CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215868Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

NDA Executive Summary

1. Application/Product Information

NDA Number.	215868
Applicant Name	Exela Pharma Sciences, LLC
Drug Product Name	midazolam in 0.8% sodium chloride injection
Dosage Form.	Injection
Proposed Strength(s)	1 mg/mL in 2 presentations; 50 mg/50 mL and 100 mg/100 mL
Route of Administration	Intravenous
Maximum Daily Dose	219 mg
Rx/OTC Dispensed	Rx
Proposed Indication	(b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] • (b) (4) [redacted] (b) (4) [redacted] [redacted]; • continuous intravenous infusion for sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.
Drug Product Description	clear, colorless solution in 50 mL or 100 mL clear glass (b) (4) [redacted] vials stoppered with (b) (4) [redacted] Gray, rubber stoppers
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	20°C–25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Gaetan Ladouceur
	Drug Product/ Labeling	Mari Chelliah	Valerie Amspacher
	Manufacturing	Yan Xu	Tianhong (Tim) Zhou
	Biopharmaceutics	Jia Yin	Ta-Chen Wu
	Microbiology	George Arhin	Elizabeth Bearr
	Other (specify):	N/A	N/A
	RBPM	Anika Lalmansingh	
	ATL	Valerie Amspacher	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The proposed shelf-life of 24 months is acceptable when stored at 20°C–25°C (68°F–77° F).

b. Additional Comments for Action – N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Based on reviews by drug substance, drug product, process/facilities, biopharmaceutics and microbiology.

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
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: N/A

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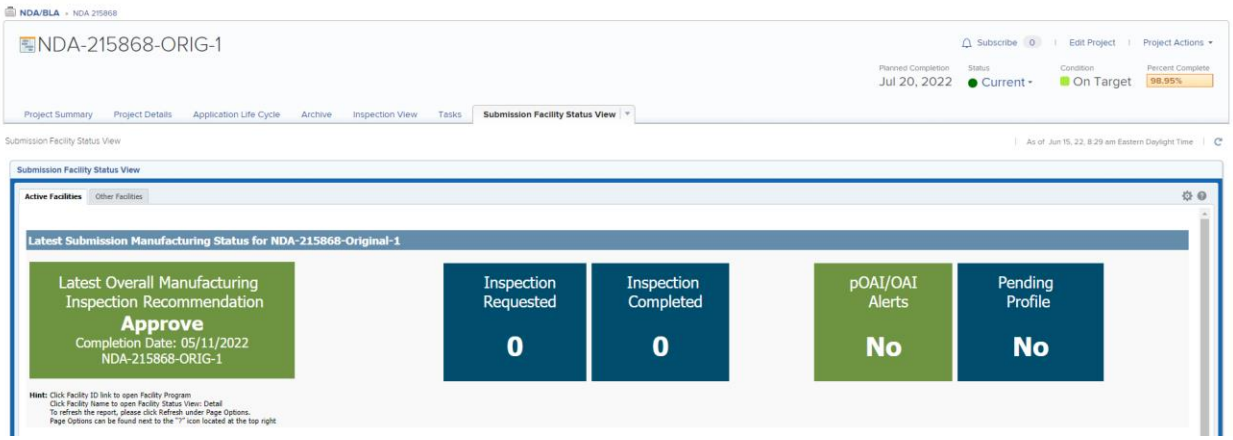

Valerie Amspacher

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items 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 Highlights		
Established name(s)[1]	Adequate	MIDAZOLAM IN 0.8% SODIUM CHLORIDE
Route(s) of administration	Adequate	for intravenous use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	50 mg per 50 mL (1 mg/mL) and 100 mg per 100 mL (1 mg/mL)
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 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.	Adequate	Single-dose
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	N/A	

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

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items 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, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
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: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	
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	Adequate	

section of the PI (e.g., Section 11).		
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 *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items 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	
Strength(s) in metric system	Adequate	
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 (Tablets: 10 mg of drug-x hydrochloride).	N/A	
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	
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 parental 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.	Adequate	

Section 11 (DESCRIPTION)

Item	Items 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)	Adequate	There is no proprietary name
Dosage form(s) and route(s) of administration	Adequate	
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)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
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.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items 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 (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).	Adequate	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items 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)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
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 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.	Adequate	
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."	Adequate	

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

Item	Items 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)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
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."*	Adequate	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items 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)
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	

2.0 PATIENT LABELING

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

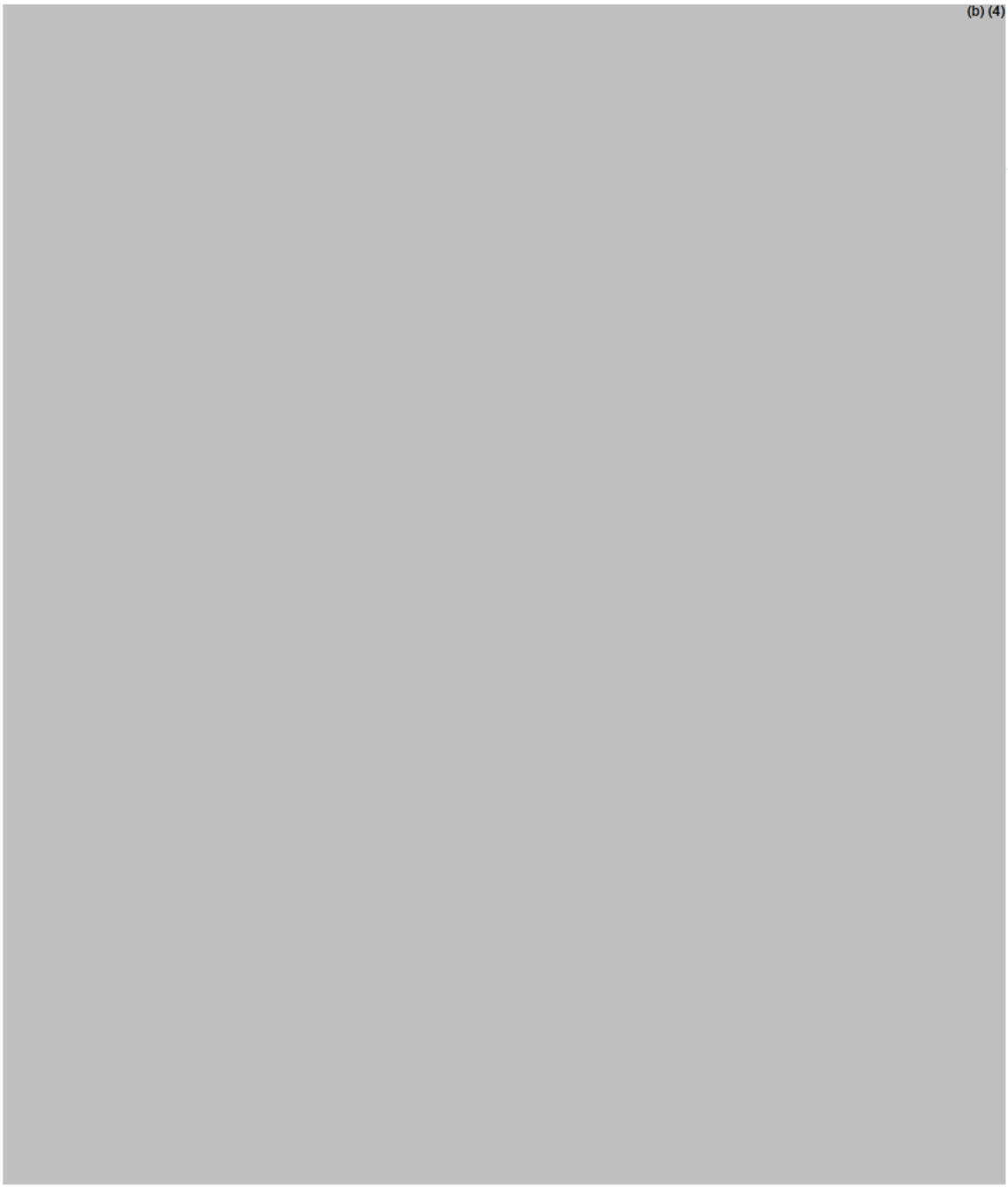
Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	N/A	Patient Labeling not applicable
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	N/A	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	N/A	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	N/A	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

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


(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
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, and these products require a "Not for direct infusion" statement.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
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, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	
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.	Inadequate	The pH of the proposed product differs from the USP monograph. The carton labels need to be edited to reflect this.
And others, if space is available.	Choose an item.	

Assessment of Carton and Container Labeling: *Adequate*

The carton labels will be edited during the labeling negotiation to indicate that the pH of the proposed product does not meet the USP monograph.

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor: Mariappan Chelliah

Secondary Assessor: Valerie Amspacher

Mariappan Chelliah

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Valerie Amspacher

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QUALITY ASSESSMENT

BIOPHARMACEUTICS

NDA: NDA-215868-ORIG-1
Submission Type: 505(b)(2)
Listed Drug: NDA 211844
Reference Standard: ANDA 075857
Drug Product Name / Strength: Midazolam in 0.8% Sodium Chloride Injection (1 mg/mL)/50 mg/50 mL and 100 mg/100 mL
Dosage Form: Injection
Route of Administration: Intravenous infusion
Applicant: Exela Pharma Sciences, LLC
Indication: Sedation of intubated and mechanically ventilated adult, pediatric, and neonatal patients as a component of anesthesia or during treatment in a critical care setting
Submission Date: 9/20/2021
Primary Reviewer: Jia Yin, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.
Tertiary Reviewer: Okponanabofa Eradiri, Ph.D.

Recommendation: Adequate

Background: The Applicant seeks approval for Midazolam in 0.8% Sodium Chloride Injection 1 mg/mL via 505(b)(2) pathway. The Listed Drug (LD), Versed® (Midazolam Hydrochloride) Injection 1 mg/mL under NDA 018654, is discontinued. The Reference Standard (RS) for this product is Preservative Free Midazolam Hydrochloride Injection 1 mg/mL under ANDA 075857. The Applicant also referenced the recently approved NDA 211844 (Midazolam in 0.9% Sodium Chloride Intravenous Solution 1 mg/mL) as a second LD because it is pharmaceutically equivalent to the proposed drug product. The Applicant submitted a request for a waiver of in vivo bioavailability/bioequivalence requirements.

REVIEW SUMMARY
Biopharmaceutics review is focused on assessing bridging of the proposed drug product to the two listed drugs.

Formulation bridging: Adequate
The proposed commercial formulation is identical to the formulation of the NDA registration batches. No bridging study is needed.

Bridging to Listed Drugs: Acceptable

A scientific bridge between the proposed drug product and the LD product (NDA 211844) is deemed acceptable per 21 CFR 320.24(b)(6).

RECOMMENDATION

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 215868 for Midazolam in 0.8% Sodium Chloride Injection 1 mg/mL (50 mg/50 mL and 100 mg/100 mL) is adequate.

BIOPHARMACEUTICS ASSESSMENT

List Submissions Being Reviewed

Received Date	Submission
9/20/2021	Original submission

Formulation Bridging

Reviewer's Assessment:

The proposed commercial formulation (**Table 1**) is identical to the formulation of the NDA registration batches. No in vivo bridging study is needed.

Table 1 Composition of proposed Midazolam Injection

Components	Quality Standard	Function	Amount			
			% w/v	mg/ mL	50 mg Vial	100 mg Vial
Midazolam Base	Active	Drug substance	0.1	1 mg	50 mg	100 mg
Sodium Chloride, USP	USP	(b) (4)	0.8	8 mg	400 mg	800 mg
Hydrochloric Acid, NF	NF	pH adjuster	N/A	pH to 3.5	(b) (4)	
Sodium Hydroxide, NF	NF	pH adjuster	N/A	pH to 3.5	pH to 3.5	pH to 3.5
Water for Injection, USP	USP	(b) (4)	N/A	q.s. to 1 mL	q.s. to 50 mL	q.s. to 100 mL

Bridging

Reviewer's Assessment:

As this is an NDA submission via 505(b)(2) pathway, biowaiver is not applicable in this case. Biopharmaceutics will assess the bridging between the proposed drug product and the listed drug (LD) under NDA 211844

Based on the submitted information and internal discussion with the Drug Product review team, a scientific bridge between the proposed product and the LD product can be established under 21 CFR 320.24(b)(6):

1) The only composition difference between the proposed drug product and the LD product is the NaCl concentration.
2) The 0.1% difference in NaCl concentrations between the proposed product and the LD product is unlikely to cause any clinical concerns, as the proposed product has the same NaCl concentration as the RS product.

The Applicant submitted a biowaiver request for both strengths and provided the following justifications (**Table 2**):

1) Midazolam in 0.8% Sodium Chloride Injection is a parenteral drug product intended for intravenous administration.
2) The proposed drug product has the same active ingredient, dosage form, route of administration (Intravenous), and indications as the LD products (NDA 018654 and NDA 211844) and the RS product (ANDA 075857).
3) The proposed drug product has the same inactive ingredient as the LD product (NDA 211844) and the RS product (ANDA 075857).
4) One of the LD products, NDA 018654, is currently discontinued. The other LD product, NDA 211844, was recently approved with 50 mg/50mL and 100 mg/100 mL presentations in IV bags. The RS product (ANDA 075857) is available as 2 mg/2 mL, 5 mg/5 mL, 5 mg/mL, and 10 mg/2 mL presentations. The composition of the proposed and the currently approved products (NDA 211844 and ANDA 075857) under the conditions of use are similar.

Table 2 Composition of the proposed drug product and the LD and RS products

Composition per mL	LD product[1] Versed (midazolam hydrochloride) Injection NDA 018654	RS Product[2] Midazolam Hydrochloride Injection ANDA075857	Midazolam in 0.9% Sodium Chloride Injection[3] NDA 211844	Exela's Proposed Midazolam in 0.8% Sodium Chloride Injection[4] NDA215868
Midazolam	1 mg/mL	1 mg/mL	1 mg/mL	1 mg/mL
Sodium chloride	8 mg/mL	8 mg/mL	9 mg/mL	8 mg/mL
Edetate disodium	0.1 mg/mL	Nil	Nil	Nil
Benzyl alcohol	10 mg/mL	Nil	Nil	Nil
Hydrochloric acid	Approx. 3	Approx. 3	q.s. to pH 2.5 - 3.5	q.s. to pH 3.5
Sodium hydroxide	Approx. 3	Approx. 3	q.s. to pH 2.5 - 3.5	q.s. to pH 3.5
Water for Injection	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL
How supplied	2/5/10 mL vials	2/5 mL vials	50/100 mL IV Bags	50/100 mL vials
Midazolam/unit	2 mg/5 mg/10 mg	2 mg/5 mg	50 mg/100 mg	50 mg/100 mg
Indications and use	As per the LD product label	As per the RS product label	As per the approved product label – intravenous infusion only	Similar to LD - Carved out for intravenous infusion only

[1] Information regarding RLD product, Versed (midazolam hydrochloride) Injection 1mg/mL of HLR Technology, was obtained from PDR, 2000.

[2]Information regarding RS product, Midazolam Hydrochloride Injection 1mg/mL, Hospira Inc., was obtained from the package insert (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1abda8b8-48a8-4995-af86-39220d1aa240).

[3]Information regarding, Midazolam in Sodium Chloride Injection 1mg/mL, Inforlife SA, was obtained from the package insert (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211844s000lbl.pdf).

[4]Information regarding, Midazolam in 0.8% Sodium Chloride Injection 1mg/mL, is provided in Module 1.14 labeling.

Jia Yin

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Okponanabofa Eradiri

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U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	
ANDA Number	215868
Assessment Cycle Number	1
Drug Product Name / Strength	Midazolam in 0.8% Sodium Chloride Injection, 1 mg/mL, (50 mL and 100 mL fill volumes)
Route of Administration	Intravenous injection
Applicant Name	Exela Pharma Sciences, LLC
Manufacturing Site	320 Cooperative Way Lenoir, NC 28645 Registration Number: 3008563008 DUNS Number: 117180896
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: N/A

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

List Submissions Being Assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
September 20, 2021 (eCTD Sequence #1)	September 20, 2021	N/A	September 29, 2021
December 30, 2021[1]	December 30, 2021	N/A	January 4, 2022

(eCTD Sequence #9)[1]			
February 22, 2022 (eCTD Sequence #13)[2]	February 22, 2022	N/A	February 22, 2022
February 28, 2022 (eCTD Sequence #15)[3]	February 28, 2022	N/A	February 28, 2022
April 4, 2022 (eCTD Sequence #18)[3]	April 4, 2022	N/A	April 4, 2022
May 6, 2022 (eCTD Sequence #19)[4]	May 6, 2022	N/A	May 6, 2022
May 13, 2022 (eCTD Sequence #)[5]	May 13, 2022	N/A	May 16, 2022

[1]December 30, 2021 submission is response to Agency's December 7, 2021 IR letter
[2]February 22, 2022 submission is response to Agency's January 25, 2022 IR letter
[3]February 28, 2022 and April 4, 2022 submissions are responses to Agency's February 25, 2022 IR letter.
[4]May 6, 2022 submission is response to Agency's April 19, 2022 IR letter.
[5]May 13, 2022 submission is IR response submission to update labeling to limit the infusion duration to 48 hours.

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

Concise Description of Outstanding Issues: None

Supporting Documents

- [redacted](b) (4) rubber [redacted](b) (4) Reviewed in Microbiology review D[redacted](b) (4)M40R01.docx dated 01/29/2020.
- Microbiology document N[redacted](b) (4)MR01.docx, dated 06/17/2020 for review of finished drug product bacterial endotoxins testing.

Select Number of Approved Comparability Protocols: 0

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  The subject drug product is a clear, colorless sterile, non-pyrogenic, preservative free solution filled as 1 mg/mL (50 mL and 100 mL fill in 50 mL and 100 mL single-dose molded clear glass[redacted](b) (4) vials respectively).

- **Drug product composition –**

Ingredient				Function
	mg/mL	50 mL fill	100 mL fill	
Midazolam Base	1 mg	50 mg	100 mg	Active Pharmaceutical Ingredient
Sodium Chloride, USP	8 mg	400 mg	800 mg	(b) (4)
Hydrochloric Acid, NF	q.s.	q.s.	q.s.	(b) (4) / pH adjuster
Sodium Hydroxide, NF	q.s.	q.s.	q.s.	pH adjuster
Water for Injection, USP	q.s. to 1 mL	q.s. to 50 mL	q.s. to 100 mL	(b) (4)

- **Description of container closure system –**

Component	Description	Manufacturer
Container	50 mL/20 mm and 100 mL molded clear USP (b) (4) glass vials	(b) (4)
Closure	20 mm, (b) (4) gray (b) (4) rubber closure (b) (4)	(b) (4)
Overseal	20 mm Overseal with Flip-off top	(b) (4)

Reviewer's Assessment: Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

(b) (4)

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