CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761248Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: 1/31/2024

1. Application/Product Information

BLA number	761248
Submission Type	Resubmission (June 12, 2023), review extension due to major amendment
Regulatory Pathway	NME 351(a), Breakthrough, Fast Track
Associated IND/BLA	IND 109157
Review Designation	Priority Review
Applicant	Eli Lilly and Company
Indication	KISUNLA is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with KISUNLA should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials.
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name:** KISUNLA
	Non-proprietary Name: donanemab-azbt
	OBP Naming: MAB HUMANIZED (IGG1) ANTI P05067 (A4_HUMAN) [LY3002813]
Drug Product Description	Donanemab is a humanized IgG-1 antibody directed at an N-terminal, third amino acid, pyroglutamate (N3pG) formation of amyloid beta (Aβ) epitope that is present only in brain amyloid plaques and is being developed as a treatment for Alzheimer's disease (AD). Donanemab consists of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains with 2 interchain disulfide bonds connecting the 2 arms.

	The mechanism of action of donanemab is targeting and removal of existing cerebral amyloid plaque through microglial-mediated phagocytosis of the deposited amyloid plaque. Donanemab targets the N3pG amyloid beta specific to amyloid plaque in the population of patients with early symptomatic AD with existing brain amyloid load.		
Dosage Form	Injection		
Strength	350 mg/20 mL (17.5 mg/mL)		
Route of Administration	Intravenous infusion		
Primary Container Closure System	Vial		
Device Information	N/A		
Co-packaged Product Information	None		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance	Ying-Xin Fan	Jacek Cieslak
	Drug product		
	Immunogenicity Assay		
	Facility	Lindsey Brown (DS) Wendy Tan (DP)	Zhong Li
	Microbiology	Lindsey Brown (DS) Wendy Tan (DP)	Maxwell Van Tassell
	RBPM	Nowrin Kakon	
	ATL	Jacek Cieslak	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability

Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761248 for KISUNLA (donanemab-azbt) manufactured by (b) (4)

The data submitted in this application are adequate to support the conclusion

that the manufacture of KISUNLA 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)

  FEI Number: (b) (4)

- **Drug Product:**

  (b) (4)

  FEI Number: (b) (4)

b. Fill size and dosage form: 350 mg/20 mL (17.5 mg/mL), injection

c. Dating Period:

- **Drug Product:** 24 months at 2°C to 8°C
- **Drug Substance:** (b) (4) months at (b) (4) °C
- **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 and drug product under 21 CFR 601.12.

d. Exempt from lot release:

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

4. Basis for Recommendation

a. Summary:

KISUNLA (donanemab-azbt) is indicated to slow disease progression of Alzheimer's disease, an irreversible, progressive neurodegenerative disease. FDA recognized the urgent and unmet medical need for effective treatments for Alzheimer's disease and particularly for treatments to delay, halt, or reverse its pathophysiological processes and donanemab received breakthrough designation

for this indication on June 21, 2021 and received Fast Track designation on July 20, 2018.

BLA 761248 was initially submitted as a rolling BLA with 3 portions: portion 1 in SN 0001 dated September 3, 2021, portion 2 in SN 0003 dated March 4, 2022, and portion 3 in SN 0002 May 18, 2022. The Agency issued a Complete Response Letter (CRL) on January 18, 2023 due to insufficient safety database to adequately characterize the long-term safety of KISUNLA in the treatment of Alzheimer's disease. The application was approvable from a product quality perspective. The following non-CR product quality additional comment was included in the CRL: Include glycosylation using a validated testing method and establish acceptance criteria for main glycan forms, high mannose, and other afucosylated species with upper and lower limits, as applicable. Provide the results of the method validation for glycosylation profiling and the data and analysis used to set acceptance criteria. Refer to the OPQ primary product quality assessments and ATL Executive Summary finalized in Panorama (December 20, 2022, January 11, and January 13, 2023) and DARRTS (January 17, 2023) for assessment of the originally submitted BLA.

In a resubmission of the BLA (SN 104 dated June 12, 2023), Lilly provided a complete response to the deficiency outlined in the CRL, i.e., information to address the insufficient long-term safety data (clinical deficiency). Lilly provided the results of the method validation for glycosylation profiling and the data and analyses used to set acceptance criteria along with updated specifications (i.e., including Oligosaccharide Profile) in SN 0132 dated September 21, 2023.

The assessment of manufacturing information provided in the application concluded that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. 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 drug substance and drug product. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. No approvability issues were identified from a product quality, sterility assurance, or microbiology product quality perspective.

Donanemab is manufactured (b) (4)

[redacted] The protocols [redacted] were submitted in the BLA and are acceptable.

The 17.5 mg/mL drug product is manufactured [redacted] The vials are 100% visually inspected and stored at 2-8°C. Accepted vials are labeled and packaged into cartons at Lilly [redacted] Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release. Container closure integrity is tested using a validated method as part of the stability program.

The donanemab drug substance will be manufactured [redacted] and the Kisunla drug product [redacted] In lieu of on-site pre-licensing inspection for the drug substance manufacturing facility, [redacted] a review of requested manufacturing site records under Section 704(a)(4) was conducted and found satisfactory. Pre-licensing inspections were conducted [redacted] was found acceptable for the manufacture of donanemab drug product. Lilly removed [redacted] as a drug product manufacturing site from the application, but the quality control testing and primary and secondary packaging/labeling of drug product operations are acceptable for this site.

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 KISUNLA (i.e., there is no specific test method described in regulation for KISUNLA that establishes an official standard of potency). We next considered whether potency is a factor for KISUNLA 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 KISUNLA for purposes of § 610.61(r) because lot variability is not a concern for KISUNLA as KISUNLA'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)

ii.

iii. Future inspection points to consider: refer to the BLA 761248 Executive Summary uploaded to DARRTS on 1/17/2023

c. Drug Product:

i. Protocols approved:
- Drug product stability protocol
- Addition of a new product into a drug product commercial multi-product facility

ii. Residual risk: none identified

iii. Future inspection points to consider: none

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

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

/s/

JACEK CIESLAK
02/07/2024 02:21:53 PM

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Product Quality Assessment III

LABELS AND LABELING ASSESSMENT

Date of Assessment:	February 1, 2024
Assessor:	Liming Lu, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Ying-Xin Fan, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XVI
Application:	BLA 761248
Applicant:	Eli Lilly and Company
Submission Date:	June 12, 2023
Product:	Kisunla (donanemab-azbt)
Dosage form(s):	Injection
Strength and Container-Closure:	350 mg/20 mL (17.5 mg/mL) in a single-dose vial
Purpose of assessment:	The Applicant re-submitted a biologics license application for the Agency assessment.
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling are **acceptable** from an OPQA III labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

CONCLUSION

The prescribing information (submitted on January 26, 2024), medication guide (submitted on June 12, 2023), container labels and carton labeling (submitted on June 12, 2023) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on June 12, 2023)
  \\CDSESUB1\EVSPROD\bla761248\0104\m1\us\proposed-uspi.docx
- Medication Guide (submitted on June 12, 2023)
  \\CDSESUB1\EVSPROD\bla761248\0104\m1\us\proposed-medguide.docx
- Container Labels (submitted on June 12, 2023)
  \\CDSESUB1\EVSPROD\bla761248\0104\m1\us\contain-350mg-vial-1ct.pdf

(b) (4)

- Carton Labeling (submitted on June 12, 2023)
  \\CDSESUB1\EVSPROD\bla761248\0104\m1\us\carton-350mg-vial-1ct.pdf

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), 21 CFR 600.3(k)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	☐ Yes ☐ No ☒ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The label is small and could be considered a partial label. Thus, the qualifying phrase "Manufactured by" and the U.S. license number are not required per 21 CFR 610.60(c).

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, Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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

[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."

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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: From the last review cycle, the Medication Guide statement was recommended by DMEPA to be relocated from the principal display panel (PDP) of the carton labeling, with the company website to the secondary display area on the side panel under the recommended dosage statement to avoid cluttering for important information.

The applicant has revised as requested in the re-submission.

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The container is enclosed in a package.

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The product contains a container label.

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

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

The applicant has confirmed that no visible text on the ferrule and cap overseal of the vials.

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

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

The applicant has confirmed that sufficient area of the vial remains uncovered for both its full height and circumference to allow for visual inspection when the label is affixed to the container. The full height visual area is located between the 2 ends of the label and is approximately 15 mm wide. The full circumference visual area is located between the bottom of the label and the bottom of the vial is approximately 10 mm high.

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

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

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

No 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

Comment/Recommendation: The label does not display text in Spanish.

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

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) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *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

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required.

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

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), 21 CFR 600.3(k)	✓ 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

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

[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.

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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *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

Comment/Recommendation: The applicant has revised storage statement to include "If refrigeration not available, may be stored at room temperature (20°C to 25°C [68°F to 77°F]) for up to 3 days" as recommended by the agency from the last review cycle.

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: The product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, anhydrous citric acid, polysorbate 80, and sodium citrate.

The established names have been revised (b) (4) (b) (4)

Revise the ingredient list as follows:
"Each mL of solution contains 17.5 mg of donanemab-xxxx, and anhydrous citric acid (0.32 mg), polysorbate 80 (0.20 mg), sodium citrate (2.15 mg), sucrose (80 mg), and Water for Injection, USP, at a pH of 5.5 - 6.5"

Resubmit an updated Description and Composition to section 3.2.P.1 adding a footnote to the table that includes (b) (4) calculations. Ensure that all inactive ingredients with a USP monograph are provided as such.

The Applicant has revised the ingredients as requested in the re-submission including the conditionally approved 4-letter suffix.

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

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

Comment/Recommendation: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with Product Quality Assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for donanemab products (i.e., there is no specific test method described in regulation for donanemab products that establishes an official standard of potency) and 2) Product Quality Assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Kisunla because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ 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) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

No 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

Comment/Recommendation: The label does not display text in Spanish.

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

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

Comment/Recommendation: The drug product does not contain phenylalanine.

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

Comment/Recommendation: The drug product does not contain sulfites.

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

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

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

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 Draft Guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: In order to reduce clutter, we recommend not including the USP descriptor within Section 2; we recommend only including this descriptor in product quality sections (Sections 3, 11, and 16), as applicable.

The applicant has 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), FD&C Act Section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: recommend revising the inactive ingredients list read as:

Each mL of solution contains 17.5 mg donanemab-azbt~~xxxx~~, anhydrous citric acid (b) (4)(0.32 mg), polysorbate 80 (0.20 mg), sodium citrate (b) (4)(2. (b) (4)15 mg), sucrose (80 mg), and Water for Injection, USP, at a pH of 5.5 to- 6.5.

The applicant has revised the inactive ingredients as requested in the re-submission.

Recommend revising the statement in the first paragraph that read "Donanemab-azbt is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against insoluble N-truncated pyroglytamate amyloid beta, and is expressed in a Chinese hamster ovary cell line."

The applicant has revised as requested.

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.	☐ Yes ☐ No ☒ N/A

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

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☐ Yes ☐ No ☒ N/A

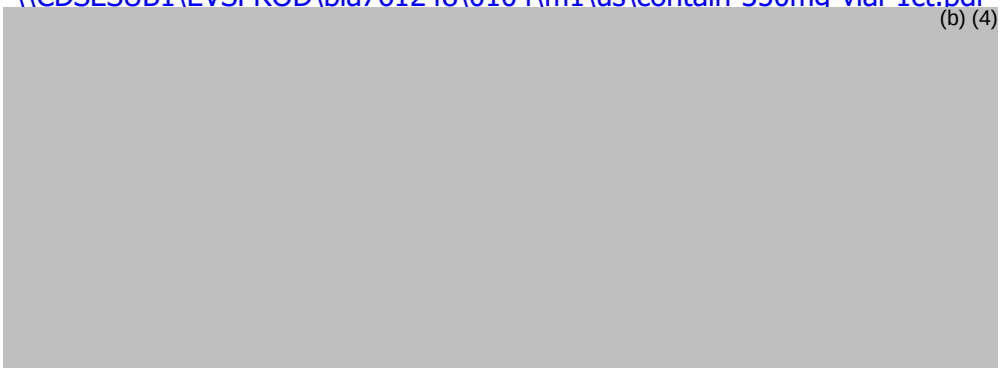
MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on January 26, 2024)
  \\CDSESUB1\EVSPROD\bla761248\0156\m1\us\proposed-uspi-clean.docx
- Medication Guide (submitted on June 12, 2023)
  \\CDSESUB1\EVSPROD\bla761248\0104\m1\us\proposed-medguide-clean.docx
- Container Labels (submitted on June 12, 2023)
  \\CDSESUB1\EVSPROD\bla761248\0104\m1\us\contain-350mg-vial-1ct.pdf

(b) (4)



- Carton Labeling (submitted on June 12, 2023)
  \\CDSESUB1\EVSPROD\bla761248\0104\m1\us\carton-350mg-vial-1ct.pdf

(b) (4)

Liming Lu

Digitally signed by Liming Lu
Date: 2/01/2024 08:38:00AM
GUID: 633d82d0001fb9cd8535e78c71271f3d

Ying Xin Fan

Digitally signed by Ying Xin Fan
Date: 2/01/2024 09:05:20AM
GUID: 508da6dc000266e7f77d37bc2e4a5a87

BLA Executive Summary
Assessment Date: 1/17/2023

1. Application/Product Information

BLA number	761248
Submission Type	Original submission
Regulatory Pathway	NME 351(a), Breakthrough, Fast Track
Associated IND/BLA	IND 109157
Review Designation	Priority Review
Applicant	Eli Lilly and Company
Indication	(b) (4)
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name:** Kisunla
	Non-proprietary Name: donanemab-azbt
	OBP Naming: MAB HUMANIZED (IGG1) ANTI P05067 (A4_HUMAN) [LY3002813]
Drug Product Description	Donanemab is a humanized IgG-1 antibody directed at an N-terminal, third amino acid, pyroglutamate (N3pG) formation of amyloid beta (Aβ) epitope that is present only in brain amyloid plaques and is being developed as a treatment for Alzheimer's disease (AD). Donanemab consists of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy

	chains with 2 interchain disulfide bonds connecting the 2 arms. The mechanism of action of donanemab is considered to be the targeting and removal of existing cerebral amyloid plaque through microglial-mediated phagocytosis of the deposited amyloid plaque. Donanemab targets the N3pG amyloid beta specific to amyloid plaque in the population of patients with early symptomatic AD with existing brain amyloid load.		
Dosage Form	Intravenous infusion		
Strength	350 mg/20 mL (17.5 mg/mL)		
Route of Administration	Intravenous infusion		
Primary Container Closure System	Vial		
Device Information	N/A		
Co-packaged Product Information	None		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance (DS)	Ying-Xin Fan	Jacek Cieslak
	Drug product (DP)	Ying-Xin Fan	Jacek Cieslak
	Immunogenicity Assay	Ying-Xin Fan	Jacek Cieslak
	Facility	Wendy Tan (DP) Lindsey Brown (DS)	Zhong Li
	Microbiology	Wendy Tan (DP) Lindsey Brown (DS)	Maxwell Van Tassell

	RBPM	Erica Keafer
	ATL	Jacek Cieslak
OPQ Issued Consults	None	

2. Recommendation and Conclusion on Approvability
OPQ Recommendation: Approval

From a product quality perspective, the Office of Pharmaceutical Quality (OPQ), CDER, does not note any product quality deficiencies that would preclude approval of BLA 761248 for Kisunla manufactured (b) (4) at this time. However, due to clinical deficiencies, this application will not be approved during this assessment cycle. The residual product quality issues listed below will be communicated to the sponsor in the FDA Complete Response (CR)

3. Additional CMC Comments to Be Included in the CR Letter:

Include glycosylation profiling in the release specification for donanemab drug substance using a validated testing method and establish acceptance criteria for main glycan forms, high mannose, and other afucosylated species with upper and lower limits, as applicable. Provide the results of the method validation for glycosylation profiling and the data and analysis used to set acceptance criteria.

4. Basis for Recommendation

a. Summary:

KISUNLA (donanemab-azbt) is indicated to slow disease progression of Alzheimer's disease, an irreversible, progressive neurodegenerative disease. The FDA recognizes the urgent and unmet medical need for effective treatments for Alzheimer's disease and particularly for treatments to delay, halt, or reverse its pathophysiological processes. Donanemab received breakthrough designation for this indication on June 21, 2021 and received Fast Track designation on July 20, 2018.

The assessment of manufacturing information provided in the application concluded that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. 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 drug substance and drug product. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their

intended purpose. No approvability issues were identified from a product quality, sterility assurance, or microbiology product quality perspective.

Donanemab is manufactured (b) (4)

The protocols (b) (4) were submitted in the BLA and are acceptable.

The 17.5 mg/mL drug product is manufactured (b) (4) The vials are 100% visually inspected and stored at 2-8°C. Accepted vials are labeled and packaged into cartons at Lilly (b) (4) Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release. Container closure integrity is tested using a validated method as part of the stability program.

The donanemab drug substance will be manufactured (b) (4) (b) (4)) and the Kisunla drug product (b) (4) (b) (4)). Pre-licensing inspections or assessments were conducted (b) (4) (b) (4) were found acceptable for the proposed operations. Lilly removed (b) (4) (b) (4) as a drug product manufacturing site from the application.

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:

Not applicable: due to clinical deficiencies this application will not be approved during this assessment cycle.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:

(b) (4)

ii. Residual risk: None identified

iii. Future inspection points to consider:

(b) (4)

(b) (4)

[redacted]

c. Drug Product:

i. Protocols approved:
- Drug Product Stability Protocol
- Addition of a New Product into a Drug Product Commercial Multi-Product Facility

ii. Residual risk: None identified

iii. Future inspection points to consider: None Identified

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.

Attachments:

B. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (type)	CQA	Risk (efficacy, PK/PD, immunogenicity and safety	Origin	Control Strategy
Identity	Identity	Safety and Efficacy	Intrinsic to molecule	(b) (4)
Potency (biological activity)	Cell-based reporter gene assay	Efficacy	Intrinsic to molecule	
	FcγRIIIa binding assay	Efficacy	Intrinsic to molecule	
	C1q binding assay	Efficacy	Intrinsic to molecule	
	FcRn binding	Efficacy	Intrinsic to molecule	
Product related variants/impurities	Charge variants (icIEF)	Efficacy	Bioreactor, (b) (4) Storage, Purification, and DS/DP Storage	
	Monomer (SEC and CE-SDS)	Efficacy	Bioreactor, (b) (4) Storage, Purification, DS/DP Storage	
	High molecular weight species (HMWS, SEC)	Efficacy or immunogenicity	Bioreactor, (b) (4) Storage, Purification, DS/DP Storage	

	Low molecular weight species (LMWS) (CE-SDS)	Efficacy	Bioreactor, (b) (4) Storage, Purification, DS/DP Storage	(b) (4)
Protein Structure	Higher Order Protein Structure (CD, DSC, AUC)	Efficacy	Intrinsic to the molecule	
	Methionine Oxidation (peptide mapping)	Biological activity, PK/PD, stability	Bioreactor, DP Storage, light exposure	
	Hydroxylation (peptide mapping)		Bioreactor, DP Storage, light exposure	
	Deamidation (peptide mapping)		Bioreactor, (b) (4) Storage, DS/DP Storage	
	Alkylation (peptide mapping)			
	Glycation (Peptide Mapping)			
Carbohydrate Structure	Main glycan forms, high mannose, and other afucosylated species	Efficacy Biological activity, PK/PD	Bioreactor	

C. Drug Substance (donanemab) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (type)	CQA	Risk	Origin	Control Strategy
	(b) (4)	Safety and immunogenicity	Bioreactor	(b) (4)
		Safety and immunogenicity	Bioreactor	
		Safety and immunogenicity	(b) (4) purification	
		Safety	Bioreactor	
		Safety	Bioreactor	
		Safety	Bioreactor	

Process-Related Impurities				(b) (4)
	(b) (4)	Safety	Bioreactor	
	Elemental Impurities	Safety	Bioreactor and purification	
	Microbial contamination (bioburden, sterility, CCIT)	Safety	MCB/WCB/ raw material, DS manufacturing process	
	Endotoxin/pyrogen	Safety	MCB/WCB/ raw material, DS manufacturing process	
	Adventitious Virus	Safety	MCB/WCB/ raw material, DS manufacturing process	
	Mycoplasma	Safety	MCB/WCB/ raw material, DS manufacturing process	
Composition and Strength	(b) (4)	Efficacy, safety, and stability	Formulation, (b) (4)	
	pH	Efficacy and safety	Formulation, (b) (4)	
	Protein Concentration (A280)	Efficacy	Formulation, (b) (4) DS/DP process	

D. Drug Product [Kisunla] 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)	CQA	Risk	Origin	Control Strategy

				(b) (4)
Particulate Matter	Visible foreign particles (visual inspection)	Safety, Immunogenicity	DP manufacturing process, CCS, and product	
	Sub-visible particles	Safety, Immunogenicity	DP manufacturing process, CCS and product	
Volume in container	Volume of injection	Efficacy/Dosing	DP process (fill)	
	Gross content	Efficacy/Dosing	DP process (fill)	
Contamination	Microbial contamination (bioburden/sterility) (bioburden, sterility, CCIT)	Safety	MCB/WCB/ raw material, DS manufacturing process	
	Endotoxin/ pyrogen	Safety	MCB/WCB/ raw material, DS manufacturing process	
Composition and strength	Protein Concentration (A280)	Efficacy	Formulation, (b) (4) DS/DP process	
	pH	Safety	Formulation	
	Polysorbate 80 Concentration	Safety and product stability	Formulation, DS/DP Process	
	Color	Safety	Intrinsic to the molecule, formulation	
	Osmolality	Safety, stability, bioactivity	Formulation	
	Excipient Concentration	Safety and product stability	Formulation, (b) (4)	

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/s/

JACEK CIESLAK
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