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RESEARCH**

APPLICATION NUMBER:

218038Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



Template Revision: 03

NDA Executive Summary – NDA 218038 Resubmission

1. Application/Product Information

NDA Number.	218038		
Applicant Name	HQ Specialty Pharma Corporation		
Drug Product Name	Diltiazem Hydrochloride in 0.72% Sodium Chloride Injection		
Dosage Form.	Injection		
Proposed Strength(s)	100 mg/100 mL (1 mg/mL); 250 mg/ 250 mL(1 mg/mL)		
Route of Administration	Intravenous		
Maximum Daily Dose	405 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	• Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. (• Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.		
Drug Product Description	Clear, colorless solution in a single-dose bag for intravenous use.		
Co-packaged product information	N/A		
Device information:	The drug product is a drug-device combination product contained in infusion bags with injection ports. No CDRH device review was required.		
Storage Temperature/ Conditions	2°C to 8°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance*</i>	Stephanie Springer	Sithamalli Chandramouli
	<i>Drug Product*/ Labeling</i>	Rao Kambhampati	Theodore Carver



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



Template Revision: 03

	<i>Manufacturing</i>	Vladimir Dragan	Sudipan Karmakar
	<i>Biopharmaceutics*</i>	Elizabeth Gray	Kevin Wei
	<i>Microbiology*</i>	BreOnna Delaine-Elias	Neal Sweeney
	<i>Other (specify):</i>	N/A	
	<i>RBPM</i>	Grafton Adams	
	<i>ATL</i>	Theodore Carver	
Consults	N/A		

*See previous Integrated Quality Assessment (IQA) dated June 26, 2024.

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 24 months is granted for the drug product when stored at 2°C to 8°C (36°F and 46°F)

b. Additional Comments for Action

None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1) Background

The Applicant has submitted NDA 218038 in accordance with Section 501(b)(2) of the Federal Food, Drug and Cosmetic Act. This NDA for a ready-to-use diltiazem hydrochloride formulation uses scientific bridging per 21 CFR 320.24(b)(6) between the proposed product and the Listed Drugs, Cardizem, NDA 020027 and Diltiazem Hydrochloride in Dextrose 5%, NDA 215252 as a basis for relying on FDA's findings of safety and effectiveness for those drugs. Because these products have been discontinued, the NDA also relies on ANDA 074617 (Diltiazem Hydrochloride, 5 mg/mL) as the Reference Standard for the physicochemical comparison for the purpose of establishing



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



Template Revision: 03

a scientific bridge to the Listed Drugs. The OPQ review of the original NDA recommended non approval of the NDA due to deficiencies identified in a cGMP inspection of the (b) (4) drug product manufacturing facility. All other disciplines recommended approval of NDA 218038. See the Integrated Quality Assessment of the original NDA submission (DARRTS review, dated June 26, 2024). Other than the manufacturing and labeling reviews, no other disciplines were required for review of the NDA submission because no new information was included in the NDA resubmission.

2) Manufacturing

Process – The manufacturing process for diltiazem hydrochloride in 0.72% sodium chloride injection involves (b) (4). The manufacturing process remains adequate.

Facilities – A CGMP inspection of the drug product manufacturing facility, (b) (4) was conducted in (b) (4) with a recommendation of preliminary Office Action Indicated (pOAI) based on deficiencies identified during the inspection. After the end of the original review period and the Complete Response Action, the inspection outcome was reclassified to Voluntary Action Indicated (VAI) based on the Applicant’s responses to deficiencies and other information. Therefore, all manufacturing facilities are currently recommended for approval.

3) Quality Labeling

Labeling comments and deficiencies identified in the previous review have been addressed by the Applicant, and any further revisions will be made as part of the final labeling review.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

- Drug Substance** - Adequate
- Drug Product** - Adequate
- Quality Labeling** - Adequate
- Manufacturing** - Adequate
- Biopharmaceutics** - Adequate
- Microbiology** - Adequate

Environmental Assessment: Categorical Exclusion - Adequate





Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



Template Revision: 03

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments:

None.





Theodore
Carver

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Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

NDA Executive Summary – Review #1

1. Application/Product Information

NDA Number.	218038		
Applicant Name	HQ Specialty Pharma Corporation		
Drug Product Name	Diltiazem Hydrochloride in 0.72% Sodium Chloride Injection		
Dosage Form.	Injection		
Proposed Strength(s)	100 mg/100 mL (1 mg/mL); 250 mg/ 250 mL(1 mg/mL)		
Route of Administration	Intravenous		
Maximum Daily Dose	405 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	• Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. (• Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.		
Drug Product Description	Clear, colorless solution in a single-dose bag for intravenous use.		
Co-packaged product information	N/A		
Device information:	Description, performance attributes or N/A		
Storage Temperature/ Conditions	2°C to 8°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Stephanie Springer	Sithamalli Chandramouli
	<i>Drug Product/ Labeling</i>	Rao Kambhampati	Theodore Carver
	<i>Manufacturing</i>	Vladimir Dragan	Sudipan Karmakar



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

	<i>Biopharmaceutics</i>	Elizabeth Gray	Kevin Wei
	<i>Microbiology</i>	BreOnna Delaine-Elias	Neal Sweeney
	<i>Other (specify):</i>	N/A	
	<i>RBPM</i>	Grafton Adams	
	<i>ATL</i>	Theodore Carver	
Consults	N/A		

2. Final Overall Recommendation - Complete Response

2. Deficiencies

Manufacturing

- Following a CGMP inspection of (b) (4) listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response. The facility's satisfactory responses are dependent on FDA's determination that the facility has come into compliance with CGMP and may require re-inspection of the facility. The deficiencies identified during the inspection may not be specific to your pending application, therefore, you should coordinate with the facility for timely resolution. Your complete response should include the date(s) of the facility's response(s) to the FDA Form 483.

Please refer to Compliance Program CP7356.002 for guidance on post inspection activities. Following resolution of the CGMP inspection, FDA may need to conduct a PAI of the facility. Satisfactory outcomes of both the PAI and the CGMP surveillance inspections will be needed prior to an approval of the application.





Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

(Include summary of deficiencies, pending issues, benefit-risk considerations, etc. according to recommendation. Not intended to be a summary of review.)

1) Background

The Applicant has submitted NDA 218038 in accordance with Section 501(b)(2) of the Federal Food, Drug and Cosmetic Act. This NDA for a ready-to-use diltiazem hydrochloride formulation uses scientific bridging per 21 CFR 320.24(b)(6) between the proposed product and the Listed Drugs, Cardizem, NDA 020027 and Diltiazem Hydrochloride in Dextrose 5%, NDA 215252 as a basis for relying on FDA's findings of safety and effectiveness for those drugs. Because these products have been discontinued, the NDA also relies on ANDA 074617 (Diltiazem Hydrochloride, 5 mg/mL) as the Reference Standard for the physicochemical comparison for the purpose of establishing a scientific bridge to the Listed Drugs.

2) Drug Substance (diltiazem hydrochloride)

This NDA cross references drug master file (DMF) (b) (4) for the diltiazem hydrochloride drug substance. This DMF was recently reviewed and found adequate to support this NDA. Control of impurities and risks with respect to residual solvents and (b) (4) impurities were evaluated and found to be low. The drug substance information was assessed to be adequate to support the NDA.

3) Drug Product (Diltiazem Hydrochloride in 0.72% Sodium Chloride Injection)

The drug product review included review of all aspects and critical quality attributes of the drug product. The review concluded that the specification, extractables leachables studies, and stability data were adequate to support approval of the drug product. In response to an information request, the Applicant conducted testing for (b) (4) and determined that levels of this impurity were below the limit of detection and therefore less than (b) (4) % of the acceptable intake (AI) limit, indicating that no additional testing is needed for this impurity. Based on the stability data provided, the drug product review concluded that a shelf life of 24 months is supported for the drug product. In addition, room temperature storage (20°C to 25°C) is supported for up to one month for the infusion bag in overwrap. The drug product information was assessed to be adequate to support the NDA.



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

4) Manufacturing

Process – The manufacturing process for diltiazem hydrochloride in 0.72% sodium chloride injection involves (b) (4)

(b) (4) After the Applicant addressed information requests related to in-process controls and limits, the manufacturing review found the process information to be adequate.

Facilities – A preapproval facility inspection for the drug substance manufacturing facility, (b) (4)

initially resulted in a preliminary Office Action Indicated (pOAI) recommendation. This outcome was downgraded to Voluntary Action Indicated (VAI) recommendation, and this facility is recommended for approval. Two other testing facilities are recommended for approval based on previous inspection history. A CGMP inspection of the drug product manufacturing facility, (b) (4) was conducted in (b) (4) with a recommendation of pOAI based on deficiencies identified during the inspection. The Office of Regulatory Affairs (ORA) has confirmed that the deficiencies identified in this facility inspection will not be resolved during the review period, and therefore, the review team has made an overall recommendation of “Withhold” for manufacturing facilities for the NDA.

5) Biopharmaceutics

The biopharmaceutics review concluded that the physicochemical comparison data provided in the NDA support a scientific bridge to the Listed Drugs (LDs), Cardizem, NDA 020027 and Diltiazem Hydrochloride in Dextrose 5%, NDA 215252, based on 21 CFR § 320.24(b)(6).

6) Microbiology

The microbiology review concluded that the supporting microbiological quality information, including validation and other supporting studies, (b) (4) (b) (4) specifications, container closure information, and facilities and monitoring, are adequate to support the drug product quality.

7) Quality Labeling

Labeling comments were communicated to the Applicant and will be included in the revised prescribing information and bag, overwrap, and carton labeling. These will be finalized during review of the resubmitted NDA after the manufacturing deficiencies have been addressed.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Inadequate
Biopharmaceutics	-	Adequate
Microbiology	-	Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

None currently.



Theodore
Carver

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Title:	NDA IQA Template CHAPTER IV- LABELING		
Document ID:	OPQ-ALL-TEM-0045		
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Template Revision: 03

CHAPTER IV: LABELING NDA 218038

NDA Number	218038
Assessment Cycle Number	1
Drug Product Name	Diltiazem hydrochloride in sodium chloride injection

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate after recommended changes are made.	
Patient Information	N/A	
Instruction for Use (IFU)	N/A	
Container Labels	Adequate after recommended changes are made.	
Carton Labeling	Adequate after recommended changes are made.	

Brief Description of Outstanding Issues: All the comments in this review were incorporated into the USPI in the sharepoint and they were communicated to the applicant. The revised USPI, bag, carton, and wrap labels will reflect the recommended changes.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eNDA 218038 (eCTD# 0001)	9/28/2023	Container (Bag), Carton, and Overwrap Labels
eNDA Amendment (eCTD# 0004)	12/18/2023	Revised USPI

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights² [21 CFR 201.57(a)(2)]		
Established name(s) ³	Adequate	DILTIAZEM HYDROCHLORIDE IN SODIUM CHLORIDE injection
Route(s) of administration	Adequate	Intravenous use only
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	1982
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Adequate	Injection; 100 mg per 100 mL (1mg/mL) and 250 mg per 250 mL (1 mg/mL)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). ⁶	Adequate	

¹ Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

² Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

³ Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

⁴ Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

⁵ Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

⁶ Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." ⁷	N/A	
For injectable drug products for parenteral 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. ⁸	Adequate	Single-dose bag

Assessment: *Adequate*

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹

(copy of proposed text)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food ¹⁰ , storage	Adequate	

⁷ Guidance: [Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation \(March 2013\)](#)

⁸ Guidance: [Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use \(October 2018\)](#); USP <659>

⁹ See § 201.57(c)(3); draft guidance: [Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format \(January 2023\)](#); Labeling Review Tool (March 2022, page 25)

¹⁰ Draft Guidance: [Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
conditions needed to maintain the stability of the reconstituted or diluted product).		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	N/A	
For parenteral products: include statement: <i>"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> ¹¹	Inadequate	A statement should be included.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. ¹² Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement <i>"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures."</i> ^x with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: Adequate

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Injection
Strength(s) in metric system	Adequate	100 mg per 100 mL (1 mg/mL) 250 mg per 250 mL (1 mg/mL)
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Adequate	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	Clear, colorless solution in a single-dose bag for intravenous use.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	Adequate	Single-dose bag

Assessment: Adequate

¹³ See § 201.57(c)(4); [Labeling Review Tool \(March 2022, page 29\)](#)

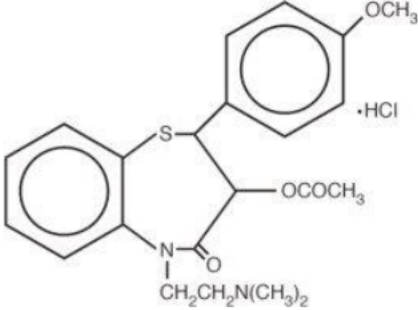
1.2.3 Section 11 (DESCRIPTION)¹⁴

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s) ¹⁵ [§ 201.57(c)(12)(i)(A)].	Adequate	No proprietary name. Established name: Diltiazem Hydrochloride in Sodium Chloride Injection
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Injection Intravenous use only
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	Adequate	Previously approved products of diltiazem hydrochloride do not contain equivalency statement.
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. ¹⁶ Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Inadequate	Not arranged alphabetically
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make	Adequate	

¹⁴ See § 201.57(c)(12); [Labeling Review Tool \(March 2022, page 56\)](#)

¹⁵ Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

¹⁶ Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	Adequate	Sterile
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	Non-dihydropyridine calcium channel-blocker
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-<i>cis</i>- with the molecular weight of 450.98 and structural formula:  The chemical structure shows a benzothiazepinone core. It features a benzene ring fused to a six-membered ring containing a sulfur atom and a nitrogen atom. The nitrogen atom is part of a five-membered ring with a carbonyl group and a dimethylaminoethyl group (-CH₂CH₂N(CH₃)₂). The sulfur atom is substituted with a 4-methoxyphenyl group (-C₆H₄OCH₃). The 3-position of the six-membered ring is substituted with an acetyloxy group (-OCOCH₃). The structure is shown as a monohydrochloride salt, indicated by ·HCl.
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	N/A	

¹⁷ Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in [FDA's Labeling Resources for Human Prescription Drugs](#) for the most recent EPC list.

¹⁸ Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement ¹⁹ (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)²⁰

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)												
HOW SUPPLIED/STORAGE AND HANDLING section														
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Injection												
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly	Adequate	<table border="1" data-bbox="711 1556 1498 1633"> <thead> <tr> <th>Total Strength per Total Volume</th> <th>Strength per mL</th> <th>Carton of 10 single-dose bags NDC</th> <th>Bag and Overwrap NDC</th> </tr> </thead> <tbody> <tr> <td>100 mg per 100 mL</td> <td>1 mg/mL</td> <td>44567-662-10</td> <td>44567-662-01</td> </tr> <tr> <td>250 mg per 250 mL</td> <td>1 mg/mL</td> <td>44567-663-10</td> <td>44567-663-01</td> </tr> </tbody> </table>	Total Strength per Total Volume	Strength per mL	Carton of 10 single-dose bags NDC	Bag and Overwrap NDC	100 mg per 100 mL	1 mg/mL	44567-662-10	44567-662-01	250 mg per 250 mL	1 mg/mL	44567-663-10	44567-663-01
Total Strength per Total Volume	Strength per mL	Carton of 10 single-dose bags NDC	Bag and Overwrap NDC											
100 mg per 100 mL	1 mg/mL	44567-662-10	44567-662-01											
250 mg per 250 mL	1 mg/mL	44567-663-10	44567-663-01											

¹⁹ Draft guidance: [Gluten in Drug Products and Associated Labeling Recommendations \(December 2017\)](#)

²⁰ See § 201.57(c)(17); [Labeling Review Tool \(March 2022, page 70\)](#). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
state whether the strength is based on the active moiety. No equivalency statement.		
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	See table above
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	See table above
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral 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 (see USP <659>).	Adequate	Single-dose bag

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.^x" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Adequate	Do not use freeze. Product should be used within 28 days of removal from aluminium wrap. Discard any unused portion.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (See USP <659>).	Adequate	Store under refrigeration at 2°C to 8°C (36°F to 46°F). The single-dose bags in their original overwraps are stable for up to one month at room temperature.
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: "<i>Not made with natural rubber latex. Avoid</i>	Adequate	The bag and port are not made with natural rubber latex, PVC, or DEHP.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
statements such as "latex-free." ²¹		
Include information about child-resistant packaging ²² (if chosen by manufacturer).	N/A	

Assessment: Adequate

Adequate after the above recommended changes are made. All comments in the above tables were incorporated into the sharepoint USPI document, which was communicated to the applicant by the clinical division. The revised document will reflect the above recommended changes.

1.2.5 Other Sections of Labeling: Not applicable

1.2.6 Manufacturing Information After Section 17 (for drug products)²³

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	Manufactured for: WG Critical Care, LLC Paramus, NJ 07652

Assessment: Adequate

²¹ Guidance: [Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex](#) (December 2014)

²² Guidance: [Child-Resistant Packaging Statements in Drug Product Labeling](#) (August 2019)

²³ § 201.1(h)(5) and 201.1(i); [Labeling Review Tool](#) (March 2022, page 74)

2.0 PATIENT LABELING: Not applicable

3.0 CONTAINER LABELING²⁴

3.1 Container Labels²⁵

Note: In the NDA, bag, carton, and overwrap labels were provided for 100 mg/100 mL and 250 mg/250 mL strengths but in this review only the representative 250 mg/250 mL strength labels are discussed.

Bag Label:



Carton Label:

²⁴ [Carton and Container Labeling Resources](#)

²⁵ Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

3.2 Bag, Carton and Overwrap Labeling:

Item	Item Proposed for Container (Bag, Carton, and Overwrap) Labeling (choose "Adequate", "Inadequate", or "N/A")		Assessor's Comments about Container (Bag, Carton, and Overwrap) Labels (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name ²⁶ , (font size and prominence) [§ 201.10(g)(2)].	Inadequate		Proprietary name was not proposed by the applicant. Established name: It should be changed to Diltiazem Hydrochloride in ^{(b)(4)} % Sodium Chloride Injection
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁷	Adequate		250 mg per 250 mL (1 mg per mL)
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate		For Intravenous Use Only
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate		Strength is based on the hydrochloride salt. Previously approved products do not contain equivalency statement, therefore, it was not included.
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁸	Adequate		250 mg per 250 mL
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate		RX only
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate		NDC 4567-663-01 and for carton NDC 4567-663-10

²⁶ Established name = [Drug] [Route of Administration] [Dosage Form]

²⁷ Express as "XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See [Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors \(May 2022\)](#)

²⁸ § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Lot number and expiration date [§ 201.18 & 201.17].	Adequate		Yes. Lot and Exp: YYYY-MM were printed.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate		Store under refrigeration at 2°C to 8°C (36°F to 46°F). The single-dose bags in their original overwraps are stable for up to one month at room temperature.
For injectable drug products for parenteral 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, and these products require a “Not for direct infusion” statement. (See USP <659>).	Adequate		Single-Dose Container. Any unused portion should be discarded. On Carton only: 10 x 250 mL Single-Dose Bags
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Inadequate		Inactive ingredients should be listed alphabetically.
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	Inadequate		Quantities were included. Statement should be included stating that hydrochloric acid NF and/or sodium hydroxide NF are added for pH adjustment.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A		
Linear Bar code [§ 201.25(c)(2)]. ²⁹	Adequate		Space was included stating UPC-FPO

²⁹ See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Adequate directions for use: “Recommended Dosage: See Prescribing Information” [§ 201.5 & 201.55].	Adequate		Recommended Dosage: See Prescribing Information
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate		Manufactured for: WG Critical Care, LLC Paramus, NJ 07652
“Keep out of reach of children” statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	N/A		
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A		
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A		
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A		
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. ³⁰	N/A		
And others if space is available.	N/A		

³⁰ USP General Notices 3.20 Indicating Conformance

Assessment of Bag, Carton, and Wrap Labels: Adequate

The above comments will be addressed in the revised bag, carton, and overwrap labels

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

All the comments shown in the above tables were communicated to the applicant by the clinical division and the responses will be included in the final revised Prescribing Information (USPI) and on Bag, Carton, and overwrap labels.

Primary Labeling Assessor Name and Date: Rao V. Kambhampati, Ph.D. 5/24/2024.



Rao
Kambhampati

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Date: 5/24/2024 07:57:55AM
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Theodore
Carver

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NDA Number	218038
Drug Product Name	Diltiazem Hydrochloride in Sodium Chloride Injection
Drug Product Description	Clear, colorless, sterile, nonpyrogenic, isotonic solution in single-dose bag for intravenous use
Strength	100 mg/100 mL and 250 mg/250 mL (1 mg/mL)
Route of Administration	Intravenous injection (bolus administration followed by continuous infusion)
Applicant Name	HQ Specialty Pharma Corporation
Proposed Indication	1. Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter 2. Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.
Product Information	Diltiazem hydrochloride in Sodium Chloride Injection is a non-dihydropyridine calcium-channel blocker

Assessor's Summary:

HQ Specialty Pharma Corporation has submitted this 505(b)(2) NDA for their proposed product, Diltiazem Hydrochloride in Sodium Chloride Injection (1 mg/mL), manufactured in two presentations, 100 mg/100 mL and 250 mg/250 mL, packaged in 100 mL and (b) (4) mL (b) (4) bags, respectively. The proposed product is a ready-to-use diltiazem hydrochloride sterile aqueous solution for intravenous injection. Diltiazem hydrochloride is a non-dihydropyridine calcium-channel blocker indicated for the temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter and for the rapid conversion of paroxysmal supraventricular tachycardias to sinus rhythm. For the proposed dosage and administration, an initial dose of 0.25 mg/kg or 20 mg is recommended to be administered as an intravenous single injection (bolus) over 2 minutes; if the response is inadequate, a second dose may be administered after 15 minutes. Immediately following bolus, the recommended initial infusion rate of diltiazem hydrochloride is 5 mg/hour and may be adjusted up to a maximum of 15 mg/hour as needed to achieve satisfactory rate control. Per the proposed prescribing information, the bolus volume should be withdrawn from the diltiazem hydrochloride infusion bag.

This 505(b)(2) NDA relies for approval on FDA's findings of safety and effectiveness of two Listed Drugs (LDs), CARDIZEM® (NDA 020027) and Diltiazem Hydrochloride in Dextrose 5% (NDA 215252). The generic reference standard (RS) product ANDA 074617 (Athenex/Sagent) was used to conduct the physicochemical property comparison studies because both relied-upon LDs are discontinued.

This Biopharmaceutics Assessment is focused on the evaluation of the information and comparative physicochemical data provided to support the bridge between the proposed drug product and the LDs via the RS. Because the formulation of the proposed drug product is not qualitatively and quantitatively (Q1/Q2) the same as that of the LDs (e.g., differences in amounts of pH adjusters due to different target pH, differences in bolus dose composition, and (b) (4) (b) (4) the biowaiver request per 21 CFR § 320.22(b)(1) is denied. However, scientific bridging per 21 CFR § 320.24(b)(6) between the proposed drug product and LDs can be established based on the following:

1. The proposed drug product is a ready-to-use formulation that has the same indication, route of administration, dosage form, active ingredient, concentration (1 mg/mL), recommended dosing frequency, and storage conditions and is also intended for bolus administration followed by continuous intravenous infusion as NDA 215252.
2. The proposed drug product has comparable physicochemical properties to the RS product (ANDA 074617) upon the dilution as per labeling in sodium chloride to 1 mg/mL (e.g., color, clarity, osmolality, density, and viscosity). The data suggest that the different pH does not impact the physicochemical properties analyzed.
3. The slight formulation differences are unlikely to alter the diltiazem pharmacokinetics and disposition.

In conclusion, the scientific bridge for the proposed drug product is adequately established to the LDs based on 21 CFR § 320.24(b)(6).

Review Recommendation: From a Biopharmaceutics perspective, NDA-218038-ORIG-1 for Diltiazem Hydrochloride in Sodium Chloride Injection, 100 mg/100 mL and 250 mg/250 mL (1 mg/mL) is adequate and is recommended for **APPROVAL**.

List of Submissions being assessed:

Document(s) Assessed	Date Received
Sequence #0001	09/18/2023
Sequence #0005	03/12/2024
Sequence #0009	04/24/2024

BIOPHARMACEUTICS ASSESSMENT

Listed Drugs (LDs) and Reference Standard (RS) products: It is stated in the electronic Orange Book that the LD CARDIZEM[®] (NDA 020027) product was not discontinued or withdrawn for safety or effectiveness reasons¹. The other LD from Exela Pharma Sciences, Diltiazem hydrochloride in Dextrose 5% (NDA 215252) received approval on October 28, 2021, relying on the FDA's finding of safety and effectiveness for CARDIZEM[®] Injectable (NDA 020027). However, this LD is similarly listed as discontinued². Subsequent to approval on February 15, 2022, Exela Pharma Sciences, LLC submitted a request for change in marketing status to 'discontinued' because of concerns regarding sterility risk during commercial production due to the manufacturing of a (b) (4) therefore, based on internal information, NDA 215252 is not discontinued due to safety or efficacy concerns. Due to the lack of LD products on market, Athenex's generic product (ANDA 074617), listed as the RS product in the electronic Orange Book, was used to generate physicochemical data for comparison to the proposed drug product. It should also be stated that the Athenex Pharmaceutical Division recently permitted a Transfer of Ownership to Sagent Pharmaceuticals⁴; this indicates that the electronic Orange Book is up to date, as it is stated that the Applicant holder of ANDA 074617 is Sagent Pharmaceuticals⁵. In this assessment, where applicable, the name Sagent Pharmaceuticals is used.

Bridging of Formulations: To support the waiver request, in response to pIND 155725, the Agency recommended that comparative physicochemical data for three lots of post-diluted RS product and three lots of the proposed drug product be provided⁶. Comparative physicochemical characterization studies, in which parameters such as pH, osmolality, and viscosity, etc. were analyzed by the Applicant, generated data that were provided for 3 batches of the 100 mg/100 mL and 3 batches of the 250 mg/250 mL test product presentations, and 3 batches of the RS drug product diluted per the labeling in sodium chloride to a 1 mg/mL solution. The comparative physicochemical data provided demonstrate similarity in most physicochemical parameters between the proposed drug product and RS diluted to 1 mg/mL in sodium chloride, supporting the scientific bridge. Dilution of the RS in sodium chloride to a concentration of 1 mg/mL aligns with the concentration of the proposed drug product. However, as aforementioned, diluted RS would only be needed for continuous intravenous infusion, not for bolus dose administration. Therefore, ideally physicochemical comparative data would be provided for the proposed drug product and Exela product (NDA 215252) that is similarly a ready-to-use formulation. However, that is not a possibility at this time given that NDA 215252

¹ https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020027#3197

² https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=215252#19883

(b) (4)

⁴ <\\CDSESUB1\EVSPROD\anda074617\0056\m1\us\12-cover-letters\cover-letter-0056.pdf>

⁵ https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=074617#25839

⁶ <https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af805fe4dc>

is discontinued. During the approval of NDA 215252, the ready-to-use Exela drug product was initially intended for continuous infusion⁷, however, the Agency conveyed recommended labeling comments that included instructions on use of the product for bolus dosing as well⁸, which suggests that no significant risk is associated with the use of a lower concentration/larger volume for bolus intravenous injection. Given the recommendations, the prescribing information was updated for NDA 215252 to include instructions for bolus dosing and continuous infusion. The dosage and administration directions for intravenous single injections (bolus) in the NDA 215252 prescribing information⁹ do not differ from the proposed draft labeling for the proposed drug product¹⁰.

It is noted that the proposed drug product differs from the Exela drug product in the (b) (4) (b) (4) used, use of sorbitol, and a different target pH range (Table 1 and Table 2). As aforementioned, per review of the RS package insert, this Assessor notes that dilution of the RS drug product, like CARDIZEM[®], is only required for continuous infusion, but not required for administration of a bolus dose¹¹. However, like the RS, the proposed drug product can similarly be used for both a bolus dose and for continuous infusion. Due to the differences in the qualitative composition and preparation between the RS and proposed drug product (Table 1), a bolus dose prepared using the RS would differ from the proposed drug product in the following ways:

1. It would lack diluent as it would contain undiluted drug product for administration, compared to diluted [in sodium chloride] ready-to-use for infusion drug product withdrawn from the infusion bag.
2. Due to the difference in the concentrations of the RS (5 mg/mL) and proposed drug product (1 mg/mL), for a defined bolus dose, to administer the same amount of the active pharmaceutical ingredient (API), diltiazem hydrochloride, a greater volume of the proposed drug product would need to be administered, in comparison to the volume of RS product that would be administered (Table 3).
3. Though the amount of inactive excipients including citric acid monohydrate, sodium citrate dihydrate, and sorbitol would be similar, given that bolus doses of CARDIZEM[®] and the RS are undiluted, due to the different target pH of the proposed drug product, it is likely that the pH of the bolus doses would also differ.

Nevertheless, as both sodium chloride (used in this proposed drug product) and dextrose (used in NDA 215252 drug product) are common diluents utilized for intravenously administered drug products, and the physicochemical comparative data suggests that the different target pH of ~5 does not impact the physicochemical parameters such as osmolality and viscosity measured, the information in totality poses no significant risk to impact the drug in vivo performance related to differences in concentrations/volumes of bolus doses to be administered (same risk assessment for approval of NDA 215252).

⁷ <https://panorama.fda.gov/task/view?ID=603fae590005775338e8a65018c8818d>

⁸ <https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af8061ba15>

⁹ <\\CDSESUB1\EVSPROD\nda215252\0015\m1\us\114-labeling\final-labeling\final-pack-insert\final-pack-insert-0015.pdf>

¹⁰ <\\CDSESUB1\EVSPROD\nda218038\0004\m1\us\114-labeling\draft\labeling\draft-labeling-text-pi-pdf.pdf>

¹¹ <\\CDSESUB1\EVSPROD\anda074617\0043\m1\us\114-labeling\final\package\package-insert.pdf>

Table 1. Qualitative and preparation comparison of the LDs, RS, and proposed drug product

	LD CARDIZEM® (NDA 020027)	LD Exela (NDA 215252)	RS Sagent Pharmaceuticals (ANDA 074617)	Proposed Drug Product
<i>Active Pharmaceutical Ingredient</i>	Diltiazem Hydrochloride	Diltiazem Hydrochloride	Diltiazem Hydrochloride	Diltiazem Hydrochloride
(b) (4)	Citric Acid	Citric Acid Monohydrate	Citric Acid (hydrous)	Citric Acid Monohydrate
	Sodium Citrate Dihydrate	Sodium Citrate Dihydrate	Sodium Citrate Dihydrate	Sodium Citrate Dihydrate
	Sorbitol solution	-	-	Sorbitol
	*	Dextrose, Anhydrous	Sorbitol solution	Sodium Chloride
<i>pH Adjusters</i>	Hydrochloric Acid or Sodium Hydroxide	Hydrochloric Acid or Sodium Hydroxide	Hydrochloric Acid or Sodium Hydroxide	Hydrochloric Acid or Sodium Hydroxide
(b) (4)	Water for Injection	Water for Injection	Water for Injection	Water for Injection
	-	-	(b) (4)	(b) (4)
Preparation				
	*For continuous intravenous infusion, aseptically transfer the appropriate quantity of diltiazem hydrochloride injection to desired volume of either normal saline, D5W, or D5W/0.45% NaCl ¹²	Ready-To-Use	For continuous intravenous infusion, aseptically transfer the appropriate quantity of diltiazem hydrochloride injection to desired volume of either normal saline, D5W, or D5W/0.45% NaCl ¹³	Ready-To-Use

Table 2. Quantitative comparison of the LDs, RS, and proposed drug product

	Undiluted LD CARDIZEM® (NDA 020027) mg / mL	LD Exela (NDA 215252) mg / mL	Undiluted RS Sagent Pharmaceuticals (ANDA 074617) mg / mL	Proposed Drug Product mg / mL
Diltiazem Hydrochloride	5	1	5	1
Citric Acid Monohydrate	0.75	0.15	0.75	0.15
Sodium Citrate Dihydrate	0.65	0.12	0.65	0.13
Sorbitol	71.4 (Sorbitol solution)*	-	71.4 (Sorbitol solution)*	10
Dextrose, Anhydrous	-	50	-	-
Sodium Chloride	-	-	-	7.2
Hydrochloric Acid	q.s. to pH 3.7 – 4.1	q.s. to pH 3.9	q.s. to pH 3.7 – 4.1	q.s. to pH 4.5 – 5.5
Sodium Hydroxide	q.s. to pH 3.7 – 4.1	q.s. to pH 3.9	q.s. to pH 3.7 – 4.1	q.s. to pH 4.5 – 5.5
Water for Injection	q.s.	q.s.	q.s.	q.s.

Note: both CARDIZEM® and RS can be diluted in Normal Saline, D5W, or D5W/0.45% NaCl

*Sorbitol solution, USP is equivalent to ~50 mg of sorbitol

¹² https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020792ap.pdf

¹³ <\\CDSESUB1\EVSPROD\anda074617\0043\m1\us\114-labeling\final\package\package-insert.pdf>

Table 3. Comparison of bolus dose volumes between RS and proposed drug product

	RS (5 mg/mL supplied as 25 mg/5 mL, 50 mg/10 mL, or 125 mg/ 25 mL vials)	Proposed product (1 mg/mL supplied in 100 mg/100 mL or 250 mg/250 mL presentations in (b) (4) bags)
20 mg bolus dose	4 mL	20 mL

Table 4. Recommendations for dilution of CARDIZEM® and the RS for continuous intravenous infusion (*dilution is not required for bolus dosing*)

Diluent Volume	Quantity of Diltiazem HCl Injection to Add	Final Concentration	Administration Dose*	Infusion Rate
100 mL	125 mg (25 mL) Final Volume 125 mL	1 mg/mL	10 mg/h 15 mg/h	10 mL/h 15 mL/h
250 mL	250 mg (50 mL) Final Volume 300 mL	0.83 mg/mL	10 mg/h 15 mg/h	12 mL/h 18 mL/h
500 mL	250 mg (50 mL) Final Volume 550 mL	0.45 mg/mL	10 mg/h 15 mg/h	22 mL/h 33 mL/h

*5 mg/h may be appropriate for some patients.

Assessment: The information provided by the Applicant, discussed in further detail in the respective sections of this Review, supports the bridge between the LD and the proposed product. The information and data that support the scientific bridge include:

1. Similarity of the proposed dosage form (injectable), route of administration (intravenous), indications, and active pharmaceutical ingredient (diltiazem hydrochloride) between the proposed drug product, relied upon LDs (NDA 020027 and NDA 215252), and RS (ANDA 074617).
2. Physicochemical comparative data generated with the proposed drug product batches and RS batches diluted to 1 mg/mL in sodium chloride as per the labeling.
3. The slight formulation differences are unlikely to alter the diltiazem pharmacokinetics and disposition.

As discussed above, the proposed drug product, like the approved drug products in NDA 020027, NDA 215252, and ANDA 047617 is used for bolus dose administration, followed by continuous infusion. Though the proposed drug product differs from NDA 215252 in the (b) (4) used, inclusion of sorbitol as a (b) (4) and target pH, it is similarly a ready-to-use product for intravenous administration. However, NDA 215252 is listed as discontinued in the electronic Orange Book and not available, therefore physicochemical comparative data could not be generated using this LD for comparison to the

proposed drug product. For this reason, the Applicant has used the drug product listed as the RS in the electronic Orange Book (ANDA 047617). For detailed assessment of the comparative physicochemical data provided, refer to the *Comparison of the proposed and the LD product formulations* section below.

Biowaiver Request: The Applicant originally submitted a waiver request of in vivo bioavailability studies under the provision of 21 CFR § 320.22(b)(1)¹⁴. It is noted that in response to pIND 155725, the Agency conveyed that based on the proposed drug product and the reference diluted with (b) (4) NaCl being identical in composition and similar in the physicochemical properties, that a biowaiver under 21 CFR § 320.22(b)(1) would be appropriate. However, based on the information provided and assessed in totality, the formulation of the proposed drug product is not qualitatively and quantitatively (Q1/Q2) the same as that of the LDs (e.g., differences in amounts of pH adjusters due to different target pH, differences in bolus dose composition, and (b) (4)). Therefore, the biowaiver request per 21 CFR § 320.22(b)(1) is denied. However, scientific bridging per 21 CFR § 320.24(b)(6) between the proposed drug product and LDs can be established. This recommendation was conveyed to the Applicant via IR #1. In response to the IR, the Applicant submitted a waiver request of in vivo bioavailability studies under the provision of 21 CFR § 320.24(b)(6)¹⁵.

This drug product can be administered as a bolus (single intravenous injection) or continuous intravenous infusion, at a recommended initial infusion rate of 5 mg/hour. The recommended initial bolus dose of 20 mg is recommended for CARDIZEM[®] Injectable, the Exela drug product, and the proposed drug product. Immediately following the bolus administration, the recommended initial infusion rate of CARDIZEM[®] Injectable is 10 mg/h. This differs from the recommendation of 5 mg/hour for the Exela drug product and proposed drug product. Nevertheless, the proposed drug product labeling does state that the infusion rate can be adjusted by 5 mg/hour increments up to a maximum of 15 mg/hour as needed. In addition to the qualitative (Table 1) and quantitative (Table 2) differences between the proposed drug product and referenced LDs arranged by this Assessor, Table 5 contains additional comparative information that was provided by the Applicant. However, this Assessor notes an error in Table 5 (see red box) specific to the Exela product, which is already diluted in dextrose, not sodium chloride.

¹⁴ <\\CDSESUB1\EVSPROD\nda218038\0001\m1\us\112-other-correspondence\request-for-waiver-of-in-vivo-bioavailability-studies.pdf>

¹⁵ <\\CDSESUB1\EVSPROD\nda218038\0005\m1\us\112-other-correspondence\request-for-waiver-of-in-vivo-bioavailability-studies.pdf>

Table 5. Comparative analysis provided by the Applicant

	CARDIZEM-RLD	Exela-RLD	HQ Diltiazem Hydrochloride in Sodium Chloride Injection	Comment
Active ingredient	Diltiazem Hydrochloride	Diltiazem Hydrochloride	Diltiazem Hydrochloride	No difference
Excipients	0.75 mg/mL Citric acid 0.65 mg/mL Sodium Citrate 71.4 mg Sorbitol Solution, NF	(b) (4) mg/ mL Citric acid (b) (4) 0.12 mg/ mL Sodium Citrate 50 mg / mL Dextrose	(b) (4) mg/ mL Citric acid (b) (4) 0.13 mg/ mL Sodium Citrate 10 mg / mL Sorbitol 7.2 Sodium Chloride	Same inactive ingredient. The concentration is the same of RLD when diluted. RLD can be diluted with multiple ingredient including sodium chloride and dextrose
Container	25 mg/ 5 mL glass vial 50 mg/ 10 mL glass vial 125 mg/ 25 mL glass vial	125 mL bag 250 mL bag	100 mL (b) (4) bag 250 mL (b) (4) bag	HQ infusion bags provide a package that is ready to use without further dilution.
Formulation	Solution that must be diluted prior to administration for continuous infusion	Pre-mix, Ready to use	Pre-mix, Ready to use	HQ formulation provides: Ready to use strength A potentially safer alternative by eliminating medication administration error
Strength	1 mg/mL* 0.83 mg / mL 0.45 mg/ mL *when reconstituted for use	1 mg/mL	1 mg/mL	Market research indicates the most common presentation is 1 mg / mL and therefore the only one developed.
Direction Intravenous preparation	Can dilute with 0.9% sodium chloride, 5% Dextrose in water or 5% Dextrose in 0.45% Sodium Chloride	No preparation required; product already diluted in sodium chloride	No preparation required; product already diluted in sodium chloride	HQ product eliminates several steps and waste in the preparation: Product is (b) (4) sterilized and provides greater assurance of sterility No need to withdraw concentrated solution from the vial

Assessment: The proposed drug product differs from the approved LDs and RS in the amount of pH adjusters used, due to the different target pH of ~5 proposed. In addition, a bolus dose of CARDIZEM® and the RS, would not contain any diluent (i.e., (b) (4) sodium chloride, 5% Dextrose in water, or 5% Dextrose/0.45% sodium chloride), given that dilution of CARDIZEM® or the RS is not required for bolus dose administration, only for continuous infusion. And to administer the same amount of API to the patient, the bolus dose volumes of CARDIZEM® and the RS would differ from the proposed drug product. If diluted in sodium chloride to a concentration of 1 mg/mL as per the labeling (Table 4) for continuous infusion, the amounts of inactive excipients (i.e., citric acid monohydrate, sodium citrate dihydrate, and sorbitol) would be similar between CARDIZEM®, the RS, and the proposed drug product. However, due to the differences in target pH, it should be noted that it is likely that the pH of the undiluted drug product would also differ.

Diltiazem Hydrochloride in Dextrose 5% (NDA 215252) is similarly a ready-to-use formulation, however, differs from the proposed drug product in the (b) (4) and fact that it does not contain sorbitol. Exela product is already diluted in dextrose, whereas the proposed drug product is already diluted in sodium chloride. The target pH of the Exela drug product and proposed drug product

also differ. Though the acceptable range for pH will be determined by the Drug Product Assessor, collectively, for the reasons above, the formulation of the proposed drug product is not qualitatively and quantitatively (Q1/Q2) the same as that of the LDs and the biowaiver request per 21 CFR § 320.22(b)(1) is denied. Nevertheless, the approval of the proposed drug product can be based on the successful establishment of a scientific bridge between the proposed and LD products, as supported by adequate data/information to demonstrate equivalence via 21 CFR § 320.24(b)(6). Thus, an IR was sent to the Applicant recommending that an appropriate waiver request would be based on 21 CFR § 320.24(b)(6). Based on the data and information in totality, the scientific bridge for the proposed drug product to the LDs via the RS in accordance with the provisions of 21 CFR § 320.24(b)(6) is adequately established.

Comparison of the proposed and the LD product formulations: The qualitative and quantitative composition of the formulations in a side-by-side comparison was provided by the Applicant (Table 6).

Table 6. Qualitative and quantitative comparison of drug product composition

	<i>RLD Cardizem</i>	<i>RLD Exela</i>	<i>Proposed HQ Diltiazem Hydrochloride Injection Ready-to-Use</i>
Component	Amount/mL (undiluted)*	Amount/mL	Amount/mL
Diltiazem HCl	5 mg	1 mg	1 mg
Sodium chloride	/	N/A	7.2 mg
Anhydrous Dextrose	/	50 mg	NA
Citric acid monohydrate (b) (4)	0.75 mg	0.1500 mg (0.1371 mg)	0.1500 mg (b) (4)
Sodium citrate dihydrate	0.65 mg	0.12 mg	0.13 mg
Sorbitol	71.4 mg (sorbitol solution, USP equivalent to about 50mg of Sorbitol)	N/A	10 mg
Hydrochloric acid	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment
Sodium hydroxide	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment
Water for injection	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL

**Concentrate Diltiazem can be diluted for continuous infusion in either Normal Saline, D5W, or D5W/0.45% NaCl.*

Assessment: As indicated in Table 6, the quantitative values for the excipients of the LD CARDIZEM[®] are for the undiluted drug product. Given that CARDIZEM[®] does not require dilution for bolus administration, the specified amounts of active and inactive excipients are representative of those that would be administered per mL of a defined bolus dose. Compared to the proposed drug product, though the amount of the API diltiazem hydrochloride would be the same as in a prepared bolus dose of CARDIZEM[®], the volume administered to the patient would be different (Table 2). Per the information provided, for the amount of diltiazem hydrochloride to be the same when administered via a bolus dose in comparison to the LD CARDIZEM[®] and the RS, five times the amount (a larger volume) of the proposed drug product is needed; therefore, though the volume administered differs, the amount of diltiazem hydrochloride would be the same and the amount of inactive ingredients administered (i.e., citric acid monohydrate, sodium citrate dihydrate, and sorbitol) would be similar.

For continuous infusion, CARDIZEM[®] and the RS would require dilution in either normal saline, D5W, or D5W/0.45% NaCl. Unlike CARDIZEM[®] and the RS, the proposed drug product is packaged in an infusion bag and does not require further dilution for continuous intravenous infusion. The volume required for dilution to 0.45 mg/mL, 0.83 mg/mL, or 1 mg/mL of CARDIZEM[®] and the RS is indicated above in Table 3. The maximum diluted concentration of 1 mg/mL matches that of the proposed ready-to-use drug product. The LD Exela drug product is similarly a ready-to-use formulation provided in 1 mg/mL strength, however, utilizes dextrose as the (b) (4) instead of sodium chloride, and does not contain sorbitol.

Comparison of physicochemical characteristics between the proposed and the LD products: The Applicant manufactured six registration batches; three for the 100 mg/100 mL presentation (1R043, 1R044, and 1R045) and three for the 250 mg/250 mL presentation (1R085, 1R086, and 1R087). All six registration batches were manufactured in November 2021 (Table 7), and the proposed expiry period is 24 months. The Applicant states that the proposed drug product should be stored between 2° - 8°C and may be stored at room temperature for up to 1 month; the acceptability of the proposed shelf life and storage conditions will be determined by Drug Product, however, were taken into consideration for the physicochemical analysis studies. The comparative physicochemical data are provided for 3 batches of the RS stored at 5 ± 3°C (Athenex product batches E003A001, E003A002, and E001A016) that were diluted to 1 mg/mL in sodium chloride according to the package insert at the expiry date (Table 10 and Table 11). The data in Table 10 compares physicochemical measurements of the RS to the 100 mg/100 mL presentation batches and Table 11 of the RS to the 250 mg/ 250 mL presentation batches. The physicochemical parameters of RS batches and proposed drug product batches were also analyzed in samples stored at 5 ± 3°C and subsequently placed at room temperature for one month (Table 12 and Table 13).

Table 7. Exhibit batch numbers and date of manufacture

Drug Product	Batch No.	Production Date
Diltiazem Hydrochloride Injection 100 mg/100 mL	1R043	November 2021
	1R044	November 2021
	1R045	November 2021
Diltiazem Hydrochloride Injection 250 mg/250 mL	1R085	November 2021
	1R086	November 2021
	1R087	November 2021

Table 8. Athenex (RS) batch numbers and expiry date

RS Batch number	Expiry Date:
E003A001	November 2021
E003A002	November 2021
E001A016	February 2022

Table 9. Comparison of excipients used in the RS and proposed test product

Component	RS Athenex Diltiazem	Applicant Diltiazem
	Amount/mL (undiluted)	Amount/mL
Sodium chloride	/*	7.2 mg
Citric acid monohydrate (b) (4)	0.75 mg	0.1500 mg (b) (4)
Sodium citrate dihydrate	0.65 mg	0.13 mg
Sorbitol	71.4 mg (sorbitol solution, USP equivalent to about 50mg of Sorbitol)	10 mg
Hydrochloric acid	q.s. for pH adjustment	q.s. for pH adjustment
Sodium hydroxide	q.s. for pH adjustment	q.s. for pH adjustment
Water for injection	q.s. to 1 mL	q.s. to 1 mL

**Concentrate Diltiazem can be diluted for continuous infusion in either Normal Saline, D5W, or D5W/0.45% NaCl.*

Table 10. Comparative physicochemical analyses for RS and 100 mg/100 mL batches on long term stability

Test	Long term stability (5±3°C) – Expiry date** RS*			Long term stability (5±3°C) – 12 months*** Applicant Drug Product			
	Batch	E001A016	E003A001	E003A002	1R043	1R044	1R045
Appearance of solution - Colour		Colorless	Colorless	Colorless	Colorless	Colorless	Colorless
Appearance of solution - Clarity		Clear	Clear	Clear	Clear	Clear	Clear
pH (pH Unit)		4.0	4.0	4.0	4.9	4.9	4.9
Osmolality (mOsmol/kg)		296	289	292	288	289	290
Assay (%)		95.9	97.3	97.2	99.7	100.4	100.3
Impurities:							
(b) (4)							(b) (4)
- Unspecified unidentified impurity (%)							
- Total impurities (%)							
Analysis Date	28 February 2022	03 November 2021	03 November 2021	December, 2022	December, 2022	December, 2022	

*RS has been diluted to 1 mg/mL in sodium chloride according to package insert

** RLD has been tested at expiry date

***12 months' time point at long term stability

Table 11. Comparative physicochemical analyses for RS and 250 mg/250 mL batches on long term stability

Test	Long term stability (5±3°C) – Expiry date** RS*			Long term stability (5±3°C) – 12 months*** Applicant Drug Product			
	Batch	E001A016	E003A001	E003A002	1R085	1R086	1R087
Appearance of solution - Colour		Colorless	Colorless	Colorless	Colorless	Colorless	Colorless
Appearance of solution - Clarity		Clear	Clear	Clear	Clear	Clear	Clear
pH (pH Unit)		4.0	4.0	4.0	5.0	5.0	5.0
Osmolality (mOsmol/kg)		296	289	292	288	291	291
Assay (%)		95.9	97.3	97.2	98.2	98.8	98.9
Impurities:							
(b) (4)							(b) (4)
- Unspecified unidentified impurity (%)							
- Total impurities (%)							
Analysis Date	28 February 2022	03 November 2021	03 November 2021	December, 2022	December, 2022	December, 2022	

*RS has been diluted to 1 mg/mL in sodium chloride according to package insert

** RLD has been tested at expiry date

***12 months' time point at long term stability

Table 12. Comparative physicochemical analyses for RS and 100 mg/100 mL batches maintained at 5±3°C for storage and placed at room temperature for 1 month

Test \ Batch	Long term stability (5±3°C) + 1 months at Room temperature** RS			1 months at Room temperature Applicant Drug Product		
	E001A016	E003A001	E003A002	1R043	1R044	1R045
Appearance of solution - Colour	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless
Appearance of solution - Clarity	Clear	Clear	Clear	Clear	Clear	Clear
pH (pH Unit)	4.0	4.0	4.0	4.8	4.9	4.9
Osmolality (mOsmol/kg)	291	293	295	289	289	287
Assay (%)	95.4	95.7	95.3	100.1	100.8	99.8
Impurities:	(b) (4)			(b) (4)		
- Unspecified unidentified impurity (%)	(b) (4)			(b) (4)		
- Total impurities (%)	(b) (4)			(b) (4)		
Analysis Date	28 February 2022	02 December 2021	02 December 2021	January 10, 2022	January 10, 2022	January 10, 2022

RLD has been diluted to 1 mg/mL in sodium chloride according to package insert

*** RLD is kept at refrigerated condition until expiry, than put one months at room temperature before the analysis.*

Table 13. Comparative physicochemical analyses for RS and 250 mg/250 mL batches maintained at 5±3°C for storage and placed at room temperature for 1 month

Test \ Batch	Long term stability (5±3°C) + 1 months at Room temperature** RS			1 months at Room temperature Applicant Drug Product		
	E001A016	E003A001	E003A002	1R085	1R086	1R087
Appearance of solution - Colour	Colorless	Colorless	Colorless	Colorless	Colorless	Colorless
Appearance of solution - Clarity	Clear	Clear	Clear	Clear	Clear	Clear
pH (pH Unit)	4.0	4.0	4.0	5.0	5.0	4.9
Osmolality (mOsmol/kg)	291	293	295	288	290	290
Assay (%)	95.4	95.7	95.3	97.9	99.0	98.7
Impurities:	(b) (4)			(b) (4)		
- Unspecified unidentified impurity (%)	(b) (4)			(b) (4)		
- Total impurities (%)	(b) (4)			(b) (4)		
Analysis Date	28 February 2022	02 December 2021	02 December 2021	January 10, 2022	January 10, 2022	January 10, 2022

RLD has been diluted to 1 mg/mL in sodium chloride according to package insert

*** RLD is kept at refrigerated condition until expiry, than put one months at room temperature before the analysis.*

As the physicochemical parameters should have been provided in triplicates, in response to the IR requests, the Applicant provided measurements for osmolality and pH in triplicates (Table 14 and Table 15, respectively) and provided additional data for density and viscosity (Table 16 and Table 17, respectively).

Table 14. Osmolality results in triplicate (mOsmol/kg) for a) RS batches and b) test product batches in 250 mg/250 mL and 100 mg/100 mL presentations

a)

Batch n°	E003A001	E003A002	E001A016
Rep 1	291	290	290
Rep 2	290	291	291
Rep 3	290	290	291
Average	290.3	290.3	290.7
RSD%	0.20	0.20	0.20
Analysis Date	March 2024	March 2024	March 2024

b)

Batch n°	1R085	1R086	1R087	1R043	1R044	1R045
Rep 1	288	288	287	289	289	289
Rep 2	291	288	287	289	291	290
Rep 3	286	290	290	287	296	291
Average	288.3	288.7	288.0	288.3	292.0	290.0
RSD%	0.87	0.40	0.60	0.40	1.23	0.34
Analysis Date	April 2024	April 2024	April 2024	April 2024	April 2024	April 2024

Table 15. pH results measured in triplicate for a) RS batches and b) test product batches in 250 mg/250 mL and 100 mg/100 mL presentations

a)

Batch n°	E003A001	E003A002	E001A016
Rep 1	3.955	3.950	3.912
Rep 2	3.954	3.947	3.911
Rep 3	3.953	3.949	3.908
Average	4.0	3.9	3.9
RSD%	0.03	0.04	0.05
Analysis Date	March 2024	March 2024	March 2024

b)

Batch n°	1R085	1R086	1R087	1R043	1R044	1R045
Rep 1	4.921	4.907	4.914	4.839	4.839	4.815
Rep 2	4.925	4.904	4.914	4.833	4.837	4.813
Rep 3	4.920	4.901	4.914	4.831	4.836	4.812
Average	4.9	4.9	4.9	4.8	4.8	4.8
RSD%	0.05	0.06	0.00	0.09	0.03	0.03
Analysis date	April 2024	April 2024	April 2024	April 2024	April 2024	April 2024

Table 16. Triplicate values for Density (g/mL) for a) RS batches and b) test product batches in 250 mg/250 mL and 100 mg/100 mL presentations

a)

Batch n°	E003A001	E003A002	E001A016
Rep 1	1.00617	1.00612	1.00615
Rep 2	1.00618	1.00612	1.00614
Rep 3	1.00616	1.00611	1.00614
Average	1.00617	1.00612	1.00614
RSD%	0.001	0.001	0.001
Analysis date	March 2024	March 2024	March 2024

b)

Batch n°	1R085	1R086	1R087	1R043	1R044	1R045
Rep 1	1.00603	1.00610	1.00610	1.00602	1.00607	1.00611
Rep 2	1.00601	1.00610	1.00609	1.00601	1.00606	1.00610
Rep 3	1.00600	1.00607	1.00610	1.00600	1.00610	1.00610
Average	1.00601	1.00609	1.00610	1.00601	1.00608	1.00610
RSD%	0.00	0.00	0.00	0.00	0.00	0.00
Analysis date	April 2024	April 2024	April 2024	April 2024	April 2024	April 2024

Table 17. Kinematic viscosity (mm²/s) values in triplicate for a) RS batches and b) test product batches in 250 mg/250 mL and 100 mg/100 mL presentations

a)

Batch n°	E003A001	E003A002	E001A016
Rep 1	93	93	93
Rep 2	93	92	92
Rep 3	92	93	93
Average	92.7	92.7	92.7
RSD%	0.6	0.6	0.6
Kinematic Viscosity	0.9448	0.9448	0.9448
Analysis date	March 2024	March 2024	March 2024

b)

Batch n°	1R085	1R086	1R087	1R043	1R044	1R045
t Rep 1	93	92	93	92	94	93
t Rep 2	93	93	92	93	93	93
t Rep 3	93	93	93	93	92	93
Average	93.0	92.7	92.7	92.7	93.0	93.0
RSD%	0.0	0.6	0.6	0.6	1.1	0.0
Kinematic Viscosity	0.9479	0.9448	0.9448	0.9448	0.9479	0.9479
Analysis date	March 2024	March 2024	March 2024	March 2024	March 2024	March 2024

Assessment: The physicochemical comparative data provided for 24-month aged RS batches stored at $5 \pm 3^\circ\text{C}$ (long-term stability) conditions and 12-month aged batches of proposed drug product in 100 mg/100 mL and 250 mg/250 mL presentations suggest that the color, clarity, and osmolality are similar between all batches (Tables 10 and 11). It is noted that the pH of the proposed drug product is higher than that of diluted RS. The acceptability of the range for pH will be evaluated by the Drug Product Assessor. Nevertheless, the Applicant proposes an average pH of $4^{(b)}$ ₍₄₎– $5^{(b)}$ ₍₄₎ for the proposed drug product based on data acquired during development and formulation studies that indicated formation of the impurity (b) (4) via hydrolysis of the API was lower at the proposed higher pH value. Given that the proposed pH is closer to normal blood pH (around 7.4) and is less acidic than the approved LDs and RS, the pH range for the proposed drug product is acceptable from a Biopharmaceutics perspective and the pH difference between the proposed product and RS product is unlikely to impact the diltiazem pharmacokinetics and disposition. The total impurities were higher for the RS compared to the proposed drug product, however, this may be due to age, given that measurements with the RS product were taken at expiry after long-term storage, in comparison to the proposed drug product that was ~12 months aged.

In Tables 12 and 13, data were acquired with RS samples that were moved to storage at room temperature after the expiration month and ~1-month aged samples stored at room temperature from batches in the proposed 100 mg/100 mL and 250 mg/250 mL presentations. The data for color, clarity, and osmolality are similar, and the pH of the proposed drug product is similarly higher than that of diluted RS. The total impurities were again higher for the RS compared to the proposed drug product, however, as previously stated may be due to the age of the RS batches. Interestingly, the total impurities for the proposed drug product in the 100 mg/100 mL and 250 mg/250 mL presentations are similar between tables 10 and 12 to the amounts measured and listed in tables 11 and 13. Given the manufacturing date of November 2021 for all batches of the proposed drug product and the dates of analysis, the data suggest that the formation of impurities may occur at an accelerated rate in product stored at room temperature in comparison to product stored at $5 \pm 3^\circ\text{C}$. For detailed assessment and information on impurities, refer to Drug Product Assessment.

Though 3 batches of RS and 3 batches of proposed drug product in each presentation were utilized for physicochemical analysis, the measurements were not acquired in triplicates, and therefore, individual unit data was not provided. The Applicant was requested to provide the individual unit data for parameters such as pH and osmolality, and in addition provide physicochemical comparative data on density and viscosity. For these additional studies to provide individual unit data, the RS batches were approximately 2 years and 5 months beyond the expiry period, and the proposed drug product batches were 7 months aged beyond the proposed shelf-life (Tables 14 – 17). However, comparison of the additional data provided for pH and osmolality (Tables 14 and 15, respectively) to the values for pH and osmolality originally reported in Tables 10 – 13, suggests that pH and osmolality remain unchanged through the storage under long-term conditions. The comparative data for density (Table 16) and viscosity (Table 17), like that provided for pH and osmolality similarly indicate that no significant differences

are observed between the RS and proposed drug product batches. Taken together, this data also suggests that though the pH of the RS and proposed drug product differ, the other physicochemical characteristics such as osmolality, density, and viscosity are comparable.

Additional Considerations: The Applicant states that there is intent to increase batch size from (b) (4) L up to (b) (4) L and (b) (4) L for each presentation, which is not more than (b) (4) old the solution volume used for the registration batches (b) (4) L (Table 18 a and b). The (b) (4) L commercial batches will be manufactured using a (b) (4) L (b) (4) and the (b) (4) L batches using a (b) (4) L (b) (4) (Table 19). The Applicant states that the manufacturing process used for the registration batches is the same for commercial production, only the (b) (4) will differ. The (b) (4) L registration batch bulk solutions were manufactured by (b) (4) the proposed drug product manufacturer¹⁶. For further details, refer to the Drug Product and Facilities Assessments, however as the same manufacturing process used for the submission batches is proposed for the commercial batches, additional bridging is not needed.

Table 18. Comparison of submission and proposed commercial formula and batch sizes for a) the 100 mg/100 mL presentation and b) the 250 mg/250 mL presentation a)

Proposed Ingredient	Amount mg/mL	Theoretical Quantity for NDA Submission Batch	Maximum Theoretical Quantity for Proposed Commercial Batch (b) (4)	Maximum Theoretical Quantity for Proposed Commercial Batch (b) (4)
*Diltiazem HCl, USP	1			
Sodium chloride, USP	7.2			
Citric Acid (b) (4) USP	(b) (4)			
Sodium Citrate dihydrate, USP	0.13			
Sorbitol, NF	10			
Hydrochloric Acid, NF	q.s. to pH			
Sodium Hydroxide, NF	q.s. to pH			
Water for Injection, USP	q.s. to ~1 mL			
Total				

(b) (4)

b)

Proposed Ingredient	Amount mg/mL	Theoretical Quantity for NDA Submission Batch	Maximum Theoretical Quantity for Proposed Commercial Batch (b) (4)	Maximum Theoretical Quantity for Proposed Commercial Batch (b) (4)
*Diltiazem HCl, USP	1	(b) (4)		
Sodium chloride, USP	7.2			
Citric Acid (b) (4) USP	(b) (4)			
Sodium Citrate dihydrate, USP	0.13			
Sorbitol, NF	10			
Hydrochloric Acid, NF	q.s. to pH			
Sodium Hydroxide, NF	q.s. to pH			
Water for Injection, USP	q.s. to ~1 mL			
Total				

Table 19. Exhibit and proposed commercial equipment comparison

Equipment			Difference exhibit batches vs commercial
Equipment	ID	Supplier	
(b) (4)			None
			None
			Different capacity
			None
			None
			None
			None
			None

Overall Assessment: HQ Specialty Pharma Corporation has submitted this New Drug Application (NDA 218038) in accordance with Section 505(b)(2) for their proposed drug product, Diltiazem Hydrochloride in Sodium Chloride injection. The Applicant states that the proposed drug product is manufactured by (b) (4) in two presentations, 100 mg/100 mL and 250 mg/250 mL, both of which are ready-to-use 1 mg/mL solutions for bolus dosing and continuous intravenous infusion. The proposed drug product is supplied in sterile aqueous solution in the form of the hydrochloride salt and does not require further dilution prior to administration.

The Applicant states that the proposed drug product formulation contains the same active ingredient, and that the route of administration is the same as CARDIZEM® (NDA 020027) and Diltiazem Hydrochloride Injection (NDA 215252 held by Exela). The proposed

intended indications, dosage form, and storage conditions are also the same. The Applicant requested a waiver for the requirement of evidence obtained to demonstrate in vivo bioequivalence of the proposed drug product that is intended solely for intravenous administration. Based on the data and information in totality, from a Biopharmaceutics perspective the establishment of the scientific bridge to the relied upon LDs is adequate and in accordance with 21 CFR § 320.24(b)(6).

BIOPHARMACEUTICS LIST OF DEFICIENCIES

IR #1 (sent on 02/29/2024):

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Applicant's Response (received on 03/12/2024):

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Reviewer's Assessment: The Applicant submitted a request for waiver of in vivo bioavailability study in accordance with 21 CFR 320.24(b)(6) for their proposed drug product, Diltiazem Hydrochloride in Sodium Chloride Injection as requested. In addition, individual unit physicochemical data for osmolality, pH, and density were only provided for the RS batches E003A001, E003A002, and E001A016, and not for the submission batches of the proposed drug product. Therefore, IR #2 was sent to the Applicant requesting the

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IR #2 (sent on 04/18/2024):

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Applicant's Response (received on 04/24/2024):

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Reviewer's Assessment: The Applicant provided the requested data. As noted in the assessment, no significant differences were noted in the data provided for osmolality, density, or viscosity; however, given that the dates of analysis were in March and April of 2024, the RS batches were approximately 2 and ½ years past the expiration date, and the proposed drug product batches were approximately 7 months beyond the proposed shelf-life. Taken together, this suggests that physicochemical parameters were not initially measured in triplicates, and the data in tables 10 – 13 of this assessment are based on single measurements. In totality, as there are no significant differences, the additional data provided is supportive.

Primary Biopharmaceutics Assessor Name and Date: Elizabeth Gray, Ph.D., May 21, 2024

Secondary Assessor Name and Date (and Secondary Summary, as needed): Kevin Wei, Ph.D., May 21, 2024



Elizabeth
Gray

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Kevin
Wei

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CHAPTER VII: MICROBIOLOGY

[IQA NDA Assessment Guide Reference](#)

Product Information	Diltiazem Hydrochloride in Sodium Chloride Injection is indicated for temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter as well as rapid conversion of paroxysmal supraventricular tachycardias to sinus rhythm.
NDA Number	218038
Assessment Cycle Number	01
Drug Product Name/ Strength	Diltiazem Hydrochloride in Sodium Chloride Injection; 1 mg/mL (100 mL and 250 mL fill)
Route of Administration	Intravenous Injection
Applicant Name	HQ Specialty Pharma Corporation 120 Route 17 North, Paramus, NJ 07652
Therapeutic Classification/ OND Division	Division of Cardiology and Nephrology
Manufacturing Site	(b) (4)
Method of Sterilization	(D) (4)

Assessment Recommendation: Adequate

Assessment Summary: The submission is recommended for approval on the basis of sterility assurance.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
SN 0001 (original submission)	September 18, 2023
SN 0008 (response to microbiology IR)	April 9, 2024

Highlight Key Issues from Last Cycle and Their Resolution: N/A. This is a first cycle review.

Remarks: This NDA application relies on the following reference listed drugs: Cardizem of NDA 020027 and Diltiazem Hydrochloride in Dextrose 5% of NDA 215252. As both products have been discontinued, the reference standard used by the applicant is ANDA 074617 held by Athenex Inc. The objective of formulation development was to have a ready-to-infuse solution of Diltiazem Hydrochloride Injection with the same qualitative formulation (when diluted), same direction for administration and same chemical stability of RLD.

The applicant's proposed Diltiazem Hydrochloride Injection, ready-to-infusion solution is 1 mg/mL, in a 100 mL (b) (4) bag and in a (b) (4) mL (b) (4) bag that is partially filled to a volume of 250 mL.

Concise Description of Outstanding Issues: N/A

Supporting Documents: Microbiology review (b) (4)
(b) (4)
(b) (4)
(b) (4)

Select Number of Approved Comparability Protocols: 0

Product Quality Microbiology Assessment

S DRUG SUBSTANCE

The drug substance is not sterile; therefore, the API information is not reviewed.

Assessment: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product** – Diltiazem Hydrochloride in Sodium Chloride Injection is a clear, colorless, sterile solution contained in a ready-to-use IV bag.
- **Drug product composition** –

Ingredient, Quality Standard	Function	Quantity (mg/mL)
Diltiazem Hydrochloride	API	1 mg
Sodium chloride, USP	(b) (4)	7.2 mg
Citric Acid monohydrate, USP*	(b) (4)	0.1500 mg
Sodium Citrate Dihydrate, USP	(b) (4)	0.13 mg
Sorbitol, NF	(b) (4)	10 mg
Hydrochloric Acid, NF	pH Adjuster	q.s to pH
Sodium Hydroxide, NF	pH Adjuster	q.s to pH
Water for Injection, USP	(b) (4)	q.s to 1 mL

*Citric acid (b) (4)

- **Description of container closure system** – The drug product container closure systems (CCS) are 100 mL and (b) (4) mL (b) (4) bags equipped with two tubing ports, one of which is a twist off port. One tubing port is (b) (4) is then sealed shut. The twist off port (winged spike) is used for administration. These bags are (b) (4) contained in an overwrapping (b) (4).

Configuration	Component Description	Supplier / DMF
100 mL and 250 mL fill bags	100 mL (b) (4) bag	(b) (4)
	(b) (4) mL (b) (4) bag	
	Connector Tubing: The external layers consist of (b) (4)	
	Twist off port: (b) (4)	
	Overwrap (b) (4) / aluminum / (b) (4)	

Assessment: Adequate

The information provided in the application adequately describes the drug product and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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/s/

THEODORE E CARVER
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