CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215887Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	215887		
Applicant Name	Biogen Inc.		
Drug Product Name	QALSODY (tofersen)		
Dosage Form.	Injection		
Proposed Strength(s)	(b) (4) (6.7 mg/mL)		
Route of Administration	Intrathecal		
Maximum Daily Dose	(b) (4) mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (*SOD1*) gene		
Drug Product Description	Clear and colorless to slightly yellow solution (b) (4)		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katharine Duncan	Gaetan Ladouceur
	Drug Product/ Labeling	Mariappan Chelliah	Martha Heimann
	Manufacturing	Suzanne Hudak	Lane Christensen
	Biopharmaceutics	N/A	N/A

	Microbiology	Jianli Xue	Nandini Bhattacharya
	Other (specify):	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval with QPA(s)

3. Action Letter Information

a. Expiration Dating:

18 months when stored at 2°C – 8°C.

b. Additional Comments for Action Letter

The post-marketing commitment (PMC) below should be included in the action letter of the NDA is approved.

- Conduct an extractable study for the rubber stopper. The aqueous extractions should use pH adjusted waters that bracket the pH of tofersen drug product as extracting solvents. The extraction should be conducted by heating at reflux conditions to ensure they represent worst-case scenarios for extractable impurities.

- Conduct a leachable study using at least three batches of tofersen drug product. The leachables should be tested at multiple time points on stability storage - from release through the proposed shelf-life.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

During the review of the NDA, the Office of Pharmaceutical Quality (OPQ) review team identified several deficiencies that were adequately addressed by the Applicant. One minor issue remains outstanding. In the NDA, the Applicant provided results from an extractable study performed by the stopper manufacturer. However, this study was not adequately conducted as the aqueous extracts were not analyzed for organic extractables. Additionally, the Applicant only conducted a simulated leachable study using a single

batch of aCSF and did not conduct a leachable study using the drug product. While the extractable and leachable studies are not considered adequate, the currently available data are acceptable on an interim basis given the unmet medical need. The applicant agreed to conduct new extractable and leachable studies post-approval.

OPQ recommends **APPROVAL with QPAs** of NDA 215887 for QALSODY (tofersen) injection (b) (4) (6.7 mg/mL) with the PMC discussed above. The applicant has provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all facilities associated with this application. The proposed labeling and labels have adequate information to meet the regulatory requirements.

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

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with QPAs**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
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: No

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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	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	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	
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)	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	
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	N/A	

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	
Dosage form(s) and route(s) of administration	Inadequate	The route of administration is missing. The PI will be edited to address this.
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.	Inadequate	The excipient list is missing the (b) (4) The PI will be edited to include this excipient.
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	Inadequate	This is currently missing. The PI will be edited to include this.
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)	Adequate	

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).	N/A	

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."*	N/A	
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	
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

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[2] 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)
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.	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.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *Adequate*

The carton and container labels meet the appropriate USP/CFR labeling regulations. Some product quality related sections of the prescribing information are currently deficient. However, once the PI becomes available for edit, it will be edited to address these deficiencies.

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 V Chelliah

Secondary Assessor: Julia Pinto

Mariappan Chelliah

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Julia Pinto

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	215887
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Tofersen/6.7 mg/ml
Route of Administration	Intrathecal Injection
Applicant Name	Biogen Inc.
Therapeutic Classification/ OND Division	CDER/OND/ON/DN1
Manufacturing Site	Biogen US Corporation 900 Davis Drive, Research Triangle Park North Carolina, 27709
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
IR response	10/6/2022
IR response	9/9/2022
IR response	8/4/2022
IR response	7/29/2022
Original submission	5/25/2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: None

Concise Description of Outstanding Issues: None

Supporting Documents: D (b) (4) doc (adequate) dated 6/7/2022 for (b) (4)

S DRUG SUBSTANCE

Assessment: ***Adequate***

(b) (4)

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Aqueous solution for intrathecal injection supplied in glass vial, 6.7 mg/ml, 15 ml/vial, single-dose.
- **Drug product composition –**

Component	Function	Quality Standard	Nominal Concentration (mg/mL)	Nominal Quantity (mg) per 15.0 mL (per vial)
Tofersen	Active Ingredient	Refer to Section 3.2.S.4.1 *Specifications*	6.7	100
(b) (4)	(b) (4)	Compendial	(b) (4)	
		Compendial		
Sodium chloride		Compendial		
Potassium chloride		Compendial		
Calcium chloride dihydrate		Compendial		
Magnesium chloride hexahydrate		Compendial		
Water for Injection		Compendial		

(b) (4)

- **Description of container closure system –** The drug product is supplied in a type I glass vial closed with a rubber stopper and sealed with a flip-off cap.

Item	Description	Supplier
Vial	• Nominal size: (b) (4) • Material: USP/Ph.Eur./JP Type I clear glass	(b) (4)
Stopper	• Nominal Size: 20mm • Material: USP/Ph.Eur./JP (b) (4) rubber • (b) (4)	
Seal	• Material: Aluminum crimp seal with (b) (4) flip-off button.	

Exhibit batches # 5000361 (b) (4), 5000362 (b) (4) 5000363 (b) (4) 5000364 (b) (4)
Proposed commercial batch: (b) (4) (p. 12/14, 3.2.P.3.5.3)

Assessment: ***Adequate***

The sponsor provided an adequate description of the drug product's composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

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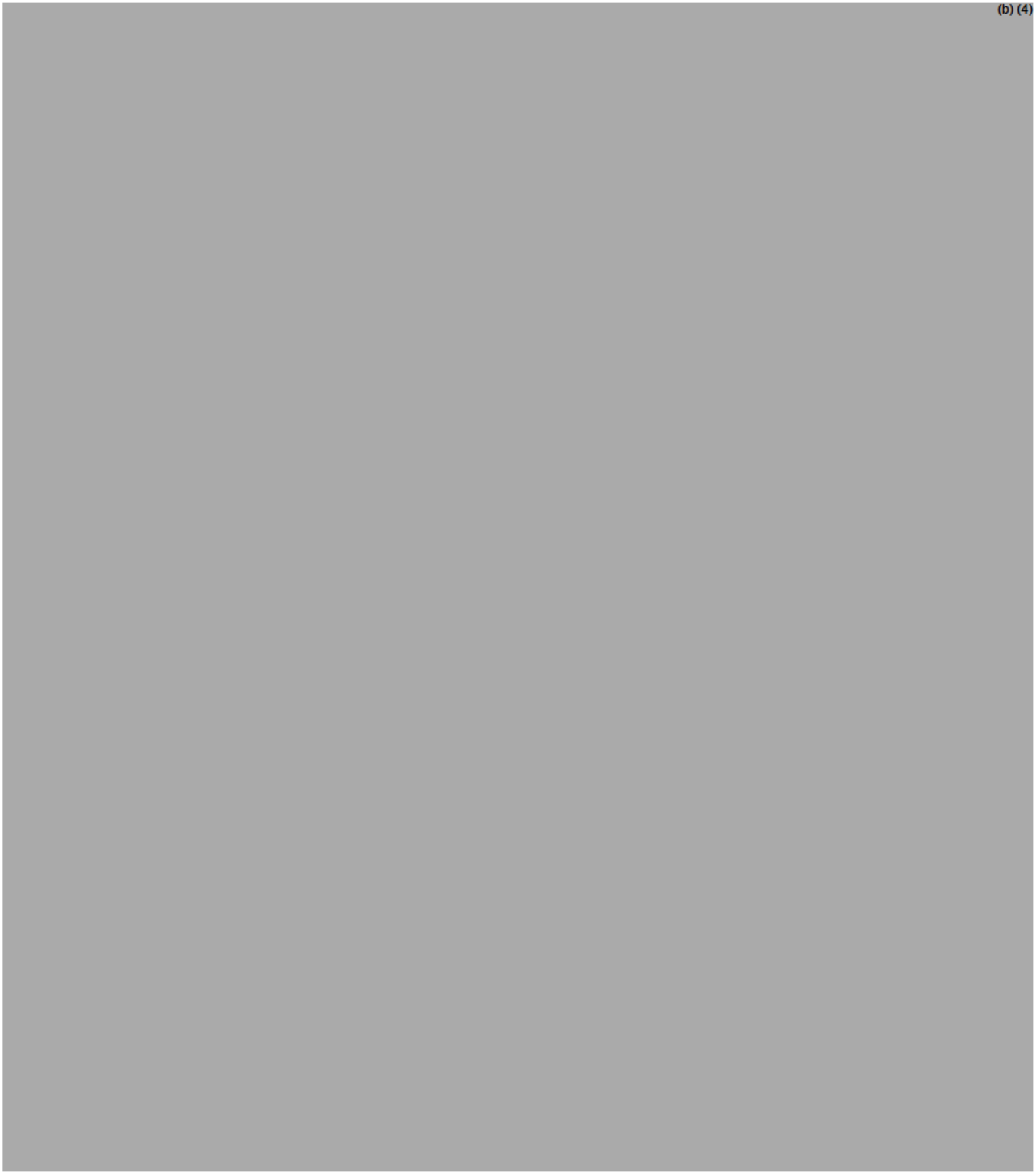

R REGIONAL INFORMATION

Executed Batch Records

Executed batch record was provided for batch#5000361, 5000362, 5000363, 5000364.

Assessment: ***Adequate***

The provided executed batch record is acceptable.

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

2.A. Prescribing Information

Store refrigerated between 2-8°C (36-46°F) in the original carton to protect from light. Do not freeze. If no refrigeration is available, QALSODY may be stored in its original carton, protected from light at or below 30°C (86°F) for up to 14 days. [redacted] (b) (4). Once drawn into the syringe, the solution should be administered immediately (within 4 hours since removal from [redacted] (b) (4)) at room temperature; otherwise, it must be discarded.

Assessment: ***Adequate***

The package insert is acceptable.

Primary Microbiology Assessor Name and Date:
Jianli Xue, Ph.D.
CDER/OPQ/OPMA/DMA I/BII
10/8/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Nandini Bhattacharya
CDER/OPQ/OPMA/DMA I/BII
10/11/2022

Jianli Xue

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Nandini Bhattacharya

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/s/

MARTHA R HEIMANN
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