CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761286Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: 06/12/2023

1. Application/Product Information

BLA number	761286
Submission Type	Original Submission
Regulatory Pathway	351(a)
Associated IND/BLA	IND 132407
Review Designation	Priority Review
Applicant	UCB, Inc
Indication	Treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name** RYSTIGGO
	Non-proprietary Name/Code Name rozanolixizumab-noli
	OBP Naming MAB Humanized (IgG4) ANTI P55899 (FCGRN_HUMAN) [UCB7655]
Drug Product Description	Rozanolixizumab (UCB7665) is a recombinant, humanized anti-neonatal Fc receptor (FcRn) immunoglobulin G4 monoclonal antibody with amino acid substitution at serine (b) (4) to proline (IgG4P) to prevent Fab arm exchange characteristic of endogenous human IgG4. Rozanolixizumab drug product is supplied as a sterile, preservative-free, colorless to pale brownish yellow, clear to slightly opalescent solution for subcutaneous injection. Each vial contains 2mL of rozanolixizumab at a nominal formulation of 140mg/mL in (b) (4) L-histidine hydrochloride monohydrate, (b) (4) mM (b) (4) proline, (b) (4) % (w/v) polysorbate 80, at pH 5.6.
Dosage Form	Injection
Strength	280 mg/2 mL
Route of Administration	subcutaneous infusion
Primary Container Closure System	6mL (b) (4) Type (b) (4) glass vials, closed with a (b) (4) stopper and sealed with an aluminum crimp seal with plastic flip off cap.
Device Information	N/A

Co-packaged Product Information	N/A		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance	João Pedras-Vasconcelos, Ph.D.	Hailin (Sheena) Wang, Ph.D.
	Drug product	Thomas Biel, Ph.D.	
	Immunogenicity Assay	João Pedras-Vasconcelos, Ph.D.	
	Facility	Hamet Touré, PharmD MPH	Madushini Dharmasena, Ph.D.
	Microbiology		
	OBP labeling	Scott Dallas, RPh	
	RBPM	Melinda Bauerlien	
	ATL	Hailin (Sheena) Wang, Ph.D.	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761286 for RYSTIGGO manufactured by (b) (4) UCB, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of RYSTIGGO 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:**

(b) (4)

- **Drug Product:**

(b) (4)

UCB Pharma SA (Drug product secondary packaging and labeling)

Chemin du Foriest
1420 Braine-l'Alleud, Belgium
FEI: 372274485

b. Fill size and dosage form: RYSTIGGO is provided as 280 mg/2 mL in a single-dose vial

c. Dating Period:
   - Drug Substance: (b) (4) months at (b) (4) °C
   - Drug Product: 24 months at 2°C - 8°C
   - For packaged products: Not packaged
   - Stability Option:
     - We have approved the post approval stability protocol(s) in the license application for drug substance and drug product.

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

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable
   CMC PMC#1 (4427-3): To develop a two-tiered reference standard system consisting of primary and working reference standards to support the rozanolixizumab-noli product lifecycle. The primary and working reference standard will be created from representative DS batches which have passed all release specifications. The first new reference standards will be qualified against the current reference standard (b) (4) according to a predefined protocol. The results for qualification of new primary and working/secondary reference standards will be submitted in a Prior Approval Supplement. Alternatively, protocols for qualification and requalification of future primary and working/secondary reference standards may be submitted as a Prior Approval Supplement, which may facilitate a reduced reporting category for implementation of new reference standards.

   Final reference standard qualification report submission date: 02/29/2024

   CMC PMC#2 (4427-4): To perform a shipping validation study under real time shipping conditions (i.e., temperature, mode of transport, shipping duration, and shipping containers and packing representative of the

minimum and maximum load) using rozanolixizumab-noli finished product in the final commercial container closure and packaging systems to verify the impact of shipping on the product quality of rozanolixizumab-noli finished product. The shipping validation data will be submitted in accordance with 21 CFR 601.12.

Final shipping validation report submission date: 04/30/2024, 07/31/2024

4. Basis for Recommendation

a. Summary:

Rozanolixizumab (UCB7665) is a recombinant, humanized anti-neonatal Fc receptor (FcRn) IgG4P monoclonal antibody with amino acid substitution at serine (b) (4) to proline to prevent Fab arm exchange characteristic of endogenous human IgG4. Rozanolixizumab decreases serum IgG concentration by inhibiting the binding of IgG to neonatal Fc receptor (FcRn) which leads to enhanced catabolism of IgGs. Thereby, rozanolixizumab decreases the concentration of pathogenic IgG autoantibodies associated with gMG.

(b) (4)

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

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

The overall rozanolixizumab-noli/RYSTIGGO control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing

process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for rozanolixizumab-noli/RYSTIGGO as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) and (b) (4), proposed for rozanolixizumab DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. The BLA is recommended for approval from a product quality, facility, microbiology and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Adequate**
Microbiology	**-**	**Adequate**

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for rozanolixizumab-noli/RYSTIGGO (i.e., there is no specific test method described in regulation for rozanolixizumab-noli/ RYSTIGGO that establishes an official standard of potency). We next considered whether potency is a factor for rozanolixizumab-noli/RYSTIGGO 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 rozanolixizumab-noli/RYSTIGGO for purposes of § 610.61(r) because lot variability is not a concern rozanolixizumab-noli/ RYSTIGGO as rozanolixizumab-noli/RYSTIGGO'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

Comments:

b. Drug Substance:

i. Protocols approved:
   1. (b) (4)
   2. (b) (4)
   3. Qualification and requalification/stability testing of New Working Cell Banks: 3.2.R
   4. Post-approval Stability Protocol: 3.2.S.7.2 Post-Approval 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 Stability Protocol: 3.2.P.8.2 Drug product post-approval 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/

HAILIN WANG
06/23/2023 09:44:09 AM

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	June 23, 2023
Assessor:	Scott Dallas, RPh Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Thomas Biel, PhD Product Quality Assessor OBP/Division of Biotechnology Review and Research 3
Application:	BLA 761286
Applicant:	UCB, Inc.
Submission Date:	October 24, 2022
Product:	RYSTIGGO (rozanolixizumab-noli)
Dosage form(s):	Injection
Strength and Container-Closure:	280 mg/2 mL (140 mg/mL) in a single-dose vial
Purpose of assessment:	The applicant submitted a biologics license application for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.
Recommendations:	The prescribing information, container label, 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

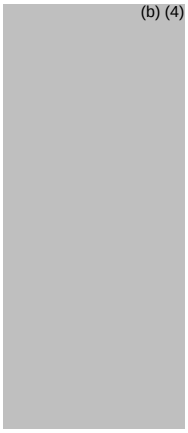
The prescribing information with accepted OBP labeling revisions under review as of June 23, 2023, and the container label, and carton labeling submitted on April 14, 2023 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective. The prescribing

information incorporated all OBP edits and revisions. However, other review disciplines may still require edits and revisions. Thus, final prescribing information was not attached to this labeling assessment.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on October 24, 2022)
  \\CDSESUB1\EVSPROD\bla761286\0001\m1\us\114-labeling\draft\labeling\cir-202209-sub.docx

- Container Label (submitted on October 24, 2022)
  (b) (4)
  

- Carton Labeling (submitted on October 24, 2022)

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

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

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
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

Comment/Recommendation:
To applicant: FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment

[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."

standards, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820. Therefore, the applicant written on Form FDA 356h is considered the following terms: license applicant, license manufacturer, or manufacturer. Revised the qualifying statement "(b) (4)" to read "Mfd. by". Applicant's Response: The "(b) (4)" statement has been revised to read "Mfd. by". OBP Labeling: The applicant's revision is acceptable.

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

Comment/Recommendation:

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Please ensure the product strength is expressed as total quantity per total volume followed by the concentration per milliliter (mL) in parenthesis. For example:

280 mg/2 mL (140 mg/mL)

Or

280 mg/2 mL
(140 mg/mL)

Applicant's Response: The applicant revised the expression of strength to appear as:

(b) (4)

OBP Labeling: The applicant's revision is acceptable.

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ 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
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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 require a Medication Guide.

No Package for container	**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**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

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

Applicant's Response: The applicant stated the lot number is printed on the side of the aluminum crimp seal (ferrule) of the vials. (b) (4) printed lot number on the aluminum crimp seal (ferrule). There is no text printed on the flip-off cap.

(b) (4)

OBP Labeling: The applicant's response is acceptable.

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

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

Applicant's Response: The applicant confirmed that sufficient area of the container remains uncovered to allow for visual inspection when the label is affixed to the vial. After application of the label on the vial, free space between both ends of the positioned label (2.0-2.5mm) remains available for visual inspection of the product.

(b) (4)

OBP Labeling: The applicant's response is acceptable.

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:

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

Comment/Recommendation:

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

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:

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

Comment/Recommendation: There are no misleading statements.

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

Comment/Recommendation:

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

Comment/Recommendation:

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:

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 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

	☒ N/A

Comment/Recommendation:

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ 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	☐ 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: The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required.

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:

To applicant: Revise the storage and handling statements to read: Store refrigerated at 36°F to 46°F (2°C to 8°C). Protect from light. Do Not Freeze or Shake.

Applicant's Response: The applicant revised the storage and handling statements to incorporate the requested additions as shown in highlighted text:
Store refrigerated at 36°F to 46°F (2°C to 8°C). Protect from light. Do Not Freeze or Shake.

OBP Labeling: The applicant's revision is acceptable.
The product quality team confirmed agitation studies were not conducted. Thus, the applicant was requested to include a "do not shake" statement.

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

Comment/Recommendation:

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

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
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[7])	✓ Yes

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

[7] 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

	☐ No ☐ N/A

Comment/Recommendation:
To applicant: FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment standards, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820. Therefore, the applicant written on Form FDA 356h is considered the following terms: license applicant, license manufacturer, or manufacturer. Revised the qualifying statement "(b) (4)" to read "Manufactured by".

Applicant's Response: The applicant revised the "(b) (4)" statement to read "Manufactured by".

OBP Labeling: The applicant's revision is acceptable.

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**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

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."

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

Comment/Recommendation: Displays a "no preservative" statement.

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
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Please ensure the product strength is expressed as total quantity per total volume followed by the concentration per milliliter (mL) in parenthesis. For example:

280 mg/2 mL (140 mg/mL)

Or

280 mg/2 mL

(140 mg/mL)

Applicant's Response: The applicant revised the expression of strength to appear as:

(b) (4)

OBP Labeling: The applicant's revision is acceptable.

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:
To applicant: Revise the Storage statement to read:

"Store vial refrigerated at 36° to 46°F (2° to 8°C) in the original carton to protect from light. Do not freeze. Do not shake.

If needed, vial may be stored at room temperature up to 77°F (25°C) for up to 30 days in the original carton to protect from light. Once vial has been stored at room temperature, do not place back in the refrigerator. Discard vial if not used within 30 days. Write the discard date in the space provided."

Revise the statement "(b) (4)" to read similar to "Discard date (30 days after removal from refrigerator):"

Applicant's Response: The applicant revised the storage and discard statement as requested above.

OBP Labeling: The applicant's revisions are acceptable.

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 handling instruction "Do not Shake" needed to be added to the labeling. The statement was added to the Storage temperature/requirements (package labeling) comment above.

Applicant's Response: The applicant revised the handling statement as requested.

OBP Labeling: The applicant's revision is acceptable.

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

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

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:

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 applicant: Revise the ingredients statement that reads "Each vial contains …" to read Each 2 mL vial contains 280 mg of rozanolixizumab-xxxx, histidine (2.1 mg), L-histidine hydrochloride monohydrate (9.74 mg), proline (57.56 mg), polysorbate 80 (0.6 mg), and Water for Injection, USP. The ingredients (b)(4) histidine and (b)(4) proline were revised to display their official established name, refer to 21 CFR 299.4.

Applicant's Response: The applicant revised the ingredients statement as requested.

OBP Labeling: The applicant's revisions are acceptable.

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 rozanolixizumab products (i.e., there is no specific test method described in regulation for rozanolixizumab 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 this product 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.

To applicant: 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.

Applicant's Response: The applicant removed the statement "No U.S. standard of potency" from the carton labeling as requested.

OBP Labeling: The applicant's revision is acceptable.

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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ 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: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

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

Comment/Recommendation:
The package type term is displayed on the principal display panel.

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:

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:

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

Comment/Recommendation:

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

Comment/Recommendation:

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	✓ Yes

	☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The label displays the statement "One sngle-dose vial" on two panels of the carton.

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

Comment/Recommendation:
To applicant: We recommend revising the statement "(b) (4) " to read "Recommended Dosage: See prescribing information". Applicant's Response: The applicant revised the dosage statement as requested. OBP Labeling: The applicant's revision is acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:

Other (package labeling)	**Acceptable**
	☐ Yes ☐ No

	☒ N/A

Comment/Recommendation:

Prescribing Information Evaluation

PRESCRIBING INFORMATION

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

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	✓ 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
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

Comment/Recommendation:

To applicant: Revised to include the strength per mL, because the product contains more than 1 mL. To read "Injection: 280 mg/2 mL (140 mg/mL) in a single-dose vial"

Applicant's Response: The applicant revised the statement as requested.

OBP Labeling: The aaplicant's revision is acceptable.

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:
To applicant: Recommend using the phrase "one-time use" to indicate how the vial is supposed to be used and not to be confused with [redacted (b) (4)].
To read: "[redacted (b) (4)]." and "RYSTIGGO vial is for one-time use only."

To applicant: A "Do not shake" statement was added, because no data was submitted to support shaking of the drug product.

To applicant: Insertion the verbatim statement per 21 CFR 201.57(c)(3)(iv).
To read: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

To applicant: Propose text to inform HCP's that the dose should be administered within 4 hours of puncturing the vial (removing the contents) or be discarded. Lack of microbial data does not support a longer time period. In addition, propose text to inform HCP's the drug product should only remain in the infusion set for up to 2 hours or be discarded. Alternatively, include text to administer immediately after preparation.

Applicant's Response: The applicant revised the statements as requested and proposed to include the statement:
- Infuse RYSTIGGO within 4 hours of puncturing the vial. RYSTIGGO should be administered immediately after priming the infusion set.

OBP Labeling: The applicant's revisions are acceptable.

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

Comment/Recommendation:
To applicant: Revised the information to appear in a more customary format.
To read: "Injection: 280 mg/2 mL (140 mg/mL) a clear to slightly opalescent, colorless to pale brownish yellow solution in a single-dose vial.

Applicant's response: The applicant revised the statement as requested.

OBP Labeling: The applicant's revision is acceptable.

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 applicant: The first paragraph was revised to be more concise, and the drug substance molecular weight, 148 kDa, was included. Please confirm.

To applicant: The Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) requires the use of the established names for drugs (i.e., drug products and ingredients) as recognized by USP as the official compendium. Thus, the inactive ingredient names (b) (4) histidine and (b) (4) proline, were revised to present their official compendial names, histidine and proline.

Applicant's response: The applicant revised the drug substance paragraph, confirmed the molecular weight, and included the official compendial names in the ingredient statement as requested.

OBP Labeling: The applicant's revisions are acceptable.

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

Comment/Recommendation:

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:
To applicant: A "Do not shake" statement was added, because no data was submitted to support shaking of the drug product.

To applicant: If the product is under the control of a healthcare provider (HCP) then the HCP should be requested to calculate and write when the product should be discarded. Thus, the discard messaging was revised to reflect the product remains in control of a HCP.
The sentence was revised to read: "[redacted (b) (4)]."

To applicant: This statement was deleted because it does not convey any unusual storage or handling condition, and the message is conveyed in the paragraph above.
The deleted sentence read: "[redacted (b) (4)]."

Applicant's response: The applicant included the "Do not Shake" statement, revised the discard statement, and deleted the "(b) (4)" statement as requested. OBP Labeling: The applicant's revisions are acceptable.

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

Comment/Recommendation:
To applicant: FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment standards, including, but not limited to, 21 CFR Parts 210, 211, 600 through 680, and 820. Therefore, the applicant written on Form FDA 356h is considered the following terms: license applicant, license manufacturer, or manufacturer. Revised the qualifying statement "(b) (4)" to read "Manufactured by".
Applicant's response: The applicant revised the manufacture qualifying statement as requested.
OBP Labeling: The applicant's revision is acceptable.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information under review as of June 23, 2023 **** The prescribing information incorporated all OBP edits and revisions. However, other review disciplines may still require edits and revisions. Thus, final prescribing information was not attached to this labeling assessment. **********

- Container Label (submitted on April 14, 2023)

(b) (4)

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

Scott Dallas

Digitally signed by Scott Dallas
Date: 6/23/2023 05:37:27PM
GUID: 508da712000294048aa136a18a6af06a

Sheena Hailin Wang

Digitally signed by Sheena Hailin Wang
Date: 6/23/2023 05:59:57PM
GUID: 5203a2110001f7235a14cac1b60d05c4