CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761339Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: August 15, 2023

1. Application/Product Information

BLA number	761339
Submission Type	Original
Regulatory Pathway	NME 351(a) Orphan Drug Designation (DRU-2020-7368) Rare Pediatrics Disease Designation (RPD-2020-281)
Associated IND/BLA	IND 142063
Review Designation	Priority
Applicant	Regeneron Pharmaceuticals, Inc.
Indication	Treatment of adults and pediatric patients 1 year of age and older with CD55-deficient protein-losing enteropathy (PLE).
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Veopoz
	Non-proprietary Name/Code Name: pozelimab-bbfg, REGN3918
	OBP Naming: MAB HUMAN (IGG4) ANTI P01031 (CO5_HUMAN) [REGN3918]
Drug Product Description	Veopoz (pozelimab-bbfg) injection is a sterile, preservative-free, 400 mg/2 mL (200 mg/mL), clear to slightly opalescent, colorless to pale yellow solution supplied in a single-dose glass vial, for intravenous or subcutaneous use. Each mL contains 200 mg pozelimab-bbfg, arginine hydrochloride (21 mg), histidine (1.15 mg), L-histidine hydrochloride monohydrate (2.65 mg), polysorbate 80 (1.5 mg), sucrose (20 mg), and Water for Injection, USP at pH 5.8. Pozelimab-bbfg, a complement inhibitor, is a recombinant monoclonal antibody (IgG4 isotype) with approximate molecular weight of 145 kDa produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells. Each heavy chain contains a serine-to-proline substitution at amino acid 228 within the hinge region of the Fc domain to promote stabilization of disulfide bonds between the two heavy chains.
Dosage Form	Liquid
Strength	400 mg/2 mL (200 mg/mL)

Route of Administration	Single loading dose by intravenous infusion followed by maintenance doses via subcutaneous injection		
Primary Container Closure System	Clear glass vial		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance	Xuhong Li	Kelley Burridge
	Drug product	Md Rahim	
	Immunogenicity Assay	Gunther Boekhoudt	Frederick Mills
	Facility	DS: Charles Yuan-Chia Kuo DP: Melissa Ray	Zhong Li
	Microbiology		Maxwell Van Tassell
	RBPM	Erica Keafer	
	ATL	Kelley Burridge	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761339 for Veopoz manufactured by Regeneron Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Veopoz 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:** Regeneron Pharmaceuticals, Inc., 81 Columbia Turnpike, Rensselaer, NY 12144; FEI 1000514603
- **Drug Product:**
  - Manufacture: (b) (4)
  - Labeling and Packaging: (b) (4)

b. Fill size and dosage form:

Veopoz is supplied as a 400 mg/2 mL (200 mg/mL) solution in a single-dose glass vial

c. Dating Period:

- **Drug Product:** 36 months at 2 to 8°C

- **Drug Substance:** (b) (4) months at ≤ (b) (4) °C, (b) (4)
- **Stability Option:**
  - 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.
  - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes, Veopoz is exempted from lot release per FR 95-29960.

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

PMC 4490-1: Re-evaluate the current anti-drug antibody (ADA) assay with the goal of improving sensitivity in the presence of the trough level of drug expected to be present during sampling. The assay validation assessments will include selectivity, system suitability specifications for negative and positive controls, effects of hemolysis, and a statistical evaluation of distribution and outlier exclusion for cutpoint samples.

Interim Report: 11/2024
Final Report Submission: 11/2025

PMC 4490-2: Re-evaluate clinical samples for anti-pozelimab antibodies (ADA) from clinical trial R3918-PLE-1878 using the assay described in PMC 4490-1. Evaluate neutralizing capacity of ADA using the assay described in PMC 4490-3 from clinical trial R3918-PLE-1878 in all confirmed ADA positive samples.

Final Report Submission: 08/2028

PMC 4490-3: Develop and validate a sensitive assay to evaluate the neutralizing capacity of anti-pozelimab antibodies (ADA) in confirmed ADA positive patient samples.

Interim Report: 08/2027
Final Report Submission: 08/2028

PMC 4490-4: Conduct a study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and safety of pozelimab in pediatric subjects with CHAPLE disease 1 to 5 years of age. The study will evaluate a minimum of 5 subjects, including at least 3 subjects less than 3 years of age. Samples will be analyzed for ADA using the assays described in PMC 4409-1 and 4409-3. Subjects will be (b) (4) for a minimum of 12 months.

Final Protocol Submission: 08/2024
Study Completion: 08/2030
Final Report Submission: (b) (4)

PMC 4490-5: Conduct a drug product (DP) shipping validation study using the first three commercial shipments of finished DP vials from the pack and label contract manufacturing organization (b) (4) to the third-party

distribution center ((b) (4)) under worst-case conditions. Include at minimum the following testing on DP samples prior to and after shipment: appearance, color, pH, particulate matter, non-reduced and reduced MCE, SE-UPLC, icIEF, potency by bioassay, protein content, volume in container and container closure integrity testing.

Final Report Submission: 09/2024

PMC 4490-6: Submit (b) (4) study data and full report.

Final Report Submission: 09/29/2023

4. Basis for Recommendation

a. Summary:

Veopoz is indicated for the treatment of adult and pediatric patients 1 year of age and older with CD55-deficient protein-losing enteropathy (PLE), also known as CHAPLE disease. Veopoz, a complement inhibitor, is an IgG4 isotype antibody produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cell suspension culture with an approximate molecular weight of 145 kDa. Veopoz is directed against the terminal complement protein C5 that inhibits terminal complement activation by blocking cleavage of C5 into C5a (anaphylatoxin) and C5b, thereby blocking the formation of the membrane-attack complex (C5b-C9, a structure-mediating cell lysis).

To fulfill its biological function, the antibody needs to bind C5, thereby preventing cell death by blocking conversion of C5 and formation of membrane attack complexes. Potency is measured through a luciferase reporter cell-based bioassay that measures the ability of Veopoz to neutralize CD20-mediated, C5-dependent cellular cytotoxicity in vitro. In the assay, complement cascade C5 activation and conversion of C5 to C5a and C5b is induced by an antibody that binds CD20, a receptor on the surface of Raji cells. Veopoz prevents cell death by binding C5. The assay measures the extent of cell death using the alanyl-alanylphenylalanyl-aminoluciferin luminogenic peptide substrate to detect the presence of proteases released upon cell lysis. The concentration-dependent luminescent signal measures dose-dependent decrease in cell death. Relative potency is calculated as the ratio between the EC50 values of the reference standard and the tested samples, multiplied by 100.

The drug substance (DS) is manufactured at (b) (4) L scale in CHO cell culture using a (b) (4). (b) (4)

(b) (4)

. The drug product (DP) manufacturing process includes (b) (4)

.

Overall, the drug substance process is under adequate microbial control.

(b) (4)

Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

All sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes. (b) (4)

. Container closure integrity testing using a validated method is included in the stability program.

The overall Veopoz control strategy incorporates control 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 Veopoz 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 product quality, facility, microbiology and sterility assurance perspectives.

The potential impact of the drug product shipping and handling process on product quality has not been directly evaluated. Evaluating the shipping impact is important because Veopoz drug product is shipped (b) (4).
The sponsor plans to perform a real-time shipping validation study using the

first three commercial drug product batches. The confirmatory shipping study in PMC number 5 includes tests to compare critical quality attributes before and after shipping.

The first of three (b) (4) studies supports the ability of the drug product manufacturing facility to perform (b) (4). The study data and full reports for two additional (b) (4) in PMC number 6 serve to demonstrate a consistent (b) (4) .

Two PMCs, numbers 1 and 3, are for improving the sensitivity of the ADA assay in the presence of drug and developing a neutralizing antibody assay. The immunogenicity assays will be used to assess clinical samples from study R3918-PLE-1878 per PMC number 2 and the new clinical study recommended in PMC number 4.

b. Subdiscipline Recommendation:

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

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 Veopoz (i.e., there is no specific test method described in regulation for Veopoz that establishes an official standard of potency). We next considered whether potency is a factor for Veopoz 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 Veopoz for purposes of § 610.61(r) because lot variability is not a concern for Veopoz as Veopoz'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. Qualification of New Working Cell Banks
2. Concurrent Lifetime for Chromatography Resins
3. (b) (4)
4. Stability/Requalification for Current Reference Standards
5. Annual Stability Protocol with Shelf-Life Extension

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocol approved:
1. Annual Stability Protocol with Shelf-Life Extension

ii. Residual risk:
1. Shipping: Under PMC, conduct a DP shipping validation study on first three commercial shipments that includes product quality testing before and after shipment.
2. (b) (4): Under PMC, submit (b) (4) study data and full report.
3. Immunogenicity: Two assay PMCs
   a. Re-evaluate the current ADA assay with the goal of improving sensitivity in the presence of the trough level of drug expected to be present during sampling.
   b. Develop and validate a sensitive assay to evaluate the neutralizing capacity of ADA in confirmed ADA positive patient samples.

iii. Future inspection points to consider: CDER/OPMA/DBM recommends the corrective actions outlined by the firm be reviewed and verified during a post-approval inspection. Refer to the DP facility review.

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.

Kelley Burridge

Digitally signed by Kelley Burridge
Date: 8/15/2023 12:50:03PM
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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/

KELLEY A BURRIDGE
08/15/2023 12:57:22 PM

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	August 15, 2023
Assessor:	Liming Lu, PharmD, RPh. Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Rahim Md, PhD. Product Quality Assessor OBP/Division of Biotechnology Review and Research 4
Application:	BLA 761339
Applicant:	Regeneron Pharmaceuticals, Inc.
Submission Date:	December 20, 2022
Product:	Veopoz (pozelimab-bbfg)
Dosage form(s):	Injection
Strength and Container-Closure:	400 mg/2 mL (200 mg/mL) single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for the approval of pozelimab-bbfg injection for the treatment of adults and pediatric patients 1 year of age and older with CD55-Deficient Protein Losing Enteropathy (PLE) also known as CHAPLE disease.
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling are **acceptable** from an OBP 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 August 15, 2023), medication guide (submitted on August 15, 2023), container labels and carton labeling (submitted on July 6, 2023) were assessed and found to be acceptable (see Appendix C) from an OBP Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on December 20, 2022)
  \\CDSESUB1\EVSPROD\bla761339\0002\m1\us\114-labeling\draft\labeling\proposed-uspi.docx
- Medication Guide (submitted on December 20, 2022)
  \\CDSESUB1\EVSPROD\bla761339\0002\m1\us\114-labeling\draft\labeling\proposed-mg.docx
- Container Labels (submitted on December 20, 2022)
  \\CDSESUB1\EVSPROD\bla761339\0002\m1\us\114-labeling\draft\carton-and-container\contain.pdf

- Carton Labeling (submitted on December 20, 2022)
  \\CDSESUB1\EVSPROD\bla761339\0002\m1\us\114-labeling\draft\carton-and-container\carton.pdf

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] 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
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

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
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

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

[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
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)	✓ Yes ☐ No ☐ N/A

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

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
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*	✓ Yes ☐ No ☐ N/A

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
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)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: See comments for carton labeling.

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

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

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

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *The applicant has confirmed that no text is present on the ferrule and cap overseal of the vials.*

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. *The applicant has confirmed that the vial remains uncovered for the full length to allow for visual inspection when the label is affixed to the vial.*

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

Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: *The applicant has revised the ROA statement from* (b) (4) *to "For Intravenous Infusion after Dilution or Subcutaneous Use" as recommended by DMEPA.*

***NDC numbers* (container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: See comments for carton labeling.

Package type term (container label)	**Acceptable**
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) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the statement "Discard unused portion." to appear after the package type term "Single-Dose Vial" if space permits.

The applicant has revised as requested.

No Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

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

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

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

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
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)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure the linear bar code are surrounded by enough white space to facilitate proper scanning.

The applicant has confirmed that the linear bar code on container label is surrounded by enough white space to facilitate proper scanning.

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

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A

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 Guidance for Industry* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Add net quantity "2mL" to the container label to appear less prominent and away from the strength.

The applicant has revised the net quantity statement to read "2 mL Single-Dose Vial" as requested.

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: See comments for carton labeling.

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: See comments for carton labeling.

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

Comment/Recommendation: See comments for carton labeling.

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

Package[6] 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
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

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
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

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

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

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

[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.

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

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

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
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*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: *The applicant has revised the storage statement to read: "Store Veopoz vial refrigerated at 2°C to 8°C (36°F to 46 °F) in the original carton to protect from light." as requested by DMEPA to be consistent with the PI.*

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

Comment/Recommendation: *The applicant has revised the handling statement to read: "Protect from freezing and shaking." as recommended by DMEPA. The applicant also removed the statement* (b) (4) *"*

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

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
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: *The applicant has revised the ROA statement from* (b) (4) *to "For Intravenous Infusion after Dilution or Subcutaneous Use" as recommended by DMEPA.*

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

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, arginine hydrochloride, histidine, L-histidine hydrochloride monohydrate. Revise the ingredient information to the compendial names and definitions to read as "…arginine hydrochloride (21 mg), histidine (1.15 mg), L-histidine hydrochloride monohydrate (2.65 mg), polysorbate 80 (1.5 mg), sucrose (20 mg), and Water for Injection, USP." We revised the amount expression of L-histidine monohydrate to be consistent with the date provided in section 3.2.P.1. Please confirm.

The applicant has confirmed, and revised inactive ingredients list as requested.

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

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

Comment/Recommendation: 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 applicant has revised as requested.

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 pozelimab products (i.e., there is no specific test method described in regulation for pozelimab 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 Veopoz/pozelimab-bbfg 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
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

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

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 *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)	✓ Yes ☐ No ☐ N/A

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

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

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 *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: recommend add statement for preparation instructions read as "Must be further diluted before intravenous infusion." to the carton labeling.

The applicant has revised to include the statement "Must dilute before intravenous infusion." to PDP.
The applicant has also added the following statement to the back panel and revised to be consistent with the prescribing information as recommended by DMEPA:

*"**Storage of Diluted Intravenous Solution (After Dilution):*** *Administer the diluted VEOPOZ solution immediately after preparation. If not used immediately, store at room temperature up to 25°C (77°F) for no more than 8 hours from the time of preparation to the end of the infusion or at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to the end of infusion. Protect diluted solution from freezing."* *The above revision is acceptable per OBP labeling perspective.*

Package type term (package labeling)	**Acceptable**
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) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

No Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: *The applicant has relocated the statement "Do not use vial if seal is broken or missing." to the side panel as requested by DMEP* (b) (4)

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

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

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

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

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
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 Guidance for Industry* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: To ensure consistency with the terminology in the Prescribing Information (PI), we recommend revising the recommended dosage statement to read, "Dosage: see Prescribing Information."

The applicant has revised as requested.

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
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	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised to the appropriate dosage form "injection" as solutions administered by injection are officially titled injections per USP Chapter <1151> Pharmaceutical Dosage Forms.

The applicant has revised as requested.

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

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
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*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**

Regulation: 21 CFR 201.57(c)(3)(iv)] *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."*	✓ Yes ☐ No ☐ N/A
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	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised to include the room temperature range according to the definition of USP controlled room temperature.

We revised this statement to verbatim statement for parenterals per 21 CFR 201.57(c)(3)(iv).

We removed the redundant information [(b) (4)]" as it has been stated in the previous paragraph.

We revised to include an appropriate discard statement with the duration for which the diluted product can be safely used under these storage conditions per Draft Guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance for Industry* (January 2023).

Detailed storage conditions for diluted products should be described in the DOSAGE AND ADMINISTRATION section rather than [(b) (4)]. Therefore, we relocated this statement "Administer the diluted VEOPOZ solution immediately after preparation" to the DOSAGE AND ADMINISTRATION and deleted it in [(b) (4)].

The applicant has revised as requested.

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
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*	✓ Yes ☐ No ☐ N/A

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)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e), the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, arginine hydrochloride, histidine, L-histidine hydrochloride monohydrate.

We revised the quantity of L-histidine hydrochloride monohydrate to be consistent with the date provided in section 3.2.P.1.

The applicant has revised as requested. The applicant also revised cell line statement to read "…in Chinese Hamster Ovary (CHO) cell suspension culture", OBP labeling considers this is acceptable after confirmed with the PQ assessor.

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
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

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised to read "Do not freeze. Do not shake." for clarity.

DMEPA has suggested edits (including statement of "Discard unused portion" at the end) for completeness of handling instruction for single-dose vial.

The applicant has revised as requested.

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
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)	✓ Yes ☐ No ☐ N/A

Medication Guide Evaluation

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

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

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

Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients), the established names for inactive ingredients in your products are revised according to the USP/NF monographs titles "arginine hydrochloride, histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose, and Water for Injection." *The applicant has revised as requested.*

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
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)	✓ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on August 15, 2023)
  \\CDSESUB1\EVSPROD\bla761339\0050\m1\us\114-labeling\draft\labeling\proposed-uspi.docx
- Medication Guide (submitted on August 15, 2023)
  \\CDSESUB1\EVSPROD\bla761339\0050\m1\us\114-labeling\draft\labeling\proposed-mg.docx
- Container Labels (submitted on July 6, 2023)
  \\CDSESUB1\EVSPROD\bla761339\0038\m1\us\114-labeling\draft\carton-and-container\contain-400mg-2ml.pdf

- Carton Labeling (submitted on July 6, 2023)
  \\CDSESUB1\EVSPROD\bla761339\0038\m1\us\114-labeling\draft\carton-and-container\carton-400mg-2ml.pdf

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Liming Lu

Digitally signed by Liming Lu
Date: 8/15/2023 03:00:23PM
GUID: 633d82d0001fb9cd8535e78c71271f3d

Md Al Rahim

Digitally signed by Md Al Rahim
Date: 8/15/2023 06:46:41PM
GUID: 62b48896000601d292e48bc49e70c983