CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761279Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: 10/26/2023

1. Application/Product Information

BLA number	761279
Submission Type	Resubmission
Regulatory Pathway	NME 351(a)
Associated IND/BLA	IND 125444
Review Designation	Standard Review
Applicant	Eli Lilly and Company
Indication	Ulcerative Colitis
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Omvoh
	Non-proprietary Name/Code Name: mirikizumab-mrkz
	OBP Naming: MAB HUMANIZED (IGG4) ANTI Q9NPF7 (IL23A_HUMAN) [LY3074828]
Drug Product Description	Omvoh (mirikizumab-mrkz) is a recombinant humanized IgG4 monoclonal antibody produced in a Chinese Hamster Ovary (CHO) cell line. The antibody binds with high affinity and specificity to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor. Omvoh (mirikizumab-mrkz) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow to slightly brown solution containing either 20 mg/mL mirikizumab-mrkz in single-dose vials, or 100 mg/mL mirikizumab-mrkz in single-dose prefilled pens.

Dosage Form	Solution, injection		
Strength	• 300 mg/15 mL (20 mg/mL) solution in a single-dose vial • 100 mg/1 mL solution in a single-dose prefilled pen		
Route of Administration	• Intravenous Infusion (vials) • Subcutaneous Injection (prefilled pens)		
Primary Container Closure System	• Vials: 20 mL clear, (b) (4) glass tubing vial with a (b) (4) elastomer closure (stopper) (b) (4) The closure is secured in place with a two piece flip-top aluminum seal. • (b) (4) 1 mL-long, clear, (b) (4) glass syringe barrel with small round flange, 27G special thin wall x 1/2" staked needle, and closed with a (b) (4) elastomeric plunger and rigid needle shield.		
Device Information	The prefilled pens ((b) (4) are 1 mL needle-based injection system (NIS) used to deliver the drug product. The components of prefilled pens do not contact the drug product solution. Device information is assessed by CDRH and the review will be documented separately.		
Co-packaged Product Information	Not applicable		
	Discipline	Primary	Secondary
	Drug substance	Mercy Oyugi	Nailing Zhang
	Drug product	Mercy Oyugi	Nailing Zhang
	Immunogenicity Assay	Marco Cardone	Daniela Verthelyi

OPQ Review Team	Facility	Hamet Touré (DS) / Maria Gutierrez-Hoffman (DP)	Michael Shanks
	Microbiology	Hamet Touré (DS) / Maria Gutierrez-Hoffman (DP)	Virginia Carroll
	RBPM	Shazma Aftab	N/A
	ATL	Nailing Zhang	
	Review Chief	Maria-Teresa Gutierrez-Lugo	
OPQ Issued Consults	None. A CDRH consult was requested by OND and the review will be documented separately.		

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761279 for Omvoh (mirikizumab-mrkz) manufactured by Eli Lilly and Company. The data submitted in this application are adequate to support the conclusion that the manufacture of Omvoh (mirikizumab-mrkz) 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: Eli Lilly Kinsale Limited, Dunderrow, Kinsale, County Cork, Ireland (FEI: 3002806888)
      - Drug Product: Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, USA (FEI: 1819470)
        (This is also the drug product packaging, labeling, and device assembly site.)

   b. Fill size and dosage form:
      - 300 mg/15 mL (20 mg/mL) solution in a single-dose vial
      - 100 mg/1 mL solution in a single-dose prefilled pen

c. Dating Period:

- **Drug Product:** 24 months at 2°C - 8°C, protected from light
- **Drug Substance:** (b) (4) months at (b) (4) °C

d. Exempt from lot release:

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

4. Basis for Recommendation

a. Summary:

Omvoh (mirikizumab-mrkz) is indicated for the treatment of moderately to severely active ulcerative colitis in adults. It is a humanized IgG4 monoclonal antibody that binds with high affinity and specificity to the p19 subunit of human IL-23 cytokine to inhibit its interaction with the IL-23 receptor. The mirikizumab/IL-23 complex does not interfere with IL-12 signaling since the p19 subunit where mirikizumab binds is specific to IL-23, even though IL-23 shares its p40 subunit with IL-12.

Potency of Omvoh (mirikizumab-mrkz) is controlled using a cell-based reporter assay that measures its ability to inhibit IL-23 induced luciferase reporter activity (b) (4) . Potency results are reported as percentage relative to a qualified reference material.

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

No approvability issues were identified from a sterility assurance or microbiology product quality perspective. All facilities used for the manufacture and quality control testing were found acceptable for the

proposed operations. In lieu of on-site pre-licensing inspections (PLI) for the DS manufacturing facility, Eli Lilly Kinsale Limited (Kinsale, County Cork, Ireland), a review of requested manufacturing site records under Section 704(a)(4) of the Federal Food Drug and Cosmetic Act was conducted and found satisfactory. An on-site PLI for the DP manufacturing facility, Eli Lilly and Company (Indianapolis, Indiana, USA), was conducted in June 2023 and found satisfactory.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of Omvoh (mirikizumab-mrkz) at concentrations presented in the patient samples. The neutralizing anti-drug antibody (NADA) assay used a target interference assay format that measures the reduction in target binding due to blocking the drug's complementarity-determining region (CDR) by ADA. This strategy relies on pre-binding of the drug to IL-23 and may not accurately test samples for neutralizing activity. However, the immunogenicity assays assessment team concluded that although the assay is not considered a suitable neutralization assay, the development of a new neutralizing assay will not be requested as a new neutralizing assay will not provide additional information, because a high correlation between titers and loss of product exposure and efficacy was observed in 1/3 of the subjects with titers >160.

The overall Omvoh (mirikizumab-mrkz) 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 Omvoh (mirikizumab-mrkz) 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 the 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 Omvoh (i.e., there is no specific test method described in regulation for Omvoh that establishes an official standard of potency). We next considered whether potency is a factor for Omvoh 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 Omvoh for purposes of § 610.61(r) because lot variability is not a concern for Omvoh as Omvoh'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: The applicant states that the BLA does not include an Established Conditions proposal as described in ICH Q12 and post-approval changes will follow the regulations and recommendations in the guidance.

b. Drug Substance:

i. Protocols approved:

(b) (4)

(b) (4)

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:

- Post-approval stability protocols for drug product
- (b) (4)

ii. Residual risk: None

iii. Future inspection points to consider: None

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

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

/s/

NAILING ZHANG
10/26/2023 10:11:59 AM

MARIA T GUTIERREZ LUGO
10/26/2023 10:27:30 AM

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	October 25, 2023
Assessor:	Jennifer Kim, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Mercy Oyugi, PhD Product Quality Assessor OBP/Division of Biotechnology Review and Research 3
Application:	BLA 761279
Applicant:	Eli Lilly and Company
Submission Date:	March 30, 2022 and May 24, 2023
Product:	Omvoh (mirikizumab-mrkz)
Dosage form(s):	Injection
Strength and Container-Closure:	300 mg/15 mL (20 mg/mL) in single-dose vial 100 mg/mL in a single-dose prefilled pen
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of mirikizumab-mrkz for the treatment of adult patients with moderately to severely active ulcerative colitis.
Recommendations:	The prescribing information, medication guide, instructions for use, 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 October 13, 2023, medication guide, instructions for use, container labels, and carton labeling submitted on October 3, 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 May 24, 2023)
  \\CDSESUB1\EVSPROD\bla761279\0059\m1\us\proposed-uspi-clean.docx
- Medication Guide (submitted on May 24, 2023)
  \\CDSESUB1\EVSPROD\bla761279\0059\m1\us\proposed-medguide-clean.docx
- Instructions for Use (submitted on May 24, 2023)
  \\CDSESUB1\EVSPROD\bla761279\0062\m1\us\mirikizumab-ai-ifu-new-draft-clean.docx
- Container Labels (submitted on May 24, 2023)

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

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and 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
Comment/Recommendation: *The licensed manufacturer is the only manufacturer information and the qualifying phrase "Manufactured by" can be omitted.*	

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, 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

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: 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

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: 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

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Partial label limited space considerations. See carton.	

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 confirms that there is no visible text 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 confirms that sufficient area of the vial, prefilled syringe and prefilled pen remains uncovered for both its full height and circumference to allow for visual inspection when the label is affixed to the container.*	

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: We recommend revising the route of administration from [redacted] (b) (4) to "For Intravenous Infusion After Dilution" for added clarity. We also recommend removing the statement, "[redacted] (b) (4) as this statement is no longer needed. *The applicant revised as requested.*	

***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: 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

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

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 *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

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: 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

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: Partial label limited space considerations for pen label. See carton.	

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: Partial label limited space considerations for pen label. See carton.	

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: Partial label limited space considerations for pen label. See carton.	

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

[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.

	☐ 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
Comment/Recommendation: *The licensed manufacturer is the only manufacturer information and the qualifying phrase "Manufactured by" may be omitted.*	

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

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: 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

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

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

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: We recommend revising the route of administration from (b) (4) to "For Intravenous Infusion After Dilution" for added clarity. We also recommend removing the statement, "(b) (4) as this statement is no longer needed. *The applicant revised as requested.*	

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

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: *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 mirikizumab products (i.e., there is no specific test method described in regulation for mirikizumab 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 Omvoh 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: 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

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* *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

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: 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

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: As currently presented the discard statement "Discard Unused Portion" is on the side panel. Including the discard statement in close proximity to the package type helps to increase the intended technique of use. In this instance that is using the vial to achieve a single dose and discarding product remaining in the vial thereafter. Relocate the discard statement "Discard Unused Portion" to the PDP. For example, "Single-dose vial – Discard Unused Portion." *The applicant revised as requested.*	

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

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: 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

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

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

Other (package labeling)	**Acceptable**
	☐ 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

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

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

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

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: *The licensed manufacturer is the only manufacturer information and the qualifying phrase "Manufactured by" may be omitted.*	

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

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
Comment/Recommendation: *The licensed manufacturer is the only manufacturer information and the qualifying phrase "Manufactured by" may be omitted.*	

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	✓ Yes ☐ No ☐ N/A

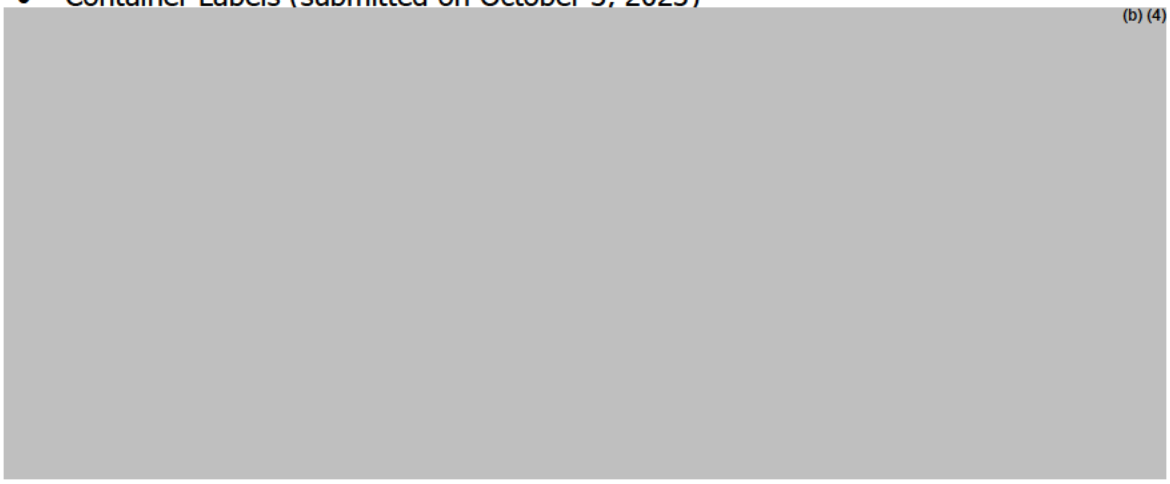
INSTRUCTIONS FOR USE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	☐ Yes ☐ No ☒ N/A

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). *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 October 13, 2023)
  \\CDSESUB1\EVSPROD\bla761279\0071\m1\us\proposed-uspi-clean.docx
- Medication Guide (submitted on October 3, 2023)
  \\CDSESUB1\EVSPROD\bla761279\0069\m1\us\proposed-medguide-clean.docx
- Instructions for Use (submitted on October 3, 2023)
  \\CDSESUB1\EVSPROD\bla761279\0069\m1\us\proposed-ifu-100mg-pen-clean.docx
- Container Labels (submitted on October 3, 2023)

(b) (4)



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

Jennifer Kim

Digitally signed by Jennifer Kim
Date: 10/25/2023 11:09:30AM
GUID: 5e5438d2008138bdbae1db8d4abc0580

Mercy Oyugi

Digitally signed by Mercy Oyugi
Date: 10/25/2023 12:06:15PM
GUID: 6140a4ed009e6d425294f2f7cd73c287

BLA Executive Summary
Assessment Date: 02/16/2023

1. Application/Product Information

BLA number	761279
Submission Type	Original BLA
Regulatory Pathway	351(a)
Associated IND/BLA	IND 125444
Review Designation	Standard
Applicant	Eli Lilly and Company
Indication	Ulcerative Colitis
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Omvoh
	Non-proprietary Name/Code Name: mirikizumab-mrkz
	OBP Naming: MAB HUMANIZED (IGG4) ANTI Q9NPF7 (IL23A_HUMAN) [LY3074828]
Drug Product Description	Omvoh (mirikizumab-mrkz) is a recombinant humanized IgG4 monoclonal antibody produced in a Chinese Hamster Ovary (CHO) cell line. The antibody binds with high affinity and specificity to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor. Omvoh (mirikizumab-mrkz) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow to slightly brown solution containing either 20 mg/mL mirikizumab-mrkz in single-dose vials, or 100 mg/mL mirikizumab-mrkz in single-dose prefilled pens (b) (4)

Dosage Form	Injection Solution		
Strength	• 300 mg/15 mL (20 mg/mL) solution in a single-dose vial • 100 mg/1 mL solution in a single-dose prefilled pen (b) (4)		
Route of Administration	• Intravenous Infusion (vials) • Subcutaneous Injection (prefilled pens (b) (4)		
Primary Container Closure System	• Vials: 20 mL clear, (b) (4) glass tubing vial with a (b) (4) elastomer closure (stopper) (b) (4) The closure is secured in place with a two-piece flip-top aluminum seal. • (b) (4) 1 mL-long, clear, (b) (4) glass syringe barrel with small round flange, 27G special thin wall x 1/2" staked needle, and closed with a (b) (4) elastomeric plunger and rigid needle shield.		
Device Information	(b) (4) prefilled pens (b) (4) are 1 mL needle-based injection system (NIS) used to deliver the drug product. The components of prefilled pens (b) (4) do not contact the drug product solution. Device information is assessed by CDRH, and the recommendation is approvable. The CDRH review will be documented separately.		
Co-packaged Product Information	Not applicable		
	Discipline	Primary	Secondary
	Drug substance	Mercy Oyugi	Nailing Zhang
	Drug product	Mercy Oyugi	Nailing Zhang

OPQ Review Team	Immunogenicity Assay	Marco Cardone	Daniela Verthelyi
	Facility	Hamet Touré (DS) / Maria Gutierrez-Hoffman (DP)	Michael Shanks
	Microbiology	Hamet Touré (DS) / Maria Gutierrez-Hoffman (DP)	Virginia Carroll
	RBPM	Rabiya Haider / Shazma Aftab	N/A
	ATL	Nailing Zhang	
	Review Chief	Maria-Teresa Gutierrez-Lugo	
OPQ Issued Consults	None. A CDRH consult was requested by OND and the review will be documented separately.		

2. Recommendation and Conclusion on Approvability

Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761279 for Omvoh (mirikizumab-mrkz) manufactured by Eli Lilly and Company. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Omvoh (mirikizumab-mrkz) is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Eli Lilly and Company to outline the deficiencies noted below and the information and data that will be required to support approval.

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

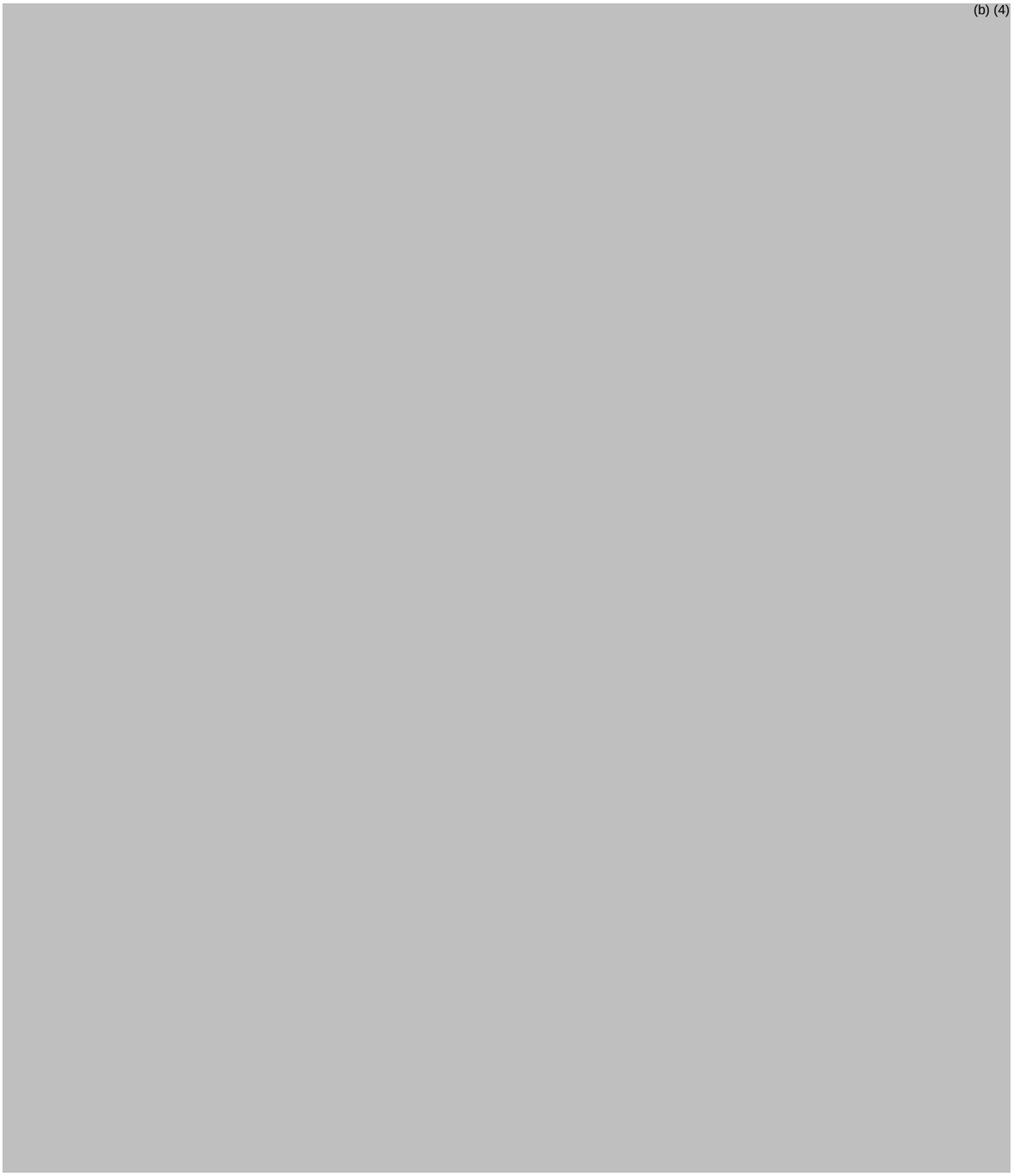
Facility Complete Response Comment (provided by OPMA):

Following pre-license inspection of the ELI LILLY AND COMPANY, Indianapolis, Indiana (FEI 1819470), manufacturing facility listed in this application, FDA

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

Additional Microbiology Comments (provided by OPMA):

(b) (4)



Additional Product Quality Comment (provided by OBP):

- Per 21 CFR 601.20(b)(1), issuance of a biologics license requires that "the product intended for introduction into interstate commerce is available for examination". To be consistent with 21 CFR 601.20(b)(1), the BLA should contain data for at least one drug product lot suitable for commercial release. (b) (4) Clarify whether a drug product lot(s) manufactured using validated drug substance and drug product processes will be available for launch, should your BLA be approved, and indicate the timeline for manufacture.

4. Basis for Recommendation

a. Summary:

Omvoh (mirikizumab-mrkz) is indicated for the treatment of moderately to severely active ulcerative colitis in adults. It is a humanized immunoglobulin G4 (IgG4) anti-IL-23 monoclonal antibody that binds with high affinity and specificity to the p19 subunit of human IL-23 cytokine to inhibit its interaction with the IL-23 receptor. Potency of Omvoh (mirikizumab-mrkz) is controlled by a cell-based reporter assay demonstrating the inhibition of IL-23 induced luciferase reporter activity (b) (4) the biologic activity relative to an established reference material is calculated and reported.

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

includes (b) (4) .

The overall control strategy for Omvoh (mirikizumab-mrkz) manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the DS and DP. The manufacturing processes and overall control strategies for Omvoh (mirikizumab-mrkz) as described in the application 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 the product quality, microbiology and sterility assurance, and device constituent performance perspectives. However, facility deficiencies were identified during the pre-license inspection of the DP manufacturing facility ELI LILLY AND COMPANY, Indianapolis, Indiana (FEI 1819470). Satisfactory resolution of these deficiencies is required before this application may be approved. Therefore, from an OPQ perspective, this BLA is not recommended for approval in its present form until the above-mentioned facility deficiencies are satisfactorily resolved.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of Omvoh (mirikizumab-mrkz) at concentrations presented in the patient samples. The neutralizing anti-drug antibody (NADA) assay used a target interference assay format that measures the reduction in target binding due to blocking the drug's complementarity-determining region (CDR) by ADA. This strategy relies on pre-binding of the drug to IL-23 and may not accurately test samples for neutralizing activity. However, the immunogenicity assays assessment team concluded that although the assay is not considered a suitable neutralization assay, the development of a new neutralizing assay will not be requested as a new neutralizing assay will not provide additional information, because a high correlation between titers and loss of product exposure and efficacy was observed in 1/3 of the subjects with titers >160.

b. Subdiscipline Recommendation:

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

Facilities	-	Inadequate
Microbiology	-	Adequate

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

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

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

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

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

/s/

NAILING ZHANG
02/17/2023 01:57:54 PM

MARIA T GUTIERREZ LUGO
02/17/2023 04:27:49 PM