CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761063Orig1s000

PRODUCT QUALITY REVIEW(S)

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

LABELS AND LABELING REVIEW

Date:	September 27, 2018
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Nailing Zhang, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761063
Applicant:	Eli Lilly and Company
Submission Date(s):	September 27, 2017, December 20, 2017
Product:	Emgality (galcanezumab-gnlm)
Dosage form(s):	Injection
Strength and Container-Closure:	120 mg/mL in a single-dose prefilled syringe or single-dose prefilled pen
Indication, dose, route, and frequency of administration:	prophylaxis of migraine in adults: 120 mg subcutaneously once monthly, with a 240 mg loading dose
Background and Summary Description:	The applicant submitted a biologics license application for the prophylaxis of migraine in adults
Recommendations:	The container labels and carton labeling (submitted on May 3, 2018), prescribing information and patient information (submitted on September 26, 2018), and the instructions for use (submitted on September 21, 2018) are acceptable (see Appendix D) from an OBP labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	**Appendix Section**
Proposed Labels and Labeling	A
Other	B
Relevant Code of Federal Regulations, FDA Guidance, and United States Pharmacopeia (USP) standards	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance to the applicable requirements in the Code of Federal Regulations, FDA Guidance, and United States Pharmacopeia (USP) standards (see Appendix C).

The prescribing information, patient information, instructions for use, and container labels and carton labeling for Emgality (galcanezumab-gnlm) injection 120 mg/mL in single-dose prefilled syringe or single-dose prefilled pen were reviewed and found to comply with relevant regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100), FDA Guidance, and USP standards. The container labels and carton labeling (submitted on May 3, 2018), prescribing information and patient information (submitted on September 26, 2018), and the instructions for use (submitted on September 21, 2018) are acceptable (see Appendix D) from an OBP labeling perspective.

APPENDICES

Appendix A: **Proposed Labeling**

Prescribing Information (submitted December 20, 2017
\\cdsesub1\evsprod\bla761063\0016\m1\us\proposed-uspi.docx)

Patient information (submitted September 27, 2017
\\cdsesub1\evsprod\bla761063\0001\m1\us\proposed-ppi.docx)

Instructions for Use (submitted September 27, 2017
\\cdsesub1\evsprod\bla761063\0001\m1\us\proposed-ifu-pen.docx and
\\cdsesub1\evsprod\bla761063\0001\m1\us\proposed-ifu-pfs.docx)

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

Package Label[5] Evaluation

Prefilled Syringe

Regulations, Guidance and CDER Best Labeling Practices	Conforms
Proper name (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	☐ No ☒ Yes ☐ N/A
Manufacturer name, address, and license number 21CFR 610.61	☐ No ☒ Yes ☐ N/A
Lot number or other lot identification 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Expiration date 21 CFR 610.61 21 CFR 201.17	☐ No ☒ Yes ☐ N/A
Preservative 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Number of containers 21 CFR 610.61 (b) (4)	☐ No ☒ Yes ☐ N/A
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100 **Comment/Recommendation:** Increase the prominence of the strength statement *The Applicant revised as requested*	☐ No ☒ Yes ☐ N/A
Storage temperature/requirements 21 CFR 610.61 **Comment/Recommendation:** Revise the storage information for consistency with the prescribing information to read as follows: "Refrigerate at 36°F to 46°F (2°C to 8°C) in original carton to protect from light until use. DO NOT FREEZE. DO NOT SHAKE. If needed, Emgality may be stored out of refrigeration in the original carton at temperatures up to 30°C (86°F) for up to 7 days. Once stored out of refrigeration, do not place back in the refrigerator. Discard after 7 days. Write the date removed	☐ No ☒ Yes ☐ N/A

[5] 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.

from the refrigerator ___/___/___." *The Applicant revised as requested*	
Handling: [redacted] (b) (4) (21 CFR 610.61)	☐ No ☒ Yes ☐ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Known sensitizing substances 21CFR 610.61	☐ No ☐ Yes ☒ N/A
Inactive ingredients 21 CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Source of the product 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
Minimum potency of product 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Rx only 21CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Divided manufacturing 21 CFR 610.63	☐ No ☐ Yes ☒ N/A
Distributor 21 CFR 610.64	☐ No ☐ Yes ☒ N/A
Bar code 21 CFR 610.67 21 CFR 201.25	☐ No ☒ Yes ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A
Preparation instructions 21 CFR 201.5	☐ No ☐ Yes ☒ N/A
Package type term 21 CFR 201.5	☐ No ☒ Yes

	☐ N/A
Drugs **Misleading statements** 21 CFR 201.6	☐ No ☒ Yes ☐ N/A
Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	☐ No ☐ Yes ☒ N/A

PEN

Regulations, Guidance and CDER Best Labeling Practices	Conforms
Proper name (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	☐ No ☒ Yes ☐ N/A
Manufacturer name, address, and license number 21CFR 610.61	☐ No ☒ Yes ☐ N/A
Lot number or other lot identification 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Expiration date 21 CFR 610.61 21 CFR 201.17	☐ No ☒ Yes ☐ N/A

Preservative 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Number of containers 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
(b) (4)	
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: Increase the prominence of the strength statement *The Applicant revised as requested*	
Storage temperature/requirements 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Comment/Recommendation: Revise the storage information for consistency with the prescribing information to read as follows: "Refrigerate at 36°F to 46°F (2°C to 8°C) in original carton to protect from light until use. DO NOT FREEZE. DO NOT SHAKE. If needed, Emgality may be stored out of refrigeration in the original carton at temperatures up to 30°C (86°F) for up to 7 days. Once stored out of refrigeration, do not place back in the refrigerator. Discard after 7 days. Write the date removed from the refrigerator ___/___/___." *The Applicant revised as requested*	
(b) (4) (21 CFR 610.61)	☐ No ☒ Yes ☐ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.61	☐ No ☐ Yes ☒ N/A
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Known sensitizing substances 21CFR 610.61	☐ No ☐ Yes ☒ N/A
Inactive ingredients 21 CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Source of the product 21 CFR 610.61	☐ No ☐ Yes

	☒ N/A
Minimum potency of product 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Rx only 21 CFR 610.61 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Divided manufacturing 21 CFR 610.63	☐ No ☐ Yes ☒ N/A
Distributor 21 CFR 610.64	☐ No ☐ Yes ☒ N/A
Bar code 21 CFR 610.67 21 CFR 201.25	☐ No ☒ Yes ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A
Preparation instructions 21 CFR 201.5	☐ No ☐ Yes ☒ N/A
Package type term 21 CFR 201.5	☐ No ☒ Yes ☐ N/A
Drugs **Misleading statements** 21 CFR 201.6	☐ No ☒ Yes ☐ N/A
Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Net quantity	☐ No

21 CFR 201.51	☒ Yes ☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24	☐ No ☐ Yes ☒ N/A

Prescribing Information and Patient Labeling Evaluation

Regulations	Conforms
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	☐ No ☒ Yes ☐ N/A
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	☐ No ☒ Yes ☐ N/A
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	☐ No ☒ Yes ☐ N/A
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	☐ No ☒ Yes ☐ N/A
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4) **Comment/Recommendation:** Confirm your product's identifying characteristics *The applicant revised to "clear to opalescent, colorless to slightly yellow to slightly brown" OBP labeling determined this is acceptable*	☐ No ☒ Yes ☐ N/A
6.2 IMMUNOGENICITY Draft Guidance for Industry: Labeling for Biosimilar Products	☐ No ☒ Yes ☐ N/A
11 DESCRIPTION (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)) **Comment/Recommendation:** We added the dosage form per 21 CFR 201.57(c)(12). *The applicant revised as requested* Also, confirm your product's identifying characteristics.	☒ No ☐ Yes ☐ N/A

The applicant revised as requested

We added the pharmacological class per 21 CFR 201.57(c)(12) (b) (4)

The applicant revised as requested

16 HOW SUPPLIED/ STORAGE AND HANDLING
21 CFR 201.57(c)(17)

☒ No
☐ Yes
☐ N/A

Comment/Recommendation: The expression of strength for this injectable product should be strength per mL.
The applicant revised as requested

We revised the storage requirements for clarity: "EMGALITY may be stored out of refrigeration in the original carton at temperatures up to 30°C (86°F) for up to 7 days. Once stored out of refrigeration, do not place back in the refrigerator."
The applicant revised as requested

MANUFACTURER INFORMATION
21 CFR 610.61, 21 CFR 610.64

☐ No
☒ Yes
☐ N/A

Comment/Recommendation: For BLAs, the license manufacturer's name (i.e., the applicant on Form 356h) must appear along with the license manufacturer's address and U.S. license number. Use the phrase "Manufactured by." The distributor's or marketer's name and address may also be included (e.g., "Distributed by" or "Marketed by") (see 21 CFR 610.64).

Applicant's response: Lilly proposes to keep the Signature Block as originally submitted. FDA asked for the addition of "manufactured by" to be added to the signature statement, however, the current statement already reflects the Manufacturer's name, Eli Lilly and Company. Lilly functions as the manufacturer, distributor and marketer. Therefore, the current signature statement is accurate, compliant and consistent with all other approved Lilly BLAs.

OBP labeling: It is historical practice to include the phrase "Manufactured by:". We note that most of the applicant's approved BLAs do not include the phrase "Manufactured by:" in the prescribing information when only the manufacturer information is present but the phrase is included when the applicant also includes the name and address of the marketer. We agree with their rationale.

INSTRUCTIONS FOR USE AND PATIENT INFORMATION

TITLE (NAMES AND DOSAGE FORM)

☐ No
☒ Yes
☐ N/A

STORAGE AND HANDLING

☐ No
☒ Yes
☐ N/A

Comment/Recommendation: For the IFU and Patient Information, under storage and handling, add the statement "Once stored unrefrigerated, do not place back in the refrigerator."
The applicant revised as requested

Revise the statement to read as follows: "Store in the original carton to protect…"
The applicant revised as requested

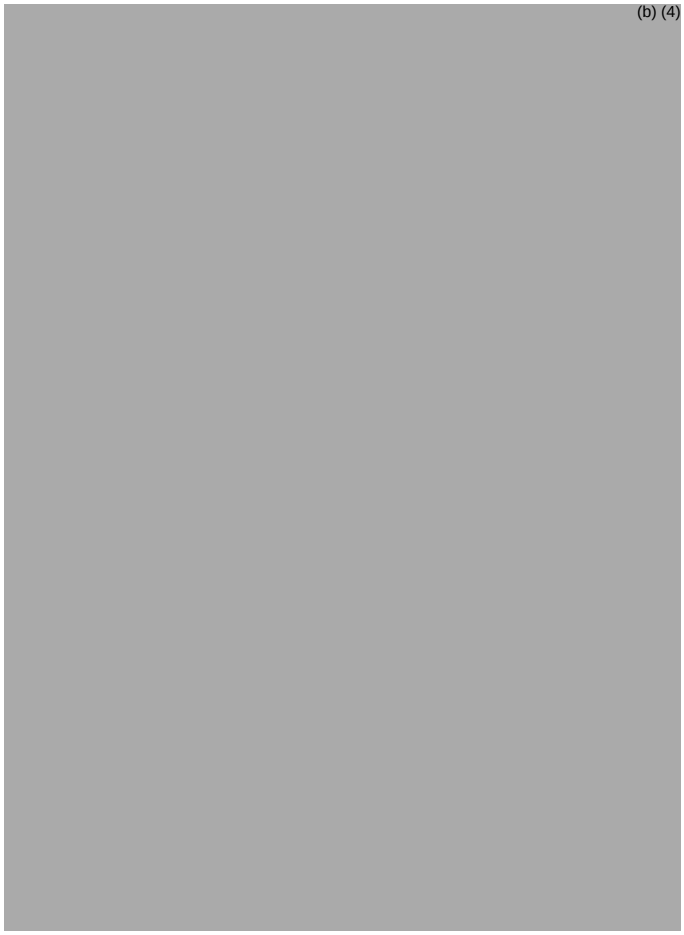
INGREDIENTS	☐ No ☒ Yes ☐ N/A
MANUFACTURER INFORMATION 21 CFR 610.61, 21 CFR 610.64	☐ No ☒ Yes ☐ N/A

APPENDIX D. Acceptable Labels and Labeling

Prescribing Information (submitted on September 26, 2018 \\cdsesub1\evsprod\bla761063\0071\m1\us\proposed-uspi-clean.docx)

Instructions for Use (submitted on September 21, 2018 **\\cdsesub1\evsprod\bla761063\0068\m1\us\proposed-ifu-pfs-clean.docx** and **\\cdsesub1\evsprod\bla761063\0068\m1\us\proposed-ifu-pen-clean.docx**)

Patient Information (submitted on September 26, 2018 **\\cdsesub1\evsprod\bla761063\0071\m1\us\proposed-ppi-clean.docx**)



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Vicky Borders-Hemphill

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Date: 9/27/2018 01:20:41PM
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Nailing Zhang

Digitally signed by Nailing Zhang
Date: 9/27/2018 01:30:01PM
GUID: 57a4df210075186d6ef8d82accd1f44e

Office of Pharmaceutical Quality Integrated Review
BLA 761063 EMGALITY (galcanezumab)

May 31, 2018

First Approval for Indication
Recommendation: BLA Approval

Drug Name/Dosage Form	EMGALITY (galcanezumab) Injection (liquid in pre-filled syringe and autoinjector)
Strength/Potency	120 mg/(b) (4) mL
Route of Administration	Subcutaneous
Rx/OTC dispensed	Rx
Indication	Migraine prophylaxis for adult
Applicant/Sponsor	Eli Lilly and Company

Product Overview

Galcanezumab is a humanized IgG4 kappa monoclonal antibody produced in CHO cells. Galcanezumab targets calcitonin gene-related peptide (CGRP) and blocks the binding of CGRP and the CGRP receptor, resulting in neutralization of the biological effects of CGRP in adults with increased plasma or serum levels of CGRP for the treatment of migraine headaches. Galcanezumab drug product (DP) is supplied at 120 mg/(b) (4) mL as a single-dose, sterile, preservative-free, clear and colorless to slightly yellow solution for subcutaneous (SC) injection in (b) (4) prefilled syringes (PFS) or (b) (4) autoinjector (prefilled pen). The recommended dose is 120 mg injected subcutaneously once monthly, with a 240 mg loading dose as the initial dose.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Nailing Zhang	OPQ/OBP/DBRRIV
Drug Product	Nailing Zhang	OPQ/OBP/DBRRIV
Immunogenicity	Yan Wang	OPQ/OBP/DBRRIV
Labeling	Nailing Zhang Vicky Borders-Hemphill	OPQ/OBP/DBRRIV OPQ/OBP
Facility	Ziyang Su	OPQ/OPF/DIA
Microbiology	Maria (Reyes) Candau-Chacon (Drug Substance) Jessica Hankins (Drug Product)	OPQ/OPF/DMA-IV OPQ/OPF/DMA-IV
Team Lead	Yan Wang Patricia Hughes Peter Qiu	OPQ/OBP/DBRRIV OPQ/OPF/DMA-IV OPQ/OPF/DIA
Application Team Lead	Yan Wang	OPQ/OBP/DBRRIV

Mutidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Emilios A. Papanastasiou	OND/ODEI/DNP
Cross-disciplinary Team Lead	Heather Fitter	OND/ODEI/DNP
Medical Officer	Suhail Kasim Lourdes Villalba	OND/ODEI/DNP OND/ODEI/DNP
Pharm/Tox	Edmund Nesti	CDER/OND

Clinical Pharmacology	Bilal AbuAsal Gopichand Gottipati	CDER/OTS/OCP/DCPII
Statistics	Cara Alfaro	CDER/OTS/OB/DBII

Product Names:

a. Proprietary Name: EMGALITY
b. Trade Name: EMGALITYTM
c. Non-Proprietary Name/USAN: Galcanezumab
d. CAS Registry Number: 1578199-75-3
e. Common Name: Immunoglobulin G4, anti-(human calcitonin gene-related peptide) (human-Mus musculus clone III heavy chain), disulfide with human-Mus musculus clone III κ-chain, dimer
f. INN Name: Galcanezumab
g. OBP systematic name: MAB HUMANIZED (IGG4) ANTI P06881 (CALCA_HUMAN) [LY2951742]
h. Other name(s): LY2951742 (company code)

Submissions Reviewed

Submission(s) Reviewed	**Document Date** (disciplines affected)
STN 761063/SN0001	September 27, 2017 (OBP, DMA, DIA)
STN 761063/SN0006	November 8, 017 (DMA)
STN 761063/SN0007	November 13, 2017 (DIA)
STN 761063/SN00017	December 21, 2017 (OBP)
STN 761063/SN0034	March 16, 2018 (OBP, DMA)
STN 761063/SN0036	April 6, 2018 (OBP)
STN 761063/SN0043	April 20, 2018 (OBP, DMA)
STN 761063/SN0044	April 27, 2018 (DMA)
STN 761063/SN0047	May 2, 2018 (DMA)
STN 761063/SN0048	May 9, 2018 (OBP)
STN 761063/SN0051	May 9, 2018 (OBP, DMA)
STN 761063/SN0052	May 9, 2018 (DMA)
STN 761063/SN0053	May 15, 2018 (OBP, DMA, DIA)
STN 761063/SN0054	May 21, 2018 (OBP, DMA)

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]**
(b) (4)	III		(b) (4)	3	N/A
	III			3	N/A

(b) (4)	II		(b) (4)	3	N/A
	V	Eli Lilly and Company		3	N/A
	III		(b) (4)	3	N/A
	III			3	N/A
	III			3	N/A
	V			2	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: None

3. Consults:
The device reviews for the PFS and autoinjector were performed by CDRH. Consult request for CDRH/DOE (Office of Device Evaluation) was processed by OND. Consult request for CDRH/OC (Office of Compliance) was processed by OPQ. Consult memos can be found in DARRTS.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:
The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761063 for galcanezumab manufactured by Eli Lilly and Company. The data submitted in this application are adequate to support the conclusion that the manufacture of galcanezumab 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.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance: ImClone Systems LLC, Branchburg, New Jersey
  - Drug Product: Eli Lilly and Company, Indianapolis, Indiana

- Fill size and dosage form:
  - Prefilled Syringe: 120 mg/(b) (4) mL
  - Autoinjector: 120 mg/(b) (4) mL

- Dating period:
  - Drug Product: 24 months at 2-8°C
  - Drug Substance: (b) (4) months at no more than (b) (4)C
  - For packaged products: Not packaged
  - Stability option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
    - For stability protocols: We have approved the stability protocol(s) in your license application for the purpose of (b) (4) under 21 CFR 601.12.

- Exempt from lot release in accordance with 21 CFR 601.2a. Galcanezumab is a specified product.

C. Benefit/Risk Considerations:

Galcanezumab is an IgG4 monoclonal antibody and it specifically targets CGRP. The level of neuropeptide CGRP as a potent vasodilator is increased in plasma or serum of patients with migraine headaches. There is unmet medical need for new treatments for migraine that are more specific and efficacious.

Review of manufacturing has identified that the methodologies used for drug substance (DS) and DP manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The DS manufacturing process is robust (b) (4) The BLA is recommended for approval from a sterility

assurance and microbiology product quality perspective. We also recommend approval of the commercial manufacture of galcanezumab DS at ImClone Systems LLC, Branchburg, New Jersey and of galcanezumab DP at Eli Lilly and Company, Indianapolis, Indiana. The OBP (Office of Biotechnology Products) product quality and immunogenicity assay, DMA (Division of Microbiology Assessment) microbiological drug substance and drug product, DIA (Division of Inspectional Assessment) facility, and OBP labeling technical assessments are located as separate documents in Panorama.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable: None

II. Summary of Quality Assessments:

A. Molecular Critical Quality Attributes Identification, Risk and Lifecycle Knowledge Management for Galcanezumab

Table 1 below summarizes the critical quality attributes (CQAs) and their control strategy that are relevant specifically to galcanezumab Active Pharmaceutical Ingredient (API) identification, risk and lifecycle Knowledge management.

CQA	Risk	Origin	Control Strategy	Other Notes
Binding to CGRP and prevention of CGRP binding to its receptors. (b) (4)	Efficacy	Intrinsic to the molecule impacted by oxidation, aggregation and fragmentation	(b) (4)	Galcanezumab is an IgG4 monoclonal antibody and Phe233Ala and Leu234Ala have been included into the Fc portion. No ADCC and CDC activities were detected
Identity	Efficacy and safety	Intrinsic to the molecule		N/A
High Molecular Weight (HMW) species/Aggregates (Product related impurity)	Efficacy, Pharmacokinetics, and Safety, Immunogenicity	Manufacturing process (b) (4) (b) (4)		(b) (4)

		(b) (4)	
Low Molecular Weight (LMW) species/Fragments (Product related impurity)	Efficacy	Manufacturing process (b) (4) Minimal change is expected on stability	N/A
Heavy chain (b) (4)	Efficacy	Manufacturing process (b) (4) Minimal change is expected on stability	(b) (4)
Heavy chain (b) (4)	Pharmacokinetics	Manufacturing process (b) (4) Minimal change is expected on stability	
(b) (4)	Pharmacokinetics	Bioreactor conditions Minimal change is expected on stability	(b) (4)
Charge variant profile	Efficacy, PK	Manufacturing process (b) (4)	(b) (4)

(Basic variants)		(b) (4)	(b) (4)	(b) (4)

B. Drug Substance Galcanezumab Quality Summary

Table 2 below summarizes the CQAs and their control strategy that are relevant specifically to galcanezumab DS CQA process risk identification and lifecycle knowledge management.

CQA	Risk	Origin	Control Strategy	Other Notes
		(b) (4)	(b) (4)	N/A
Quantity	Efficacy	Manufacturing process		N/A
pH (General)	Efficacy and stability	Formulation components and stability		N/A
Osmolality (General)	Stability	Composition of the DS		N/A
Description (include clarity and color of solution) (General)	Stability	Formulation components and stability		N/A
Host Cell DNA (Process related impurity)	Safety	(b) (4)		(b) (4)

			(b) (4)
Host Cell Protein (Process related impurity)	Immunogenicity	(b) (4)	(b) (4)
(b) (4) (Process related impurity)	Safety	(b) (4)	
(b) (4) viruses, virus (Process related impurity)	Safety	Cell banks, raw materials	
(b) (4) (Process related impurity)	Safety	Cell banks, raw materials	
Endotoxin (contaminant)	Safety and purity	Endotoxin can be introduced by raw materials and throughout the manufacturing process	
Bioburden (contaminant)	Safety, purity and efficacy (degradation or modification of	Bioburden can be introduced by raw materials and throughout the	

	the product by contaminating microorganisms)	manufacturing process.	(b) (4)	
Leachables (Process-related impurity)	Safety, stability	from manufacturing contact material and the DS container closure system (CCS)		Risk for leachables from CCS is low (b) (4)
(b) (4)	Safety	(b) (4)		(b) (4)
Culture medium (b) (4)	Safety	Cell bank (b) (4)		Levels are below toxicological concern based on the risk assessment
Elemental Impurities	Safety	Cell culture medium, product-contact surfaces, raw materials, excipients, and water		(b) (4) levels are consistently below PDE

- Description:
  Galcanezumab is a recombinant, humanized IgG4 monoclonal antibody and consists of two identical kappa light chains that are each composed of 217 amino acids and two identical gamma heavy chains that are each composed of 445 amino acids. Each heavy chain contains N-linked glycosylation site at Asn296. The predominant form of oligosaccharides at the Asn296 site on either arm is G0F. In addition, each heavy chain contains Gln1 at the N-terminus, which can cyclize to form pyroglutamic acid. Thus, the overall molecular weight of galcanezumab calculated from the peptide backbone (144,084 Da), pyroglutamic acid formation of Gln1, and oligosaccharides (G0F/G0F, 1445 Da for each) is 146,940 Da.

(b) (4)

- Mechanism of Action (MoA):
  Galcanezumab targets CGRP and blocks the binding of CGRP to the CGRP receptor. Although CGRP has two high homologue isoforms (i.e., αCGRP and βCGRP), αCGRP is the predominant isoform and expressed mainly in the peripheral and central nervous system while βCGRP is expressed mostly in the enteric nervous system. CGRP receptor is a heteromeric receptor composed of a G protein-coupled receptor (i.e., calcitonin receptor-like receptor-CRLR) and a receptor activity-modifying protein 1 (i.e., RAMP1). CGRP receptors are expressed mainly in the central nervous system, peripheral nervous system, and cardiovascular system. CGRP is a potent vasodilator and increased plasma or serum levels of CGRP have been associated with painful syndromes such as migraine headache.

- Potency Assay:
  A cell based bioassay uses a human CGRP receptor expressing SK-N-MC-CRE-Luciferase cell line (human supra-orbital neuroepithelioma cell line which has been stably transfected with a CRE-driven luciferase gene) to monitor the level of cAMP activation. Inhibition of CGRP by galcanezumab can be measured by monitoring the decrease in luciferase signal that occurs when cells are exposed to both CGRP and galcanezumab. Potency is defined as percent activity relative to reference standard.

  Note that galcanezumab is highly unlikely to induce Fc-mediated biological effects *in vivo* due to it does not bind to Fcγ receptors tested (CD16a, CD32a, and CD64) nor to the complement component C1q *in vitro*.

- Reference Materials:
  A two-tiered reference material system is in place as per ICH Q6B recommendations.
  (b) (4)

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

- Manufacturing process summary:
  (b) (4)

(b) (4)

- Container closure:
  DS is stored in a (b) (4)

- Dating period and storage conditions:
  The dating period for the DS is (b) (4) months when stored at no more than (b) (4) C. Due to the Agency's request, Lilly agreed (b) (4) in the post-approval stability protocol.

C. Drug Product Galcanezumab Quality Summary:

Table 3 below summarizes the CQAs and their control strategy that are relevant specifically to galcanezumab DP CQA process risk identification and lifecycle knowledge management.

CQA	Risk	Origin	Control Strategy	Other Notes
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process.	(b) (4)	
Endotoxin	Safety, Purity,	Raw materials,		Endotoxin is

(contaminant)	and Immunogenicity	contamination may be introduced throughout the DP manufacturing process	(b) (4)	(b) (4)
Container closure integrity (contaminant)	Safety	Container closure breaches during storage		
Quantity	Efficacy	Manufacturing process		N/A
Description (include clarity, color, and visible particles of solution) (General)	Stability	Formulation components and stability		N/A
Particulate Matter for subvisible particles (product or process related impurities)	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles		N/A
Polysorbate 80 Concentration	Efficacy (b) (4) stability	Formulation component		N/A
pH (General)	Efficacy and stability	Formulation components and stability		N/A
Osmolality (General)	Stability	Composition of the DP.		N/A
Volume of Injection (General)	Efficacy/Dosing	Fill process		N/A
Break-loose and Glide Force (General)	Efficacy and Safety	Device performance		N/A
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS		N/A
Dose Accuracy	Usability impacting Safety and efficacy	(b) (4) device performance		N/A
Visual Inspection	Safety	Device performance		N/A
Injection Process	Usability	Device performance		N/A

	impacting Safety and efficacy			
Button Activation Force	Usability impacting Safety and efficacy	Device performance	(b) (4)	N/A

- Potency and Strength:
  Galcanezumab is supplied as 120 mg/mL solution in two presentations. Potency is defined as the percent activity relative to the current galcanezumab reference standard. The potency assay is the same as described in the DS section of this memo.

- Summary of Product Design:
  Galcanezumab is supplied as a sterile, single-dose, preservative-free solution for subcutaneous injection in two different presentations: PFS and autoinjector. The extractable volume for both PFS and autoinjector is (b) (4)

- List of Excipients:
  (b) (4) histidine, (b) (4) NaCl, (b) (4) polysorbate 80, pH (b) (4)

- Reference Materials:
  The same reference material is used for DS and DP.

- Manufacturing process summary:
  (b) (4)

- Container closure:
  (b) (4)

(b) (4)

- Dating period and storage conditions:
  The dating period for the DP is 24 months when stored at 2-8°C. The data included in the BLA support storage for up to 7 days when stored at temperatures up to 30°C once removed from refrigerator, as described in the labeling.

- List of co-package components, if applicable: none

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Store refrigerated at 2°C to 8°C
- Protect EMGALITY from light until use
- Do not freeze
- Do not shake
- EMGALITY may be stored outside of refrigeration for up to 7 days when stored at temperatures up to 30°C

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture, testing & release. (b) (4)	ImClone Systems LLC 33 ImClone Dr Branchburg, NJ 08876, USA	FEI 3002889358	Pre-license inspection requested	VAI	Approve
(b) (4)			Acceptable based on file review	N/A	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP Manufacture, (b) (4)	Eli Lilly and Company Lilly Corporate Center,	FEI 1819470	Acceptable based on file review	Inspection waived	Approve

(b) (4)	Indianapolis, IN 46285, USA				

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for ImClone Systems LLC (FEI 3002889358) and Eli Lilly and Company (FEI 1819470) proposed for galcanezumab DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable on the basis of their currently acceptable CGMP compliance status and recent relevant inspectional coverage. BLA 761063 is recommended for approval from a facilities assessment perspective.

H. Lifecycle Knowledge Management:

a. Drug Substance:
   i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Proposed reporting category committed in 3.2.R.4 in the BLA submission
3.2.S.2.3.2.4	(b) (4)		
3.2.S.2.5			
3.2.S.2.5			
3.2.S.2.5			
3.2.S.2.5			

3.2.S.2.5	(b) (4)
3.2.S.5	
3.2.S.7.2	
3.2.R.4	
3.2.R.4	
3.2.R.4	

ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Proposed reporting category committed in 3.2.R.4 in the BLA submission
3.2.P.8.2	(b) (4)		
3.2.R.4			

	(b) (4)
3.2.R.4	
3.2.R.4	
3.2.R.4	
3.2.R.4	
3.2.R.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]				X
	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 tem			X	
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN assigned name		X		
20.	Other [fill in]				X
	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}				X

Yan Wang (CDER/OPQ/OBP)

Digitally signed by Yan Wang (CDER/OPQ/OBP)
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Zhihao Peter Qiu

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Patricia Hughes Troost

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Joel Welch

Digitally signed by Joel Welch
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BLA STN 761063

EMGALITY™ (galcanezumab)

Eli Lilly and Company

Nailing Zhang, Ph.D., Primary Reviewer
Yan Wang, Ph.D., Application Technical Lead
Joel Welch, Ph.D., Review Chief

Division of Biotechnology Review & Research IV (DBRR IV)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP CMC Review Data Sheet

1. BLA#: STN 761063

2. Review Date: May 23, 2018

3. Primary Review Team:
   a. **Medical Officer**: Suhail Kasim, Lourdes Villalba and Heather Fitter (TL)
   b**. Pharm/Tox**: Edmund Nesti and Lois Freed (TL)
   c. **Product Quality Team**:
      OPQ/OBP: Nailing Zhang, Yan Wang (ATL) and Joel Welch (Review Chief)
      OPQ/OPF/DMA: Maria (Reyes) Candau-Chacon (DS), Jessica Hankins (DP) and Patricia Hughes (QAL)
      OPQ/OPF/DIA: Ziyang Su and Peter Qiu (QAL)
      OPQ/OBP (labeling): Vicky Borders-Hemphill
   d. **Clinical Pharmacology**: Bilal AbuAsal, Gopichand Gottipati, Sreedharan Sabarinath (TL) and Kevin Krudys (TL)
   e. **Statistics**: Junshan Qiu and Kun Lin (TL)
   f. **CDRH:**
      ODE: Keith Marin and Alan Stevens (TL)
      OC: Katelyn Bittleman and Matthew Krueger (TL)
   g. **RBPM**: Emilios A. Papanastasiou (OND/ODEI/DNP) and Anita Brown (OPQ)

4. Major GRMP Deadlines:
   a. Filing meeting: 11/02/2017
   b. Application orientation meeting: 11/09/2017
   c. Mid-cycle internal meeting: 02/21/2018
   d. Mid-cycle communication: 03/12/2018
   e. Late-cycle internal meeting: 05/23/2018
   f. Late-cycle sponsor meeting: 06/12/2018
   g. Primary review due: 05/27/2018
   h. Secondary review due: 06/03/2018
   i. Wrap-up meeting: 08/02/2018
   j. PDUFA action date: 09/27/2018

5. Communications and submissions:

Communication/Document	Date	Submission	Review status
CMC Pre-BLA Meeting	07/18/2017		Complete
Original submission		STN 761063/SN 0001, 9/27/2017	Complete
Filing review memo	11/16/2017		Complete
Information Request #1	2/19/2018	STN 761063/SN 0034, 3/16/2018	Complete
Information Request #2	3/16/2018	STN 761063/SN 0036, 4/6/2018	Complete
Information Request #3	4/9/2018	STN 761063/SN 0043, 4/20/2018	Complete
Information Request #4	4/27/2018	STN 761063/SN 0048, 5/9/2018	Complete
Information Request #5	5/3/2018	STN 761063/SN 0051, 5/9/2018	Complete
Information Request #6	5/9/2018	STN 761063/SN 0053, 5/15/2018	Complete
Information Request #7	5/17/2018	STN 761063/SN 0054, 5/21/2018	Complete

6. Drug Product Name/Code/Type:
   a. Proprietary Name: EMGALITY
   b. Trade Name: EMGALITY™
   c. Non-Proprietary Name/USAN: Galcanezumab
   d. CAS Registry Number: 1578199-75-3
   e. Common Name: Immunoglobulin G4, anti-(human calcitonin gene-related peptide) (human-*Mus musculus* clone III heavy chain), disulfide with human-*Mus musculus* clone III κ-chain, dimer
   f. INN Name: Galcanezumab
   g. OBP systematic name: MAB HUMANIZED (IGG4) ANTI P06881 (CALCA_HUMAN) [LY2951742]
   h. Other name(s): LY2951742 (company code)

7. Pharmacological Category: Therapeutic monoclonal antibody to the human calcitonin gene-related peptide (CGRP) / migraine prophylaxis.

8. Dosage Form: liquid in pre-filled syringe and autoinjector

9. Strength/Potency:
   (i): The concentration/strength of the Drug Product: 120 mg (b) (4) mL
   (ii): Type of potency assay(s): Potency is defined as percent activity relative to reference standard, using the (b) (4) cell line which has been stably transfected with a (b) (4) to monitor the level of cAMP activation. Inhibition of CGRP by galcanezumab can be measured by monitoring the decrease in (b) (4) signal that occurs when cells are exposed to both CGRP and galcanezumab.

10. Route of Administration: subcutaneous injection

11. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA.
			Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA
			Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA
			Yes	Defer to the DMA and DIA reviewers
			Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA
			Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA
			Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA
			Yes	No review was required as all information related to safety and compatibility with the

		(b) (4)		product was provided in the BLA

12. Inspectional Activities: The pre-license inspection on the drug substance manufacturing site at ImClone Systems, LLC (33 ImClone Dr, Branchburg, NJ 08876-3903) was conducted on (b) (4) The inspection covered the manufacture of drug substance from (b) (4) The inspection was system-based and covered Quality, Production, Laboratory Control, Materials, and Facilities and Equipment Systems. Form FDA 483 was issued with two observations (b) (4) Lilly responded to Form 483 on March 27, 2018. It was recommended that the inspection be classified as voluntary action indicated.

The pre-license inspection on the drug product manufacturing site at Eli Lilly and Company, Indianapolis, IN was waived.

13. Consults Requested by OBP: The device components of the (b) (4) prefilled syringe (PFS), and Autoinjector are reviewed by CDRH. Consult requests were processed by OND and OPQ.

14. Quality by Design Elements: The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment/Risk Management
	(b) (4) Process Control
	Process Analytical Technology
	Expanded Change Protocol

15. Precedents: None.

16. Administrative:
Signature Block

Name and Title	Signature and Date
Joel Welch, Ph.D. Review Chief, DBRRIV/OBP/OPQ/CDER	See electronic signature and date
Yan Wang, Ph.D. Application Technical Lead, DBRRIV/OBP/OPQ/CDER	See electronic signature and date
Nailing Zhang, Ph.D. Primary reviewer, DBRRIV/OBP/OPQ/CDER	See electronic signature and date

Summary of Quality Assessments

1. Primary Reviewer Summary Recommendation:
The data submitted in this Biologics License Application (STN 761063) support the conclusion that the manufacture of EMGALITY™ (galcanezumab) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents and meets the standards

recommended by FDA. The conditions used in the manufacturing process had been adequately validated, and the product had been consistently manufactured from (b) (4). It is recommended that EMGALITY™ (galcanezumab) be approved for human use under conditions specified in the package insert.

2. List of Deficiencies to be Communicated: None.

3. List of Post-Marketing Commitments/Requirements: None.

Product quality-related protocols to be approved within BLA 761063 are listed in the table below:

(b) (4)

Product quality-related commitments to be approved within BLA 761063 are listed in the table below:

(b) (4)

[redacted]

4. Review of Common Technical Document - Quality Module 1:

A. Environmental Assessment of Claim of Categorical Exclusion

Eli Lilly and Company claims a categorical exclusion from the requirements of environmental assessment (BLA section 1.12.14) based on 21 CFR §25.15(d) under the provisions of 21 CFR 25.31(b and c). Thus, no environmental assessment needs to be performed. Categorical Exclusion is appropriate for this product and should be granted.

5. Primary Container Labeling Review:

The carton and container labels are reviewed by OBP. The OBP carton and container labeling review will be uploaded as a separate file in Panorama.

6. Review of Common Technical Document - Quality Module 3.2 and Module 2.3 Quality Overall Summary: The review of Modules 2.3 and 3.2 is included in this review memorandum.

7. Review of Immunogenicity Assays - Module 5.3.1.4:

The current immunogenicity assay, a modified enzyme-linked immunosorbent assay (ELISA), has neat sufficient sensitivity (b) (4)

[redacted]

the parameters such as sensitivity, drug tolerance, selectivity, robustness and stability were not necessary to be performed in the neutralization assay validation. The parameters specific for neutralization assay (i.e., assay cut point, precision and specificity) were validated. The immunogenicity assays were adequately validated. The review of the assays is included in this review memorandum.

BLA EDR Location: \\CDSESUB5\evsprod\BLA761063\761063.enx

TABLE OF CONTENTS

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

2.3 – QUALITY OVERALL SUMMARY (QOS)

Review of the QOS did not identify anything that was not included in Module 3. Therefore, all information will be covered in Module 3. It should be noted that as of finalization of this review, although many updates have occurred to Module 3, the matching updates have not yet been implemented in Module 2.3.

The Figures and Tables in the review were directly copied from the current and previous submissions unless otherwise noted. The reviewer comments are addressed in *italics*.

S. DRUG SUBSTANCE

3.2.S.1 General information

3.2.S.1.2 Structure

Galcanezumab is a humanized immunoglobulin G4 (IgG4) isotype monoclonal antibody composed of two identical immunoglobulin kappa light chains (LC) (23,330 Da each) and two identical immunoglobulin gamma heavy chains (HC) (48,728 Da each). Each CH contains a single N-linked glycosylation site at Asn296. The predominant form of oligosaccharides at the Asn296 site on either arm is G0F. In addition, each CH contains Gln1 at the N-terminus, which can cyclize to form pyroglutamic acid. Thus, the overall molecular weight of galcanezumab calculated from the peptide backbone (144,084 Da), pyroglutamic acid formation of Gln1, and oligosaccharides (G0F/G0F, 1445 Da for each) is 146,940 Da.

The higher order structure of galcanezumab was characterized using (b) (4) techniques. The secondary structure is predominantly β-sheet, the tertiary structure is consistent with a natively folded protein, and the quaternary structure/association state is consistent with the aforementioned chemical structure. Additional details are provided in Section 3.2.S.3.1 *Elucidation of Structure and Other Characteristics*.

The overall structure of galcanezumab and the protein sequences for the LC and the HC are provided in figures below (Note that variable region is shown in blue, complementarity determining regions (CDRs) in red, and constant region in black).

Figure 3.2.S.1.2-3 Schematic Diagram of Galcanezumab

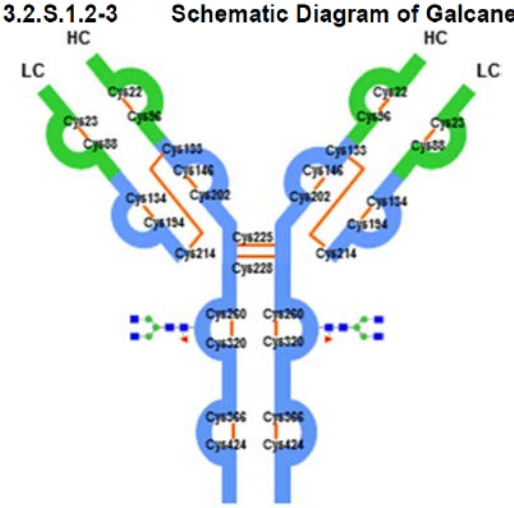

Figure 3.2.S.1.2-1 Light Chain Amino Acid Sequence of Galcanezumab

```
        10         20         30         40         50         60
DIQMTQSPSS LSASVGDRVT ITCRASKDIS KYLNWYQQKP GKAPKLLIYY TSGYHSGVPS

        70         80         90        100        110        120
RFSGSGSGTD FTLTISSLQP EDFATYYCQQ GDALPPTFGG GTKVEIKRTV AAPSVFIFPP

       130        140        150        160        170        180
SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT

       190        200        210  214
LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC
```

Figure 3.2.S.1.2-2 Heavy Chain Amino Acid Sequence of Galcanezumab

```
        10         20         30         40         50         60
QVQLVQSGAE VKKPGSSVKV SCKASGYTFG NYWMQWVRQA PGQGLEWMGA IYEGTGKTVY

        70         80         90        100        110        120
IQKFADRVTI TADKSTSTAY MELSSLRSED TAVYYCARLS DYVSGFGYWG QGTTVTVSSA

       130        140        150        160        170        180
STKGPSVFPL APCSRSTSES TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG

       190        200        210        220        230        240
LYSLSSVVTV PSSSLGTKTY TCNVDHKPSN TKVDKRVESK YGPPCPPCPA PEAAGGPSVF

       250        260        270        280        290        300
LFPPKPKDTL MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR

       310        320        330        340        350        360
VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL PPSQEEMTKN

       370        380        390        400        410        420
QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD GSFFLYSRLT VDKSRWQEGN

       430        440   445
VFSCSVMHEA LHNHYTQKSL SLSLG
```

3.2.S.1.3 General Properties

Galcanezumab is designed to bind calcitonin gene-related peptide (CGRP), inhibiting its activity as a sensory neuropeptide in the trigeminal system - an important mechanism in the pathophysiology of migraine. The characteristics of this macromolecule are outlined below:

- Molecular Mass: 144,084 Da (non-glycosylated, disulfide linked).
- Description: Clear to opalescent, colorless to slightly yellow to slightly brown solution, free of visible particles.
- pI: (b) (4)
- Extinction Coefficient (theoretical): (b) (4)
- Solubility at 25°C: > 147 mg/mL in (b) (4) Histidine buffer formulation at pH (b) (4)

Reviewer Comment: *The experimentally determined extinction coefficient is 1.57 $(mg/mL)^{-1}cm^{-1}$. The applicant stated that since the extinction coefficient values differ by ≤10%, the historical theoretical extinction coefficient of 1.52 $(mg/mL)^{-1}cm^{-1}$ is used to support commercial manufacturing. This is acceptable.*

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The addresses of the manufacturing, storage, and control facilities are provided in the table below.

	Facility Name	Address	Establishment Identification Number

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Nailing Zhang

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Yan Wang (CDER/OPQ/OBP)

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Joel Welch

Digitally signed by Joel Welch
Date: 5/23/2018 04:08:16PM
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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Jessica Hankins, Ph.D.
BRANCH CHIEF: Patricia Hughes, Ph.D.

BLA:	761063
Applicant:	Eli Lilly and Company
US License Number:	1891
Submission Reviewed:	Original BLA
Product:	galcanezumab (Emgality)
Indication:	Migraine prophylaxis
Dosage Form:	Solution for injection (120 mg/(b)(4)mL)
Manufacturing Sites:	Eli Lilly and Company Indianapolis, IN USA (FEI: 1819470)
FDA Receipt Date:	9/26/2017
Action Date:	9/27/2018

Conclusion and Approvability Recommendation

The drug product portion of this BLA, as amended, is recommended for approval from a product quality microbiology and sterility assurance perspective.

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	09/27/2017	Original BLA
0006	11/08/2017	Response to Information Request
0034	03/16/2018	Response to Information Request
0043	04/20/2018	Response to Information Request
0044	04/27/2018	Response to Information Request

0047	05/02/2018	Response to Information Request
0051	05/07/2018	Response to Information Request
0053	05/15/2018	Response to Information Request
0054	05/21/2018	Response to Information Request

Reviewer comment: The BLA references the sponsor's Type V DMF (b) (4) *for background information regarding the* (b) (4) *at the Eli Lilly site and a letter of authorization was provided. The sponsor's DMF was not reviewed because the necessary data required for review of* (b) (4) *of the galcanezumab was provided in the BLA.*

Module 3.2

P.1 Description and Composition of the Drug Product (b) (4)

The DP is supplied as a 120 mg/mL solution in a (b) (4), type (b) (4) glass syringe barrel with (b) (4) plunger. The container closure system (CCS) is (b) (4) a delivery device for patient administration.

The composition of the DP is listed below (copied from the submission).

Table 3.2.P.1.2-1 Composition of Galcanezumab Injection

Ingredient	Quantity (mg) per Syringe[1]	Function	Reference to Standards
Active Ingredient			
Galcanezumab	120	Drug Substance	Internal Standard: See Section 3.2.S.4.1, Specification
Other Ingredients			
L-Histidine	0.5	(b) (4)	USP, Ph. Eur.
L-Histidine Hydrochloride Monohydrate	1.5		Ph. Eur.
Sodium Chloride	8.8		USP, Ph. Eur.
Polysorbate 80	0.5		USP, Ph. Eur.
Water for Injection	*q.s.* (b) (4)		USP, Ph. Eur.

Abbreviation: Ph. Eur. = European Pharmacopoeia; *q.s.* = quantity sufficient; USP = United States Pharmacopoeia.
[1] An overfill volume of 0.06 mL is included to enable delivery of 1 mL. Quantities in the table do not include overfill.

Reviewer comment: (b) (4) (b) (4)

in sequence 0034.

DESCRIPTION IS SATISFACTORY

P.2 Pharmaceutical Development

(b) (4)

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(b) (4)

Conclusion

I. The BLA, as amended, is recommended for approval from a sterility assurance and product quality perspective.

II. Product quality aspects other than microbiology should be reviewed by OBP.

III. Inspection follow-up items were not identified.

Quality Microbiology Information Requests Sent

(b) (4)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 5/20/2018
To: Administrative File, STN 761063/0
From: Ziyang Su, Ph.D., Chemist, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License: 1891
Applicant: Eli Lilly and Company
Mfg. Facility: Drug Substance — *ImClone Systems LLC*, Branchburg, NJ, USA FEI 3002889358
Drug Product — *Eli Lilly and Company*, Indianapolis, IN, USA FEI 1819470
Product: Emgality™ (Galcanezumab), Solution for Injection
Dosage: 120 mg/mL
Indication: Migraine Prophylaxis
Due Date: 5/27/2018

RECOMMENDATION:

Approval: This submission is recommended for approval from a facilities assessment perspective.

SUMMARY

The subject BLA proposes commercial manufacture of Galcanezumab DS at ImClone Systems LLC, Branchburg, NJ (FEI 3002889358), and Galcanezumab DP at Eli Lilly and Company, Indianapolis, IN (FEI 1819470). (b) (4)

Galcanezumab (calcitonin-gene related peptide [CGRP] neutralizing antibody) is a humanized monoclonal IgG4 antibody (120 mg/mL) developed for prevention of migraine headache. Galcanezumab binds to CGRP, which is released from activated trigeminal sensory nerves and plays a role in neurotransmission and the dilation of intracranial and extracranial blood vessels. CGRP binds CGRP G-protein-coupled receptors on the cell surface of neurons and other cells and activates the cyclic adenosine monophosphate signaling pathway and causes many of the symptoms of migraine and cluster headache. The commercial Galcanezumab injection is a ready-to-inject, fixed-dose, single-use, sterile solution formulation suitable for patient self-administration.

Galcanezumab drug product, 120 mg/mL, is a clear to opalescent, colorless to slightly yellow to slightly brown, steril (b) (4) parenteral solution for subcutaneous (*s.c.*) administration. It is

contained in a (b) (4) glass syringe barrel with an (b) (4) plunger. The container closure system filled with drug product is referred to as the (b) (4) delivery device for patient administration.

ASSESSMENT

(b) (4)

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(b) (4)

CONCLUSION

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for ImClone Systems LLC (FEI 3002889358) and Eli Lilly and Company (FEI 1819470) proposed for galcanezumab DS and DP manufacture. All

proposed manufacturing and testing facilities are acceptable on the basis of their currently acceptable CGMP compliance status and recent relevant inspectional coverage.

BLA 761063 is recommended for approval from a facilities assessment perspective.

Ziyang Su -S

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Date: 2018.05.21 15:32:08 -04'00'

Ziyang Su, Ph.D.
Chemist
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -S

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Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: May 16, 2018
To: Administrative File, STN 761063/0
From: Reyes Candau-Chacon, Ph.D., Reviewer, OPQ/OPF/DMA/BIV
Through: Patricia Hughes, Ph.D., Branch Chief, OPQ/OPF/DMA/BIV
Subject: New Biologic License Application (BLA)
US License: 1891
Applicant: Eli Lilly and Company
Facilities: ImClone Systems LLC, 33 ImClone Dr., Branchburg, NJ 08876, (FEI # 3002889358)
Product: galcanezumab
Dosage: solution for injection (120 mg (b) (4) mL)
Indication: Migraine Prophylaxis
Due date: PDUFA date September 27, 2018 (Primary review due May 27, 2018)

Recommendation for Approvability: BLA 761063 is recommended for approval from a microbial control and microbiology product quality perspective.

Review Summary

Eli Lilly and Company has submitted BLA 761063 to license galcanezumab and the associated drug substance and drug product manufacturing processes. In addition, several comparability protocols are included in the Regional Section of the BLA.

BLA 761063 was submitted in eCTD on September 27, 2017. This review contains the assessment of the manufacturing process of galcanezumab (b) (4) from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Hankins.

Amendments Reviewed for Drug Substance Quality

Information Request date	Question numbers	Amendment sequence	Amendment date
February 19, 2018	Microbiology DS 1 to 3	0034	March 16, 2018
April 20, 2018	Microbiology DS 1 to 3	0044	April 27, 2018
May 4, 2018	Questions 1 to 7	0052	May 9, 2018
May 9, 2018	Microbiology DS 1a to 1d	0053	May 15, 2018

(b) (4)

Conclusion

I. The drug substance part of BLA 761063 was reviewed from a microbial control and microbiology product quality perspective and is recommended for approval.

II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by an OBP reviewer.

III. Refer to Panorama for cGMP status of the relevant facilities.

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