CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761258Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary (Round #2)
Assessment Date: April 1, 2025

1. Application/Product Information

BLA number	761258
Submission Type	Resubmission (Class 2)
Regulatory Pathway	New Molecular Entity Application 351(a)
Associated IND/BLA	IND 138576
Review Designation	Standard Review
Applicant	Akeso Biopharma Co., Ltd.
Indication	Treatment of adults in combination with either cisplatin, or carboplatin and gemcitabine, for first-line treatment of adults with recurrent or metastatic non-keratinizing nasopharyngeal carcinoma (NPC); or as a single agent in adults with metastatic non-keratinizing NPC and disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: No proprietary name proposed
	Non-proprietary Name/Code Name: penpulimab-kcqx; AK105
	OBP Naming: MAB Humanized (IGG1) ANTI Q15116 (PDCD1_Human) [AK105]
Drug Product Description	Sterile, preservative-free, clear to slightly opalescent, colorless to yellowish solution for dilution (with 0.9% sodium chloride injection), supplied in a single-dose glass vial. Each single dose vial contains 100 mg penpulimab-kcqx, 25.2 mg sodium acetate, 0.9 mg acetic acid, 450.0 mg

	sorbitol, 2.0 mg polysorbate 80, Water for Injection (USP), pH 5.8. Penpulimab-kcqx is a therapeutic recombinant humanized IgG1 monoclonal antibody.		
Dosage Form	Liquid		
Strength	100 mg/10 mL (Vial)		
Route of Administration	Intravenous infusion		
Primary Container Closure System	Single dose vial		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Michael Moses	Andrea George
	Drug product		
	Facility	Bo Chi	Zhong Li
	Microbiology	Bo Chi	Maxwell Van Tassell
	RBPM	Musse Olani	N/A
	ATL	Andrea George	
OPQ Issued Consults	N/A		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761258 for penpulimab-kcqx manufactured by Akeso Biopharma Co., Ltd. The data submitted in this application are adequate to support the conclusion that the manufacture of penpulimab-kcqx 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: Akeso Biopharma Co., Ltd., Zhongshan, China (FEI: 3017057933)
      - Drug Product: Akeso Biopharma Co., Ltd., Zhongshan, China (FEI: 3017057933)
   b. Fill size and dosage form: 100 mg/10 mL single dose vial
   c. Dating Period:
      - Drug Product: 36 months at 5°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: penpulimab-kcqx is exempted from lot release per FR 95-29960.

   e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable

      - Develop, validate, and implement an alternative biological activity assay for an improved control of potency for penpulimab-kcqx drug substance and drug product lot release and stability testing. Submit the analytical procedure, method validation report, proposed acceptance criterion, and justification for the proposed acceptance criterion, to support the implementation of alternative potency assay in a PAS to the BLA by September 30, 2025.

4. Basis for Recommendation
   a. Summary:

   Penpulimab-kcqx (AK105) is a recombinant humanized IgG1 monoclonal antibody directed against human programmed cell death 1 (PD-1) to inhibit its' interaction with programmed cell death ligand 1 (PD-L1) and PD-L2. Penpulimab-

kcqx drug product is manufactured as a sterile, preservative-free, clear to slightly opalescent, colorless to yellowish solution, supplied as a 100 mg/10 mL single dose vial.

PD-1, which is expressed on lymphocytes, normally functions as an immune checkpoint by which binding of PD-1 to its ligands PD-L1/PD-L2 expressed on tumor cells leads to suppression of anti-tumor immune responses, particularly by CD8+ T cells. Penpulimab-kcqx was designed to act as a checkpoint inhibitor to prevent tumor-mediated immune suppression and thereby modulates anti-tumor responses. Penpulimab-kcqx has been engineered with two mutations in the Fc region of the antibody to minimize Fcγ receptor and complement binding.

The potency of penpulimab-kcqx is assessed using two assays. The reporter gene bioassay includes a human T cell line (Jurkat) that constitutively expresses human PD-1 with a luciferase reporter that is driven by a nuclear factor of activated T-cells (NFAT) response element and an aAPC/CHO-K1 cell line that constitutively expresses PD-L1. When these two cell lines are co-cultured, PD-L1 binding to PD-1 inhibits T cell receptor signaling and NFAT-mediated luciferase activity. In the presence of penpulimab-kcqx, PD-L1 cannot bind to PD-1, blocking the PD-L1-mediated inhibition of luciferase activity. Although PD-L2 binding to PD-1 is part of the penpulimab-kcqx MOA and the reporter gene bioassay includes only PD-L1, there is significant overlap in the PD-L1 and PD-L2 binding motifs on PD-1 such that penpulimab-kcqx-mediated inhibition of PD-L1 blocking is representative of PD-L2 blocking.

Biological activity of penpulimab-kcqx is also evaluated via an enzyme-linked immunosorbent assay (ELISA) wherein penpulimab-kcqx binding to PD-1 is detected via oxidation of a colorimetric substrate 3, 3', 5, 5'-tetramethylbenzidine by horseradish peroxidase conjugated to a secondary antibody (anti-human IgG).

To measure potency in both assays, serial dilutions of penpulimab-kcqx test articles and reference standard are co-incubated with Jurkat and CHO-K1 cells in the bioassay or with PD-1 in the ELISA and a 4-parameter unconstrained logistic analysis is used to calculate the dose response curves. Potency evaluated by both assays is reported as a percentage relative to the reference standard.

Penpulimab-kcqx drug substance (DS) is manufactured at Akeso Biopharma Co., Ltd., Zhongshan, China. (b) (4)

(b) (4)

For penpulimab-kcqx drug product (DP) manufacture at Akeso Biopharma Co., Ltd., Zhongshan, China, (b) (4)

The DP manufacturing process is adequate from microbial control and sterility assurance perspective. All sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes. (b) (4)

The overall penpulimab-kcqx 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.

During the review cycle, highly variable results for recovery and method precision were shown for method validation of PD-1 reporter gene bioassay, which indicate poor method performance to enable a robust routine control of the biological activity of penpulimab-kcqx. However, penpulimab-kcqx drug substance and drug product potency are also measured using a PD-1 binding ELISA method that has acceptable performance for routine quality control. Although the binding ELISA method does not fully represent the mechanism of action (MOA) of penpulimab-kcqx, the risk for inadequate potency control is low with the overall control strategy in place. Therefore, a post-marketing commitment (PMC) was issued to develop and implement an optimized assay that is more representative of the presumed in vivo MOA to provide better control of product potency.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate with PMCs/PMRs
Drug Product	-	Adequate with PMCs/PMRs
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 penpulimab-kcqx (i.e., there is no specific test method described in regulation for penpulimab-kcqx that establishes an official standard of potency). We next considered whether potency is a factor for penpulimab-kcqx 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 penpulimab-kcqx for purposes of § 610.61(r) because lot variability is not a concern for penpulimab-kcqx as penpulimab-kcqx’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. Residual risk: PMC to develop, validate, and implement an alternative biological activity assay. Refer to Section 4a for additional details.
iii. Future inspection points to consider: None

c. Drug Product:
   i. Protocols approved:
      - Post-approval annual stability protocol and expiry extension

   ii. Residual risk: PMC to develop, validate, and implement an alternative biological activity assay. Refer to Section 4a for additional details.
   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/

ANDREA L GEORGE
04/01/2025 06:30:09 PM

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	March 6, 2025
Assessor:	Jennifer Kim, PharmD Labeling Assessor Office of Product Quality Assessment III
Through:	Michael Moses, PhD, Product Quality Assessor OPQA III/Division of Product Quality Assessment XIII
Application:	BLA 761258
Applicant:	Akeso Biopharma Co., Ltd.
Submission Date:	October 2, 2024
Product:	Penpulimab-kcqx
Dosage form(s):	Injection
Strength and Container-Closure:	100 mg/10 mL (10 mg/mL) in single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of Penpulimab-kcqx for the treatment of metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.
Recommendations:	The prescribing information, medication guide, patient labeling, instructions for use, 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

BLA 761258 was resubmitted on October 2, 2024, and Appendix B contains labeling comments that were communicated in the previous review cycle.

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 and medication guide submitted on March 6, 025, container labels submitted on February 10, 2025, and carton labeling submitted on February 20, 2025 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 October 2, 2024)
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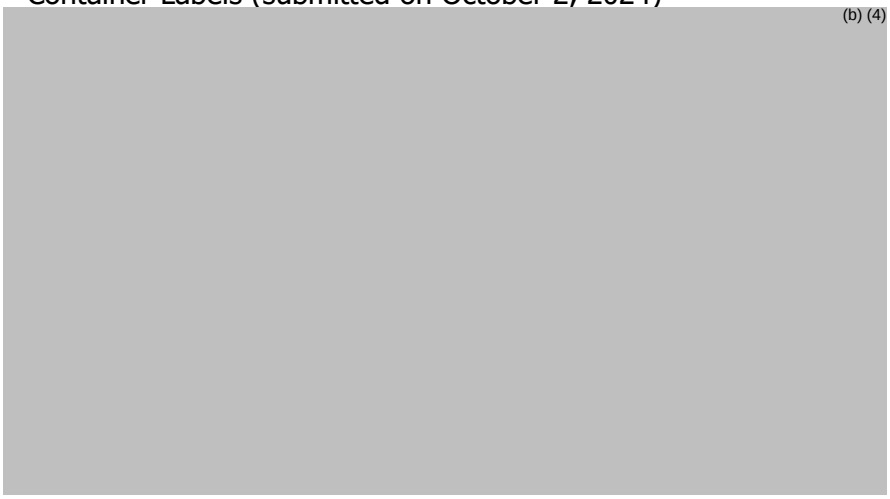
- Medication Guide (submitted on October 2, 2024)
  \\CDSESUB1\EVSPROD\bla761258\0078\m1\us\114-labeling\114a-draft-label\draftmedguide-penpulimab-bla761258-20240927-clean.doc

- Container Labels (submitted on October 2, 2024)

(b) (4)



- Carton Labeling (submitted on October 2, 2024)

(b) (4)

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 (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
Comment/Recommendation: *Approval without proprietary name.* Remove the parenthesis around the nonproprietary name and capitalize the first letter as follows: Penpulimab-kcqx Injection *The applicant revised as requested.*	

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 (i)(1), 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: *Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time*	

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

of the licensure of the BLA. The label is small and could be considered a partial label. Thus, the manufacturer address are not required per 21 CFR 610.60(c). Consider revising the abbreviated qualifying phrase from "Mfg for" and "Mfg by" to "Mfd. for" and "Mfd. by". *The applicant revised as requested.* Consider relocating the U.S. license number to appear below the manufacturer name as follows: Mfd. by: Akeso Biopharma Co., Ltd. US License No. xxxx *The applicant revised as requested.*

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 (i)(1)	✓ Yes ☐ No ☐ N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

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

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

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *The applicant confirms that there is no text on the ferrule and cap overseal of the vials.*	

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

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

(b) (4)

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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Consider relocating the package type term "Single-dose vial" to appear below the route of administration as follows: "Single-dose vial. Discard unused portion." *The applicant revised as requested.*	

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
Comment/Recommendation: Consider deleting the statement (b) (4) from the principal display panel to avoid clutter since it is redundant information. *The applicant revised as requested.*	

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

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

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Add the product's linear barcode to each individual container and carton as required per 21CFR 201.25(c)(2). *The applicant revised as requested.*	

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Consider revising the statement of dosage from "Recommended Dosage: See Prescribing Information." to "Dosage: See Prescribing Information." to avoid clutter. *The applicant revised as requested.*	

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required per 21 CFR 610.60(c).*	

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the storage statement to read "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original container to protect from light. Do not freeze." *The applicant revised as requested.*	

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

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *Approval without proprietary name.*	

[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.

Remove the parenthesis around the nonproprietary name and capitalize the first letter as follows:

Penpulimab-kcqx
Injection

The applicant revised as requested.

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

Comment/Recommendation: *Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.*

Consider revising the abbreviated qualifying phrase from "Mfg for" and "Mfg by" to "Mfd. for" and "Mfd. by".
The applicant revised as requested.

Revise to include a placeholder for the U.S. license number "US License No. xxxx" below the manufacturer address.
The applicant revised as requested.

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Revise the storage statement to read "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original container to protect from light. Do not freeze." *The applicant revised as requested.*	

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

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

Comment/Recommendation:

Include the name and amount of inactive ingredients per 21 CFR 610.61(n) on the side panel as follows:

> Each vial contains 100 mg of penpulimab-kcqx in 10 mL of solution. Each mL also contains acetic acid (0.09 mg), polysorbate 80 (0.2 mg), sodium acetate (2.52 mg), sorbitol (45 mg), and Water for Injection, USP. The pH of the solution is 5.8.
> No preservatives.

To accommodate this change, delete the statement that reads (b) (4) (b) (4) (b) (4) since it is not required.

The applicant revised as requested.

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

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for penpulimab products (i.e., there is no specific test method described in regulation for penpulimab 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 Penpulimab-kcqx 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.* Remove the statement (b) (4) from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable. *The applicant revised as requested.*	

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	✓ Yes ☐ No ☐ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Add the product's linear barcode to each individual container and carton as required per 21CFR 201.25(c)(2). *The applicant revised as requested.*	

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

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

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

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
Comment/Recommendation: Consider deleting the statement (b) (4) from the principal display panel to avoid clutter since it is redundant information. *The applicant revised as requested.*	

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

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

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

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

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A

Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Consider revising the statement of dosage from "Recommended Dosage: See Prescribing Information." to "Dosage: See Prescribing Information." to avoid clutter. *The applicant revised as requested.*	

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

Comment/Recommendation: *Approval without proprietary name.*	

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

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

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

We revised to the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit." per 21 CFR 201.57(c)(3)(iv).
This comment was not communicated to the applicant for consistency with other product labeling. The statement "Inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to yellowish. Discard the vial if the solution is cloudy, discolored, or contains visible particles." is acceptable.

We revised the storage information language to clarify that the total storage time should not exceed 4 hours.
The applicant revised as requested.

We revised the minimum concentration range based on the limitation of the infusion bag size.
The applicant revised as requested.

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

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: We revised the inactive ingredients in alphabetical order. *The applicant 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.[1]	☐ Yes ☐ No ☒ N/A

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

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

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
Comment/Recommendation: Include a placeholder for the 4-letter suffix to the proper name. *The applicant revised to the approved suffix "penpulimab-kcqx".*	

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
Comment/Recommendation: We revised the inactive ingredients in alphabetical order. *The applicant revised as requested.*	

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

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information (submitted on March 6, 2025)
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- Medication Guide (submitted on March 6, 2025)
  \\CDSESUB1\EVSPROD\bla761258\0109\m1\us\114-labeling\114a-draft-label\draft-mg-penpulimab-bla-761258-clean-20250306.docx

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Jennifer Kim

Digitally signed by Jennifer Kim
Date: 3/10/2025 12:17:27PM
GUID: 5e5438d2008138bdbae1db8d4abc0580

Michael Moses

Digitally signed by Michael Moses
Date: 3/10/2025 06:00:33PM
GUID: 5c5af420004e3a3e57d04c387a30231a

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/

ASHLEY R LANE
03/22/2025 01:27:58 AM

BLA Executive Summary
Assessment Date: November 30, 2023

1. Application/Product Information

BLA number	761258
Submission Type	Original Submission
Regulatory Pathway	New Molecular Entity Application 351(a)
Associated IND/BLA	IND 138576
Review Designation	Standard Review
Applicant	Akeso Biopharma Co., Ltd.
Indication	Treatment of adult (b) (4) with metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name No proprietary name proposed
	Non-proprietary Name/Code Name penpulimab-kcqx; AK105
	OBP Naming MAB Humanized (IGG1) ANTI Q15116 (PDCD1_Human) [AK105]
Drug Product Description	Sterile, preservative-free, clear to slightly opalescent, colorless to yellowish solution for dilution (with 0.9% sodium chloride injection), supplied in a single-dose glass vial. Each single dose vial contains 100 mg penpulimab-kcqx, 25.2 mg sodium acetate, 0.9 mg acetic acid, 450.0 mg

	sorbitol, 2.0 mg polysorbate 80, Water for Injection (USP), pH 5.8. Penpulimab-kcqx is a therapeutic recombinant humanized IgG1 monoclonal antibody.		
Dosage Form	Liquid		
Strength	100 mg/10 mL (Vial)		
Route of Administration	Intravenous infusion		
Primary Container Closure System	Single dose vial		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Michael Moses	Riley Myers/ Andrea George
	Drug product	Milos Dokmanovic	Riley Myers
	Immunogenicity Assay	Milos Dokmanovic	Riley Myers
	Facility	Yun Wu/ Bo Chi	Zhong Li
	Microbiology	Yun Wu (DS)/ Bo Chi (DP)	Maxwell Van Tassell
	RBPM	Anita Brown/ Musse Olani	N/A
	ATL	Riley Myers/ Andrea George	
OPQ Issued Consults	N/A		

2. Recommendation and Conclusion on Approvability
Recommendation: Complete Response

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761258 for penpulimab-kcqx manufactured by Akeso Biopharma Co., Ltd. The data submitted in this application are not sufficient to support a conclusion that the manufacture of penpulimab-kcqx is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Akeso Biopharma Co., Ltd. to outline the deficiencies noted below and the information and data that will be required to support approval.

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

Per 21 CFR 601.20 (c) "No product shall be licensed if any part of the process of or relating to the manufacture of such product…would impair the assurances of continued safety, purity, and potency…".

1. Following the pre-license inspection (PLI) of Akeso Biopharma, Co., Ltd., Guangdong, China (FEI 3017057933), the drug substance and drug product manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. FDA has reviewed the responses from the facility, and not all deficiencies have been satisfactorily resolved. Satisfactory responses to these deficiencies should be provided by the facility to the email address provided on the Form FDA 483 Inspectional Observations, prior to submitting your complete response. Your complete response should include the date of the facility's response to the Post-action Letter. The assessment of application approvability and the resolution of inspection deficiencies would be evaluated upon receipt of the complete response and may require re-inspection of the facility.

2. Reference is made to information and data provided during the PLI at Akeso BioPharma Co., Ltd. (FEI 3017057933; Zhongshan, China), and in response to the Agency's IRs dated February 24, 2022, March 11, 2022, May 12, 2022, and September 28, 2023, concerning the cell bank (b) (4)

Taken together, an adequate, well-controlled, and stable production cell bank(s) is currently unavailable for the manufacture of penpulimab-kcqx with continued product quality and sustainable commercial supply.

To resolve these deficiencies, provide data and information to support the qualification of an adequate and well-controlled cell bank(s) to ensure the manufacture of penpulimab-kcqx that is of continued product safety, purity, and potency. These should include, but not be limited to, safety testing results for the new cell bank(s), available cell bank stability test results, comparisons of cell growth data (e.g., growth kinetics, viability, VCD, characteristics of fermentation process, etc.), drug substance release data, and extended analytical characterization data (e.g., glycan analyses, primary, secondary and higher structure, results for product variants using sufficiently sensitive methods, etc.) from materials produced using the new cell bank(s) to historical at-scale manufacturing experience with properly qualified cell bank(s) and clinical experience (where applicable).

3. Reference is made to information provided in the original submission and in response to the Agency's IRs dated March 11, 2022, and August 18, 2022. The totality of information and data provided is inadequate to support the suitability of the following quality control methods for their intended use.

(b) (4)

To resolve these deficiencies, further optimize these methods and validate the optimized methods for their intended use. Provide updated method procedures (if applicable) and method validation/revalidation results to support the suitability of these methods for routine process and product control.

4. Reference is made to the information and data provided in the original submission and in response to the Agency's IR dated September 9, 2021, concerning the penpulimab-kcqx drug product (DP) manufacturing process control strategy. The information provided is insufficient to support the following process control ranges.

(b) (4)

(b) (4)

To resolve these deficiencies, provide additional information and data from appropriate process validation and stability studies to support these process control ranges for routine manufacture.

4. Basis for Recommendation

a. Summary:

Penpulimab-kcqx (AK105) is a recombinant humanized IgG1 monoclonal antibody directed against human programmed cell death 1 (PD-1) to inhibit its' interaction with programmed cell death ligand 1 (PD-L1) and PD-L2. Penpulimab-kcqx drug product is manufactured as a sterile, preservative-free, clear to slightly opalescent, colorless to yellowish solution for dilution (with 0.9% sodium chloride injection), supplied as a 100 mg/10 mL single dose vial.

PD-1, which is expressed on lymphocytes, normally functions as an immune checkpoint by which binding of PD-1 to its ligands PD-L1/PD-L2 leads to a downregulation of immune cell responses. Expression of PD-L1/PD-L2 on tumor cells similarly leads to suppression of anti-tumor immune responses, particularly by CD8+ T cells. Penpulimab-kcqx was designed to act as a checkpoint inhibitor to prevent tumor-mediated immune suppression and thereby modulates anti-tumor responses. Penpulimab-kcqx has been engineered with two mutations in the Fc region of the antibody to minimize Fcγ receptor and complement binding.

The potency of penpulimab-kcqx is assessed using two assays. The reporter gene bioassay includes a human T cell line (Jurkat) that constitutively expresses human PD-1 with a luciferase reporter that is driven by a nuclear factor of activated T-cells (NFAT) response element and a CHO-K1 cell line that

constitutively expresses PD-L1. When these two cell lines are co-cultured, PD-L1 binding to PD-1 inhibits T cell receptor signaling and NFAT-mediated luciferase activity. In the presence of penpulimab-kcqx, PD-L1 cannot bind to PD-1, blocking the PD-L1-mediated inhibition of luciferase activity. Although PD-L2 binding to PD-1 is part of the penpulimab-kcqx MOA and the reporter gene bioassay includes only PD-L1, there is significant overlap in the PD-L1 and PD-L2 binding motifs on PD-1 such that penpulimab-kcqx-mediated inhibition of PD-L1 blocking is representative of PD-L2 blocking.

Biological activity of penpulimab-kcqx is also evaluated via an enzyme-linked immunosorbent assay (ELISA) wherein penpulimab-kcqx binding to PD-1 is detected via oxidation of a colorimetric substrate 3, 3', 5, 5'-tetramethylbenzidine by horseradish peroxidase conjugated to a secondary antibody (anti-human IgG).

To measure potency in both assays, serial dilutions of penpulimab-kcqx test articles and reference standard are co-incubated with Jurkat and CHO-K1 cells in the bioassay or with PD-1 in the ELISA and a 4-parameter unconstrained logistic analysis is used to calculate the dose response curves. Potency evaluated by both assays is reported as a percentage relative to the reference standard.

Penpulimab-kcqx drug substance (DS) is manufactured at Akeso Biopharma Co., Ltd., Zhongshan, China. (b) (4)

(b) (4)

(b) (4)

The DP manufacturing process is adequate from microbial control and sterility assurance perspective. All sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes. (b) (4)

The overall penpulimab-kcqx 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.

However, multiple deficiencies were identified during the pre-license inspection at Akeso BioPharma Co., Ltd. (FEI 3017057933) and not all deficiencies have been satisfactorily resolved. (b) (4)

Therefore, an appropriately qualified cell bank is currently unavailable to support the manufacture of product with continued safety, quality, and potency for licensure. (b) (4)

Refer to Complete Response comments listed above for details.

b. Subdiscipline Recommendation:

Drug Substance - Inadequate

Drug Product	-	Inadequate
Immunogenicity Assay	-	Adequate
Facilities	-	Inadequate
Microbiology	-	Adequate

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

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

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

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

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

/s/

ANDREA L GEORGE
11/30/2023 03:02:38 PM

QING ZHOU
11/30/2023 03:04:43 PM

Recommendation: Pending final determination of manufacturing facility compliance status

BLA Number: 761258
Assessment Date: October 4, 2022

Drug Name/Dosage Form	penpulimab-kcqx (NO TRADE NAME)/injection
Strength/Potency	100 mg/vial (10 mg/mL)
Route of Administration	intravenous infusion
Rx/OTC dispensed	Rx
Indication	Treatment of adult (b) (4) with metastatic non-keratinizing nasopharyngeal carcinoma with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy
Applicant/Sponsor	Akeso Biopharma Co., Ltd.
US agent, if applicable	Akesobio, Inc.

Product Overview:

Penpulimab-kcqx is a humanized IgG1 monoclonal antibody produced in CHO cells that targets human programmed cell death 1 (PD-1) to inhibit its interaction with programmed cell death ligand 1 (PD-L1) and PD-L2. PD-1 is expressed on lymphocytes and binding of PD-L1/PD-L2 to PD-1 downregulates an immune response, which function normally as an immune checkpoint. Tumor cells express PD-L1/PD-L2 in order to suppress an anti-tumor response, particularly by CD8+ T cells. Penpulimab-kcqx is a checkpoint inhibitor that prevents tumor-mediated immune suppression and modulates an anti-tumor response. Penpulimab-kcqx has been engineered with two mutations in the Fc region of the antibody to minimize Fcγ receptor and complement binding. Penpulimab-kcqx is manufactured as a sterile, preservative-free, 100 mg vial.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Michael Moses	DBRRI/OBP/OPQ
Drug Product	Milos Dokmanovic	DBRRI/OBP/OPQ
Labeling	Jennifer Kim	OBP/OPQ
Drug Substance Microbiology and Facility	Yun Wu	DBM/OPMA/OPQ
Drug Product Microbiology and Facility	Bo Chi	DBM/OPMA/OPQ
Microbiology Quality Assessment Lead	Maxwell Van Tassell	DBM/OPMA/OPQ
Facility Quality Assessment Lead	Zhong Li	DBM/OPMA/OPQ
Application Technical Lead	Riley Myers	DBRRI/OBP/OPQ
RBPM	Anita Brown	RBPMBI/OPRO/OPQ

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Ashley Lane	DROOD/ORO/OND
Cross-disciplinary Team Lead	Nicole Drezner	DOII/OOD/OND
Medical Officer	Erica Nakajima (efficacy) & Satinder “Mona” Choudhary (safety)	DOII/OOD/OND
Pharmacology/Toxicology	Kelie Reece	DHOT/OOD/OND
Clinical Pharmacology	Yajun Liu	DCPII/OCP/OTS

Statistics	Mengdie Yuan	DBV/OB/OTS

1. Names

a. Proprietary Name: NO TRADE NAME
b. Trade Name: NO TRADE NAME
c. Non-Proprietary Name/USAN: penpulimab-kcqx
d. CAS Name: 2350298-92-7
e. Common Name: AK105
f. INN Name: penpulimab
g. OBP systematic name: MAB Humanized (IGG1) Anti Q15116 (PDCD1_Human) [AK105]

Submissions Assessed:

Submission(s) Assessed	Document Date
STN 0001/1	May 24, 2021
STN 0002/2	May 26, 2021
STN 0004/4	June 11, 2021
STN 0006/6	July 7, 2021
STN 0007/7	July 16, 2021
STN 00011/11	July 22, 2021
STN 00014/14	August 27, 2021
STN 00015/15	September 8, 2021
STN 00016/16	September 24, 2021
STN 00023/23	November 1, 2021
STN 00027/27	January 20, 2022
STN 00029/29	February 8, 2022
STN 00030/30	February 22, 2022
STN 00031/31	February 25, 2022
STN 00033/33	March 11, 2022
STN 00035/35	March 18, 2022
STN 00037/37	April 4, 2022
STN 00040/40	April 27, 2022
STN 00043/43	May 10, 2022
STN 00044/44	May 19, 2022
STN 00045/45	May 20, 2022
STN 00046/46	May 20, 2022
STN 00049/49	May 24, 2022
STN 00050/50	May 31, 2022
STN 00051/51	June 30, 2022
STN 00054/54	July 13, 2022
STN 00056/56	August 4, 2022
STN 00057/57	August 10, 2022
STN 00060/60	August 23, 2022
STN 00061/61	August 23, 2022
STN 00062/62	September 8, 2022
STN 00063/63	September 15, 2022

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

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	3	N/A		
	III			3	N/A		
	V			2	N/A	July 2, 2021	

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

2. Action codes for Status column: 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 assessed.

B. Other documents:

Document	Application Number	Description
IND	138576	Clinical study

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion: Per 21 CFR 25.31(c), Akeso Biopharma claims a categorical exclusion from the environmental assessment requirements of 21 CFR 25.20, in agreement with FDA’s Guidance for Industry, “Environmental Assessment of Human Drug and Biologics Applications,” penpulimab is considered "naturally occurring in the environment" and when exposed to the environment, is not expected to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. Additionally, no extraordinary circumstances exist as described in 21 CFR 25.21 that

indicate that the product would significantly affect the quality of the human environment or that could trigger the requirement to prepare an environmental assessment.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommendation on approvability of STN 761258 for penpulimab-kcqx manufactured by Akeso Biopharma Co., Ltd. is deferred. Due to COVID 19 travel restriction, the final determinations of compliance status of the drug substance and drug product manufacturing facility, Akeso Biopharma Co., Ltd., Zhongshan, China (FEI: 3017057933) is pending. FDA assessment of the ability of the facility to conduct manufacturing operations in compliance with cGMP is required to support approval of the application. The Akeso Biopharma Co., Ltd facility does not have FDA inspection history and thus, alternative inspection tools could not be applied. Due to restrictions on travel, OPQ may be unable to conduct an inspection of the facility prior to the User Fee Date. OPMA will continue to monitor the public health situation as well as travel restrictions. OPMA is actively working to define an approach for scheduling outstanding inspections once safe travel may resume based on public health need and other factors.

B. Draft CMC Approval Action Letter Language: Not applicable as overall OPQ recommendation is deferred.

C. Benefit/Risk Considerations: Nasopharyngeal carcinoma (NPC) is a tumor of the head and neck which originates in the nasopharynx and is commonly associated with Epstein-Barr virus infection. Patients with NPC experience difficulty breathing and bleeding in the nose and mouth. The available treatments for NPC are platinum-based chemotherapy, radiation, and surgery, which afford an 80% 5-year survival rate. There are no approved treatments for NPC following failure of two of these frontline therapies. Therefore, penpulimab-kcqx may potentially address this unmet need.

The overall control strategy for penpulimab-kcqx manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, process monitoring tests, release, and stability testing ensures process consistency, and drug substance (DS), and drug product (DP) that have appropriate quality and are free of adventitious agents. Due to COVID 19 travel restriction, OPQ is unable to conduct an inspection of the facility at this time to determine the cGMP compliance status of the drug substance and drug product manufacturing facility.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy	Other
PD-1 binding (potency)	Potency	Intrinsic to the molecule. (b) (4)	(b) (4)	

		(b) (4)	(b) (4) (b) (4)
Identity	Safety and Efficacy	Intrinsic to the molecule.	
High molecular weight species (HMWS) (Product-related impurity)	Potency and immunogenicity	(b) (4)	
Low molecular weight species (LMWS) (Product-related impurity)	Potency		
(b) (4)	Pharmacokinetics		
	Potency and Pharmacokinetics		
	Pharmacokinetics		
Appearance of Solution (visible particulates, color and clarity)	Safety and Efficacy		

			(b) (4)	
Protein Content	Efficacy	Manufacturing process		
pH	Safety and Efficacy	Formulation process		
Osmolality	Safety and Efficacy	Formulation		
(b) (4)	Safety	Formulation		

B. Drug Substance [penpulimab-kcqx] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy	Other
Residual HCP (Process-related impurity)	Immunogenicity	(b) (4) (b) (4)	(b) (4)	
Residual DNA (Process-related impurity)	Safety	(b) (4)		
(b) (4) (Process-related	Safety and Immunogenicity	Process related impurity (b) (4)		

impurity)			(b) (4)
(b) (4) (Process-related impurities)	Safety	(b) (4) process related impurities	
Viruses (Contaminant)	Safety	Contamination during manufacture, most likely during cell culture operations.	
Mycoplasma (Contaminant)	Safety	Mycoplasma would most likely be introduced (b) (4)	
Endotoxin (Contaminant)	Safety and Purity	Raw materials and contamination during manufacturing	
Bioburden (Contaminant)	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials and manufacturing process	

- Description: Penpulimab-kcqx is a humanized monoclonal immunoglobulin G1κ consisting of two identical heavy chains (HC) and two identical light chains (LC) covalently linked through inter- and intra-chain disulfide bonds. Each HC and LC are composed of 448 and 214 amino acids, respectively. Each HC contains a leucine to alanine substitution at amino acid residues 235 and 236 and a glycine to alanine substitution at amino acid residue 238 within the Fc domain to minimize the potential for

effector function and deletion of lysine at the C terminus to reduce potential for charge heterogeneity. A single N-linked glycosylation site is in the CH2 domain of each HC at asparagine residue 298.

The extinction coefficient was calculated and confirmed experimentally to be 1.53 mL x mg^{-1} x cm^{-1} at 280 nm.

- Mechanism of Action (MoA): Penpulimab-kcqx selectively binds to PD-1 and inhibits binding of its ligands, PD-L1 and PD-L2. This, in turn, prevents tumor-mediated immune suppression via PD-L1/PD-L2 signaling through PD-1 expressed on lymphocytes and modulates an anti-tumor response.

- Potency Assay: Biological activity of penpulimab-kcqx is evaluated using two assays. The reporter gene bioassay includes a human T cell line (Jurkat) that constitutively expresses human PD-1 with a luciferase reporter that is driven by a nuclear factor of activated T-cells (NFAT) response element and a CHO-K1 cell line that constitutively expresses PD-L1. When these two cell lines are co-cultured, PD-L1 binding to PD-1 inhibits T cell receptor signaling and NFAT-mediated luciferase activity. In the presence of penpulimab-kcqx, PD-L1 cannot bind to PD-1, blocking the PD-L1-mediated inhibition of luciferase activity. Although PD-L2 binding to PD-1 is part of the penpulimab-kcqx MOA and the reporter gene bioassay includes only PD-L1, there is significant overlap in the PD-L1 and PD-L2 binding motifs on PD-1 such that penpulimab-kcqx-mediated inhibition of PD-L1 blocking is representative of PD-L2 blocking. Biological activity of penpulimab-kcqx is also evaluated via an enzyme-linked immunosorbent assay (ELISA) wherein penpulimab-kcqx binding to PD-1 is detected via oxidation of a colorimetric substrate 3, 3', 5, 5'-tetramethylbenzidine by horseradish peroxidase conjugated to a secondary antibody (anti-human IgG). To measure potency in both assays, increasing amounts of penpulimab-kcqx are co-incubated with Jurkat and CHO-K1 cells in the bioassay or with PD-1 in the ELISA and a 4-parameter unconstrained logistic analysis is used to calculate the dose response curves. Potency evaluated by both assays is reported as a percentage relative to the reference standard.

- Reference Materials: (b) (4)

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

- Manufacturing process summary: (b) (4)

(b) (4)

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

C. Drug Product [penpulimab-kcqx] Quality Summary:

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

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

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety (Infection), Purity and Efficacy (degradation or modification of products by contaminating microorganisms)	Contamination may be introduced throughout the manufacturing process, failure of the container closure integrity	(b) (4)	

			(b) (4)
Endotoxin (contaminant)	Safety and purity	Raw materials; contamination may be introduced throughout the DP manufacturing process	
Container closure integrity	Safety (Sterility assurance)	Container closure breaches during manufacture or storage.	
Extractable volume DP	Accurate dosing	(b) (4)	
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS	
Subvisible Particulate Matter (Product or Process Related Impurities)	Safety and Immunogenicity	Manufacturing process and CCS.	
Visible Particles	Safety and Immunogenicity	Through the DP manufacturing process (b) (4)	

			(b) (4)	

- Potency and Strength: Penpulimab-kcqx is supplied at 100 mg/10 mL in a single-use vial. Potency is defined as the percent activity relative to the current reference standard. The potency assay is the same as described for the DS.

- Summary of Product Design: Penpulimab-kcqx 100 mg vial is presented as a sterile, preservative-free, non-pyrogenic liquid formulation in glass vial for intravenous injection at a concentration of 10 mg/mL. The extractable volume is 10 mL.

- List of Excipients: (b) (4) sodium acetate, 45 mg/mL sorbitol, 0.02 % (w/v) polysorbate 80, pH 5.8

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

- Manufacturing process summary: (b) (4)

(b) (4)

- Container closure: The primary container closure system for penpulimab-kcqx 10 mg/mL DP consists of a 10 mL (b) (4) glass vial that is sealed with a grey 20 mm (b) (4) rubber stopper and aluminum flip cap with a (b) (4) disc. Appropriate compatibility studies were performed for the container closure system.

  The secondary container closure system consists of a box, which is sufficient for protection from light.

- Dating period and storage conditions: The dating period for penpulimab-kcqx 10 mg/mL DP is 24 months when stored at 5±3°C.

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

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations: None

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacturing, testing (in-process, release, and stability), and storage; (b) (4)	Akeso Biopharma Co., Ltd, Zhongshan, China	544314741/ 3017057933	PLI recommended	Pending PLI	Pending PLI
Safety testing of unprocessed bulk	(b) (4)		Approve Based on Previous History	N/A	Approve
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug product Manufacturing, In-process Testing, Release and Stability Testing	Akeso Biopharma Co., Ltd.	544314741/ 3017057933	PLI recommended	Pending PLI	Pending PLI

G. Facilities:
Deferred-Travel Restrictions-COVID for Akeso Biopharma Co., Ltd, Zhongshan, China (FEI: 3017057933)

An on-site PLI is recommended for the drug substance and drug product manufacturing facility, Akeso Biopharma Co., Ltd, Zhongshan, China (FEI: 3017057933) because the facility has no prior inspection history by the FDA or MRA health regulatory authorities and the Applicant is

inexperienced. Due to restrictions on travel, OPQ may be unable to conduct an inspection of this facility prior to the User Fee Date.

H. Lifecycle Knowledge Management: Not applicable as the overall OPQ recommendation is deferred.

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/s/

RILEY C MYERS
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