

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761367Orig1s000

PRODUCT QUALITY REVIEW(S)

LABELS AND LABELING ASSESSMENT

Date of Assessment:	June 4, 2025
Assessor:	Diana Pei, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Arnold Seo, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIV
Application:	BLA 761367 ORIG 1 RESUB 45
Applicant:	CSL Behring LLC
Submission Date:	December 17, 2024
Product:	Andembry (garadacimab-gxii)
Dosage form(s):	injection
Strength and Container-Closure:	200 mg/1.2 mL solution in autoinjector 200 mg/1.2 mL solution in single-dose prefilled syringe with needle safety device.
Purpose of assessment:	The Applicant submitted a biologics license application for the approval of garadacimab-gxii for the indication for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years and older.
Recommendations:	The prescribing information, patient labeling, instructions for use, 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

In the Instructions for Use (IFU), the Applicant proposed the term “(b) (4)”, while the Prescribing Information (PI) uses “slightly opalescent” as the clarity for the drug product. OPQA III Labeling and the Product Quality team recommended revising the IFU to use “slightly opalescent” to remain consistent throughout labeling. The Applicant has agreed to this change but has requested to implement it after completing the packaging of 400 units currently in process under Pre-Launch Activities Importation Requests (PLAIR). These 400 units will use the labeling submitted on May 20, 2025 [Sequence Number 0052] which includes the term “(b) (4)” in the IFU. Once this PLAIR batch is complete, the IFU labeling will be updated to use “slightly opalescent”.

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, patient information, instructions for use submitted on June 3, 2025 and the container labels, and carton labeling submitted on December 17, 2024 were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information, Patient Information, and Instructions for Use (submitted on December 17, 2024)
<\\CDSESUB1\EVSPROD\bla761367\0045\m1\us\114-labeling\annotated-draft-labeling-1-14-12.docx>
- Container Labels (submitted on December 17, 2024)



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

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:

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:

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."

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

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:

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

Comment/Recommendation: The product does not need a Medication Guide.

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:

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

Comment/Recommendation:

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:

<u>NDC numbers (container label)</u>	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

<u>Preparation instructions (container label)</u>	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:

<u>Package type term (container label)</u>	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:

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

Comment/Recommendation:

<u>Prominence of required label statements (container label)</u>	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: Guidance for Industry Bar Code Label Requirements Questions and Answers (August 2011) Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	

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

<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>	☐ No ☐ N/A

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: The label is small and could be considered a partial label. Thus, a dosage statement is not required.

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 ☐ 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:

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

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.

<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

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) 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
Regulation: 21 CFR 610.61(r)	☒ Yes ☐ No ☐ N/A

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 garadacimab products (i.e., there is no specific test method described in regulation for garadacimab 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 Andembry 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.

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
<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 (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) Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015) 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: This product does not have a Medication Guide.

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</i>	

<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> <i>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> <i>Draft Guidance Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2023)</i>	

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 (October 2018)</i> <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>	

Comment/Recommendation:

Full Prescribing Information	
15 & 16 Hazardous Drug	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv)	☐ Yes ☐ No ☒ N/A
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	

Comment/Recommendation:

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
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	
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No

<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>	☐ N/A

Comment/Recommendation:

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM) <i>Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>	Acceptable ☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING <i>Recommended labeling practices for Patient Labeling: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i>	Acceptable ☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

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

Comment/Recommendation:

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	Acceptable

21 CFR 201.1, 19 CFR 134.11	☒ 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:

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
<i>Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Guidance for Industry Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (July 2022). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	
<i>Recommended labeling practices for IFU: Guidance for Industry Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (July 2022). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i>	Acceptable ☒ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	Acceptable
21 CFR 201.1, 19 CFR 134.11	☐ Yes ☐ No ☒ N/A
Guidance for Industry <i>Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format</i> (July 2022). 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)	

Comment/Recommendation:

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information, Patient Information, and Instructions for Use (submitted on June 3, 2025)
<\\CDSESUB1\EVSPROD\bla761367\0053\m1\us\114-labeling\draft\labeling\draft-labeling-text.docx>
- Container Labels (submitted on December 17, 2024)



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

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Diana
Pei

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Arnold
Seo

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BLA Executive Summary
Assessment Date: May 20, 2025

1. Application/Product Information

BLA number	761367
Submission Type	Resubmission
Regulatory Pathway	NME 351(a)
Associated IND/BLA	IND 139936
Review Designation	Class 2 resubmission
Applicant	CSL Behring LLC
Indication	Indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients aged 12 years and older
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name ANDEMBRY
	Non-proprietary Name/Code Name Garadacimab-gxii/CSL312
	OBP Naming MAB HUMAN (IGG4) ANTI P00748 (FA12_HUMAN)[CSL312]
Drug Product Description	The ANDEMBRY injection is a sterile, preservative-free, slightly opalescent to clear, brownish-yellow to yellow solution for subcutaneous use. Each 1.2 mL ANDEMBRY prefilled syringe assembled with autoinjector or assembled with needle safety device contains 200 mg of garadacimab-gxii, arginine monohydrochloride (37.9 mg), histidine (3.7 mg), polysorbate 80 (0.24 mg),

	proline (19.3 mg), and water for injection, USP. The pH is 6.1. Garadacimab-gxii, an activated Factor XII (FXIIa) inhibitor, is a recombinant, fully human, monoclonal antibody (IgG4/λ-light chain) produced in Chinese Hamster Ovary (CHO) cells. The molecular weight is approximately 148 kDa.		
Dosage Form	Injection: • 200 mg/1.2 mL (167 mg/mL) solution in single-dose prefilled autoinjector • 200 mg/1.2 mL (167 mg/mL) solution in single-dose prefilled syringe with needle safety device		
Strength	200 mg/1.2 mL		
Route of Administration	Subcutaneous use		
Primary Container Closure System	Pre-fillable syringe		
Device Information	Autoinjector and needle safety device		
Co-packaged Product Information	Not applicable		
OPO Review Team (for BLA original)	Discipline	Primary	Secondary
	Drug substance (DS)	Arnold Seo	Lei Zhang
	Drug product (DP)		
	Immunogenicity Assay		
	Facility	DS Micro and Facility: Maria	DS Micro and Facility: Candace Gomez-
	Microbiology		

submission and resubmission)		Scott (original submission) Madushini Dharmasena DP Micro and Facility: Hamet Touré	Broughton (original submission) Madushini Dharmasena DP Micro and Facility: Virginia Carroll
	RBPM	Hannah Lee	
	ATL	Lei Zhang	
OPO Issued Consults	Original Submission: CDRH Facilities Inspection (ICCR# 00950741) and CDRH Technical Engineering/Device Design Review (ICCR# 00950756)	Janice Ferguson	Shruti Mistry
	Resubmission: CDRH Technical Engineering/Device Design Review (ICCR# 01042826)	Sarah Hanif	

2. Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761367 for ANDEMBRY manufactured by CSL Behring LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of ANDEMBRY 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:** CSL Behring (Australia) Pty Ltd, Broadmeadows, Australia, FEI 3001644620
- **Drug Product:** Semi-finished product manufacturing and filling: CSL Behring GmbH, Marburg, Germany, FEI 3003098680;
Autoinjector assembly, labeling, and packaging: (b) (4)
Needle safety device assembly, labeling, and packaging: CSL Behring GmbH, Marburg, Germany, FEI 3003098680

b. Fill size and dosage form: 200 mg/1.2 mL solution in single-dose prefilled autoinjector and in single-dose prefilled syringe with needle safety device

c. Dating Period:

- **Drug Product:** 36 months at 2°C - 8°C
- **Drug Substance:** (b) (4) months at (b) (4) °C
- **Intermediate Substance, if applicable:** N/A
- **For packaged products:** N/A
- **Stability Option:**
 - Limited stability data: Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: ANDEMBRY is exempted from lot release per FR 95-29960.

4. Basis for Recommendation

a. Summary:

ANDEMBRY is indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients aged 12 years and older. Garadacimab-gxii is an inhibitor of activated Factor XII (FXIIa). Garadacimab-gxii binds to the catalytic domain of FXIIa and inhibits its catalytic activity, which inhibits the cascade of events that leads to HAE attacks. Potency of garadacimab-gxii is controlled using an FXIIa enzyme activity inhibition assay. The biological activity relative to an established reference material is calculated and reported for garadacimab-gxii.

Garadacimab-gxii drug substance (DS) manufacturing process consists of (b) (4)

[REDACTED] (b) (4)

The garadacimab-gxii drug product (DP) is produced using [REDACTED] (b) (4)
[REDACTED] and storage at 2-8°C.

The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose.

During the original BLA review cycle, this BLA was recommended for approval from DS, immunogenicity assay, and CDRH consult perspectives. In addition, approval was recommended for the DS manufacturing facility (CSL Behring (Australia) Pty Ltd, Broadmeadows, Australia, FEI 3001644620) and autoinjector assembly facility ([REDACTED] (b) (4) [REDACTED]), together with other release, stability and device functionality performance testing facilities.

During the original BLA review cycle, multiple microbiology and product quality deficiencies were identified for the DP manufacturing process, including inadequate DP process design to minimize potential contamination of the sterile DP, insufficient DP process control to ensure consistent product quality, and insufficient DP process validation data to demonstrate consistent process performance. In addition, withhold was recommended for the DP manufacturing facility (CSL Behring GmbH, Marburg, Germany, FEI 3003098680) based on pre-license inspection and facility compliance review.

In the BLA resubmission, the Applicant adequately addressed the deficiencies identified during the original BLA review cycle. The microbial control and sterility assurance strategy of the DP manufacturing process in the BLA resubmission supports consistent manufacture of a sterile product. The product quality data and information provided in the resubmission support

adequate control to ensure consistent product quality and process performance. In addition, the DP manufacturing facility (CSL Behring GmbH, Marburg, Germany, FEI 3003098680) was recommended for approval based on the 704(a)(4) Records Request review.

The overall ANDEMBRY control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the DS and DP. The manufacturing processes and overall control strategies for ANDEMBRY are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The BLA is recommended for approval from a product quality, facility, microbiology and sterility assurance perspectives.

CDRH performed consult review for the device technical engineering and facilities, and recommended approval.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate
Device (CDRH Consult)	-	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 garadacimab (i.e., there is no specific test method described in regulation for garadacimab that establishes an official standard of potency). We next considered whether potency is a factor for garadacimab 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 ANDEMBRY for purposes of § 610.61(r) because lot variability is not a concern for ANDEMBRY as ANDEMBRY's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:

- 1) Requalification protocol (storage stability protocol) for master cell bank and working cell bank
- 2) Qualification and requalification protocols for primary and secondary reference standards

3) (b) (4)

- 4) Post-approval annual stability protocol and stability commitment

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:

- 1) Post-approval annual stability protocol and stability commitment

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/

LEI N ZHANG
05/20/2025 05:42:47 PM

BLA Executive Summary
Assessment Date: August 26, 2024

1. Application/Product Information

BLA number	761367
Submission Type	Original Submission
Regulatory Pathway	NME 351 (a)
Associated IND/BLA	IND 139936
Review Designation	Standard review
Applicant	CSL Behring LLC
Indication	For the indication of prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and adolescent patients 12 years and older
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name ANDEMBRY (proposed)
	Non-proprietary Name/Code Name Garadacimab-gxii / CSL312
	OBP Naming MAB HUMAN (IGG4) ANTI P00748 (FA12_HUMAN)[CSL312]
Drug Product Description	The CSL312 injection is a sterile, preservative-free, slightly opalescent to clear, brownish-yellow to yellow solution for subcutaneous use. Each 1.2 mL CSL312 prefilled syringe assembled with autoinjector or assembled with needle safety device contains 200 mg of CSL312, arginine monohydrochloride (37.9 mg),

	histidine (3.7 mg), polysorbate 80 (0.24 mg), proline (19.3 mg), and water for injection, USP. The pH is 6.1. The CSL312 active ingredient, an activated Factor XII (FXIIa) inhibitor, is a recombinant, fully human, monoclonal antibody (IgG4/λ-light chain) produced in Chinese Hamster Ovary (CHO) cells. The molecular weight is approximately 148 kDa.		
Dosage Form	Injection: • 200 mg/1.2 mL (167 mg/mL) solution in single-dose prefilled autoinjector • 200 mg/1.2 mL (167 mg/mL) solution in single-dose prefilled syringe with needle safety device		
Strength	200 mg/1.2 mL		
Route of Administration	Subcutaneous use		
Primary Container Closure System	Pre-fillable glass syringe		
Device Information	Autoinjector and needle safety device		
Co-packaged Product Information	Not applicable		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance (DS)	Arnold Seo	Lei Zhang
	Drug product (DP)		
	Immunogenicity Assay		
	Facility	DS Micro and Facility: Maria Scott	DS Micro and Facility:
	Microbiology		

		DP Micro and Facility: Hamet Touré	Madushini Dharmasena DP Micro and Facility: Virginia Carroll
	RBPM	Hannah Lee	
	ATL	Lei Zhang	
OPQ Issued Consults	CDRH Facilities Inspection (ICCR# 00950741) and CDRH Technical Engineering/Device Review (ICCR# 00950756)	Janice Ferguson	Shruti Mistry

2. Recommendation and Conclusion on Approvability

Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761367 for CSL312 manufactured by CSL Behring LLC. The data submitted in this application are not sufficient to support a conclusion that the manufacture of CSL312 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 CSL Behring LLC 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):

Facility Inspection

1. Following pre-license inspection of CSL Behring GmbH, Emil-von-Behring-Strasse 76, Marburg, Hesse, Germany (FEI 3003098680), listed in this application, FDA conveyed deficiencies to the representative of the facility. The facility should provide satisfactory responses to these deficiencies to the FDA office indicated on the FDA 483 prior to your complete response to your application. Your complete response should include the date(s) of the

facility's response to the FDA Form 483. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

Microbiology

2. The manufacturing process for CSL312 semi-finished product (SFP) is not designed to minimize potential contamination of the sterile drug product. (b) (4)

(b) (4)

. A process performance qualification (PPQ) protocol and the results of the first (b) (4) PPQ batch were provided in the amendment received July 12, 2024; however, additional process validation and other supporting data are needed to support the process change. The amendment received August 9, 2024, was submitted late in the review cycle and was not reviewed. In the BLA resubmission, provide complete process validation data for the CSL312 SFP manufacturing process with (b) (4) and update Module 3.2.P of the BLA to reflect the new process accordingly. Include (b) (4) and sufficient stability data to support consistency, stability and proposed shelf life of the CSL312 SFP manufactured using the new process. In addition, provide a summary of sterilization validation data for (b) (4).

Product Quality

3. Based on the information provided in the original BLA submission and amendments to the BLA received on June 3, 2024 and June 20, 2024, there is concern that the control for CSL312 drug product manufacturing process is insufficient to ensure consistent product quality. Specifically, a process control of (b) (4) was not adequately established. In addition, the proposed process control strategy of (b) (4) is inappropriate to ensure consistent and acceptable filling weight/volume of individual syringes during the filling process. In your resubmission, establish an adequate control strategy for (b) (4) that is supported by relevant data. In addition, you should consider the

(b) (4)
[redacted] process control to ensure accurate monitoring of the filled weight/volume. Additionally, a clear description of the actions taken for failure of in-process checks should be provided.

4. The process validation data for CSL312 drug product manufacturing are insufficient to demonstrate consistent process performance. Specifically, (b) (4)
[redacted] In addition, the (b) (4)
data from the PPQ batches are derived from a limited number of samples and insufficient sampling points. This is a concern considering (b) (4)
[redacted] during the routine manufacturing process. In your resubmission, provide sufficient (b) (4)
[redacted] results for the drug product filling process (refer to the information requests issued on May 22, 2024 and June 11, 2024). Additionally, provide filling capability data that are derived from sufficient samples and multiple sampling points of PPQ batches to demonstrate that the filling process is capable of filling syringes with consistent filling weight/volume.

Comments/recommendations that are not approvability issues:

Microbiology

1. The plunger movement study described in section 3.2.P.2.5 was not conducted with syringes with the largest air bubble allowed by the process controls; therefore, the study was not performed under worst-case conditions for plunger movement during (b) (4) transport. The amendment received June 11, 2024, noted that a new plunger movement study will be conducted using 15 filled syringes with plunger stopper positions manipulated manually to create a (b) (4) mm air bubble. Provide results from the repeated plunger movement study conducted with syringes with the largest air bubble allowed in the syringe to ensure that sterility of the drug product will be maintained during routine (b) (4) transport under worst-case conditions.

2. [redacted] (b) (4)

(b) (4)

Product Quality

3. We acknowledge that you provided product quality data from relevant studies to support risk assessment of the commercial drug product shipping; however, you did not provide real-time/real-condition drug product shipping validation data in the BLA submission. In the information request response dated June 3, 2024, you agreed to commit to perform a real-time/real-condition shipping validation study and to submit the data in a future annual report. Submitting the shipping validation data without an approved shipping validation protocol for prospective validation of the actual commercial drug product shipping to a future annual report is inappropriate because product quality cannot be ensured during the actual commercial drug product shipment. Therefore, in your resubmission, we recommend you provide drug product real-time/real-condition shipping validation data.

Device

4. In the information request dated January 29, 2024, FDA requested device performance testing (either real-time or accelerated aged testing) on a total of 3 batches of the subject prefilled syringe (PFS) with needle safety device (NSD) to include dose accuracy, peak force, injection force, and NSD activation force to demonstrate that the device will perform as intended to the end of its proposed shelf life of 36 months. The Agency also requested testing for a total of 3 batches of the subject autoinjector (AI) to include dose accuracy, injection time, activation force, extended needle length, and lockout force to demonstrate that the device will perform as intended to the end of its proposed shelf-life of 36 months. In the response dated February 5, 2024, it is noted that two additional drug product batches of CSL312 PFS assembled with NSD and CSL312 PFS assembled with AI will be placed on stability, and this data will be provided in an annual report. In your resubmission, please provide the results of the additional stability data rather than in an annual report.

4. Basis for Recommendation

a. Summary:

CSL312 is an inhibitor of activated Factor XII (FXIIa). CSL312 binds to the catalytic domain of activated FXIIa and inhibits its catalytic activity. The inhibition of FXIIa inhibits the cascade of events that leads to a hereditary angioedema (HAE) attack. Potency of CSL312 is controlled using an FXIIa

enzyme activity inhibition assay; the biological activity relative to an established reference material is calculated and reported.

CSL312 drug substance (DS) manufacturing process consists of (b) (4)

(b) (4)

The drug product (DP) is produced using (b) (4)

(b) (4) and storage.

The overall control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the DS and DP. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. CDRH performed consult review for the device technical engineering and facilities, and recommended approval. In addition, approval is recommended for the following facilities: DS manufacturing facility (CSL Behring (Australia) Pty Ltd, Victoria, Australia, FEI 3001644620), AI device functionality performance testing site ((b) (4)), and AI assembly facility ((b) (4)).

Although this BLA is recommended for approval from DS, immunogenicity assay, and CDRH consult perspectives, multiple microbiology and product quality deficiencies were identified for the DP process and these deficiencies cannot be adequately addressed during the assessment period. These deficiencies include:

- Inadequate DP process design to minimize potential contamination of the sterile DP,
- Insufficient DP process control to ensure consistent product quality,

- Insufficient DP process validation data to demonstrate consistent process performance.

In addition, during the inspection of the DP manufacturing facility (CSL Behring GmbH, Marburg, Germany, FEI 3003098680), the field investigators issued a 7-item FDA Form 483 conveying deficiencies to the representatives of the facility, and the initial field recommendation was withhold. Based on the facility compliance review of the facility's responses to the FDA Form 483, OPMA recommended a withhold for the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Inadequate
Immunogenicity Assay	-	Adequate
Facilities	-	Inadequate
Microbiology	-	Inadequate
CDRH consult	-	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/

LEI N ZHANG
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MADUSHINI N DHARMASENA
08/26/2024 03:55:22 PM

YAN WANG
08/26/2024 04:03:42 PM