CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761180Orig1s000

PRODUCT QUALITY REVIEW(S)

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	December 16, 2021
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Samuel Mindaye, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 2
Application:	BLA 761180
Applicant:	LEO Pharma A/S
Submission Date:	July 2, 2021
Product:	Adbry (tralokinumab-ldrm)
Dosage form(s):	injection
Strength and Container-Closure:	150 mg/mL solution in a single-dose prefilled syringe with needle guard
Purpose of assessment:	The Applicant resubmitted a biologics license application for Agency assessment to address deficiencies outlined in the complete response letter dated April 23, 2021. The Applicant resubmitted labeling.
Recommendations:	The prescribing information, patient labeling, and instructions for use and container labels and carton labeling (submitted on December 14, 2021) were assessed and found to be acceptable (see Appendix C) 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 (N/A)
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 and for consistency with recommended labeling practices in a previous assessment.[1] The Applicant resubmitted a biologics license application for Agency assessment to address deficiencies outlined in the complete response letter dated April 23, 2021. The Applicant resubmitted labeling revised to include a different proprietary name than that provided in the previously approved labeling (See Appendix A). OBP Labeling previously determined that prescribing information, patient labeling, and instructions for use, container and carton labeling submitted on March 25, 2021 were acceptable.

This assessment confirms revisions to OBP sections of prescribing information, patient labeling, and instructions for use and container and carton labeling submitted on December 14, 2021 revised only the proprietary name and are acceptable.

CONCLUSION

The prescribing information, patient labeling, instructions for use, and container labels and carton labeling (submitted on December 14, 2021) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling
Prescribing Information (submitted on July 2, 2021 \\CDSESUB1\evsprod\bla761180\0041\m1\us\draft-labeling-text-uspi-clean.pdf)
Medication Guide (N/A)
Patient Information Labeling (submitted on July 2, 2021 \\CDSESUB1\evsprod\bla761180\0041\m1\us\draft-labeling-text-ppi-clean.pdf)
Instructions for Use (submitted on July 2, 2021 \\CDSESUB1\evsprod\bla761180\0041\m1\us\draft-labeling-text-ifu-clean.pdf)

9 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[1] V. Borders-Hemphill. STN 761180 tralokinumab labeling assessment. April 15, 2021. P32.

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 12/16/2021 08:55:47AM
GUID: 50814c7000007a3d59329f660d8ddf02

Samuel Mindaye

Digitally signed by Samuel Mindaye
Date: 12/16/2021 09:32:29AM
GUID: 5dd2d3f60048d8672219510df16c7dd8

First Approval for Indication/First Biosimilar/Expedited or Breakthrough Review: No

Recommendation: Complete Response

BLA Number: 761180
Review Number: 2
Review Date: 04/16/2021

Drug Name/Dosage Form	(b) (4) tralokinumab-ldrm/Injection
Strength/Potency	150 mg in a volume of 1 mL in a single-dose, accessorized prefilled syringe (APFS)
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Moderate-to-severe atopic dermatitis with or without topical corticosteroids (TCS) in adults who are candidates for systemic therapy
Applicant/Sponsor	LEO Pharma A/S
US agent, if applicable	LEO Pharma Inc.

Summary

The drug substance manufacturing facility at Astrazeneca Pharmaceuticals LP Frederich Manufacturing Center (FEI 3002617771) was not inspected at the time of finalization of the original OPQ Executive Summary due to the travel restriction during COVID-19 pandemics. The current addendum provides a summary of the inspection conclusion and OPQ recommendations. Refer to the original OPQ Executive Summary for the detailed benefit/risk considerations, action letter language, product issues for BLA 761180.

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The application will not be approved during this assessment cycle due to Center for Devices and Radiological Health (CDRH) deficiencies. From the product quality and sterility assurance perspective, the Office of Pharmaceutical Quality (OPQ), CDER, does not note any product quality deficiencies that would preclude approval of STN 761180 for (b) (4) manufactured by LEO Pharma A/S at this time. Because the application will not be approved in this cycle, the product quality issues listed below will be communicated to the sponsor in the FDA Complete Response (CR) letter. If manufacturing changes are made before the sponsor submits their responses to the CR deficiencies, additional assessment may be needed during the next assessment cycle.

B. Complete Response Letter Language:

No CMC Complete Response Issues.

C. Benefit/Risk Considerations:

The OPMA assessor is recommending approval of the commercial manufacture of tralokinumab-ldrm DS at AstraZeneca Pharmacruticals LP Frederick Manufacturing Center, 633 Research Court, Frederick, MD 21703 FEI: 3002617771.

D. Additional Product Quality Comments (not CR Issues):

The applicant will conduct a real time transport study covering shipment from Catalent Indiana LLC (b) (4) The acceptance criteria will be specified in the transport study protocol and will include container closure integrity and microbiology quality as requested.

A. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacture, freeze/thaw, storage, release, and stability testing Preparation of future Working cell banks Storage and stability testing of Master and Working Cell Banks	AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center 633 Research Court, Frederick, MD 21703	968459953/ 3002617771	On-site inspection needed.	(b) (4)	Approve

B. **Facilities:**

In advance of or in lieu of a pre-license on-site inspection (PLI) for the drug substance manufacturing facility, AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FEI 3002617771), a review of requested manufacturing site records under section 704(a)(4) was conducted. Based on the records review, a PLI is recommended.

A pre-license inspection for tralokinumab-ldrm drug substance manufacture was conducted on March 02-19, 2021 at AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center. A 3-item FDA Form 483 was issued, and the initial recommendation was withhold pending the firm's adequate response to objectionable conditions. The final classification of the AZ FMC pre-license inspection was acceptable.

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/

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	April 15, 2021
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Samuel Mindaye, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 2
Application:	BLA 761180
Applicant:	LEO Pharma A/S
Submission Date:	April 27, 2020
Product:	(b) (4) (tralokinumab-ldrm)
Dosage form(s):	injection
Strength and Container-Closure:	150 mg/mL solution in a single-dose prefilled syringe with needle guard
Purpose of assessment:	The Applicant submitted a biologics license application Agency assessment
Recommendations:	The prescribing information, patient labeling, and instructions for use (submitted on March 23, 2021), and container labels and carton labeling (submitted on March 25, 2021) were assessed and found to be acceptable (see Appendix C) 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, patient labeling, and instructions for use (submitted on March 23, 2021), and container labels and carton labeling (submitted on March 25, 2021) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling
Prescribing Information (submitted on April 27, 2020
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Medication Guide (N/A)
Patient Information Labeling (submitted on April 27, 2020
\\CDSESUB1\evsprod\bla761180\0001\m1\us\draft-labeling-text-ppi.doc)

Instructions for Use (submitted on April 27, 2020
\\CDSESUB1\evsprod\bla761180\0001\m1\us\draft-labeling-text-ifu.doc)

5 Pages 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: For BLAs, the name of the applicant in Field 2 of the form FDA 356h is the name of the license holder or manufacturer for the BLA. This was revised to LEO Pharma A/S. Revise to "Mfd. by: LEO Pharma A/S"
The Applicant revised as requested

[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."

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

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	✓ Yes ☐ No

Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	☐ N/A

Comment/Recommendation: Ensure that Rx only appears on the container label *The Applicant's response as partial label is acceptable*

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

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

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

Comment/Recommendation: Per 3.2.P.1 Acceptable

(b) (4)

[redacted]

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: *partial label space considerations*

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

Comment/Recommendation: *partial label space considerations*

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,	☐ Yes ☐ No ☒ N/A

April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	

Comment/Recommendation: *partial label space considerations*

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: *partial label space considerations*

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 space considerations*

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 space considerations*

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 space considerations*

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

Package[6] Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: For BLAs, the name of the applicant in Field 2 of the form FDA 356h is the name of the license holder or manufacturer for the BLA. This was revised to LEO Pharma A/S. Revise to:
"Manufactured by: LEO Pharma A/S
Industriparken 55 Ballerup, Denmark DK-2750
The Applicant revised as requested

[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.

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

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: According to the drug master file for this (b) (4) (b) (4). Add "The needle cap (b) (4) contains dry natural rubber (a derivative of latex) which may cause allergic reactions."
Applicant's response: LEO Pharma's supplier, (b) (4) *has confirmed* (b) (4) (b) (4)
Applicant's confirmation was determined to be acceptable from product quality perspective

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: Revise to match your proposed prescribing information as follows: "Each prefilled syringe delivers 150 mg of tralokinumab-ldrm in 1 mL and the inactive ingredients: acetic acid (0.3 mg), polysorbate 80 (0.1 mg), sodium acetate trihydrate (6 mg), sodium chloride (5 mg), and Water for Injection, USP at an approximate pH of 5.5"
The Applicant revised as requested

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

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

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	✓ Yes ☐ No ☐ N/A

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*	

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

Comment/Recommendation: Consider revising the statement of dosage (b) (4) (b) (4) to read "Dosage: See Prescribing Information"

The Applicant revised as requested

The proposed dosage regimen includes an initial dose of 600 mg (four 150 mg injections) followed by 300 mg (two 150 mg injections) administered every other week. The proposed packaging configuration includes a two-count carton and a four count carton. Only the two-count carton includes the statements (b) (4) (b) (4) (b) (4) *Noting concurrence with DMEPA's recommendation to mitigate dosing confusion by removing these statements from the two-count carto* (b) (4) (b) (4)

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Recommend revising to "Before injection, remove (b) (4) prefilled syringes from the refrigerator and allow them to reach room temperature for 30 minutes without removing the needle cap."
The Applicant revised as requested

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Added the pharmacological class ("an interleukin-13 receptor antagonist") *The Applicant revised as requested*

Added the dosage form *The Applicant revised as requested*

Revised the ingredient paragraph to "Each prefilled syringe delivers 150 mg of tralokinumab-ldrm in 1 mL and the inactive ingredients: acetic acid (0.3 mg), polysorbate 80 (0.1 mg), sodium acetate trihydrate (6 mg), sodium chloride (5 mg), and Water for Injection, USP at an approximate pH of 5.5" *The Applicant revised as requested*

According to the drug master file [redacted]. Added [redacted]

Applicant's response: [redacted] *Applicant added "None of the components of the prefilled syringe or the needle guard are made with natural rubber latex."*
Applicant's confirmation and addition was determined to be acceptable from product quality perspective

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

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

Comment/Recommendation: Consider adding the needle gauge and length as "27-gauge, ½ inch needle" *The Applicant revised as requested*

Added "Do not Freeze" to be consistent with carton labeling *The Applicant revised as requested*

According to the drug master file [redacted] (b) (4)
[redacted] (b) (4))
[redacted] (b) (4)
Applicant's response: [redacted] (b) (4)
(b) (4)
Applicant's confirmation was determined to be acceptable from product quality perspective

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 name of the applicant in Field 2 of the form FDA 356h is the name of the license holder or manufacturer for the BLA. This was revised to LEO Pharma A/S Industriparken 55 Ballerup, Denmark DK-2750
The Applicant revised as requested and acceptably added the distributor information

Medication Guide Evaluation (N/A)

Patient Information Labeling Evaluation

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

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

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

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ 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 name of the applicant in Field 2 of the form FDA 356h is the name of the license holder or manufacturer for the BLA. This was revised to LEO Pharma A/S Industriparken 55 Ballerup, Denmark DK-2750
The Applicant revised as requested

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

Comment/Recommendation: The name of the applicant in Field 2 of the form FDA 356h is the name of the license holder or manufacturer for the BLA. This was revised to LEO Pharma A/S Industriparken 55 Ballerup, Denmark DK-2750
The Applicant revised as requested

APPENDIX C. Acceptable Labels and Labeling
Prescribing Information (submitted on March 23, 2021 \\CDSESUB1\evsprod\bla761180\0034\m1\us\final-package-insert-uspi.pdf)
Instructions for Use (submitted on March 23, 2021 \\CDSESUB1\evsprod\bla761180\0034\m1\us\final-package-insert-ifu.pdf)
Patient Information (submitted on March 23, 2021 \\CDSESUB1\evsprod\bla761180\0034\m1\us\final-package-insert-ppi.pdf)

5 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 4/15/2021 03:26:59PM
GUID: 50814c7000007a3d59329f660d8ddf02

Samuel Mindaye

Digitally signed by Samuel Mindaye
Date: 4/15/2021 03:45:32PM
GUID: 5dd2d3f60048d8672219510df16c7dd8

First Approval for Indication/First Biosimilar/Expedited or Breakthrough Review: No

Recommendation: pending

BLA Number: 761180
Review Number: 1
Review Date: 02/03/2021

Drug Name/Dosage Form	(b) (4) - tralokinumab-ldrm/Injection
Strength/Potency	150 mg in a volume of 1 mL in a single-dose, accessorized prefilled syringe (APFS)
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Moderate-to-severe atopic dermatitis with or without topical corticosteroids (TCS) in adults who are candidates for systemic therapy
Applicant/Sponsor	LEO Pharma A/S
US agent, if applicable	LEO Pharma Inc.

Product Overview

(b) (4) (tralokinumab-ldrm) is a recombinant human monoclonal antibody of the IgG4 subclass. Tralokinumab-ldrm specifically binds to human interleukin-13 (IL-13) and inhibits its interaction with the IL-13 receptor α1 and α2 subunits (IL-13Rα1 and IL-13Rα2). IL-13 is a naturally occurring cytokine of the Type 2 immune response. Tralokinumab-ldrm inhibits IL-13-induced responses including the release of proinflammatory cytokines, chemokines and IgE. Tralokinumab-ldrm is produced in mouse myeloma cells by recombinant DNA technology, (b) (4) (tralokinumab-ldrm) injection is a sterile, preservative-free clear to opalescent, colorless to pale yellow solution for subcutaneous use, supplied as a single-dose prefilled syringe with needle guard in a siliconized Type-1 clear glass syringe. (b) (4) drug product is formulated in acetic acid (0.3 mg), polysorbate 80 (0.1 mg), sodium acetate trihydrate (6 mg), sodium chloride (5 mg), and Water for Injection, at an approximate pH of 5.5.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Samuel Mindaye	OPQ/OBP/DBRR II
Drug Product		
Immunogenicity	Bruce Huang	OPQ/OBP/DBRR II
Labeling	Vicky Borders-Hemphill	OPQ/OBP
DS Microbiology and Facility	Zhao (Joe) Wang	OPQ/OPMA/DBM
DP Microbiology and Facility	Yarery Smith	OPQ/OPMA/DBM
Facility Team Lead	Viviana Matta	OPQ/OPMA/DBM
Microbiology Team Lead	Candace Gomez-Broughton	OPQ/OPMA/DBM
Regulatory Business Project Manager	Kelly Ballard	OPQ/OPRO/DRBPMI/RBPMBI
Application Team Lead	Yanming An	OPQ/OBP/DBRR II
OBP Tertiary Reviewer	Xianghong Jing	OPQ/OBP/DBRR II

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Strother Dixon	ORO/DRO II
Cross-disciplinary Team Lead	David Kettl	OII/DDD
Medical Officer	Hamid Tabatabai	OII/DDD
Pharm/Tox	Renqin Duan/Barbara Hill	OII/DPT II
Clinical Pharmacology	Da Zhang/Chinmay Shukla	OCP/DIIP
Statistics	Marilena Flouri / Mohamed Alosh	OB/DB III

1. Names:
   a. Proprietary Name: (b) (4)
   b. Trade Name: (b) (4)
   c. Non-Proprietary/USAN: tralokinumab-ldrm
   d. INN Name: tralokinumab-ldrm
   e. CAS Registry Number: 1044515-88-9
   f. OBP systematic name: MABFRAG(IGG4) ANTI P35225 (IL13_HUMAN) [CAT354]
   g. Other name(s): CAT-354

Submissions Reviewed:

Submission	Date Received	Review Completed (Yes/No)
STN 761180/0001 (submission)	04/27/2020	Yes
STN 761180/0003 (response to IR #1 OPMA)	05/19/2020	Yes
STN 761180/0008 (response to IR #2 OBP)	07/31/2020	Yes
STN 761180/0014 (response to IR #3 OBP)	09/30/2020	Yes
STN 761180/0016 (response to IR #4 OBP)	10/09/2020	Yes
STN 761180/0023 (response to IR #5 OPMA)	12/22/2020	Yes
STN 761180/0024 (response to IR #6 OPMA)	01/11/2021	Yes
STN 761180/0025 (response to IR #7 OPMA)	01/21/2021	Yes
STN 761180/0027 (response to IR #8 OBP)	01/26/2021	Yes

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed
(b) (4)	3	(b) (4)		2	Adequate	N/A

(b) (4)	3	(b) (4)	2	Adequate	N/A
	3		2	Adequate	N/A
	3		2	Adequate	N/A

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

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed).

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	123797	LEO Pharma-sponsored IND under which tralokinumab was developed and meetings were held

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Assessor
CDRH/OPEQ/OHTIII	06/02/2020	Completed	Complete Response	Stephen Retta Rumi Young (TL)

4. Environmental Assessment of Claim of Categorical Exclusion:

LEO Pharma Inc. claimed a categorical exclusion from the requirements of environmental assessment for tralokinumab-ldrm in accordance with 21 CFR 25.31 (c). The claim is because the estimated concentration of the substance at the point of entry into the aquatic environment will nonetheless be below 1 ppb. To the best of the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommendation on approvability of STN 761180 for (b) (4) manufactured by LEO Pharma A/S is pending the final determinations of compliance status of the (b) (4) (tralokinumab-ldrm) drug substance manufacturing facility. The scheduled Pre-license inspection is on 02/23- 03/03/2021 at AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FEI 3002617771). FDA assessment of the ability of these facilities to conduct manufacturing operations in compliance with CGMP is required to support approval of the application.

From the product quality and sterility assurance perspective, OPQ, CDER, does not note any product quality deficiencies that would preclude approval of STN 761180 for (b) (4) manufactured by LEO Pharma A/S at this time. This memo will be amended with the outcome of the facility assessment in the future.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance:
    AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center
    633 Research Court
    Frederick, MD 21703
    FEI: 3002617771

  - Drug Product:
    Catalent Indiana, LLC
    1300 South Patterson Dr.
    Bloomington, IN 47403
    FEI: 3005949964

- Fill size and dosage form:
  150 mg/1 mL accessorized prefilled syringe (APFS)

- Dating period:
  - Drug Product: 36 months: 5 ± 3 °C, 14 days at room temperature (≤ 30°C) after storage at long-term conditions (5 ± 3 °C) for up to 36 months.
  - Drug Substance: (b) (4) months: (b) (4) °C
  - For packaged products: "Not packaged"
  - Stability Option:
    We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release
  - Yes
  - Rationale, if exempted: Per FR notice 95-29960 well-characterized therapeutic recombinant DNA-derived and monoclonal antibody biotechnology products are exempt from 21 CFR 601.2a lot release requirement.

C. Benefit/Risk Considerations:

Tralokinumab-ldrm is a recombinant human monoclonal antibody of the IgG4 subclass that binds specifically to human interleukin 13 (IL-13) and blocks interactions with the IL-13 receptors. Atopic dermatitis (AD) has traditionally been considered a type 2 immunity (Th2 cell)- driven disease. IL-13 has been suggested to be the key type 2 cytokine driving inflammation in the periphery. IL-13 is overexpressed locally and has a significant impact on skin biology, including the recruitment of inflammatory cells, the alteration of the skin microbiome, and the decrease in the epidermal barrier function. Targeting the IL-13 cytokine has the potential for treating the underlying pathology of AD and reducing the type 2 inflammatory responses. LEO Pharma seeks licensure for the following indication:

Adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

The overall control strategy includes control of raw materials, facilities and equipment, manufacturing process, and adventitious agents. The conditions used in manufacturing have been sufficiently validated, and the data submitted in this application support the conclusion that the manufacture of tralokinumab-ldrm is well controlled and yields a consistently high-quality product.

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The BLA is recommended for approval from a sterility assurance and microbiology product quality perspective.

The OPMA assessor is recommending approval of (b) (4) DP at Catalent Indiana, LLC, 1300 South Patterson Dr., Bloomington, IN 47403 FEI: 3005949964. The assessment is pending for tralokinumab-ldrm DS at AstraZeneca Pharmacruticals LP Frederick Manufacturing Center, 633 Research Court, Frederick, MD 21703 FEI: 3002617771.

The OBP assessments including DS quality, DP quality, and validation of immunogenicity assays, OPMA DS microbiology and facility assessment, and DP microbiology and facility assessment are located as separate documents in Panorama.

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

The applicant will conduct a real time transport study covering shipment from Catalent Indiana LL (b) (4) The acceptance criteria will be specified in the transport study protocol and will include container closure integrity and microbiology quality as requested. The applicant has committed to conduct a real-time shipping study of commercial product as a Post Marketing Commitment (PMC) with a final report submission of July 2022.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and the associated control strategies for attributes that are relevant to both Drug Substance and Drug Product. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by OBP/DBRRII and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPMA/DBM.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Binding IL-13 and blocking the interaction with IL-13 receptors. (Potency)	Efficacy	Intrinsic to molecule	(b) (4)	The mechanism of action is based on binding to IL-13 without Fc region effector functions.
Appearance, color and clarity	Safety	Manufacturing process		
Identity, primary Sequence and corresponding variants	Efficacy, pharmacokinetics and immunogenicity	Intrinsic to molecule		
Total protein	Efficacy, pharmacokinetics, safety	Manufacturing process		
pH	Efficacy, safety	Formulation and stability		
High-molecular weight species (aggregates) (product-related impurity)	Efficacy, pharmacokinetics, and immunogenicity	Manufacturing process and storage conditions. Can form due to agitation, temperature, or light exposure.		
Low-molecular weight species (fragments) (product-related impurities)	Efficacy, pharmacokinetics, and immunogenicity	Manufacturing process and storage conditions. May be caused by agitation, temperature, or light		
(b) (4)	Pharmacokinetics and half-life	DS manufacturing process and storage conditions		(b) (4)
	Efficacy	DS manufacturing process and storage conditions		
	Efficacy, immunogenicity, safety	DS manufacturing process		
	Pharmacokinetics	DS manufacturing process		

CQA (type)	Risk	Origin	Control Strategy	Other
Higher order structure	Efficacy immunogenicity	Intrinsic to molecule	Controlled by the fermentation process. Indirectly controlled by reporter gene bioassay for DS and DP potency release testing.	

B. Drug Substance [Tralokinumab-ldrm] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2 below summarizes the critical quality attributes and their control strategy that are relevant specifically to the Drug Substance. For additional information, see the primary reviews, including the Drug Substance Quality Review and Drug Product Quality Review by OBP/DBRRII and the Drug Substance Microbiology Review and the Drug Product Microbiology Review by OPMA/DBM.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Host Cell Proteins (process-related impurity)	Safety and immunogenicity	Derived from host cell line	(b) (4)	N/A
Host Cell DNA (process-related impurity)	Safety and immunogenicity	Derived from host cell line		N/A
(b) (4) (process-related impurity)	Safety and immunogenicity	Process-related impurity (b) (4)		N/A
(b) (4) (process-related impurity)	Safety and immunogenicity	(b) (4)		N/A
(b) (4)	Safety, stability	Manufacturing process		N/A
Virus (enveloped and non-enveloped (contaminant)	Safety	Contamination during manufacture		N/A
Endotoxin	Safety, Purity	Endotoxin (b) (4)		N/A
Bioburden	Safety, Purity and Efficacy (b) (4)	Bioburden (b) (4)		N/A

- Description: tralokinumab-ldrm is a recombinant human IgG4λ consisting of two identical heavy chains of 49.4 kDa each, and two identical light chains of 22.7 kDa each. The molecular weight of tralokinumab is approximately 147 kDa. Tralokinumab has an N-linked oligosaccharide attachment site in the Fc region at residue Asn-299. The oligosaccharides are predominantly fucosylated biantennary complex-type oligosaccharides. (b) (4)

- Mechanism of Action (MoA): tralokinumab binds specifically to and neutralizes the activity of the immunoregulatory human interleukin 13 (IL-13), blocking interactions with the IL-13 receptor. Atopic dermatitis (AD) is a common inflammatory skin condition that has traditionally been considered a type 2 immunity (Th2 cell)- driven disease. IL-13 has been suggested to be the key type 2 cytokine driving inflammation in the periphery. IL-13 is overexpressed locally and has a significant impact on skin biology, including the recruitment of inflammatory cells, the alteration of the skin microbiome, and the decrease in the epidermal barrier function. Targeting the IL-13 cytokine has the potential for treating the underlying pathology of AD and reducing the type 2 inflammatory responses, thereby restoring the skin barrier function and reducing inflammation, itch, and skin thickening.

- Potency Assay: A cell-based reporter gene assay measures inhibition of IL-13 activity. HEK-Blue cells express the IL-13 receptor subunits, IL13Rα1 and IL4Rα and express a secreted embryonic alkaline phosphatase (SEAP) gene under the control of STAT6 promoter. In the presence of IL-13, IL13Rα1/IL4Rα heterodimerization results in the activation of STAT6 with subsequent production of SEAP. SEAP activity is determined using a colorimetric substrate QUANTI-Blue, resulting in a product which absorbs at 650 nm. Tralokinumab causes a dose-dependent inhibition of IL-13 mediated SEAP activity in HEK-Blue cells. The relative potency of the test sample is reported by dividing the IC50 of the reference standard by the IC50 of the test sample.

- Reference Materials: (b) (4)

- Critical starting materials or intermediates: (b) (4)

(b) (4)

- Manufacturing process summary: (b) (4)

(b) (4)

- Container closure: (b) (4)

- Dating period and storage conditions: (b) (4)

The stability testing program is adequate and consistent with ICH Q5C recommendations.

C. Drug Product [(b) (4)] Quality Summary:

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

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

CQA (type)	Risk	Origin	Control Strategy	Other
Deliverable Volume	Control of dosing	Manufacturing process	(b) (4)	N/A
Particles (visible and sub-visible) (general)	Efficacy, immunogenicity and Safety	Manufacturing process, product degradation		N/A
Osmolality	Safety, stability	Formulation		N/A
Endotoxin (contaminant)	Safety, purity and immunogenicity	Raw materials; microbial contamination during the manufacturing process		N/A
Sterility (contaminant)	Safety, purity, efficacy (b) (4))	Contamination may be introduced during DP manufacture or through a container closure integrity failure		N/A
Container closure integrity	Safety (maintenance of sterility during shelf-life)	Container closure (b) (4) . May be impacted by storage conditions.		N/A

- Potency and Strength: Potency of tralokinumab is considered, for the purposes of this review, as the percent inhibition of SEAP activity relative to the current reference standard. The potency assay is the same as those described in the Drug Substance section of this review.

  Tralokinumab is supplied as 150 mg/1 mL solution of tralokinumab-ldrm.

- Summary of Product Design: Tralokinumab injection will be supplied in a single-dose accessorized prefilled syringe (APFS) for subcutaneous administration. The primary container is PFS.

- List of Excipients: Excipients include sodium acetate trihydrate, acetic acid glacial, polysorbate 80, and sodium chloride. Except for the protein itself, all ingredients meet compendial requirements (USP/NF, Ph. Eur. and/or JP) and are commonly used for formulation of biopharmaceuticals. No excipients are of human or animal origin.

- Reference Materials: The same reference standard is used for Drug Product as for Drug Substance. Refer to the Drug Substance reference standard section above.

- Manufacturing process summary: (b) (4)

- Container closure: (b) (4)

- Dating period and storage conditions: The applicant conducted real-time, accelerated, and thermal-stressed stability studies on 3 PPQ lots and 6 clinical Drug Product lots. These data support a dating period (b) (4)

- List of co-package components: None.

D. Biopharmaceutics Considerations: None

E. Novel Approaches/Precedents: None

F. Any Special Product Quality Labeling Recommendations: None

G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacture, freeze/thaw, storage, release, and stability testing	AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center	968459953/ 3002617771	On-site inspection needed.		pending

Preparation of future Working cell banks Storage and stability testing of Master and Working Cell Banks	633 Research Court, Frederick, MD 21703				
Manufacture of Master cell bank	(b) (4)		-----	Waived	Approve
Manufacture of working cell bank			-----	Waived	Approve
In vitro adventitious agent testing for (b) (4)			-----	Waived	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug product manufacture, assembly, labeling and packaging Storage of drug product Quality control testing for batch release	Catalent Indiana, LLC 1300 South Patterson Dr. Bloomington, IN 47403	172209277/ 3005949964	-----	Waived	Approve
Release of product	LEO Pharma A/S Industriparken 55 2750 Ballerup Denmark	306218108/ 3002807496	-----	Waived	Approve
Quality control testing for batch release Stability testing	(b) (4)		----	Waived	Approve
			----	Waived	Approve

H. **Facilities:**

In advance of or in lieu of a pre-license on-site inspection (PLI) for the drug substance manufacturing facility, AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FEI 3002617771), a review of requested

manufacturing site records under section 704(a)(4) was conducted. Based on the records review, a PLI is recommended.

The pre-license inspection of the drug product site Catalent Indiana, LLC was waived because of the site's compliance status and its recent surveillance inspection (October 2019).

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved: Stability protocol for the extension of shelf life, annual stability protocol, Production of a replacement WCB, annual stability protocol for primary and working reference standards.
ii. Outstanding review issues/residual risk: Drug substance manufacturing facility on-site pre-license inspection is scheduled on 02/23-03/03/2021. An addendum will be added with the final recommendation of the PLI.
iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved: stability protocol for the extension of shelf life, annual stability protocol, (b) (4)
ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product		x		
2.	Naturally Derived Product			x	
3.	Botanical			x	
4.	Human Cell Substrate/source material			x	
5.	Non-Human Primate Cell Substrate/Source Material			x	
6.	Non-Primate Mammalian Cell Substrate/source material		x		
7.	Non-Mammalian Cell Substrate/Source Material			x	
8.	Transgenic Animal source			x	
9.	Transgenic Plant source			x	
10.	New Molecular Entity		x		
11.	PEPFAR drug			x	
12.	PET drug			x	
13.	Sterile Drug Product		x		
14.	Other: [fill in information]				
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			x	
16.	Comparability Protocol(s)			x	
17.	End of Phase II/Pre-NDA Agreements term			x	
18.	SPOTS (special products on-line tracking system)			x	
19.	USAN assigned name		x		
20.	Other [fill in]				
	Quality Considerations				
21.	Drug Substance Overage			x	
22.	Design Space	Formulation		x	
23.		Process		x	
24.		Analytical Methods		x	
25.		Other		x	
26.	Other QbD Elements			x	
27.	Real Time release testing (RTRT)			x	
28.	Parametric release in lieu of Sterility testing			x	
29.	Alternative Microbiological test methods			x	
30.	Process Analytical Technology in Commercial Production			x	
31.	Non-compendial analytical procedures	Drug Product	x		
32.		Excipients		x	
33.		Drug Substance	x		
34.	Excipients	Human or Animal Origin		x	
35.		Novel		x	
36.	Nanomaterials			x	
37.	Genotoxic Impurities or Structural Alerts			x	
38.	Continuous Manufacturing			x	
39.	Use of Models for Release			x	
40.	Other {fill-in}				

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/s/

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