amendment	4/24/2017	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product	Caroline Strasinger	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Yuesheng Ye	CDER/OPQ/OPF/ DPAIII/PABVIII
Microbiology	Julie Nemecek	OMPT/CDER/OPQ/OPF/DM A/MABIII
Facility	Carl Lee	CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	Hansong Chen	CDER/OPQ/ONDP/ DB/BBII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMBI/RBPMBI
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
ORA Lead	Paul Perdue Jr.	ORA/OO/OMPTO/ DMPTPO/MDTP
Environmental Analysis (EA)	Caroline Strasinger	CDER/OPQ/ONDP/ DNDPII/NDPBV

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	March 3, 2016	LoA May 18, 2016
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	020988	Exela is relying on the investigations performed by the NDA holder, Wyeth Pharmaceuticals, Inc. for PRORONIX® I.V. (pantoprazole sodium) for Injection, to which the FDA has made a finding of safety and effectiveness.

2. CONSULTS: None

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

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The Office of Process and Facilities (OPF) has made a final overall “Approval” recommendation for the facilities involved in this application as of this review.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

However, the issues on label/labeling has *not* been completely resolved yet as of this review. (see the **List of Deficiencies**)

Therefore, from the OPQ perspective, this NDA is *not* deemed ready for approval in its present form per 21 CFR 314.125(b)(6) until the label/labeling issues are satisfactorily resolved.

II. Summary of Quality Assessments

A. Product Overview

Pantoprazole sodium for injection is a proton pump inhibitor. It is supplied in a vial as sterile lyophilized powder containing 40 mg of pantoprazole equivalent to 45.1 mg of pantoprazole sodium. The drug product is reconstituted with 10 mL 0.9% Sodium Chloride Injection, USP and administered as a “Two Minute Infusion” or the reconstituted solution can be admixed with 100 mL of 5% Dextrose Injection, 0.9% Sodium Chloride Injection or Lactated Ringer’s solution and administered as a “Fifteen Minute Infusion”.

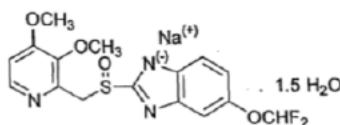
Proposed Indication(s) including Intended Patient Population	Pantoprazole sodium for injection is indicated for treatment of GERD and pathological hyper secretory conditions, including ZE Syndrome.
Duration of Treatment	7 to 10 days
Maximum Daily Dose	Recommended adult dose is 40 mg given once daily by intravenous infusion
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

The active pharmaceutical ingredient (API) in the drug product is pantoprazole sodium, USP. It is manufactured by (b) (4). The CMC information is provided in DMF (b) (4). The applicant provided an LoA to reference the DMF for CMC information in support of this NDA. The DMF was reviewed by Dr. Lauren E. Woodard on March 3, 2017, and it was deemed adequate. There are no CMC related updates since the last review.

Pantoprazole sodium, USP is a white to almost white powder. Its chemical name is 5-(Difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridyl)methyl]sulfinyl] benzimidazole, sodium salt, sesquihydrate. Its molecular weight is 432.37 and molecular formula is $C_{16}H_{14}F_2N_3NaO_4S \cdot 1.5 H_2O$. The structural formula of pantoprazole sodium is the following:



It is freely soluble in water and ethanol but practically insoluble in hexane. It is not hygroscopic and manufactured as the sesquihydrate form which melts at ~190°C. Its pKa value is 8.29 and the pH of 2% w/v solution in water is between 9.0 and 11.5. It is a BCS Class III compound with high water solubility and low permeability.

The quality of pantoprazole sodium, USP is controlled by its specification which includes identification by IR and UV spectroscopy; purity by HPLC, heavy metals per UPS <231> Method II, impurities and residual solvents etc. The API particle size is not important because during the drug product manufacturing process it is completely dissolved in water. The API specification deemed adequate per drug substance reviewer Dr. Sukhamaya Bain. (see the **Drug Substance** review)

The information regarding container closure and stability is provided in DMF (b) (4). Based on the stability data, the API re-test period of (b) (4) was established. However, Exela follows a retest period of (b) (4) for pantoprazole sodium, USP.

The Office of Process and Facilities (OPF) reviewer, Dr. Carl Lee, has made an “Adequate” recommendation for the drug substance manufacturing and testing facility (see the **Process** review).

Pantoprazole sodium, USP is manufactured and controlled according to the procedure described in DMF (b) (4) from (b) (4). It conforms to the requirements (specification) for drug product formulation of pantoprazole sodium for injection.

Drug Product:

Pantoprazole sodium for injection is supplied in single-dose 10 mL/20 mm USP (b) (4) clear glass vials as a white to off-white sterile lyophilized powder for reconstitution containing 40 mg of pantoprazole (equivalent to 45.1 mg of pantoprazole sodium). The vials are stoppered with gray (b) (4) stoppers and capped with 20 mm white flip-off overseals. The drug product formulation (b) (4)

The drug product manufacturing process involves (b) (4)

The drug product manufacturing process was reviewed by Dr. Yuesheng Ye and was found to be acceptable. (see the **Process** review)

The overall control strategy for the drug product is deemed adequate based on raw material controls, drug product specification including description, identity, assay, impurities, water content, content uniformity, dissolution, heavy metals and microbial and endotoxin limits, and also stability data assuring the identity, strength, purity, and quality during the 24-month of expiration dating period when stored at room temperature in the proposed container closure system according to drug product reviewer, Dr. Caroline Strasinger (see the **Drug Product** review).

The microbiology reviewer, Dr. Julie Nemecek, reviewed the manufacturing steps involving (b) (4)

(b) (4) in drug product specification, etc., and concluded that the applicant has met regulatory expectations for the product release (see the **Microbiology** review).

The Office of Process and Facilities (OPF) reviewer, Dr. Carl Lee, has made an "Adequate" recommendation for the drug product manufacturing and testing facilities (see the **Facility** review).

Based on the stability data provided, a 24-month of expiration dating period for the drug product is granted when stored at room temperature in the proposed container closure system.

The applicant provided a claim for a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31(a) and a statement of no extraordinary circumstances existed was included. The claim was reviewed and found to be acceptable.

The Biopharmaceutics reviewer, Dr. Hansong Chen, concluded that in accordance with 21 CFR 320.24(b)(6) the applicant has provided adequate information to establish a scientific bridge between the relative bioavailability of the drug product and Agency's finding of safety and efficacy of the Reference Listed Drug, Protonix I.V. (pantoprazole sodium) for injection, 40 mg. Therefore, additional in vivo bioequivalence (BE) bridging study is not needed. (see the **Biopharmaceutics** review)

Protonix I.V. (pantoprazole sodium) for injection, 40 mg from Wyeth Pharmaceuticals was approved in January 2001 (NDA 020988).

(b) (4)

The proposed drug product by Exela (b) (4) to RLD except that it does not contain EDTA. Exela also claimed that there is no significant precipitates formation during reconstitution of the drug product. Exela compared precipitates formation in side by side comparison of both RLD and drug product in different IV diluents and different pH. The results confirmed that there was less precipitation in the drug product solution than RLD even though the drug product does not contain EDTA. Thus, with respect to quality, the drug product from Exela appears to be comparable to RLD.

The proposed labels and labeling are under review and they are not deemed adequate from the CMC perspective according to Dr. Caroline Strasinger (see **Labels/Labeling** review), and the issues have not been completely resolved as of this review (see the **List of Deficiencies**).

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies:

1. Regarding PI

#3: Dosage Forms and Strengths

(b) (4)

#11: Description

- Modify the name, structure, formula, and molecular weight to be consistent with USP and adjust the equivalency statement accordingly

2. Regarding of the Container/Carton Labels:

- Modify equivalency statement content and format
- Sterility of the product should be indicated in the labels.

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II

Hitesh N.
Shroff -S

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BIOPHARMACEUTICS**Product Background:****NDA/ANDA:** NDA 209463**Drug Product Name / Strength:** Pantoprazole Sodium for Injection, 40 mg/vial**Route of Administration:** IV injection**Applicant Name:** Exela Pharma Sciences, LLC***Review Summary:***

The Listed Drug PROTONIX® I.V. (pantoprazole sodium) for Injection, developed by Wyeth Pharmaceuticals Inc., was approved by the FDA under NDA 020988 on 3/22/2001, which did not contain EDTA (b) (4) initially. Later, Wyeth reformulated the product by adding EDTA, which was approved by FDA in 2004. It is indicated for short term gastric acid suppression in gastroesophageal reflux disease patients who are unable to take oral medication.

Exela Pharma Sciences, LLC developed Pantoprazole Sodium for Injection, 40 mg/vial and submitted the application under NDA 209463 via 505(b)(2) pathway on 6/7/2016 to seek approval referencing PROTONIX® I.V (NDA 20988) .

The Biopharmaceutics review focuses on the side-by-side comparison between the proposed product and the Listed Drug for the active and inactive ingredients including pH, viscosity, and osmolality, as well as the Applicant's waiver request on the in vivo BA/BE for its proposed drug product.

From the Biopharmaceutics perspective, NDA 209463 for Pantoprazole Sodium for Injection, 40 mg/vial is reviewed and found adequate, and the waiver request with justifications submitted under 21 CFR 320.24(b)(6) for the proposed product is also considered adequate. This NDA is, therefore, recommended for approval.

List Submissions being reviewed (table):

Submission	Submission date
Original submission (sequence #0000)	6/7/2016
Quality/Response to Information Request	12/9/2016

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

BCS Designation

Reviewer's Assessment: Not reported.

Solubility: Not reported.

Permeability: not reported.

Dissolution: N/A

Bridging of Formulations

Reviewer's Assessment:

Biowaiver Request

Reviewer's Assessment:

1. Background

The Applicant developed Pantoprazole Sodium for Injection, 40 mg/vial and submitted this application under NDA 209463 on 6/7/2016 seeking approval through 505(b) (2) path. The listed drug is PROTONIX® I.V. (pantoprazole sodium) 40 mg/vial for Injection. The proposed product and the Listed Drug, PROTONIX®, have the same active ingredient with the same concentration, but they have different inactive ingredients. A waiver request was also submitted under 21 CFR.320.24(b)(6).

Here is the side-by-side comparison of the components and composition of these two products.

Table 1. Formulation Comparison between Exela' Pantoprazole Sodium for Injection, 40 mg/vial and Listed Drug, PROTONIX® I.V.

Components of the drug	Proposed pantoprazole Sodium	PROTONIX® I.V.
------------------------	------------------------------	----------------

product	for Injection, 40 mg/vial	
pantoprazole sodium	40 mg/vial as base	40 mg/vial as base
Edetate disodium	----- (Absent)	Edetate Disodium 1 mg/vial
Sodium Hydroxide, NF	To adjust pH to 11.3 (target)	To adjust pH

The Applicant removed Edetate Disodium from its drug product formulation, which is currently included in the Listed Drug. The Applicant did not provide if these two products have similar pH, osmolality, viscosity, and tonicity.

2. Information Request (IR)

On 11/1/2016, the FDA sent an IR to the Applicant. On 12/23/2016, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this Reviewer's comment.

IR

Submit a detailed side-by-side comparison between your proposed product and the Listed Drug to include justification on differences in pH, viscosity, tonicity, and osmolality. Provide supporting data (e.g., literature articles/data and/or your study results) to demonstrate that any differences between the two formulations in terms of inactive ingredients and in terms of physicochemical properties, e.g., pH, viscosity, tonicity, and osmolality) will not affect its In Vivo PK performance and clinical outcome on efficacy/safety.

The Applicant's response

1) Physicochemical Properties

The Applicant reconstituted the Listed Drug PROTONIX IV and proposed product with 10 mL of Sodium Chloride Injection, (0.9%), USP, and evaluated their physicochemical properties. A side-by-side comparison of the physicochemical properties of the two products is listed in the following table.

Table 2. Side-by-Side Comparison of Physiochemical Characteristics between the Listed Drug and Proposed Formulation

Physicochemical Property	PROTONIX IV Lot # 360315	Pantoprazole Sodium for Injection Lot # XLNF1431
Measured Reconstituted Product pH	9.83	9.96
pH Range for the Reconstituted Product	9.0 – 10.5 (as per label)	(b) (4) (based on 24 month stability data for 3 lots XLNF1429, XLNF1431, and XLNF1432)
Osmolarity	310 mOsm/kg	310 mOsm/kg
Tonicity	Isotonic	Isotonic
Viscosity	0.016292 Centistokes	0.016292 Centistokes

The data in Table 2 show that the two products have the same osmolality, tonicity, and viscosity. The pHs of the two reconstituted solutions are also considered similar.

2) No EDTA in the Proposed Drug

The Applicant reviewed the approved labeling of two pantoprazole IV products (the one without EDTA, which was initially approved by FDA under NDA 020988 in 2001 and the currently reformulated product with EDTA, which was approved by FDA in 2004), and concluded that the removal of EDTA has no negative effect on the pharmacokinetics and clinical outcome of safety/efficacy of the Listed Drug. Therefore, the absence of EDTA in the proposed drug has no impact on the proposed product as well.

In addition, the Applicant reviewed the Listed Drug labels, labeling of all approved PPIs, and literature generally with respect to PPIs and EDTA-containing non-PPI injectable products, and concluded that the proposed product (without EDTA) is likely to have a lower incidence rate of hypersensitivity and skin reaction than that of the RLD. The Applicant's justification is acceptable.

Overall, no EDTA in the proposed drug product does not affect its in vivo PK performance and clinical outcome on efficacy/safety.

Reviewer's comment:

The response is adequate. The Listed Drug PROTONIX IV and proposed product have almost identical physicochemical properties. Absence of EDTA does not affect the proposed product's in vivo PK performance and bring extra safety issues. Therefore, the difference between the two products would not be expected to alter the pharmacologic activity of the proposed product.

3. **Biowaiver Request**

The Applicant requested the waiver of the in vivo BA/BE for its proposed product by citing 21 CFR 320.22(b). The Applicant stated that both drug products have the same active ingredient with the same concentration. Although they have different inactive ingredients, the differences in the inactive ingredients are not expected to affect the performance of the proposed drug.

Reviewer's comment:

Although the criteria for a biowaiver under 21 CFR 320.22(b)(1) is not fully met, based on 21 CFR 320.24(b)(6), the FDA can rely on any other approach deemed adequate by FDA to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products.

Specifically for NDA 209463, the absence of EDTA in the formulation of the proposed drug product is not expected to affect the bioavailability of Pantoprazole Sodium for Injection following intravenous (IV) administration. The rationales are as follows:

- 1. The proposed and the listed Drug are for intravenous use, their bioavailability is self-evident.*
- 2. The difference in pH between two formulations does not bring any safety issues.*
- 3. Absence of EDTA would not be expected to alter the pharmacologic activity of the product.*

Conclusion

As consistent with 21 CFR 320.24(b)(6), the FDA deemed adequate information supporting the relative bioavailability of Exela's proposed drug product to the Listed Drug and a scientific bridge has been established to the Agency's finding of safety and effectiveness for the Listed Drug. Thus, additional in vivo bioequivalence (BE) bridging study is not needed. This Reviewer recommends that NDA 209463 for Pantoprazole Sodium for Injection, 40 mg/vial be approved from the Biopharmaceutics perspective.

R Regional Information

Comparability Protocols

Reviewer's Assessment:

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations

List of Deficiencies: N/A

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, 1/27/2017, 4/23/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur. 04/25/17

Tien-Mien Chen, PhD.

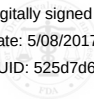
Acting Biopharm Lead

DB/ONDP/OPQ



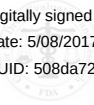
Hansong
Chen

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Tien Mien
Chen

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LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

PANTOPRAZOLE SODIUM for injection, for intravenous use
Initial U.S. Approval: 2000

2) DOSAGE FORMS AND STRENGTHS

For Injection: 40 mg pantoprazole lyophilized powder in single-dose vial for reconstitution (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: N/A Established Name: Pantoprazole Sodium for Injection	Adequate
Dosage form, route of administration	Dosage: For Injection Route: Intravenous	Adequate
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		
Summary of dosage form and strength	. For Injection: 40 mg pantoprazole	Adequate

Reviewer Assessment: ADEQUATE

2. “FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

Item	Information Provided in NDA	Reviewer’s Comment and Recommendations
Available dosage forms	For Injection	Adequate
Strengths: in metric system	40 mg	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	“40mg pantoprazole” should be revised to “40mg pantoprazole (equivalent to 45.1mg of pantoprazole sodium)”	Inadequate; Equivalency statement should be added.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	lyophilized powder in single dose vial	Adequate

Reviewer Assessment: Inadequate

(b) (4)

2) #11: DESCRIPTION

11 DESCRIPTION

The active ingredient in Pantoprazole Sodium for Injection, a PPI, is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is

Comment [SC14]: To the Sponsor: Changes requested to be consistent with Pantoprazole Sodium, USP

$C_{16}H_{14}F_2N_4NaO_4S \cdot 1.5 H_2O$, with a molecular weight of 432.37 (b) (4) The structural formula is:

Comment [M0M15]: To the Sponsor: We replaced the structure, consistent with the revised formula as found in the USP. You may replace with your own revised figure.

Formatted: Subscript

Pantoprazole sodium is a white to off-white crystalline powder and is racemic. Pantoprazole sodium is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane. The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. The reconstituted solution of Pantoprazole Sodium for Injection is in the pH range 9.5 to 11.5.

Pantoprazole Sodium for Injection is supplied for intravenous administration as a sterile lyophilized powder in a single-dose clear glass vial fitted with a rubber stopper and crimp seal. Each vial contains 40 mg pantoprazole (equivalent to 45.12-3 mg of pantoprazole sodium), and sodium hydroxide to adjust pH.

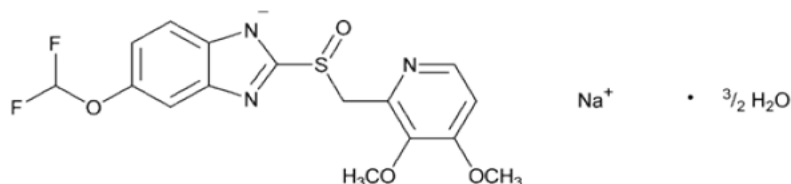
Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	Pantoprazole Sodium for Injection	Adequate
Dosage form and route of administration	For Injection	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	40 mg pantoprazole (equivalent to (b) (4) mg of pantoprazole sodium)	INADEQUATE the equivalency should be 45.1 mg based on the USP MW of the pantoprazole sodium (which includes sesquihydrate)
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Sodium hydroxide	Adequate
Statement of being sterile (if applicable)	Sterile lyophilized powder	Adequate
Pharmacological/ therapeutic class	Proton pump inhibitor	Adequate
Chemical name, structural formula, molecular weight	(b) (4) Structure and Molecular Weight Presented	INADEQUATE the equivalency should be 45.1 mg based on the USP MW

		of the pantoprazole sodium (which includes sesquihydrate)
If radioactive, statement of important nuclear characteristics.	NA	Adequate
Other important chemical or physical properties (such as pKa or pH)	solubility	Adequate

Reviewer Assessment: **INADEQUATE** During review it was noted the Applicant had calculated the equivalency based on the anhydrous structure and molecular weight. The USP Monograph utilizes the following for the Pantoprazole Sodium:

Pantoprazole Sodium

(pan toe' pra zole soe' dee um)



C₁₆H₁₄F₂N₃NaO₄S · 1.5H₂O 432.37

5-(Difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]benzimidazole, sodium salt, sesquihydrate [164579-32-2].

As such the Applicant has been requested to modify the appropriate sections of section 11 Description and the Container/Carton.

The correction above has been communicated to OND on 4/28/2017. The edits noted above will be corrected by the Applicant during labeling negotiations.

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

Pantoprazole Sodium for Injection is supplied in a single-dose vial as a white to off-white sterile lyophilized powder for reconstitution containing 40 mg of pantoprazole.

Pantoprazole Sodium for Injection is available as follows:

NDC Number	Strength	Package
0143-9284-01	40 mg pantoprazole	Single vial

0143-9284-10

40 mg pantoprazole

Package of 10 vials

Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° – 30°C (59° – 86°F) [see USP Controlled Room Temperature].

Protect from light.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	40mg	Adequate
Available units (e.g., bottles of 100 tablets)	Single vial; 10 vials	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	single-dose vial as a white to off-white sterile lyophilized powder	Adequate
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	Protect from light	Adequate
Storage conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° – 30°C (59° – 86°F) [see USP Controlled Room Temperature].	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured by Exela Pharma Sciences, LLC Distributed by West-Ward Pharmaceuticals Corp.	Adequate

Reviewer Assessment: **ADEQUATE**

II. Labels

1. IMMEDIATE CONTAINER LABEL

The below container label was provided on April 21, 2017)



(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	No Proprietary Name. Exempt from Salt Policy due to history of PPI: Pantoprazole Sodium for Injection is correct	Adequate
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	40 mg (equivalency statement format and content to side panel to be adjusted to 45.1)	INADEQUATE
Net contents	40mg Per vial	Adequate
"Rx only" displayed prominently on the main panel	Rx only	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Presnet on front panel	Adequate
Lot number and expiration date (21 CFR 201.17)	Location present	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store 20-25C excursions permitted; protect from light	Adequate
Bar code (21CFR 201.25)	Present	Adequate
Name of manufacturer/distributor	Present	Adequate
And others, if space is available		

Reviewer Assessment: **INADEQUATE.** The equivalency statement included on the side panel is based on the anhydrous structure and molecular weight. Additionally, the formatting of the equivalency statement on the side panel is not consistent with that of the FDA Guidance for Industry: Naming of Drug Products Containing Salt Drug Substances.

The following information was communicated to the Applicant on 04/28/2017.

Comments on Carton/Container – NDA 209463

We refer to the revised carton/container labeling submitted on April 21, 2017.

We would like to emphasize that the format for the equivalency statement on the side panel of both the carton and container should be as follows (note the number of lines of text and the words found on each line):

If you are unable to follow these recommendations due to space constraints, please provide a rationale for any revisions that use different formatting.

No changes to the front panels are recommended.

The equivalency statement should be consistent with the molecular weight and structure of Pantoprazole Sodium, USP monograph which utilizes the sesquihydrate. We will provide you with comments and modifications to Section 11 Description in the PI regarding this information in a future communication.

2. CARTON LABELS:

(b) (4)



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	No Proprietary Name. Exempt from Salt Policy due to history of PPI: Pantoprazole Sodium for Injection is correct	INADEQUATE
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	40 mg (equivalency statement format and content to side panel to be adjusted to 45.1)	Adequate
Net quantity of dosage form	40mg per vial	Adequate
"Rx only" displayed prominently on the main panel	Displayed on front and back panel	Adequate
Lot number and expiration date	Located on bottom	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° – 30°C (59° – 86°F) [see USP Controlled Room Temperature]. Protect from light; use of vial carton recommended	Adequate
Bar code (21CFR 201.25)	Side panel	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Front and back panel	Adequate
Manufacturer/distributor's name	Side panel	Adequate
Quantitative ingredient information (injectables)	Pantoprazole Sodium; NaOH not required to be included as it is a pH adjuster	Adequate
Statement of being sterile (if applicable)	No statement	
"See package insert for dosage information"	Side panel	Adequate
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Not applicable	Adequate

Reviewer Assessment: INADEQUATE. The equivalency statement included on the side panel is based on the anhydrous structure and molecular weight. Additionally, the formatting of the equivalency statement on the side panel is not consistent with that of the FDA Guidance for Industry: Naming of Drug Products Containing Salt Drug Substances. Refer to the comments communicated to the Applicant above on 04/28/17 for additional information.

III. LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlight Section

b) Full Prescribing Information

#3: Dosage Forms and Strengths

(b) (4)

#11: Description

- Modify the name, structure, formula, and molecular weight to be consistent with USP and adjust the equivalency statement accordingly

#16: How Supplied/Storage and Handling

B. Regarding of the Container/Carton Labels:

- Modify equivalency statement content and format
- Sterility of the product should be indicated in the labels.

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

The Label and Labeling of NDA 209463 is inadequate due to the deficiencies noted above for Section 3 and 11 of the PI and the Container and Carton Labels.

Therefore, this application is not deemed ready for approval in its present form per 21CFR 314.125(b)(6) from the label/labeling perspective until the deficiencies noted above are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Caroline Strasinger, PhD 01-MAY-2017

OPQ, ONDP, DNDP II, BV

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Strasinger's assessment on the labeling and labels and concur with her recommendation that this application is ***not*** deemed ready for approval as of this review.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP



Moo Jhong
Rhee

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Caroline
Strasinger

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MICROBIOLOGY**Product Background:**

NDA: 209463

Drug Product Name / Strength: Pantoprazole Sodium for Injection

Route of Administration: Intravenous injection

Applicant Name: Exela Pharma Sciences, LLC

Manufacturing Site: Exela Pharma Sciences, 1325 William White Place, Lenoir, NC 28645

Method of Sterilization: (b) (4)

Review Summary: Recommended for Approval.

List Submissions being reviewed: 6/2/2016, 11/11/2016, 12/9/2016, 1/26/2017, 2/27/2017, 2/28/2017, and 3/24/2017.

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents: DMF (b) (4) (Type V), 11648mic31.doc, 8/25/2015, (b) (4) (b) (4), Adequate.

DMF (b) (4) (Type II), D (b) (4) MR02R01.doc, 12/15/2016, for the (b) (4) (b) (4), Adequate.

(b) (4)

Remarks Section: This is a non-eCTD submission. An IR was conveyed to the applicant on 8/23/2016. The applicant responded to the IR in two submissions (11/11/2016 and 12/9/2016). The 11/11/2016 submission lacks four referenced attachments. The applicant provided the attachments in the 1/26/2017 submission. A second IR was conveyed to the applicant on 1/27/2016 and the applicant responded on 2/28/2017. A third IR was conveyed to the applicant on 3/16/2017 and the applicant responded on 3/24/2017.

The reviewer was provided with an updated package insert by email on 3/7/2017. As of 3/10/2017, this updated package insert has not been added to the platform/Global Submit

Review. There are no changes to the package insert that impact sterility assurance and this review.

S Drug Substance

Not applicable.

P.1 Description of the Composition of the Drug Product

- Description of drug product – The subject drug product is a sterile lyophilized powder.
- Drug product composition –

Ingredient	Content per vial
Pantoprazole sodium	42.3 mg/vial
Sodium hydroxide	q.s. to pH 11.3
	(b) (4)

- Description of container closure system –

Component	Manufacturer
Vial, 10 mL, USP (b) (4) clear glass tubing	(b) (4)
Stopper, (b) (4)	
Seal, (b) (4)	

Acceptable

Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

(microbiological-attributes.pdf)

- The applicant states that helium leak testing is performed in lieu of microbial ingress testing as it is a more sensitive method.
- The container-closure system used for validation is the same as the drug product (10 mL vial, 20 mm stopper). Twelve vials from 3 lots were tested at release and after six months. The samples were taken from the accelerated stability study.
- Study date: 11/4/2014, 2/11/2015, 7/27/2015
- Range of the method: (b) (4) std cc/sec

- Sensitivity: (b) (4) std cc/sec. This appears to be outside the method range. However, the critical leak rate for which the probability of microbial ingress is (b) (4) is indicated as (b) (4).
- Acceptance criterion: Actual helium leak rate is less than (b) (4) std cc/sec.
- All units met the stated acceptance criterion. The helium leak rate results were lower than the critical leak rate and acceptance criterion of (b) (4) std cc/sec. for the test vials. The values ranged from (b) (4) (microbiological-attributes.pdf, pages 4-9 of 28).

Acceptable

Reviewer's Assessment: The observed (b) (4) std cc/sec result indicated for some of the challenged vials is marginally below the range of the method (i.e., (b) (4) std cc/sec). However, the data is acceptable since the results show some of the challenged vials had leak rates that were smaller than the applicant's leak rate measurements. The overall results indicate that the product's container closure system provides an effective barrier against microbial ingress and meets regulatory expectations for a sterile pharmaceutical product.

Antimicrobial Effectiveness Testing

Not applicable.

Acceptable

Reviewer's Assessment: The subject drug product is packaged in a single-use vial; antimicrobial effectiveness testing is not required.

P.3 Manufacture

P.3.1 Manufacturers

Drug product

Exela Pharma Sciences
1325 William White Place
Lenoir, NC 28645

(b) (4)

Acceptable

Reviewer's Assessment: The applicant has met regulatory expectations for the actions performed after media fill failure.

P.5 Control of Drug Product**P. 5.1 Specification**

(specifications.pdf, page 3 of 6)

The product release specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	USP <85>	NMT (b) (4) EU/mL of Panto (b) (4) le Sodium for Injection (Equivalent to (b) (4) EU/mg as Pantoprazole Base)
Sterility	USP <71>	No growth is observed
Container/Closure Integrity	Helium Leak Test	NMT (b) (4) std cc/sec

Acceptable

Reviewer's Assessment: The applicant has met regulatory expectations for the product release specifications.

P.5.2 Analytical Procedures

See P.5.1 and P.5.3

P.5.3 Validation of Analytical Procedures

Endotoxins

(2014-QMMV-121.pdf)

Test Method: Kinetic turbidimetric assay per USP <85>. Inhibition and enhancement testing was conducted.

Endotoxins Specification: NMT (b) (4) EU/mg; USP Monograph limit: N/A;
Lysate sensitivity: (b) (4) EU/mL; Drug potency: 4 mg/mL;
Calculated MVD: (b) (4);

Reviewer calculated MVD:

$$(b) (4) \text{ EU/mg} \times 4 \text{ mg/mL} \div 0.01 \text{ EU/mL} = (b) (4)$$

Acceptance criteria for method validation:

- Absolute Value of Coefficient of Correlation must be $\leq$ (b) (4)
- Positive Product Control (PPC) recovery be (b) (4) %

The absolute value of coefficient of correlation was (b) (4) for the tested batch.
The PPC ranged from (b) (4) %. The acceptance criteria were met.

Validation of the test shows no inhibition or enhancement using a dilution of 1:10.
The dilution used for routine testing is not stated.

Finished lots XLNF1429, XLNF1431, and XLNF1432 contain < (b) (4) EU/mL
(batch-analyses.pdf).

Maximum dose according to the package insert: 80 mg delivered by a 15 minute infusion. Per the label, the safety and effectiveness of this drug product in pediatrics patients has not been established.

Calculated endotoxin dose at the proposed endotoxins specification and maximum dose:

(b) (4)

The endotoxin dose at the proposed endotoxins specification and maximum dose as calculated by this reviewer is within the USP <85> recommendation of 5EU/kg/hr.

Deficiency sent to the Applicant on August 23, 2016:

We acknowledge the information provided in module 3.2.P.5.3 regarding endotoxins testing and method verification. However, provide the dilution proposed for testing commercial batches of the drug product during routine production.

Summary of response received on November 11, 2016:

The applicant states that a 1:10 dilution will be used for routine testing.

B comment sent to the Applicant on August 23, 2016:

It is indicated in the 3.2.P.8.1-stability-summary.pdf document that the Limulus Amoebocyte Lysate (LAL) USP <85> test will be conducted on a pool of three (3) reconstituted vials. Note that validation data was provided only for the kinetic turbidimetric assay and that pooling of samples produces an additional dilution corresponding to the number of vials pooled, and requires an adjustment of the maximum valid dilution (MVD).

Summary of response received on November 11, 2016:

The applicant clarifies that endotoxins testing is performed on three individual vials and vials are not pooled.

Acceptable

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the endotoxins test that will be performed on the drug product prior to its release.

Sterility

(b) (4)

The subject drug product did not inhibit recovery of the test organisms.

Finished lots XLNF1429, XLNF1431, and XLNF1432 met the release specification of "no growth observed" (batch-analyses.pdf).

Acceptable

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the sterility test that will be performed on the drug product prior to its release.

P.7 Container Closure

See P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(stability-summary.pdf, page 17 of 18)

Proposed expiry: 24 months

Acceptable

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the proposed expiration date.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(postapproval-stability.pdf)

(b) (4)

Acceptable

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life.

P.8.3 Stability Data

(stability-summary.pdf)

Long-term and accelerated stability studies were performed for batches XLNF1429, XLNF1431, and XLNF1432 and the provided results were acceptable.

Acceptable

Reviewer's Assessment: The stability data submitted to date support the microbiological quality of the subject drug product.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not applicable.

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not applicable.

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not applicable.

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not applicable.

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: Not applicable.

R Regional Information

Executed Batch Records

Executed batch records were provided for lots XLNF1429, XLNF1431, and XLNF1432.

Acceptable

Reviewer's Assessment: The applicant has met the regulatory expectations regarding the executed batch records.

Comparability Protocols: No CP was included in the application.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

- **Post-dilution/constitution hold time**

The lyophilized powder is reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, and further diluted with 100 mL of 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer's Injection to a final concentration of approximately 0.4 mg/mL or 4 mg/mL.

Storage times per the package insert:

- Lyophilized powder: 20-25 °C
- Reconstituted product: 6 hours at room temperature
- Diluted product: 24 hours at room temperature

The applicant did not provide microbiological studies in support of these proposed storage times.

Deficiency sent to the Applicant on August 23, 2016:

Microbiological studies in support of the post-constitution or post-dilution storage time (as stated in the proposed product labeling) have not been provided. Please provide a risk assessment summarizing studies that demonstrate adventitious microbial contamination does not grow under the specified storage conditions [(i.e., 6 hours at room temperature and 24 hours at room temperature) after reconstitution and further dilution with the specified diluents)]. Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Please include a description of the test methods and results of studies that are designed using a minimum countable inoculum (b) (4) /mL) to simulate potential microbial contamination that may occur during product constitution and dilution. It is generally accepted that growth is evident when the population increases more than 0.5 log₁₀, however other evidence of growth may be significant. Please perform the test using the storage conditions (temperature and duration) and diluents specified in product labeling. Please provide justification for the selected test conditions and/or diluents as necessary. Periodic intermediate sample times are recommended, as well as extended sample time points demonstrating that the reconstituted and diluted product does not support microbial

growth for at least the maximum storage periods under the specified storage conditions. Challenge organisms may include strains described in USP <51> plus typical skin flora and species associated with nosocomial infection. Please provide a positive control that demonstrates the viability of the organisms over the duration of the test period.

Summary of response received on November 11, 2016 and December 9, 2016:

The applicant provided study report 2016-ES-278 dated December 9, 2016 in support of the storage conditions for the post-constitution and post-dilution storage times (6 hours at room temperature and 24 hours at room temperature). Per the proposed product labeling, the drug product was reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, and further diluted with 100 mL of 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer's Injection to a final concentration of 0.4 mg/mL or 4 mg/mL. The RLD was not tested in parallel.

Samples of the reconstituted drug product were tested for viable CFU at 0, 2, 4, 6, 8, and 12 hours at room temperature. Samples of the diluted drug product were tested for viable CFU at 0, 6, 12, 24, 36, and 48 hours at room temperature. Positive controls were not described.

Acceptance criterion: NMT (b) (4) $\log_{10}$ increase in growth from the initial time point.

In the response, the applicant states that the study data did not meet the specified acceptance criterion (1.3.6.2-Formal-IR-Response (08-23-16).pdf, page 72 of 87). An increase in growth was seen for several microorganisms in both the reconstituted and the diluted drug product during the proposed hold times. The following is a list of the conditions in which an increase in growth was seen in the 15 minute infusion (0.4 mg/mL) stored 12-48 hours at room temperature. The provided results for the 2 minute infusion (4 mg/mL) were similar.

Condition	Organism	Time point, log increase					
		0 hr	2 hr	4 hr	6 hr	8 hr	12 hr
Reconstituted, 0.9% Sodium Chloride Injection, USP	<i>E. coli</i>	(b) (4)					
	<i>P. aeruginosa</i>						
	<i>C. albicans</i> (SAB)						
		0 hr	6 hr	12 hr	24 hr	36 hr	48 hr
Admix, 0.9% Sodium Chloride Injection, USP	<i>E. coli</i>	(b) (4)					
	<i>P. aeruginosa</i>						
	<i>C. albicans</i>						
	<i>C. albicans</i> (SAB)						
Admix, 5% Dextrose Injection, USP	<i>E. coli</i>						
	<i>P. aeruginosa</i>						
	<i>S. aureus</i>						
	<i>C. albicans</i>						
	<i>C. albicans</i> (SAB)						

Admix, Lactated Ringer's Solution	<i>E. coli</i>	(b) (4)
	<i>P. aeruginosa</i>	
	<i>C. albicans</i>	
	<i>C. albicans</i> (SAB)	

Deficiency sent to the Applicant on January 27, 2017:

We acknowledge the information provided in the response regarding microbiological studies in support of the post-constitution and post-dilution storage time. However, additional information is required to assess the acceptability of the proposed storage times. We note that the reconstituted and diluted drug product supports microbial growth under the labeled storage conditions. Provide additional results for studies performed with the RLD tested in parallel to demonstrate equivalence.

Summary of the response provided by the applicant on February 29, 2017:

The applicant provided results from Study 2017-ES-093 dated February 20, 2017 in support of the storage conditions for the post-constitution and post-dilution storage times (6 hours at room temperature and 24 hours at room temperature). Per the proposed product labeling, the RLD was reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, and further diluted with 100 mL of 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer's Injection to a final concentration of 0.4 mg/mL or 4 mg/mL.

Samples of the reconstituted RLD were tested for viable CFU at 0, 2, 4, 6, 8, and 12 hours at room temperature. Samples of the diluted RLD were tested for viable CFU at 0, 6, 12, 24, 36, and 48 hours at room temperature. Positive controls were not described.

Acceptance criterion: NMT (b) (4) $\log_{10}$ increase in growth from the initial time point.

An increase in growth was seen for several microorganisms in the diluted RLD during the proposed hold times. The following is a list of the conditions in which an increase in growth was seen in the 15 minute infusion (0.4 mg/mL) stored at room temperature. Growth was not seen in 2 minute infusion (4 mg/mL) or in the reconstituted RLD.

15 Minute Infusion, Admix: 0.9% Sodium Chloride Injection, USP						
	0 hr (log)	6 hr (log)	12 hr (log)	24 hr (log)	36 hr (log)	48 hr (log)
(b) (4)						

Table 6 – 15 Minute Infusion, Admix: 0.9% Sodium Chloride Injection, USP Log Values

15 Minute Infusion, Admix: 5% Dextrose Injection, USP						
	0 hr (log)	6 hr (log)	12 hr (log)	24 hr (log)	36 hr (log)	48 hr (log)
(b) (4)						

Table 8 – 15 Minute Infusion, Admix: 5% Dextrose Injection, USP Log Values

15 Minute Infusion, Admix: Lactated Ringer's Injection, USP						
	0 hr (log)	6 hr (log)	12 hr (log)	24 hr (log)	36 hr (log)	48 hr (log)
(b) (4)						

Table 10 – 15 Minute Infusion, Admix: Lactated Ringer's Injection, USP Log Values

Acceptable

Reviewer's Assessment: The applicant has demonstrated that the drug product and RLD support equivalent microbial growth under the storage conditions indicated in the package insert.

Post-Approval Commitments: Not applicable

Lifecycle Management Considerations: Not applicable.

List of Deficiencies: Not applicable.

Primary Microbiology Reviewer Name and Date: Julie Nemecek, Ph.D., 3/28/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Dupeh Palmer, 3/30/17; "I concur".



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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 209463

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranki ng	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Consideratio ns/ Comments
Assay	Formulation, Raw materials, Process Parameters, Scale/equipment	L	Assay is determined by a validated HPLC method. Critical manufacturing process steps were identified and controlled. The long term and accelerated stability studies show that the assay is consistent during the time tested.	The dose strength of the drug product is expected to be within the specification during the entire shelf life from product quality perspective. None	None
Impurities	Raw materials, process parameters,	M	The related substances/ impurities are fully characterized and controlled by DS specification and DP specification. The test results during the stability studies are within the specification. The impurities are assessed by validated HPLC methods.	The degradation/impurities of the drug product are expected to be controlled and the drug product is safe for IV administration during the entire shelf life from product quality perspective. Low	None
Bioburden	Manufacturing environment and processes	M	Applicant's environmental monitoring program is consistant with	Bioburden is controlled in the drug product at release and stability. Low	None

			regulatory requirement for (b) (4).		
Sterility	Sterilization	M	<p>The bulk solution^{(b) (4)}</p> <p>Vials and rubber stoppers are (b) (4) prior to use.</p>	<p>Sterility is controlled in drug product at release and stability.</p> <p>Low</p>	None

1 Document History

Document History		
Author: Integrated Quality Assessment Team, and Don Henry.		
<p>Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team.</p> <p>Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.</p>	<p>This process (CDER OPQ Integrated Quality Assessment Template) will be reviewed at the following intervals and changes to the work aid will be captured as needed:</p> <p>This process will be reviewed approximately 150 days from date issued (February 18, 2016).</p>	
Version	Summary of Changes Issued	Date
03	Content update	02/18/2016



Hitesh
Shroff

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