CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215252Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 215252
Review 1

Drug Name/Dosage Form	Diltiazem Hydrochloride Injection
Strength	125 mg/125 mL (1 mg/mL) and 250 mg/250 mL (1 mg/mL)
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	Exela Pharma Sciences, LLC
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
001 (Original submission)	12/30/20	Quality modules 3, 1.14, and 1.11
0002	1/28/2021	DP
0004	3/3/2021	DP, Biopharmaceutics,
0005	3/17/2021	DP
0006	5/7/2021	Manufacturing, Microbiology
0008	6/3/2021	Biopharmaceutics

Quality Review Team

Discipline	Reviewer/Secondary	Branch/division
Drug Substance	Ben Zhang/ Suong Tran	Branch III/Division of New Drug Active Pharmaceutical Ingredients
Drug Product	Dhanalakshmi Kasi/ Mohan Sapru	Branch V/New Drug Products III of Office of New Drug Products
Process/ Facility	John Metcalfe/ Vidya Pai	Branch II/ Office of Pharmaceutical Manufacturing Assessment
Biopharmaceutics	Rebecca Moody/ Poonam Delvadia	
Microbiology	Bernard Marasa/ Yuansha Chen	Office of Pharmaceutical Manufacturing Assessment
Regulatory Business Process Manager	Grafton Adams/ Hamet Toure	Branch I/Regulatory Business Process Management I
Application Technical Lead	Theodore Carver	Branch V/New Drug Products III of Office of New Drug Products
Environmental Analysis (EA)	Dhanalakshmi Kasi/ Mohan Sapru	Branch V/New Drug Products III of Office of New Drug Products

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	adequate	DMF reviewed for this NDA 9/2/21	LOA dated 10/21/19; found adequate 9/15/10
	II			Information in NDA found adequate	NDA only reviewed.	LOA dated 2/26/2020
	III			Information in NDA found adequate.	NDA only reviewed.	LOA dated 2/25/2020
	III			Information in NDA found adequate.	NDA only reviewed.	LOA dated 3/6/2020
	III			Information in NDA found adequate.	NDA only reviewed.	LOA dated 3/23/2020
	III			Information in NDA found adequate.	NDA only reviewed.	LOA dated 3/6/2020
	III			Information in NDA found adequate	NDA only reviewed.	LOA dated 3/6/2020

*Sufficient information provided in the NA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	074617	Diltiazem HCl Injection; reference standard for scientific bridge.
NDA	020027	Diltiazem HCl Injection; listed drug.

2. CONSULTS: None.

Executive Summary

1. **Recommendations and Conclusions on Approvability**

The Office of Pharmaceutical Quality Review team has assessed NDA 215252 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports to have. As such OPQ recommends approval of this NDA from a quality perspective.

2. **Background Summary**

The Applicant, Exela Pharma Sciences, LLC, is seeking marketing approval for Diltiazem Hydrochloride injection, 125 mg/125 mL (1 mg/mL) and 250 mg/250 ml (1 mg/mL), in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Diltiazem HCl is indicated for either the temporary control of rapid ventricular rate in atrial fibrillation in adults or the rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. To support approval of diltiazem for these indications, the Applicant relies on FDA's finding of safety and effectiveness for the reference listed drug Cardizem Injectable (diltiazem hydrochloride injection, 5 mg/mL 25 mg/5 mL), NDA 020027 approved on October 24, 1991. The proposed product is a sterile solution to be administered by continuous intravenous infusion and is packaged as 125 mg/125 mL and 250 mg/250 mL solutions in 250 mL IV bags with the concentration of 1 mg/mL

3. **Summary of Quality Assessments**

Diltiazem hydrochloride injection is a clear, colorless, sterile, nonpyrogenic solution and is intended for continuous intravenous infusion. The drug product is to be marketed as two presentations of same concentration of diltiazem HCl, 125 mg/125 mL and 250 mg/250 mL. In terms of excipients, the drug product contains dextrose (b) (4) (b) (4), sodium citrate dihydrate and citric acid monohydrate (b) (4), sodium hydroxide and hydrochloric acid as pH-adjusting agents for a target pH of 3.9, and water for injection. The drug product is filled as either 125 mL or 250 mL solutions in a 250 mL IV bag sealed with (b) (4) Por (b) (4). Each bag is packaged in an (b) (4) pouch and ten pouches are packed into a case containing one package insert. The OPQ integrated quality assessment includes reviews of drug substance, drug product, manufacturing, biopharmaceutics, and microbiology information in the NDA.

3.1 Drug Substance (diltiazem hydrochloride)

The diltiazem HCl drug substance information was reviewed by Dr. Ben Zhang and found to be adequate. All chemistry, manufacturing, and controls information was cross-referenced to the Type II DMF (b) (4) which was reviewed by Dr. Zhang and found to be adequate to support this NDA. The diltiazem

HCl drug substance is a white, odorless, crystalline powder consisting of a single diastereomer with a molecular weight of 450.98. It is freely soluble in water and methanol, and, since the drug substance is fully dissolved in the drug product, particle size and polymorphic form are not attributes of the drug substance that are critical to the drug product. The retest period is (b) (4) months for diltiazem HCl drug substance, with a shorter retest period of (b) (4) months used by the drug product manufacturer.

3.2 Drug product (diltiazem HCl)

A) Product Design and Specification: The product design and specification information were reviewed by Dr Dhanalakshmi Kasi and found to be adequate. The diltiazem HCl drug product is a sterile product for continuous infusions that is manufactured as 125 mg/125 mL in a (b) (4) 250 mL IV bag and 250 mg/250 mL in a 250 mL (b) (4) IV bag at a concentration of 1 mg/mL for both presentations. The drug product contains dextrose (b) (4), sodium citrate dihydrate, and citrate acid monohydrate, (b) (4), sodium hydroxide, and hydrochloric acid, are pH adjusters, and water is used as a solvent. The maximum daily exposures for each excipient was found to be within limits for approved products for intravenous use. The Applicant conducted controlled extractable and leachable studies, and no leachables were detected at above the threshold for toxicological concern. The drug product specification includes appropriate tests and thresholds for impurities.

B) Drug Product Manufacturing: Dr. John Metcalfe reviewed the drug product manufacturing. The drug product is manufactured by (b) (4) The drug product manufacturing process and controls were reviewed and found to be adequate.

C) Biopharmaceutics Aspects: Dr. Rebecca Moody performed the biopharmaceutics review of the application. The Applicant initially requested a biowaiver under 21 CFR 320.22(b)(1), which was not feasible due to quantitative and qualitative differences in composition between the proposed and listed drug products. However, the Applicant performed comparative physicochemical studies to establish a scientific bridge between the proposed drug product and an appropriate generic reference standard product, the subject of ANDA 074617. These studies included comparisons of pH, osmolality, viscosity, and specific gravity. The biopharmaceutics review concluded that these data are adequate to establish a scientific bridge between the two products based on 21 CFR 320.24(b)(6), and the biopharmaceutics information is adequate to support approval of the NDA.

D) Microbiological Aspects: Dr. Bernard Marasa performed the quality microbiology review of the drug product, including (b) (4), microbiological test methods and acceptance criteria for sterility, endotoxins, and container closure integrity; (b) (4) ; information regarding building, facilities, equipment, environmental monitoring program; product labeling, stability data and

stability commitments. The microbiology review concluded that the microbiological controls are adequate to support the NDA.

E) Container Closure System: The container closure information was reviewed by Dr. Dhanalakshmi Kasi and found to be adequate. The drug product is light sensitive and must be protected from light by the container closure system. The container closure system for the 125 mg/125 mL presentation is 250 mL (b) (4) IV bags and 250 mL (b) (4) bags sealed with port (b) (4). The bags are individually packaged in (b) (4) pouches to protect from light, and (b) (4) bags are packed into a single carton with product insert. DMF references and letters of authorization were provided for each primary packaging component. The engineering drawings, specifications, and certificates of analysis were found to be adequate to support control of the container closure system. Photostability studies indicated that the product is adequately protected from light and stable when stored in the (b) (4) pouch.

4. **Assessment of Manufacturing Facilities**

Facility compliance information for the drug substance and drug product were reviewed by Dr. John Metcalfe. The drug substance manufacturing facility was approved based on inspectional history, and the drug product manufacturing facility was approved for LVP based on its previous history. All facilities have been found acceptable after OPMA review (see table below), and the overall manufacturing recommendation for NDA 215252 is approval.

Table of Manufacturing Facilities for NDA 215252:

Facility name and address	FEI	Responsibilities	Current Recommendation
Exela Pharma Sciences, LLC. P.O. Box 818 1245 Blowing Rock Blvd., Lenoir, NC, USA, 28645	3008563008	Raw Material Receipt and Testing, Quality Control Chemistry Testing, Visual Inspection, Packaging and Labeling, Warehousing of Packaged Drug Product, Stability Testing and Container Closure Integrity Testing	Approve - Based on Previous History
Exela Pharma Sciences, LLC 320 Cooperative Way, Lenoir, N.C., USA, 28645	3008563008	(b) (4) (b) (4) Drug Product Containers, Quality Control Environmental Microbiology Testing, Quality Control Product Sterility Testing and Quality Control In-process Drug Product Testing	Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History

5. **Environmental Assessment**: The Applicant claims that approval of this NDA qualifies for a categorical exclusion in accordance with 21 CFR 25.31(a) and that, to the best of the Applicant's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment. The information to support this categorical exclusion was reviewed by Dr. Kasi and found to be adequate to grant this request.

6. **Expiration Dating and Storage Conditions**: The Applicant submitted 24 months long-term and 6 months accelerated stability data in the NDA, for 3 primary stability batches. Stability data showed significant trending in assay and impurities; therefore, the proposed shelf life of 24 months is based on available long-term stability data. Freeze-thaw and photostability studies were performed. An expiration period of 24 months is granted for the drug product stored at 2 to 8°C (36°F to 46°F).

7. **Quality Labeling**: The container and carton label were reviewed as part of the drug product review. The dosage form description, strength, established name, NDC #, Lot #/Expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements for labeling. Comments regarding the draft USPI were conveyed to the Applicant, and it will be finalized as part of the review. Refer to the labeling review for additional information.

8. **List of CMC Deficiencies:** None

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, process, microbiology, and environmental analysis sections of this NDA. The OPQ overall recommendation for NDA 215252 is *approval.*

Theodore Carver, Ph.D. 10/3/2021
Senior Pharmaceutical Quality Assessor
Application Technical Lead

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate with revisions provided below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	**Revised Version:** DILTIAZEM HYDROCHLORIDE injection, for intravenous use only (USP salt policy not applied in this case as the applicant is following the nomenclature of the approved drug Cardizem (NDA 020027). Other approved ANDA's 074617, 074894, 075004 also use the same nomenclature.
Established name(s)		
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Injection: Clear, colorless solution in a single-dose bag for intravenous use. 125 mg/125 mL (1 mg/mL) 250 mg/ 250 mL (1 mg/mL)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		

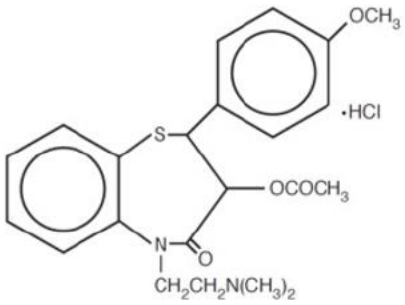
1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)		

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4)	Injection: Clear, colorless solution in a single-dose bag for intravenous use. 125 mg/125 mL (1 mg/mL) 250 mg /250 mL (1 mg/mL).
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		

Item		Assessor's Comments
DESCRIPTION:		
Proprietary and established name(s)	(b) (4)	Diltiazem Hydrochloride Injection is a nondihydropyridine calcium channel-blocker. Diltiazem hydrochloride is 1,5-benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2, 3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis- with the molecular weight of 450.98 and structural formula :  Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. Diltiazem Hydrochloride Injection is a clear, colorless, sterile, nonpyrogenic, isotonic solution for intravenous use only. Each
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Statement of being sterile (if applicable)		
Pharmacological/ therapeutic class		
Chemical name, structural formula, molecular weight		
If radioactive, statement of important nuclear characteristics.		

Other important chemical or physical properties (such as pKa or pH)	(b) (4)	mL contains 1 mg diltiazem hydrochloride, USP, 50 mg, anhydrous dextrose, USP, 0.15 mg citric acid monohydrate, USP and 0.12 mg sodium citrate dihydrate, USP, sodium hydroxide, NF and/or hydrochloric acid, NF to adjust pH to 3.9, and water for injection.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	None.	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None.	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	(b) (4)	Diltiazem Hydrochloride Injection is a sterile, clear, colorless solution in a single-dose bag supplied as: 125 mg/125 mL (NDC 51754-3000-1) 250 mg/ 250 mL (NDC 51754-3500-1) Discard any unused portion. Store under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. The single-dose bags in their original pouches are stable for up to one month at room temperature.
Strength(s) in metric system		
Available units (e.g., bottles of 100 tablets)		
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	(b) (4)	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	See above	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above.	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	No Information included.	

1.2.3 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	(b) (4)	Manufactured and Distributed by: Exela Pharma Sciences, LLC Lenoir, NC 28645

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

No Information included.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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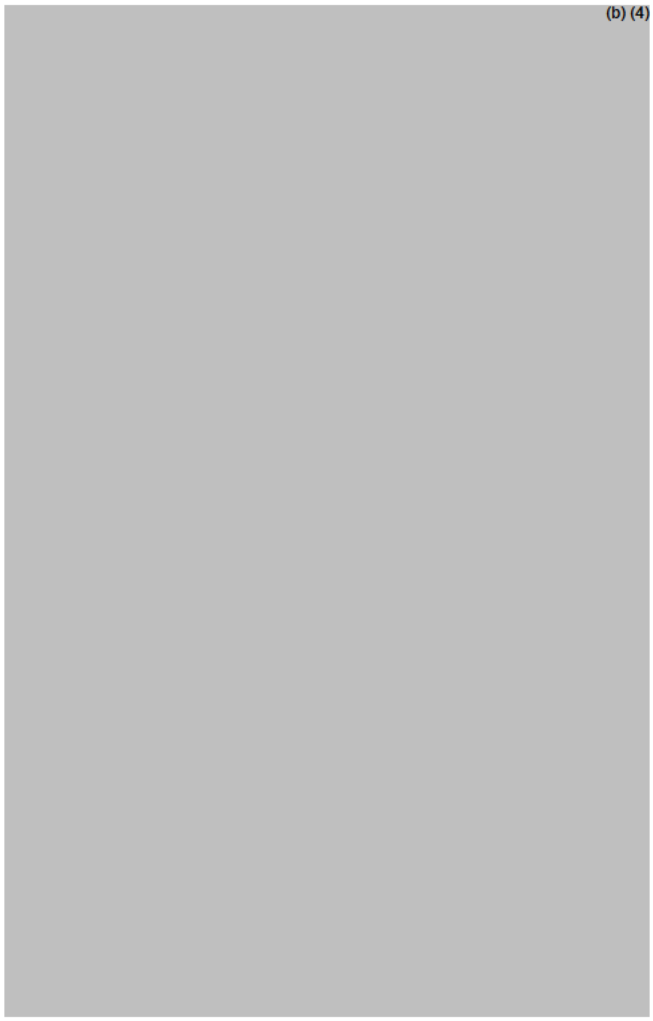

Assessment of Carton and Container Labeling: *Adequate*

The applicant will be asked to revise the following from the carton and container label:

1. Revise "(b) (4)" to "For intravenous use only"
2. Remove "(b) (4)".
3. DMEPA will be consulted for the caution statement: "**CAUTIONS:** Check for minute leaks (b) (4). Do not use unless solution is clear. Do not add supplemental medication. Must not be used in series connections."

Overall Assessment and Recommendation:

The labeling/labels will be adequate from a quality perspective after the recommended changes have been made.

Dhanalakshmi Kasi

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Mohan Sapru

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CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	215252
Assessment Cycle Number	# 1
Drug Product Name/ Strength	Diltiazem Hydrochloride Injection, 1 mg/mL with 125 mL and 250mL fill volumes in 250 mL IV bags
Route of Administration	Intravenous (IV) infusion
Applicant Name	Exela Pharma Sciences
Therapeutic Classification/OND Division	Calcium Channel Blocker/ Division of Cardiology and Nephrology (DCN)
RLD/RS Number	NDA 020027/ANDA 074617
Proposed Indication	(1) Temporal control of rapid ventricular rate in atrial fibrillation or atrial flutter. (2) Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.
Primary Assessors	*Rebecca Moody, Ph.D..*
Secondary Assessors	*Poonam Delvadia, Ph.D.*
Assessment	**Adequate**
Recommendation	Based on the assessment of the overall information, from a Biopharmaceutics perspective, NDA 215252 for Diltiazem Hydrochloride Injection 1 mg/mL (250 mg/250 mL and 125 mg/125 mL), is recommended for **APPROVAL**.

Background

This 505 (b)(2) application seeks approval for Diltiazem Hydrochloride Injection, 1 mg/mL with 125 mL and 250mL fill volumes in 250 mL IV bags for continuous intravenous (IV) infusion, which is indicated for (1) temporal control of rapid ventricular rate in atrial fibrillation or atrial flutter and (2) rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.

This application relies on the FDA's finding of safety and effectiveness for the reference listed drug, Cardizem Injectable (diltiazem hydrochloride injection, 5 mg/mL) (NDA 020027, Biovail Laboratories International SRL).

Assessment Summary:

The Applicant initially requested a biowaiver; however, because the formulation of the proposed drug product is not qualitatively and quantitatively (Q1/Q2) the same as the LD, a biowaiver under 21 CFR 320.22(b)(1) is not feasible. Nevertheless, a scientific bridge may be established between the proposed Diltiazem Hydrochloride Injection and the LD as per 21 CFR 320.24(b)(6). The Applicant used an approved generic manufactured by West-Ward Corp to conduct the bridging studies because the LD, Cardizem Injectable, is discontinued (not for safety or efficacy reasons). In an IR dated 5/11/2021, the Applicant was informed that the generic reference standard (RS) product, ANDA 074617, should be used for comparative physicochemical studies to establish the scientific bridge. This

Biopharmaceutics Review evaluated the overall data supporting the bridge between the proposed drug product and the LD/RS.

The LD/RS, provided at 5 mg/mL, is intended for bolus intravenous injection or continuous intravenous infusion. For continuous intravenous infusion, the LD/RS is to be diluted in 5% Dextrose, normal saline, or 5% Dextrose/0.45% NaCl. Exela's product, provided in 250 mL IV bags, is intended to be a ready-to-use drug product for continuous intravenous infusion at 1 mg/mL.

The proposed drug product shares the active ingredient, dosage form, route of administration and instructions for administration as the LD/RS. In addition, the excipients are the same with the exception of the (b) (4) (sorbitol solution in the LD/RS vs. dextrose in the proposed drug product). The difference (b) (4), however, is not likely to affect disposition kinetics of diltiazem hydrochloride. The Applicant also provided sufficient physicochemical data demonstrating the pH, osmolality, viscosity, and specific gravity are comparable between their proposed drug product and the RS. Based on the totality of the data, the scientific bridge between the proposed Diltiazem Hydrochloride Injection (1 mg/mL) is adequately established to the LD/RS based on 21 CFR 320.24(b)(6).

List Submissions being assessed:

Document(s) Assessed	Date Received
0001 (1) Original Submission	**December 30, 2020**
0004 (4) (IR Response)	**March 3, 2021**
0008 (8) (IR Response)	**June 3, 2021**

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues: None

Recommendation: Based on the assessment of the overall information, from a Biopharmaceutics perspective, NDA 215252 for Diltiazem Hydrochloride Injection 1 mg/mL (250 mg/250 mL and 125 mg/125 mL), is recommended for **APPROVAL**.

B.1 DRUG SUBSTANCE

The active ingredient of Exela Pharma Sciences' proposed drug product is diltiazem hydrochloride, USP, which is the same as the approved LD, Cardizem Injectable (N020027).

Diltiazem hydrochloride is a white, odorless crystalline powder (or small crystals) and is sparingly soluble in water. However, the solubility of diltiazem hydrochloride in water and the formulation vehicle is greater than the concentration in the proposed drug product (1 mg/mL) at room temperature and at 2-8°C (the long term storage condition of the finished product).

(b) (4)

B.2 DRUG PRODUCT

The composition of the proposed Diltiazem Hydrochloride Injection is shown in **Error! Reference source not found.** APPEARS THIS WAY ON ORIGINAL

Table 1: Composition of Diltiazem Hydrochloride Injection

Component	Quality Standard	Function	Amount		
			% w/v	mg/ mL	mg/ 250 mL Bag
Diltiazem Hydrochloride, USP	USP	Active	0.1%	1.0	250
Dextrose, Anhydrous, USP	USP	(b) (4)	5.0%	50	12,500
Citric Acid ,Monohydrate, USP	USP		0.015%	0.15	37.5
Sodium Citrate, Dihydrate, USP	USP		0.012%	0.12	30
Sodium Hydroxide, NF	NF	pH Adjuster	q.s. to 3.9 pH	q.s. to 3.9 pH	q.s. to 3.9 pH
Hydrochloric Acid, NF	NF	pH Adjuster	q.s. to 3.9 pH	q.s. to 3.9 pH	q.s. to 3.9 pH
Water for Injection	USP	Solvent	q.s to 100%	q.s. to 1.0 mL	q.s. to 250.0 mL

B.3 BRIDGE BETWEEN THE PROPOSED DRUG PRODUCT AND THE LISTED DRUG PRODUCT

The following information is evaluated in support of the bridging between the proposed drug product and the listed drug product:

1. Formulation, dosage form, and administered volume
2. Comparative physicochemical data

1) Formulation, dosage form and administered volume

Exela's proposed drug products, Diltiazem Hydrochloride Injection, 125 mg/125 mL and 250 mg/250 mL, are supplied as a clear, colorless, sterile, nonpyrogenic, unpreserved solution intended for intravenous infusion in 250 mL IV bags.

The LD, on the other hand, is supplied at 5 mg/mL and can be administered via intravenous bolus injection or continuous intravenous infusion. To prepare the LD for continuous intravenous infusion, it must be diluted with normal saline, D5W, or D5W/0.45% NaCl to a concentration of 1 mg/mL or 0.83 mg/mL or 0.45 mg/mL.

Exela's proposed drug product, supplied at 1 mg/mL, is a ready-to-use (RTU) formulation for continuous intravenous infusion. Exela's diltiazem hydrochloride injection is ***not*** for direct intravenous single injections (i.e., bolus). The comparison between the proposed drug product formulation and the LD/RS is provided below in Tables 2 and 3.

Table 2: Comparison between LD product, Cardizem Injectable, and the proposed Diltiazem Hydrochloride Injection (1 mg/mL)

	RLD product, Cardizem[1] Injectable 5 mg/mL	Proposed Diltiazem Hydrochloride 1 mg/mL
Composition per mL		
Diltiazem Hydrochloride	5 mg	1 mg
Citric acid, USP	0.75 mg	0.15 mg
Sodium citrate, dihydrate, USP	0.65 mg	0.12 mg
Sorbitol solution, USP	71.4 mg	Nil
Dextrose, anhydrous, USP	Nil	50 mg
Hydrochloric acid	q.s. to pH 3.7 – 4.1	q.s. to pH 3.9
Sodium hydroxide	q.s. to pH 3.7 – 4.1	q.s. to pH 3.9
Water for Injection	q.s. to 1 mL	q.s. to 1 mL

How supplied	5/10 mL vials	125/250 mL IV bags
Diltiazem Hydrochloride/unit	25 mg/50 mg	125 mg/250 mg
Indications and use	As per the RLD product label	Same as the RLD product
Dose and administration	As per the RLD product label	Same as the RLD product
Preparation	May be diluted before administration	Premixed and ready to use
Storage and handling	To be stored under refrigeration 2 to 8°C (36 to 46°F). Do not freeze.	To be stored under refrigeration 2 to 8°C (36 to 46°F). Do not freeze.

[1] Information regarding Cardizem Injectable product was obtained from PDR 2000.

Table 3: Comparison between the Athenex RS product Diltiazem Hydrochloride Injection, and the proposed Diltiazem Hydrochloride Injection (1 mg/mL)

Component	RS product, Diltiazem Hydrochloride Injection Solution 5 mg/mL[1]	Proposed Diltiazem Hydrochloride 1 mg/mL
	Composition per mL	
Diltiazem Hydrochloride	5 mg	1 mg
Citric Acid Monohydrate	0.75 mg	0.15 mg
(b) (4) sodium Citrate, Dihydrate	0.65 mg	0.12 mg
Sorbitol	71.4 mg	Nil
Dextrose, anhydrous	Nil	50 mg
Hydrochloric acid	q.s. to pH 3.7 – 4.1	q.s. to pH 3.9 (b) (4)
Sodium hydroxide	q.s. to pH 3.7 – 4.1	q.s. to pH 3.9
Water for Injection	q.s. to 1 mL	q.s. to 1 mL
How supplied	5/10/25 mL vials	125/250 mL IV bags
Diltiazem Hydrochloride/unit	25 mg/50 mg/125 mg	125 mg/250 mg
Indications and use	As per the RLD product label	Same as the RLD product
Dose and administration	As per the RLD product label	Same as the RLD product
Preparation	May be diluted before administration	Premixed and ready to use
Storage and handling	To be stored under refrigeration 2 to 8°C (36 to 46°F). Do not freeze.	To be stored under refrigeration 2 to 8°C (36 to 46°F). Do not freeze.
Storage And Handling	To be stored under refrigeration 2 to 8°C (36 to 46°F). Do not freeze.	To be stored under refrigeration 2 to 8°C (36 to 46°F). Do not freeze.

[1] Information regarding Athenex's Diltiazem Hydrochloride Injection Solution was obtained from DailyMed

Reviewer's Assessment:

The proposed drug product has the same active ingredient, dosage form, route of administration (intravenous) and indications as the LD/RS. After the LD/RS is diluted for continuous intravenous infusion, the concentrations of the active ingredient and inactive ingredients are very similar. Aside from the starting concentrations (e.g. 5 mg/mL in the LD vs. 1 mg/mL in the proposed drug product), the only other difference between the LD and Exela's proposed drug product is the (b) (4) In the LD, sorbitol solution is used (b) (4) whereas the proposed drug product uses dextrose. The change from sorbitol solution to dextrose in the proposed drug product is not expected to have any impact on the disposition kinetics of diltiazem hydrochloride.

2) **Comparative Physicochemical Data**

The Applicant provided chemical characterization data of the proposed Diltiazem Hydrochloride Injection and the "RLD" at room temperature (Table 4) and after 24 hours of storage at 2-8°C (Table 5). The "RLD" was diluted to 1 mg/mL in 5% Dextrose (D5W). Of note, the LD has been discontinued, so the Applicant substituted an approved generic of Diltiazem Hydrochloride Injection (manufactured by West-Ward Corp) for the RLD in admixture studies. In response to the IR dated 5/11/2021, the Applicant also provided comparative physicochemical data for their proposed drug product (Table 6) and the RS, Athenex's Diltiazem Hydrochloride Injection (A074617), (Table 7).

Table 4: Comparison between the RLD and the proposed Diltiazem Hydrochloride Injection (1 mg/mL) at Room Temperature

Product Name	Appearance and Description	pH	Particulate Matter	Assay	Total Impurities
			(b) (4)		(b) (4)
RLD (Diltiazem Hydrochloride Injection) (after dilution)	Pass	3.9 – 4.1		96.5% - 100.98%	
Exela's Diltiazem Hydrochloride Injection	Pass	3.9 – 4.0		99.7% - 101.6%	

Table 5: Comparison between the RLD and the proposed Diltiazem Hydrochloride Injection (1 mg/mL) at 2-8°C

Product Name	Appearance and Description	pH	Particulate Matter	Assay	Total Impurities
			(b) (4)		(b) (4)
RLD (Diltiazem Hydrochloride Injection) (after dilution)	Pass	4.1		99.3% - 100.8%	
Exela's Diltiazem Hydrochloride Injection	Pass	3.9 – 4.0		99.6% - 101.6%	

Table 6: Physicochemical Properties of Exela's Proposed Drug Product

Product	Manufacturer	Lot Number	Expiry	Physical Appearance	pH	Osmolality (mOsm/kg)	Viscosity (cSt)
Diltiazem Hydrochloride Injection (1 mg/mL)	Exela	X0000091B	TBD	Clear, Colorless Solution	3.9	304	0.9
					3.9	298	0.9
					3.9	305	0.9
Diltiazem Hydrochloride Injection (1 mg/mL)	Exela	X0000092B	TBD	Clear, Colorless Solution	4.0	304	0.9
					3.9	300	0.9
					3.9	302	0.9
Diltiazem Hydrochloride Injection (1 mg/mL)	Exela	X0000093B	TBD	Clear, Colorless Solution	3.9	302	0.9
					4.0	300	0.9
					4.0	300	0.9

Table 7: Physicochemical Properties of RS, Athenex's Diltiazem Hydrochloride Injection (A074617) after dilution in D5W to 1 mg/mL

Product	Manufacturer	Lot Number	Expiry	Physical Appearance	pH	Osmolality (mOsm/kg)	Viscosity (cSt)
Diltiazem Hydrochloride Injection (5 mg/mL)	Athenex	E001A009	12/2021	Clear, Colorless Solution	4.2	275	0.9
					4.2	275	0.9
					4.2	275	0.9
Diltiazem Hydrochloride Injection (5 mg/mL)	Athenex	E003A002	11/2021	Clear, Colorless Solution	4.1	276	0.9
					4.1	273	0.9
					4.1	274	0.9
Diltiazem Hydrochloride Injection (5 mg/mL)	Athenex	E002A005	02/2022	Clear, Colorless Solution	4.1	277	0.9
					4.1	278	0.9
					4.1	275	0.9

Reviewer's Assessment:

The pH, osmolality, viscosity, and physical appearance are comparable between Exela's proposed Diltiazem Hydrochloride Injection and the RS.

The Applicant has provided sufficient evidence to support a scientific bridge between their proposed drug product and the LD/RS. In accordance with 21 CFR 320.24(b)(6), a scientific bridge has been established between the proposed drug product and the LD/RS, based on the following:

1. The proposed drug product shares the same active ingredient, dosage form, route of administration (continuous intravenous infusion), and indications as the LD/RS.
2. The proposed drug product has comparable physicochemical data (i.e., pH, osmolality, viscosity, and specific gravity) to the LD/RS (diluted from 5 mg/mL to 1 mg/mL).

APPENDIX I: Biopharmaceutics Information Request (2/22/2021) and Applicant's Response (3/3/2021)[1]

1. *You requested a biowaiver under regulation 21 CFR 320.22 (b)(1); however, the formulation of your proposed drug product is not qualitatively and quantitatively the same as the formulation of the listed drug product. The listed drug is also discontinued. Therefore, a biowaiver request under 21 CFR 320.22 (b)(1) is not feasible for your proposed drug product.*

   Nevertheless, you may establish a scientific bridge between your drug product and the reference standard under 21 CFR 320.24 (b)(6). The reference standard (RS) currently designated in the orange book is A074617. Submit the following information in support of the bridge under 21 CFR 320.24 (b)(6):

   1. *Side-by-side comparison of the qualitative and quantitative compositions between your proposed drug product and the RS.*
   2. *Comparative physiochemical data (such as pH, osmolality, viscosity, specific gravity, color and clarity) for at least 3 productions lots of your proposed drug product and 3 lots of the RS. The measurements should be done in triplicate for each lot tested.*
   3. *Justification that any difference between the proposed drug product and the RS, in terms of formulation, physiochemical characteristics, mode of administration, administered volume, etc., will not affect the in vivo performance of your product.*

   As the RS is intended for both direct intravenous bolus injection (without dilution) and continuous intravenous infusion (post dilution), provide data on the RS, before and after dilution (i.e., to 1 mg/mL), in comparison with your proposed drug product.

Applicant's Response to IR 1:

The LD, Cardizem Injectable, was discontinued and Athenex Pharmaceuticals Division, LLC (A074617) was designated as the RS. The Applicant claims the RS was not available for testing at the time of their NDA submission. Therefore, they obtained three lots of an approved generic, Diltiazem Hydrochloride Injection (5 mg/mL) manufactured by West-Ward Corp to represent the LD/RS during admixture and comparison studies. The Applicant further claimed that due to limited quantities of the approved generic, they prioritized admixture studies using diluted "LD/RS" as this most closely aligned with their proposed ready-to-use product. Only two lots had sufficient quantities for physical

[1] NDA 215425 Biopharmaceutics Information Request (dated February 10, 2021) and IR response (dated February 23, 2021)

comparison studies. The comparison of the physicochemical properties between Exela's and West-Ward Corp's Diltiazem Hydrochloride Injection are provided below in Table 8.

Table 8: Comparison of physicochemical properties between Exela's Diltiazem Hydrochloride Injection (1 mg/mL) and Approved Generic Diltiazem Hydrochloride Injection (5 mg/mL) manufactured by West-Ward Corp.

Product	Lot Number	Expiry/Date of Manufacture	Color and Clarity	Osmolality	pH	Specific Gravity
Diltiazem Hydrochloride Injection (5 mg/mL), West-Ward Corp	057364	Exp. 05/2019	Clear, Colorless Solution	319 mOsm/kg	3.9	1.0194
				324 mOsm/kg	3.9	
				321 mOsm/kg	3.9	
Diltiazem Hydrochloride Injection (5 mg/mL), West-Ward Corp	108366	Exp. 10/2020	Clear, Colorless Solution	323 mOsm/kg	3.9	1.0194
				323 mOsm/kg	3.9	
				321 mOsm/kg	3.9	
Diltiazem Hydrochloride Injection (1 mg/mL), Exela	X0000091A (125 mL)	Mfg. 03/2020	[1]Clear, Colorless Solution	[1]299 mOsm/kg	[1]4.0	1.0194
			[2]Clear, Colorless Solution	[2]303 mOsm/kg	[2]3.9	1.0194
			[3]Clear, Colorless Solution	[3]302 mOsm/kg	[3]3.9	1.0196
Diltiazem Hydrochloride Injection (1 mg/mL), Exela	X0000091B (250 mL)	Mfg. 03/2020	[1]Clear, Colorless Solution	[1]300 mOsm/kg	[1]4.0	1.0195
			[2]Clear, Colorless Solution	[2]300 mOsm/kg	[2]3.9	1.0195
			[3]Clear, Colorless Solution	[3]301 mOsm/kg	[3]4.0	1.0195
Diltiazem Hydrochloride Injection (1 mg/mL), Exela	X0000092A (125 mL)	Mfg. 03/2020	[1]Clear, Colorless Solution	[1]302 mOsm/kg	[1]3.9	1.0191
			[2]Clear, Colorless Solution	[2]305 mOsm/kg	[2]3.9	1.0188
			[3]Clear, Colorless Solution	[3]301 mOsm/kg	[3]4.0	1.0187
Diltiazem Hydrochloride Injection (1 mg/mL), Exela	X0000092B (250 mL)	Mfg. 03/2020	[1]Clear, Colorless Solution	[1]300 mOsm/kg	[1]4.0	1.0195
			[2]Clear, Colorless Solution	[2]302 mOsm/kg	[2]3.9	1.0196
			[3]Clear, Colorless Solution	[3]300 mOsm/kg	[3]3.9	1.0195
Diltiazem Hydrochloride Injection (1 mg/mL), Exela	X0000093A (125 mL)	Mfg. 03/2020	[1]Clear, Colorless Solution	[1]302 mOsm/kg	[1]3.9	1.0196
			[2]Clear, Colorless Solution	[2]300 mOsm/kg	[2]3.9	1.0195
			[3]Clear, Colorless Solution	[3]303 mOsm/kg	[3]4.1	1.0195
Diltiazem Hydrochloride Injection (1 mg/mL), Exela	X0000093B (250 mL)	Mfg. 03/2020	[1]Clear, Colorless Solution	[1]301 mOsm/kg	[1]4.0	1.0195
			[2]Clear, Colorless Solution	[2]300 mOsm/kg	[2]4.0	1.0194
			[3]Clear, Colorless Solution	[3]303 mOsm/kg	[3]4.0	1.0194

[1] Release Stability Data
[2] 1 Month 5°C Stability Data
[3] 3 Month 5°C Stability Data

Reviewer's Assessment:

While the physicochemical data for West-Ward Corp's and Exela's Diltiazem Hydrochloride Injection (at 1 mg/mL) are comparable, the use of West-Ward Corp's drug product to represent the LD/RS is not acceptable as the RS has not been discontinued. The Applicant was informed in a subsequent IR (IR #2, Appendix II) to provide comparative data using the appropriate RS, Athenex Diltiazem Hydrochloride Injection (A074617). Further, the Applicant only provided data on the diluted "LD/RS." However,

since the proposed drug product is most similar in use and composition as the diluted LD/RS, this is acceptable.

APPENDIX II: Biopharmaceutics Information Request (5/11/2021) and Applicant's Response (6/3/2021)[2]

1. *The use of Diltiazem Hydrochloride Injection (5 mg/mL) manufactured by West-Ward Corp to represent the RLD/RS during admixture and comparison studies is not acceptable. The reference standard (RS) currently designated in the orange book, A074617, has not been discontinued and therefore, should be used to establish the scientific bridge for your proposed drug product. Provide comparative physiochemical data (such as PH, osmolality, viscosity, specific gravity, color, and clarity) between your proposed drug product and the RS post-dilution. We recommend testing in triplicate and using at least 3 lots of your proposed drug product and 3 lots of the RS. If any differences in the physicochemical properties of the diluted products are observed, provide justification that it will not impact in vivo performance of your proposed drug product.*

Applicant's Response to IR 2:
The Applicant provided pH, osmolality, specific gravity, viscosity, and physical appearance data for three lots of the RS in comparison with the proposed NDA product.

Reviewer's Assessment:
The Applicant's response is acceptable. The data demonstrates there are no significant differences in the physicochemical properties of the diluted drug products.

[2] NDA 215425 Biopharmaceutics Information Request (dated April 13, 2021) and IR response (dated June 22, 2021).

Poonam Delvadia

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Rebecca Moody

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	215252
Assessment Cycle Number	#1
Drug Product Name/ Strength	Diltiazem Hydrochloride Injection
Route of Administration	Intravenous Injection
Applicant Name	Exela Pharma Sciences, LLC. P.O Box 818 1245 Blowing Rock Blvd Lenoir, NC 28645
Therapeutic Classification/ OND Division	Atrial Fibrillation
Manufacturing Site	Exela Pharma Sciences Augusta Manufacturing Facility 320 Cooperative Way Lenoir, NC 28645
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: Diltiazem Hydrochloride Injection is (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) .

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq 0001	**12/30/2020**
Seq 0006*	**05/07/2021**

***Applicant Response to Information Request**

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

Remarks: Application is in eCTD format. Some table are copied from the submission. Applicant responded to Agency's Information Request dated April 23, 2021 with a Response to Information Request dated May 07, 2021 which upon review was deemed adequate. The Agency Information Request comments are highlighted in italics followed by Applicant's Response in bold within the submission.

Supporting Documents: None.

S DRUG SUBSTANCE

Assessment: ***{Adequate}***
The drug substance is received non-sterile and will not be subject to sterility assurance review.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Diltiazem Hydrochloride Injection, 1 mg/mL, is supplied as a clear, colorless, sterile, non-pyrogenic, unpreserved solution intended for intravenous infusion. The proposed drug product is available in two strengths, 125 mg/125 mL and 250 mg/250 mL, both in 250 mL IV bags sealed with port (b) (4).

- **Drug product composition –**

Table 1: Function and Percentage of Ingredients for Diltiazem Hydrochloride Injection, 1 mg/mL

Component	Quality Standard	Function	Amount			
			% w/v	mg/mL	mg/250 mL Bag	mg/125 mL Bag
Diltiazem Hydrochloride, USP	USP	Active	0.1%	1.0	250	125
Dextrose, Anhydrous, USP	USP	(b) (4)	5.0%	50	12,500	6,250
Citrate Acid Monohydrate, USP	USP		0.015%	0.15	37.5	18.75
Sodium Citrate Dihydrate, USP	USP		0.012%	0.12	30	15
Sodium Hydroxide, NF	NF	pH Adjuster	q.s. to 3.9 pH	q.s. to 3.9 pH	q.s. to 3.9 pH	q.s. to 3.9 pH
Hydrochloric Acid, NF	NF	pH Adjuster	q.s. to 3.9 pH	q.s. to 3.9 pH	q.s. to 3.9 pH	q.s. to 3.9 pH
Water for Injection	USP	Solvent	q.s to 100%	q.s. to 1.0 mL	q.s. to 250.0 mL	q.s. to 125.0 mL

- **Description of container closure system –**

Table 1: Diltiazem Hydrochloride Injection Container Closure Components

Product Description	IV Bag Type	IV Bag Closure
Diltiazem Hydrochloride Injection (1 g/mL), 125 mL/125 mL bag and 250 mL/250 mL bag	250 mL IV Bag, (b) (4)	(b) (4) Port (b) (4) (b) (4) (For exhibit batch)
Diltiazem Hydrochloride Injection (1 g/mL), 125 mL/125 mL bag and 250 mL/250 mL bag	250 mL IV Bag (b) (4)	(b) (4) Port (b) (4) (b) (4)

Note to Reviewer: Drawings of the C/C system are provided (Section 3.2P.7-Container Closure System Results Drug Product seq 0001, page 16 of 383 for (b) (4) bags and page 26 of 383 for (b) (4) bags).

Reviewer's Assessment: *Adequate*
Adequate description and composition of the drug product was provided along with the container closure system used for packaging.

P.2 Pharmaceutical Development

(b) (4)

[redacted]

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

R REGIONAL INFORMATION

R.1 Executed Batch Record

Executed lot #(s): lot # X0000091A, X0000091B, X00000092A, X0000092B, X0000093A and X0000093B

The batch records confirm that validated (b) (4) (b) (4) manufacturing processes were used for the manufacture of the exhibit batch.

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

R.2 Comparability Protocol – No CP was included in the application.

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

A. PACKAGE INSERT

Storage temperature: 2°C to 8°C (36°F to 46°F). ; Route of administration: IV; Container: Single dose

Pre-use storage: 2°C to 8°C (36°F to 46°F). The single dose bags are stable up to one month at room temperature without significant loss of potency.

Further product dilution: None.

Reviewer's Assessment: *Adequate*

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

2.A. Prescribing Information

- Post-dilution/constitution hold time: No reconstitution or further dilution is indicated in the package insert.

Assessment: *Adequate*

Post-Approval Commitments: None.

Assessment: *Adequate*

MICROBIOLOGY LIST OF DEFICIENCIES- None.

Primary Microbiology Assessor Name and Date:

Bernard S. Marasa, Ph.D. May 20, 2021

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

Yuansha Chen, Ph. D. May 21, 2021

Yuansha Chen

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/s/

THEODORE E CARVER
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