CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761306Orig1s000

PRODUCT QUALITY REVIEW(S)

This is a corrected review that does not change the overall recommendations/conclusions of the original review dated August 27, 2024.

BLA Executive Summary
Assessment Date: August 26, 2024

1. Application/Product Information

BLA number	761306
Submission Type	Resubmission (Round 2)
Regulatory Pathway	351(a)
Associated IND/BLA	IND 119866
Review Designation	Standard
Applicant	Eli Lilly and Company
Indication	Moderate to severe chronic atopic dermatitis
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name Ebglyss
	Non-proprietary Name/Code Name lebrikizumab-lbkz
	OBP Naming MAB HUMANIZED (IGG4) ANTI P35225 (IL13_HUMAN) [LY3650150]
Drug Product Description	Lebrikizumab is supplied as a sterile 250 mg/2 mL solution formulated in 6.2 mg (b) (4) histidine, 1.8 mg glacial acetic acid, 119.6 mg sucrose, 0.6 mg polysorbate 20, and Water for Injection (b) (4) Lebrikizumab is a humanized IgG4 monoclonal antibody consisting of two heavy chains (HC) and two light chains (LC) that are held together via 12 intra-chain disulfide bonds and 4 inter-chain disulfide bonds. A

	S226P mutation was introduced to the hinge region (b) (4) .		
Dosage Form	Liquid		
Strength	250 mg/2 mL		
Route of Administration	Subcutaneous		
Primary Container Closure System	The DP is stored in a 2.25 mL, Type (b) (4) glass syringe barrel with a (b) (4) elastomeric plunger (b) (4) .		
Device Information	The (b) (4) is assembled with device components to prepare the two presentations— pre-filled syringe with needle safety device (PFS-NSD) and autoinjector (AI).		
Co-packaged Product Information	None		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Amy Hsu	Kristen Nickens
	Drug product		
	Immunogenicity Assay		
	Facility	Bo Chi (DS)/Melissa Ray (DP)	Zhong Li
	Microbiology	Bo Chi (DS)/Melissa Ray (DP)	Maxwell Van Tassel
	RBPM	Andrew Shiber (June 1, 2023 – current); Anh-Thy Ly (until May 31, 2023)	

	ATL	Kristen Nickens
OPQ Issued Consults	During the original review cycle, two CDRH ICCRs (# 00878385 and 00878369) were requested by OPQ for the device quality review and facility inspection. See DARRTS and the ICCR database for the ICCRs and associated memos from Courtney Evans for PFS-NSD review and Florencia Wilson for autoinjector review, and Porsche Bennett for device facility review.	

2. Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761306 for Ebglyss manufactured by Eli Lilly and Company. The data submitted in this application are adequate to support the conclusion that the manufacture of Ebglyss is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** (b) (4)
- **Drug Product:**
  - DP manufacture, PFS-NSD assembly/primary and secondary packaging/labeling: (b) (4)
  - DP manufacture, AI assembly/primary and secondary packaging/labeling: Eli Lilly and Company, Lilly Corporate Center Indianapolis, Indiana 46285 USA (FEI: 1819470)

b. Fill size and dosage form: 250 mg/2 mL solution in a PFS-NSD or AI

c. Dating Period:

- **Drug Product:**
  - PFS-NSD: 36 months, 2°C to 8°C, protected from light
  - AI: 24 months, 2°C to 8°C, protected from light
- **Drug Substance:**
  - (b) (4)
  -
- **For packaged products:** Not packaged

- **Stability Option:**
  - For stability protocols:
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance stored [redacted] (b) (4) and drug product autoinjector presentation under 21 CFR 601.12.

d. Exempt from lot release:

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

4. Basis for Recommendation

a. Summary:

Lebrikizumab binds human interleukin 13 (IL-13) and selectively inhibits IL-13 signaling through the IL-4Rα/IL-13Rα1 pathway, thereby blocking the downstream effects of IL-13 signaling. Further, lebrikizumab-bound IL-13 maintains the ability to bind the IL-13Rα2, thereby allowing subsequent internalization and clearance of IL-13. Potency of lebrikizumab is controlled using a cell-based reporter gene assay that measures the ability of lebrikizumab to bind IL-13 and inhibit the IL-13-induced downstream expression of STAT6-activated luciferase in engineered human bronchial epithelial L-BEAS-2B cells. The biological activity is calculated and reported relative to an established reference material.

The lebrikizumab drug substance (DS) manufacturing process consists of [redacted] (b) (4)

During the original review cycle, facility-related concerns were identified as part of the remote regulatory assessment (RRA) and a subsequent on-site inspection of the (b) (4) DS manufacturing facility was performed. Several observations were made related to data integrity issues that led to the inability to reliably interpret relevant data sets submitted to the BLA and issuance of a complete response (CR) letter dated September 28, 2023. In the resubmission, newly generated data sets were provided to replace relevant impacted data sets originally submitted to the BLA. The CR issues have been resolved.

Ultimately, the overall control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the DS and DP. The assays used for the immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) ; and Eli Lilly and Company, Lilly Corporate Center Indianapolis, Indiana 46285 USA (FEI: 1819470) for the lebrikizumab-lbkz DS, Ebglyss PFS-NSD DP, and Ebglyss autoinjector DP, respectively. All proposed manufacturing (including device) and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. The BLA is recommended for approval from a product quality, facility, microbiology, sterility assurance, and device 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 lebrikizumab (i.e., there is no specific test method described in regulation for lebrikizumab that establishes an official standard of potency). We next considered whether potency is a factor for lebrikizumab 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 Ebglyss for purposes of § 610.61(r) because lot variability is not a concern for Ebglyss as Ebglyss's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved: (b) (4) , Primary Reference and Working Reference Standard Requalification Protocols, Qualification Protocol for Replacement Working Reference Standards, Post-Approval Stability Protocol with shelf-life extension for DS stored (b) (4) , New Product Introduction into Drug Substance Commercial Multi-Product Facility

ii. Residual risk: N/A

iii. Future inspection points to consider: N/A

c. Drug Product:

i. Protocols approved: Primary Reference and Working Reference Standard Requalification Protocols, Qualification Protocol for Replacement Working Reference Standards, Post-Approval Stability Protocol with shelf-life extension for the DP filled in autoinjector, New Product Introduction into Drug Product Commercial Multi-Product Facility

ii. Residual risk: N/A

iii. Future inspection points to consider: N/A

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.

APPEARS THIS WAY ON ORIGINAL

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/

KRISTEN P NICKENS
09/12/2024 05:31:09 PM

BLA Executive Summary
Assessment Date: September 27, 2023

1. Application/Product Information

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Associated IND/BLA	IND 119866
Review Designation	Standard
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Dosage Form	Liquid

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	for the ICCRs and associated memos from Courtney Evans for PFS-NSD review and Florencia Wilson for autoinjector review, and Porsche Bennett for device facility review.

2. Recommendation and Conclusion on Approvability
Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761306 for Ebglyss manufactured by Eli Lilly and Company. The information and data provided to support licensure are not sufficient to support a conclusion that the manufacture of Ebglyss 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):

Complete Response Comment (provided by DBM and OBP):

1. As part of the facility evaluation of (b) (4) drug substance (DS) manufacturing facility, a Remote Regulatory Assessment (RRA) was performed. FDA identified issues during the RRA and conducted a pre-license inspection (PLI) to further evaluate the facility. Following the PLI, FDA conveyed deficiencies to the representative of the facility. FDA has reviewed the responses from the facility, and all deficiencies have not been satisfactorily resolved. Satisfactory responses to these deficiencies should be provided to the inspection team prior to submitting your complete response. Your complete response should include the date of the facility's response to the FDA Form 483. The assessment of the application approvability and resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may include a re-inspection of the facility. Please work with the facility in resolving the related deficiencies.

2. Following evaluation of the inspection findings noted above, and the response to those findings, the Agency has identified concerns regarding the reliability of data generated at (b) (4) in your BLA submission. The

concerns impact data that supports comparability between commercial and clinical materials to ensure expected clinical outcome demonstrated by clinical material can be achieved by commercial material. Further, the adequacy of the proposed lebrikizumab DS manufacturing process and overall control strategy cannot be determined at this time to support the licensure of lebrikizumab. For resolution, we recommend you engage with an independent third party to develop a protocol for, and conduct, a comprehensive assessment on the impacted information and data submitted in your application to justify the acceptability of using these data and information to support licensure. We recommend you also confirm with the FDA that the protocol to ensure that the audit will cover the data reliability concerns identified. If any impacted data are removed from the application and/or changes are made to the control strategy to address the facility deficiencies, provide additional information and data (e.g., testing results from repeated studies) that are reliable and accurate to support that consistent process performance and product quality is achieved.

Additional Product Quality Comment (provided by OBP):

1. Reference is made to your September 13, 2023 response to Question 2 of the FDA September 7, 2023 information request (IR) with respect to the pre-filled syringe needle safety device (PFS-NSD) drug product (DP) manufacturing process at (b) (4). While a re-evaluation of the process validation data against the new (b) (4) was performed (response to Question 2b), this assessment alone is not sufficient to fully support that the (b) (4) process controlled using the revised (b) (4) limits is validated for commercial manufacture. Provide additional process validation data, using a scientifically justified number of PFS-NSD process run(s) controlled using the revised (b) (4) limits, to fully support the validation of DP (b) (4) process.

4. Basis for Recommendation

a. Summary:

Lebrikizumab binds human interleukin 13 (IL-13) and selectively inhibits IL-13 signaling through the IL-4Rα/IL-13Rα1 pathway, thereby blocking the downstream effects of IL-13 signaling. Further, lebrikizumab-bound IL-13 maintains the ability to bind the IL-13Rα2, thereby allowing subsequent internalization and clearance of IL-13. Potency of lebrikizumab is controlled using a cell-based reporter gene assay that measures the ability of lebrikizumab to bind IL-13 and inhibit the IL-13-induced downstream

expression of STAT6-activated luciferase in engineered human bronchial epithelial L-BEAS-2B cells. The biological activity is calculated and reported relative to an established reference material.

The lebrikizumab drug substance (DS) manufacturing process consists of

The overall control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the DS and DP. The assays used for the immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. However, facility deficiencies were identified during the on-site inspection of the (b) (4) DS manufacturing facility and following OPMA/DBM's expedited review of (b) (4) responses (provided 9/22/2023) to the FDA Form 483 observations, the responses were considered inadequate. Due to the unresolved facility deficiencies, there is an inability to reliably interpret the data sets submitted to the BLA intended to support comparability between the material used in the clinical studies and commercial material, DS process validation and the DS control strategy (refer to CR comments above).

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Inadequate due to facility deficiency (refer to Section 4)**
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/

KRISTEN P NICKENS
09/27/2023 07:33:21 PM

QING ZHOU
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