

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761225Orig1s000

PRODUCT QUALITY REVIEW(S)

LABELS AND LABELING ASSESSMENT

Date of Assessment:	February 7, 2024
Assessor:	Diana Pei, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Asha Hewarathna, PhD Product Quality Assessor OPQ III/Division of Product Quality Assessment XV
Application:	BLA 761225 ORIG 1 RESUB 29
Applicant:	Hugel, Inc.
Submission Date:	August 31, 2023 (resubmission)
Product:	Letybo (letibotulinumtoxinA-wlbq)
Dosage form(s):	For injection
Strength and Container-Closure:	50 Units or 100 Units freeze-dried powder in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of Letybo (letibotulinumtoxinA-wlbq) for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling are acceptable from an OPQA III labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

CONCLUSION

The prescribing information submitted on February 16, 2024, the medication guide submitted on February 14, 2024, and the carton labeling submitted on August 31, 2023 and carton labeling submitted on January 30, 2024 were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Medication Guide (submitted on August 31, 2023)
<\\CDSESUB1\EVSPROD\bla761225\0029\m1\us\114-labeling\draft\labeling\letibotulinumtoxina-bla-pi-17mar2021-tracked-changes.docx>
- Container Label (submitted on August 31, 2023)

(b) (4)

Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Proper Name (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	

Comment/Recommendation:

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	
<i>Recommended labeling practices (U.S license number for container bearing a partial label⁵)</i>	

Comment/Recommendation:

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

⁵ Per 21 CFR 610.60(c) *Partial Label*. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.

Lot number or other lot identification (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	

Comment/Recommendation:

Beyond Use Date (Multiple-dose containers) (container label)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Product Strength (container label)	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (expression of strength for injectable drugs) references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022) USP General Chapters: <7> Labeling</i>	

Comment/Recommendation:

Multiple-dose containers (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 <i>(recommended individual dose)</i>	☐ Yes ☐ No

	☒ N/A
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Comment/Recommendation:

Statement: "Rx only" (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (prominence of Rx Only statement) reference: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	

Comment/Recommendation: The label is small and could be considered a partial label. Thus, a "Rx only" statement is not required per 21 CFR 610.60(c).

Medication Guide (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

No Package for container (container label)	Acceptable
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The container is enclosed in a package.

No container label (container label)	Acceptable
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The product contains a container label.

Ferrule and cap overseal (for vials only)	Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials.

Applicant's response: The sponsor confirms there is no additional text added onto the fixed aluminum and cap on vial.

Visual inspection	Acceptable
Regulation: 21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.

Applicant's response: The sponsor confirms that a sufficient area of the container remains uncovered for visual inspection for both 50 Unit and 100 Unit vials. The vial label spacing is approximately 4 mm (picture below).



Route of administration (container label)	Acceptable
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	

Comment/Recommendation:

NDC numbers (container label)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No

	☐ N/A
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Comment/Recommendation:

Preparation instructions (container label)	Acceptable
Regulation: 21 CFR 201.5(g)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	

Comment/Recommendation:

Package type term (container label)	Acceptable
<i>Recommended labeling practices: Guidance for Industry 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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

No misleading statements (container label)	Acceptable
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Prominence of required label statements (container label)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Spanish-language (Drugs) (container label)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label does not display text in Spanish.

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

Bar code label requirements (container label)	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references:</i> Guidance for Industry <i>Bar Code Label Requirements Questions and Answers</i> (August 2011) Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022)	

Comment/Recommendation:

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Net quantity (container label)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references:</i> Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022) Guidance for Industry <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products</i> (June 2015) <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	

Comment/Recommendation:

Statement of Dosage (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	

Comment/Recommendation: The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required.

Storage requirements (container label)	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: The label is small and could be considered a partial label.

Dispensing container (container label)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Package⁶ Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	☒ Yes

⁶ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

	☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	

Comment/Recommendation:

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	

Comment/Recommendation:
Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.

Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Expiration date (package labeling)	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Beyond Use Date (Multiple-dose containers) (package labeling)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Preservative (package labeling)	Acceptable
Regulation: 21 CFR 610.61(e)	☒ Yes

	☐ No ☐ N/A
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Comment/Recommendation:

Number of containers (package labeling)	Acceptable
Regulation: 21 CFR 610.61(f)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Product Strength (package labeling)	Acceptable
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>USP General Chapters: <7> Labeling</i>	

Comment/Recommendation:

Storage temperature/requirements (package labeling)	Acceptable
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	

Comment/Recommendation:

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	Acceptable
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Multiple dose containers (recommended individual dose) (package labeling)	Acceptable
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Route of administration (package labeling)	Acceptable
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	

Comment/Recommendation:

Known sensitizing substances (package labeling)	Acceptable
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: The drug product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).

Inactive ingredients (package labeling)	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	

Comment/Recommendation:

Source of the product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(p)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Minimum potency of product (package labeling)	Acceptable
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Regulation: 21 CFR 610.61(r)	☒ Yes ☐ No ☐ N/A
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Comment/Recommendation:

Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for letibotulinumtoxinA products (i.e., there is no specific test method described in regulation for letibotulinumtoxinA products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Letybo because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

In the original submission, OPQIII Labeling recommended the Applicant to "Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable." The statement was removed from the carton when labeling was resubmitted on August 31, 2023.

Rx only (package labeling)	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	

Comment/Recommendation:

Divided manufacturing (package labeling)	Acceptable
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Distributor (package labeling)	Acceptable
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Bar code (package labeling)	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry <i>Bar Code Label Requirements Questions and Answers</i> (August 2011) Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022)	

Comment/Recommendation:

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

NDC numbers (package labeling)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Preparation instructions (package labeling)	Acceptable
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022) <i>USP General Chapters <7> Labeling</i>	

Comment/Recommendation:

Package type term (package labeling)	Acceptable
Recommended labeling practices: Guidance for Industry <i>Selection of the Appropriate Package Type Terms and Recommendations for Labeling</i>	☒ Yes ☐ No

<i>Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☐ N/A
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Comment/Recommendation:

No misleading statements (package labeling)	Acceptable
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Prominence of required label statements (package labeling)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Spanish-language (Drugs) (package labeling)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label does not display text in Spanish.

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

Phenylalanine as a component of aspartame (package labeling)	Acceptable
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain phenylalanine.

Sulfites; required warning statements (package labeling)	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain sulfites.

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	

Comment/Recommendation:

Statement of Dosage (package labeling)	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Dispensing container (package labeling)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Medication Guide (package labeling)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Other (package labeling)	Acceptable
	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: Draft Guidance for Industry on 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), which, when finalized, will represent FDA's current thinking on topic</i>	

Comment/Recommendation:

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	Acceptable
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	Acceptable
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry 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 chapter <659> Packaging and Storage Requirements USP General Chapters: <7> Labeling</i>	

Comment/Recommendation:

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv) <i>Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components</i> Draft Guidance <i>Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry</i> (January 2023)	

Comment/Recommendation:

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	Acceptable
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry 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</i> (October 2018) <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	

Comment/Recommendation:

Full Prescribing Information	
11 DESCRIPTION	Acceptable
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q), FD&C Act Section 502(e)	☒ Yes ☐ No ☐ N/A

<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	
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Comment/Recommendation:

Full Prescribing Information	
<u>15 & 16 Hazardous Drug</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures. ¹	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Full Prescribing Information	
<u>16 HOW SUPPLIED/ STORAGE AND HANDLING</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	

Comment/Recommendation:

Full Prescribing Information	
<u>MANUFACTURER INFORMATION</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	

Comment/Recommendation:

To Applicant: The address of the manufacturer should be the same as the address of the applicant on the FDA form 356h form which is:

"61-20 Sinbuk-ro, Sinbuk-eup
Chuncheon, 24206 Korea"

Please correct as appropriate.

Applicant made revisions as recommended.

Medication Guide Evaluation

MEDICATION GUIDE	
<u>TITLE (NAMES AND DOSAGE FORM)</u>	<u>Acceptable</u>
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Add in the route of administration to match other labeling.

Applicant made revisions as recommended.

MEDICATION GUIDE	
<u>STORAGE AND HANDLING</u>	<u>Acceptable</u>
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

MEDICATION GUIDE	
<u>INGREDIENTS</u>	<u>Acceptable</u>
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

MEDICATION GUIDE

MANUFACTURER INFORMATION	Acceptable
21 CFR 208.20(b)(8)(iii)	☒ Yes ☐ No ☐ N/A
<i>21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	

Comment/Recommendation:

To Applicant: The name of the manufacturer should match the name of the Applicant on the FDA form 356h which is: "Hugel, Inc." Please ensure the comma is added.

Applicant made revisions as recommended.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on February 16, 2024)
<\\CDSESUB1\EVSPROD\bla761225\0036\m1\us\114-labeling\draft\labeling\letibotulinumtoxina-bla-pi-30jan2024.docx>
- Medication Guide (submitted on February 14, 2024)
<\\CDSESUB1\EVSPROD\bla761225\0035\m1\us\114-labeling\draft\labeling\letibotulinumtoxina-bla-medication-guide-14feb2024.docx>
- Container Labels (submitted on August 31, 2023)

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



Diana
Pei

Digitally signed by Diana Pei

Date: 2/27/2024 09:42:52AM

GUID: 6352da2c009ad0777a2c3b47ec094b9a



Sheena Hailin
Wang

Digitally signed by Sheena Hailin Wang

Date: 2/27/2024 09:45:51AM

GUID: 5203a2110001f7235a14cac1b60d05c4

BLA Executive Summary #3

Assessment Date: 02/21/2024

1. Application/Product Information

BLA number	761225 Sequence 0029		
Submission Type	Resubmission #2		
Regulatory Pathway	351(a)		
Associated IND/BLA	IND 123178		
Review Designation	Standard Complete Response Resubmission		
Applicant	Hugel, Inc.		
Indication	Treatment of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients		
Rx/OTC dispensed	Rx		
Drug Product Name	Proprietary Name LETYBO		
	Non-proprietary Name/Code Name letibotulinumtoxinA-wlbg		
	OBP Naming PROT P0DPI1 (BXA1_CLOBH) BOTULINUM NEUROTOXIN TYPE A [ADS01]		
Drug Product Description	LetibotulinumtoxinA-wlbg is a 900 kDa botulinum toxin typeA complex produced by anaerobic fermentation of <i>Clostridium botulinum</i> type A CBFC26 strain (b) (4) in South Korea. LetibotulinumtoxinA-wlbg drug product is supplied as a sterile, preservative-free, white, freeze-dried powder in a single-dose vial for intramuscular use after reconstitution. Each vial contains either 50 Units of letibotulinumtoxinA-wlbg, albumin human (0.25 mg) and sodium chloride (0.45 mg); or 100 Units of letibotulinumtoxinA-wlbg, albumin human (0.5 mg) and sodium chloride (0.9 mg).		
Dosage Form	For injection		
Strength	50 Units/vial or 100 Units/vial		
Route of Administration	Intramuscular (IM) injection		
Primary Container Closure System	a clear, (b) (4) glass vial (5 mL nominal volume) closed with a rubber stopper and an aluminum cap		
Device Information	N/A		
Co-packaged Product Information	N/A		
	Discipline	Primary	Secondary
	Drug substance	Asha Hewarathna,	Hailin (Sheena)
	Drug product		Wang

For use with OPQ-OBP-SOP-3104: OPQ-OBP-TEM-0010-07 [BLA executive summary non-annotated template]

OPQ Review Team		Joao Pedras-Vasconcelos	
	Immunogenicity Assay	Asha Hewarathna	
	Facility	Madushini Dharmasena	Candace Gomez-Broughton
	Microbiology		
	RBPM	Melinda Bauerlien	
	ATL	Hailin (Sheena) Wang	
OPQ Issued Consults	Statistical consult to evaluate the Applicant's response to additional comment #3 in the CR letter issued on 04/12/2023		

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761225 for LETYBO manufactured by Hugel, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of LETYBO is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- Drug Substance:
Hugel Geodu plant
23, Geodudanji 1-gil
Dongnae-myeon, Chuncheon-si
Gangwon-do
Republic of Korea
FEI: 3012163998
- Drug Product:
Hugel Geodu plant
23, Geodudanji 1-gil
Dongnae-myeon, Chuncheon-si
Gangwon-do
Republic of Korea
FEI: 3012163998

b. Fill size and dosage form: LETYBO is provided as 50 Units or 100 Units freeze-dried powder in a single-dose vial

c. Dating Period:

- Drug Substance: (b) (4)
- Drug Product: 36 months at 2°C - 8°C
- For packaged products: Not packaged
- Stability Option: N/A

d. Exempt from lot release:

- Yes
- Rationale, if exempted: LETYBO is exempted from lot release per FR 95-29960. The overall control strategy, including manufacturing and release controls, is adequate to control lot-to-lot variability and product quality over the proposed shelf-life.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable

CMC PMC#1 (4587-1): To investigate the development and implementation of a non-animal-based potency assay for drug substance and drug product release and stability testing.

Final report submission date: December 2028

4. Basis for Recommendation

a. Summary:

The BLA 761225 resubmission #1 SN 0022 received a complete response recommendation on 04/12/2023 due to the withhold determination for the drug substance (DS) and drug product (DP) manufacturing and testing facility Hugel Inc. (FEI #3012163998).

A facility reinspection was conducted from January 25, 2024, through February 01, 2024. Based on reinspection findings at Hugel Inc. (FEI #3012163998), in support of BLA 761225 (SN 0029, Resubmission#2), the manufacturer resolved the inspectional deficiencies cited during the previous FDA re-inspection at Hugel Inc. in support of BLA 761225 resubmission #1 SN 0022. Both DS and DP facility is now recommended for approval.

In addition, the Applicant submitted updated information to Chemistry, Manufacturing, and Controls modules and in response to the additional

comments provided in the Complete Response Action Letter which have been addressed adequately in the current assessment period.

LetibotulinumtoxinA is a purified type A neurotoxin complex produced by anaerobic fermentation of *Clostridium botulinum* type A CBFC26 strain (b) (4) in South Korea. The 900 kDa complex is composed of a type A botulinum neurotoxi (b) (4)

LetibotulinumtoxinA blocks neuromuscular transmission by binding to receptor sites on motor nerve terminals, entering the nerve terminals and inhibiting acetylcholine release.

(b) (4)

The letibotulinumtoxinA DS manufacturing process comprises (b) (4)

The overall letibotulinumtoxinA-wlb/LETYBO control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for letibotulinumtoxinA-wlb/LETYBO

as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for Hugel, Inc. (FEI: 3012163998) proposed for letibotulinumtoxinA-wlb主 DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

The BLA is recommended for approval from a product quality, immunogenicity, facility, microbiology and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate with PMCs/PMRs
Drug Product	-	Adequate with PMCs/PMRs
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for letibotulinumtoxinA-wlb主/LETYBO (i.e., there is no specific test method described in regulation for letibotulinumtoxinA-wlb主/LETYBO that establishes an official standard of potency). We next considered whether potency is a factor for letibotulinumtoxinA-wlb主/LETYBO within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if “potency is a factor” and “no U.S. standard of potency has been prescribed.” We have determined that potency is not a factor for letibotulinumtoxinA-wlb主/LETYBO for purposes of § 610.61(r) because lot variability is not a concern for letibotulinumtoxinA-wlb主/LETYBO as letibotulinumtoxinA-wlb主/LETYBO’s manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

For use with OPQ-OBP-SOP-3104: OPQ-OBP-TEM-0010-07 [BLA executive summary non-annotated template]

a. Established Conditions based on ICH Q12 principles: No
Comments: N/A

b. Drug Substance:

i. Protocols approved:

(b) (4)

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:

(b) (4)

ii. Residual risk: None

iii. Future inspection points to consider: None

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAILIN WANG
02/27/2024 10:58:08 AM

BLA Executive Summary

Assessment Date: 03/31/2023

1. Application/Product Information

BLA number	761225		
Submission Type	Resubmission		
Regulatory Pathway	351(a)		
Associated IND/BLA	IND 123178		
Review Designation	Standard Complete Response Resubmission		
Applicant	Hugel, Inc.		
Indication	Treatment of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients		
Rx/OTC dispensed	Rx		
Drug Product Name	Proprietary Name LETYBO		
	Non-proprietary Name/Code Name letibotulinumtoxin A-xxxx		
	OBP Naming PROT P0DPI1 (BXA1_CLOBH) BOTULINUM NEUROTOXIN TYPE A [ADS01]		
Drug Product Description	LETYBO (letibotulinumtoxinA), sterile lyophilized powder for injection		
Dosage Form	Injection, Powder, LYOPHILIZED, FOR SOLUTION		
Strength	50 Units/vial or 100 Units/vial		
Route of Administration	Intramuscular (IM) injection		
Primary Container Closure System	a clear, (b) (4) glass vial (5 mL nominal volume) closed with a rubber stopper and an aluminum cap		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Asha Hewarathna	Hailin (Sheena) Wang
	Drug product		
	Immunogenicity Assay		
	Facility	Madushini Dharmasena	Candace Gomez-Broughton
	Microbiology		
	RBPM	Melinda Bauerlien	
	ATL	Hailin (Sheena) Wang	

OPQ Issued Consults

(b) (4)

2. Recommendation and Conclusion on Approvability

Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761225 for LETYBO manufactured by Hugel, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of LETYBO is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Hugel, Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

3. Draft Complete Response Comments and Additional Comments (if applicable):

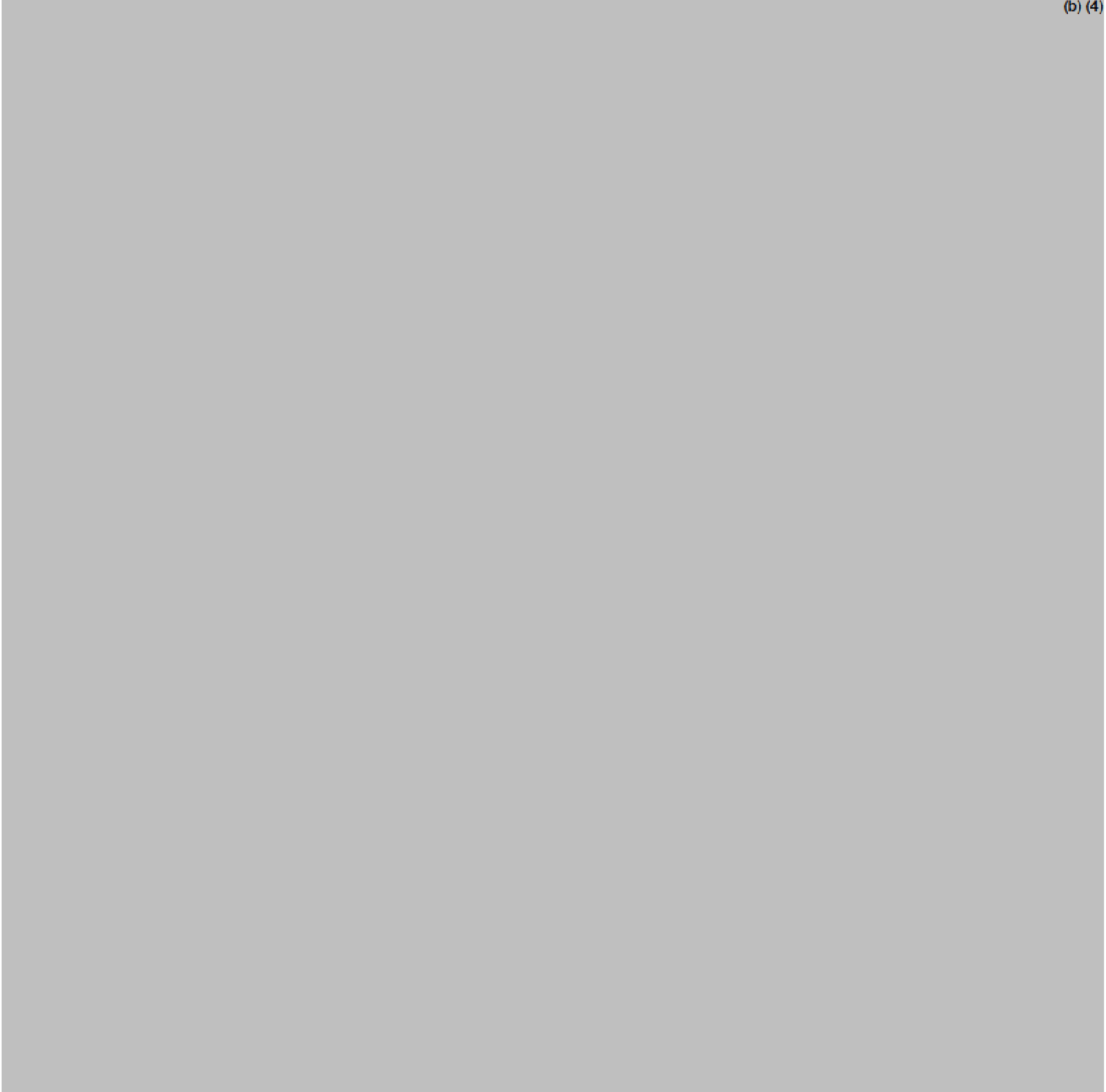
Product Quality Complete Response Comments (provided by OPMA):

During a recent inspection of the Hugel, Inc. (FEI 3012163998) manufacturing and testing facility of drug substance and drug product for this application, our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Additional Product Quality Comments (provided by OBP):

(b) (4)

(b) (4)

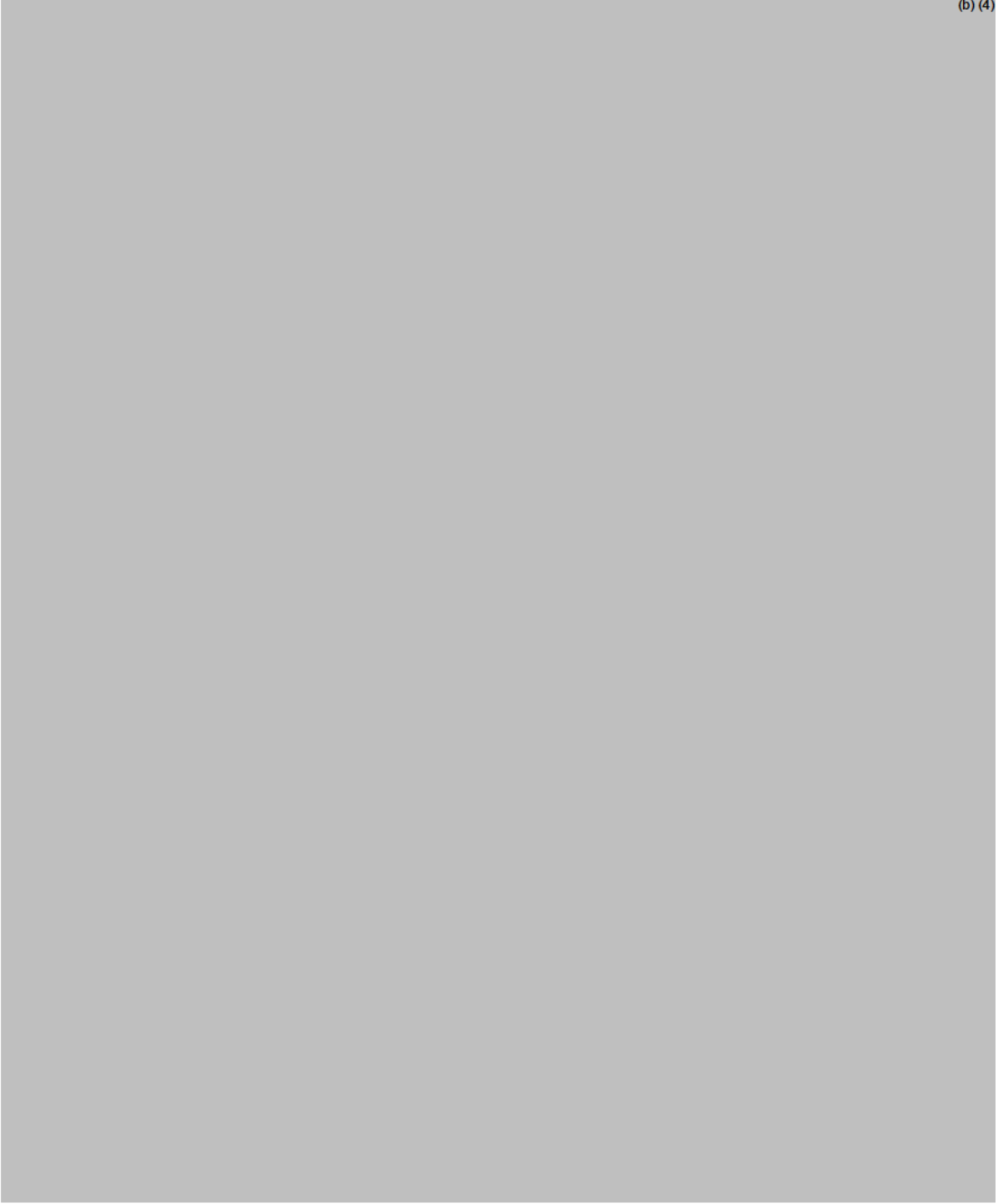


**Additional Microbiology and Facility Inspections Comments (provided by
OPMA):**

(b) (4)



(b) (4)



4. Basis for Recommendation

a. Summary:

The original BLA 761225 submission received a complete response recommendation due to major deficiencies related to the manufacturing and control of DS and DP, microbiological control strategy, as well as the

For use with OPQ-OBP-SOP-3104: OPQ-OBP-TEM-0010-07 [BLA executive summary non-annotated template]

withhold determination for the DS and DP manufacturing and testing facility Hugel Inc. (FEI #3012163998).

Following a compliance review of the reinspection findings at Hugel Inc. (FEI #3012163998), in support of BLA 761225 (SN 0024, Resubmission) there are still significant, outstanding manufacturing risks that prevent approval of this application and the facility recommendation remains withhold approval. Satisfactory resolution of the inspectional deficiencies cited during the recent FDA re-inspection at Hugel Inc. is required before this application may be approved. Therefore, the unacceptable status of the facility is considered deficiency and will be communicated in the CR letter. (b) (4)

In addition, the Applicant submitted updated information to Chemistry, Manufacturing, and Controls modules and in response to the complete response comments and additional comments provided in the Complete Response Action Letter which have been addressed adequately in current assessment period except (b) (4)

These deficiencies (include, but are not limited to) which do not preclude approval will be communicated as additional comments in the CR letter for the BLA resubmission:

Refer to the previous Quality Executive Summary and Integrated Quality Assessment memorandum for BLA 761225 for more detailed information on product and process description, MOA in relation to the proposed indication and how potency is controlled.

b. Subdiscipline Recommendation:

Drug Substance	-	Pending
Drug Product	-	Pending

Immunogenicity Assay	-	Adequate
Facilities	-	Inadequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
Not applicable as OPQ does not recommend approval of this application.

5. Life-Cycle Considerations
Not applicable as OPQ does not recommend approval of this application.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAILIN WANG
03/31/2023 05:12:00 PM

FRANCES NAMUSWE
03/31/2023 05:18:30 PM

Recommendation: Complete Response

OPQ EXECUTIVE SUMMARY

BLA Number: 761225

Assessment Number: 1

Assessment Date: March 29, 2022

Drug Name/Dosage Form	LETYBO (letibotulinumtoxinA), sterile lyophilized powder for injection
Strength/Potency	50 Units/vial or 100 Units/vial
Route of Administration	Intramuscular (IM) injection
Rx/OTC dispensed	Rx
Indication	Treatment of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients
Applicant/Sponsor	Hugel, Inc.

Product Overview

LetibotulinumtoxinA is a purified type A neurotoxin complex produced by anaerobic fermentation of *Clostridium botulinum* type A CBFC26 strain (b) (4) in South Korea. The 900 kDa complex is composed of a type A botulinum (b) (4)

LetibotulinumtoxinA is supplied as a sterile, single use freeze-dried powder for reconstitution in a single use vial containing 50 or 100 Units of botulinum toxin type A neurotoxin complex, human serum albumin (HSA, 0.25 mg or 0.5 mg), and sodium chloride (0.45 mg or 0.9 mg).

LetibotulinumtoxinA blocks neuromuscular transmission by binding to receptor sites on motor nerve terminals, entering the nerve terminals and inhibiting acetylcholine release. It is intended for intramuscular use. (b) (4)

Quality Assessment Team

Discipline	Assessor	Branch/Division
Product Quality (DS and DP)	Asha Hewarathna	CDER/OPQ/OBP/DBRR III
Immunogenicity	Asha Hewarathna	CDER/OPQ/OBP/DBRR III
Labeling	James Barlow	CDER/OPQ/OBP
Facility	Michael Shanks	CDER/OPQ/OPMA/DBM2
Microbiology	Candace Gomez-Broughton	CDER/OPQ/OPMA/DBM2
Team Lead	Zhenzhen Liu (Product quality) Zhenzhen Liu (Immunogenicity) Madushini Dharmasena (Micro and Facilities)	CDER/OPQ/OBP/DBRR III CDER/OPQ/OBP/DBRR III CDER/OPQ/OPMA/DBM2

Application Technical Lead	Zhenzhen Liu	CDER/OPQ/OBP/DBRR III
OPQ RBPM	Rabiya Haider	CDER/OPQ/OPRO/DRBPMI/RBPMBI

Multidisciplinary Assessment Team

Discipline	Assessor	Office/Division
RPM	H. F. Van Horn	CDER/OND/ORO/DROI
Cross-disciplinary Team Lead	Snezana Trajkovic	CDER/OND/OII/DDD
Medical Officer	Tong Li-Masters	CDER/OND/OII/DDD
Pharmacology/Toxicology	Xinguang (Cindy) Li / Barbara Hill (TL)	CDER/OND/OII/DPTII
Clinical Pharmacology	Soo Hyeon Shin / Chinmay Shukla (TL)	CDER/OTS/OCF/DIIP

1. Names:

- Proprietary Name: LETYBO (proposed)
- Trade Name: LETYBO (proposed)
- Non-Proprietary Name/USAN: letibotulinumtoxin A
- CAS Name: 1800016-51-6
- Common Name: letibotulinumtoxin A, BoNT/A
- INN name: None
- OBP systematic name:
PROT P0DPI1 (BXA1_CLOBH) BOTULINUM NEUROTOXIN TYPE A [ADS01]

2. Pharmacological class: Acetylcholine Release Inhibitor, neuromuscular blocking agent

Submissions Assessed

Submission(s) Assessed	Document Date	Review Completed by:
STN 761225/0001- Original BLA submission	03/31/2021	OBP and OPMA
STN 761225/0004- Response to 06/08/2021 IR	06/11/2021	OPMA Facility
STN 761225/0005- Response to 06/07/2021 IR	07/02/2021	OBP Quality
STN 761225/0007- Response to 07/23/2021 IR	08/04/2021	OBP Quality
STN 761225/0009- Response to 07/23/2021 IR	08/23/2021	OPMA Micro
STN 761225/0012- Response to 09/20/2021 IR	10/01/2021	OBP Quality
STN 761225/0013- Response to 09/20/2021 IR	10/12/2021	OBP Quality
STN 761225/0014- Response to 12/13/2021 LCM Request	12/27/2021	OPMA Micro
STN 761225/0016- Response to 01/11/2022 IR	01/31/2022	OBP Quality
STN 761225/0017- Response to 12/12/2021 LCM Request	02/14/2022	OPMA Quality

Quality Assessment Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Comments
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	Provided in Seq 0001
	III			3	Adequate	Provided in Seq 0001
	III			3	Adequate	Provided in Seq 0001

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows:
2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be assessed).

B. Other documents: IND 123178 (letibotulinumtoxinA), BLA 125154 (HSA (b) (4) %)

3. Consults: OBP sent a consult to CDER/OTS/OB (b) (4)

4. Environmental Assessment or Claim of Categorical Exclusion:

Hugel Inc. requests a categorical exclusion for letibotulinumtoxinA from preparation of an environmental assessment under 21 CFR 25.31 (a). As this product is a natural substance in the environment, the Applicant should revise their claim of categorical exclusion to align with 21 CFR 25.31(c). A comment to amend the categorical exclusion claim will be sent to the Applicant in the CR letter.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **Complete Response**

The Office of Pharmaceutical Quality (OPQ), CDER, has completed product quality assessment of STN 761225 for letibotulinumtoxinA manufactured by Hugel Inc. The information and data submitted in this application are not adequate to support a conclusion that the manufacture of letibotulinumtoxinA is well-controlled and will lead to a product that is safe, pure, and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Hugel Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

B. Summary of Complete Response Issues:

The Office of Biotechnology Products (OBP) and the Office of Pharmaceutical Manufacturing Assessment (OPMA) under OPQ identified several product quality deficiencies during the review of Module 3 of BLA 761225. The deficiencies do not support that the manufacture and testing of letibotulinumtoxinA is well-controlled and will lead to a product that is safe, pure, and potent for the duration of the shelf-life. These deficiencies include, but are not limited to

(b) (4)

In addition, following a review of the pre-license inspection (PLI) findings at Hugel Inc. (FEI #3012163998, the proposed DS and DP manufacturing facility), in support of BLA 761225, there are significant, outstanding manufacturing risks that prevent approval of this application (refer to EIR assessment memos in CMS, WA#414192). Satisfactory resolution of the deficiencies cited during the recent FDA inspections at Hugel Inc. is required before this application may be approved. Therefore, the unacceptable status of the facility is considered deficiency and will be communicated in the CR letter.

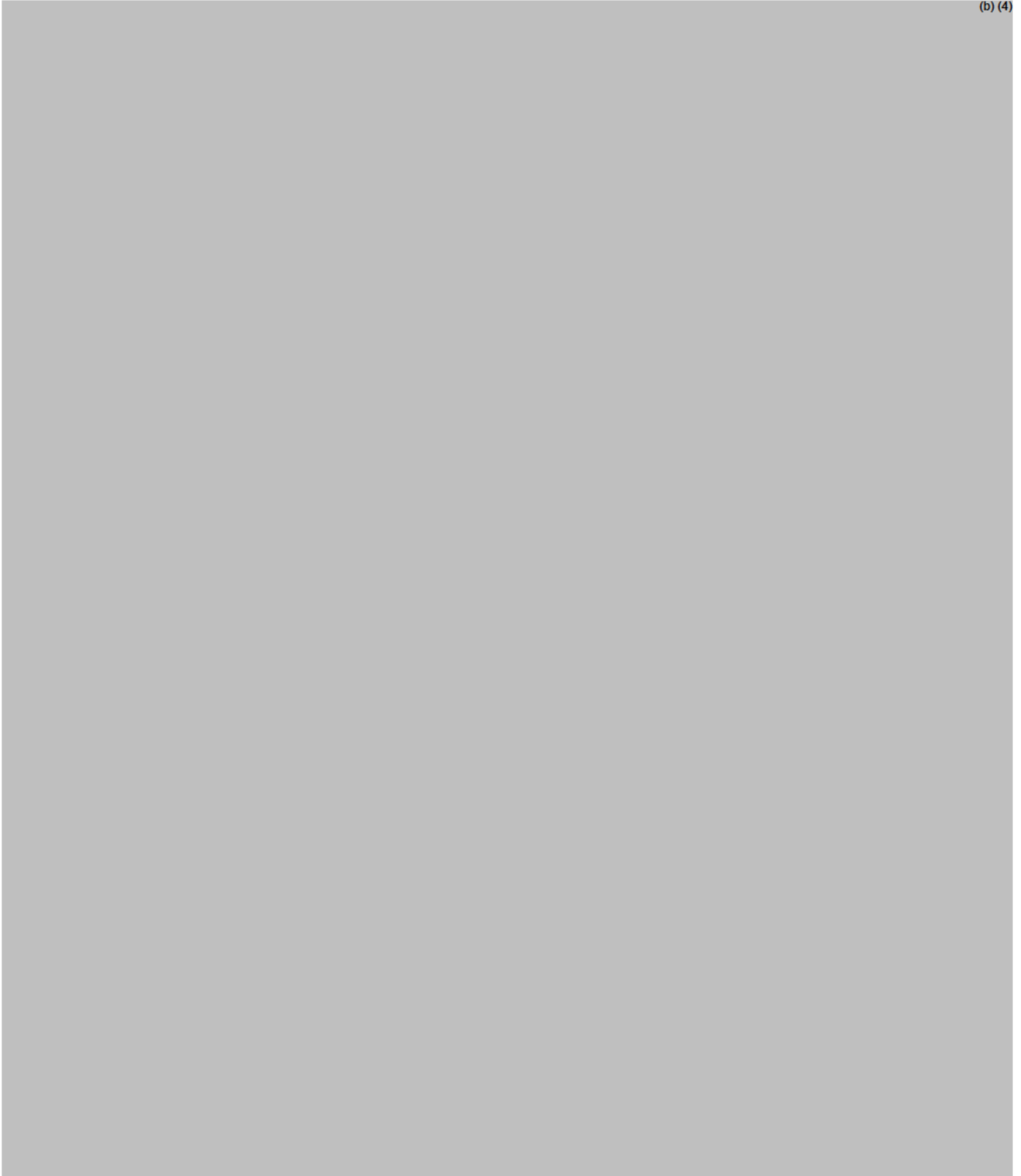
C. Complete Response Letter Draft Language:

Facilities CR Comment (provided by OPMA)

1. During a recent inspection of the Hugel, Inc. (FEI 3012163998) manufacturing and testing facility of drug substance and drug product for this application, our field investigator conveyed

deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Microbiology CR Comment (provided by OPMA)



(b) (4)

D. Benefit/Risk Considerations:

The overall control strategy for letibotulinumtoxinA incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, release of DS and DP, and stability of these materials. Numerous deficiencies were identified during the review period and during the pre-license inspection of the Hugel facility. The facility deficiencies were not resolved, and significant review issues were not adequately addressed during the review period; therefore, the information and data provided in BLA 761225, and its amendments, do not demonstrate that the manufacturing process and control strategy of letibotulinumtoxinA are sufficient to ensure that the manufacturing process is well-controlled and leads to a product of acceptable quality to ensure drug safety and effectiveness for patients. In addition to adequately addressing the deficiencies in the next review cycle, re-inspection of the Hugel facility will be necessary to support BLA approval.

Individual assessments for each discipline, (1) product quality evaluation of DS and DP [OBP], (2) immunogenicity assay validation [OBP], (3) microbiology evaluation of DS and DP [OPMA/DBM], and (4) facility evaluation of DS and DP [OPMA/DBM] are located as separate documents in Panorama.

E. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

There are no recommended post-marketing commitments, requirements, agreements, and/or risk management steps at this time.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 is a summary of product-related critical quality attributes (CQA), intrinsic to the molecule, that are relevant to both DS and DP. The table includes the identification of the various attributes along with their risk management.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Molecular Mass	Safety and Efficacy	Intrinsic to the molecule	(b) (4)	
Identity	Safety and Efficacy	Intrinsic to the molecule		
pH	Efficacy	Formulation		
Potency	Safety and Efficacy	Intrinsic to the molecule		

Purity of toxin complex	Efficacy and safety	May change during manufacturing process and storage	(b) (4)
High molecular weight species (HMWS) / Aggregates (product-related impurities)	Potency, safety, and immunogenicity The risk for immunogenicity is low because of the low amount of the product injected into patients and because the product does not have an endogenous counterpart.	(b) (4) manufacturing process.	
Low molecular weight species (LMWS, product-related impurities)	Efficacy and potency	LMWS are introduced by the manufacturing process.	

B. Drug Substance Quality Summary

Table 2 provides a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes, including process-related impurities.

Table 2: Drug Substance CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance (general)	Safety and Immunogenicity	Manufacturing process, formulation		(b) (4)
pH	Safety	Manufacturing process, formulation		
Protein Concentration (strength)	Bioactivity and efficacy	Manufacturing process		
Neurotoxin Content (strength)	Bioactivity and efficacy	Manufacturing process		
Host cell DNA (Process-related impurities)	safety	Production strain		
Host cell protein (Process-related impurities)	safety	Production strain		
Media-derived residual Impurities (Process-related impurities)	Safety	Raw materials		
(b) (4) (Process-related impurities)	Safety	Raw materials		
(b) (4) (Process-related impurities)	Safety	Raw materials		
(b) (4)	safety	Raw materials		

Bioburden (Process-related impurities, adventitious agents)	Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms)	Can be introduced from raw materials and throughout the manufacturing process	(b) (4)
Endotoxin (Process-related impurities, adventitious agents)	Safety, purity		
Oxidized Species (Product-related substances)	Bioactivity, PK, PD, immunogenicity, and efficacy	Intrinsic to the molecule, and the relative abundance can change during manufacturing process and storage	

- **Description:** LetibotulinumtoxinA drug substance (BoNT/A-DS) is a purified 900 kDa neurotoxin protein complex (b) (4)

It is purified from the anaerobic culture of *Clostridium botulinum* type A CBFC26 strain. The heavy chain and the light chain of the neurotoxin protein are linked by a single disulfide bond. An additional intramolecular disulfide bond is located in the heavy chain. The light chain poses a Zn²⁺-dependent protease activity.

- **Mechanism of Action (MoA):** The neurotoxin complex is stable under acidic conditions and dissociated quickly after injection. The heavy chain of neurotoxin binds with its receptors (integral membrane protein SV2 and sialic acid-containing glycosphingolipids and gangliosides) and the toxin is internalized. The light chain of neurotoxin is released to the cytosol of the nerve terminal and cleaves its target protein SNAP-25, which is essential for exocytosis of acetylcholine vesicles located in peripheral motor neurons. This inhibits the release of acetylcholine and reduce muscle activity in neuromuscular junction which in turn is leading to relaxation and reduction of glabellar lines and mimic wrinkles.

- **Potency Assay:** (b) (4)

(b) (4)

- **Reference Standards:**

(b) (4)

- **Critical starting materials or intermediates:**

(b) (4)

(b) (4)

- **Manufacturing process summary:** The letibotulinumtoxinA DS manufacturing process

(b) (4)

- **Container closure:** The container closure system for the DS

- **Dating period and storage conditions:**

(b) (4)

C. Drug Product Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety, purity, and efficacy (degradation or modification of the product by	Contamination may be introduced throughout the DP manufacturing process or by	(b) (4)	

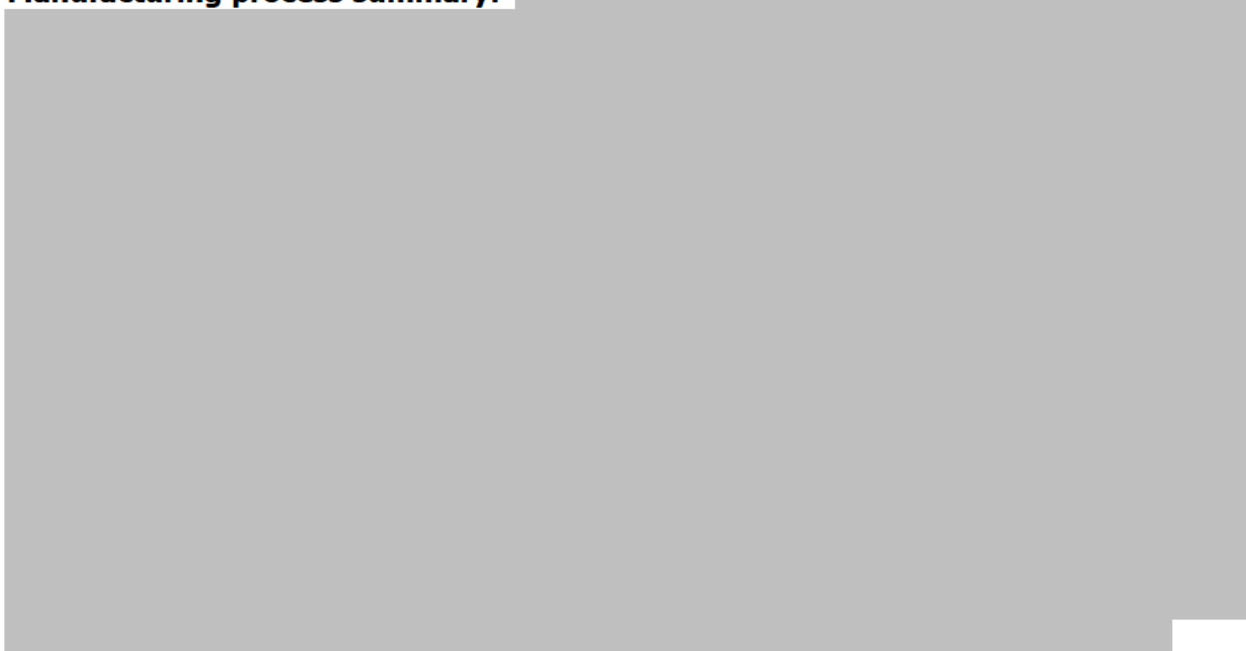
	contaminating microorganisms)	container closure integrity failure	(b) (4)
Endotoxin (contaminant)	Safety and purity	DP manufacturing process and by raw materials	
Container closure integrity (contaminant)	Safety (Failure in closure integrity may lead to contamination through a loss of sterility) or evaporation/leakage (impacting concentration or content)	Breach during the manufacturing process May be impacted by storage conditions	
Appearance	Safety	DP Manufacturing process	
Visible Particles (Appearance)	Safety	DP manufacturing process, CCS, and product	
Subvisible particles (general)	Safety	DP manufacturing process, CCS, and product	
pH (general)	Safety Efficacy	Impacted by the Formulation, reconstitution buffer, and potentially stability by a breach in the container closure system or presence of leachables	
Solubility/reconstitution time (general)	Efficacy	DP manufacturing process, DP stability	
(b) (4) (general)	safety	(b) (4) process	
Extractable volume/overfill (general)	Safety and Efficacy	Filling process	

			(b) (4)
(b) (4)	safety	Filling process	
Total protein content (quantity)	Efficacy Stability (b) (4)	DP manufacturing process, formulation	
Neurotoxin content	Efficacy	DP manufacturing process, formulation	
HSA content (composition)	Safety and Efficacy	DP manufacturing process, formulation	

- Potency and Strength:** 50 or 100 Units of letibotulinumtoxinA per vial. (b) (4)
 (b) (4)
 (b) (4)
 For DP, potency is reported relative to the reference standard.
- Summary of Product Design:** LetibotulinumtoxinA is supplied as a sterile, single use freeze-dried powder in glass vials for intramuscular injection. Prior to administration, the DP must be reconstituted in 1.25 ml or 2.5 mL of injectable physiological saline (b) (4) to obtain a solution at a concentration of 4 Units/0.1 mL and a total treatment dose of 20 Units in 0.5 mL. Reconstituted DP should be stored at 2-8 °C protected from light and must be used within 24 hours of reconstitution. Data to support chemical and microbial stability of the reconstituted solution up to 24 hours at 2-8 °C were provided.
- List of Excipients:** The 50U and 100U DP are formulated with 0.25 or 0.5 mg human serum albumin (HSA) (b) (4) and 0.45 or 0.9 mg sodium chloride (b) (4). The HSA is FDA approved (refer to BLA 125154).
- Reference Materials:** Same as the reference standards used for DS testing.

- **Manufacturing process summary:**

(b) (4)



- **Container closure:** The primary container closure system is comprised of a clear, (b) (4) glass vial (5 mL nominal volume) with a rubber stopper, and an aluminum cap. The DP stability studies were carried out in the same container closure system and the data support that the DP is compatible with these primary container closure components. The leachable study results were provided and support the suitability of the proposed primary CCS for DP. The secondary packaging is an individual cardboard carton per each vial and will serve to protect from light during storage.
- **Dating period and storage conditions:** 36 months at 2 – 8 °C. Thirty-six (36) months long term stability data were provided for the 50U DP, while only 12 months stability data were provided for the 100U DP. It is unclear whether the 36 months shelf life for the 50U DP can be applied to the 100U DP. Hugel will be asked to provide updated stability data in their complete response.
- **List of co-package components, if applicable:** None.

D. Novel Approaches/Precedents: None.

E. Any Special Product Quality Labeling Recommendations: N/A.

F. Establishment Information:

Overall Recommendation: CR					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
- production and characterization of WCB - storage of MCB and WCB - DS and DP manufacture	Hugel Geodu plant 23, Geodudanji 1-gil Dongnae-myeon, Chuncheon-si Gangwon-do	3012163998	PLI Required	PLI: 7-item FDA Form 483*	Withhold – based on inspection

- DS Storage - DS and DP release and stability testing - Batch release of DP	Republic of Korea				
- production and characterization of MCB and WCB - storage of WCB	Hugel Sinbuk plant: 61-20, Sinbuk-ro, Sinbuk-eup, Chuncheon-si, Gangwon-do, Republic of Korea	3012072120	Facility was found compliant based on file review	N/A	Approve – Based on Previous History

*7-i

(b) (4)

G. Facilities:

A pre-license inspection of Hugel, Inc. (FEI: 3012163998), Gangwon, Korea, was conducted from 08/12/2021 to 08/20/2021 in support of the new Biologics License Application (BLA) 761225/0 for letibotulinumtoxin A (BoNT/A). Hugel is responsible for manufacturing of letibotulinumtoxin A drug substance (DS), drug product (DP), release and stability testing, and storage of DS, DP, and master and working cell banks. This inspection was conducted by CDER/OPQ/OPMA/DBM2 and CDER/OPQ/OBP/DBRRIII under eNSpect operation ID122192. The inspection covered the Quality, Facilities and Equipment, Production, Material, and Laboratory Control systems, used in the manufacturing and testing of letibotulinumtoxinA DS and DP. The profile classes covered were CBI and SVL. This inspection resulted in a seven-item FDA Form 483. Based on the review of the EIR, associated exhibits, and the firm's response to the issued FDA Form 483, it was concluded that the firm's capability and readiness to manufacture Letibotulinumtoxin A drug substance and drug product should be reassessed during a re-inspection of the facility for BLA 761225. During this re-inspection of Hugel, Inc. (FEI 3012163998), an assessment of the corrective actions and commitments for

Observations 1, 2, 3, and 7, is require before an approval recommendation can be made for BLA 761225.

In summary, CDER/OPQ recommends WITHHOLD for BLA 761225 in part due to the unacceptable CGMP status for Hugel Inc. (see CMS WA# 414192 and CR Comments #1).

H. Lifecycle Knowledge Management:

a. Drug Substance:

- i. Protocols approved: Not Applicable.
- ii. Outstanding assessment issues/residual risk: See CR comments in Section I.C.
- iii. Future inspection points to consider:
 - an assessment of the corrective actions and commitments for Observations 1 and 2 documented in FDA Form 483.
 - Check documents such as batch record or batch release SOP to verify the update of batch rejection criteria: a batch that fails to meet any AR for CPP or AC for IPC will be rejected.
 - Check failed DS and DP lots and whether corresponding CAPA are established.
 - Compare SDS-PAGE gels for the forced degradation samples (i.e., temperature stressed v.s. freeze/thaw) and determine whether these gels are duplicated. Particularly, the gels appear to be the same when comparing the bands for the native/control samples between these two gels.

b. Drug Product

- i. Protocols approved: Not Applicable.
- ii. Outstanding assessment issues/residual risk: See CR comments in Section I.C.
- iii. Future inspection points to consider for PBL:
 - an assessment of the corrective actions and commitments for Observations 3 and 7 documented in FDA Form 483.

c. Immunogenicity Assay Validation

- i. Protocols approved: N/A.
- ii. Outstanding assessment issues/residual risk: None.
- iii. Future inspection points to consider: None.

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/s/

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03/29/2022 01:52:17 PM

SUSAN L KIRSHNER
03/29/2022 02:21:19 PM