CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761258Orig1s000

OTHER ACTION LETTERS

BLA 761258

COMPLETE RESPONSE

Akeso Biopharma Co., Ltd.
c/o Akesobio, Inc.
Attention: Liang Liu (U.S. Agent)
81 Belhaven Avenue
Daly City, CA 94015

Dear Liang Liu:

Please refer to your biologics license application (BLA) dated July 15, 2021, received July 16, 2021, and your amendments, submitted under section 351(a) of the Public Health Service Act for AK105.

We acknowledge receipt of your major amendment dated June 14, 2022, which extended the goal date by three months.

We also refer to the general advice letter, issued October 14, 2022, notifying you that the extended PDUFA date of October 16, 2022, would be missed due to travel restrictions preventing the inspection of Akeso Biopharma Co., Ltd.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. Given the changing treatment landscape for nasopharyngeal carcinoma (NPC), current results of Study AK105-202 in patients with metastatic non-keratinizing NPC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy treated with penpulimab-kcqx do not provide a meaningful advantage over currently available therapy, as required by Section 21 of the Code of Federal Regulations (CFR) 601.41 Subpart E for accelerated approval.

Potential path forward for clinical deficiencies

2. You should conduct a multiregional randomized clinical trial comparing penpulimab-kcqx to an acceptable control in patients with metastatic NPC which should utilize progression-free survival (PFS) and overall survival (OS) endpoints. The trial should enroll an adequate representation of U.S. patients,

with demographics that reflect the more ethnically diverse population of patients with NPC and should include adolescent patients.

PRODUCT QUALITY

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…".

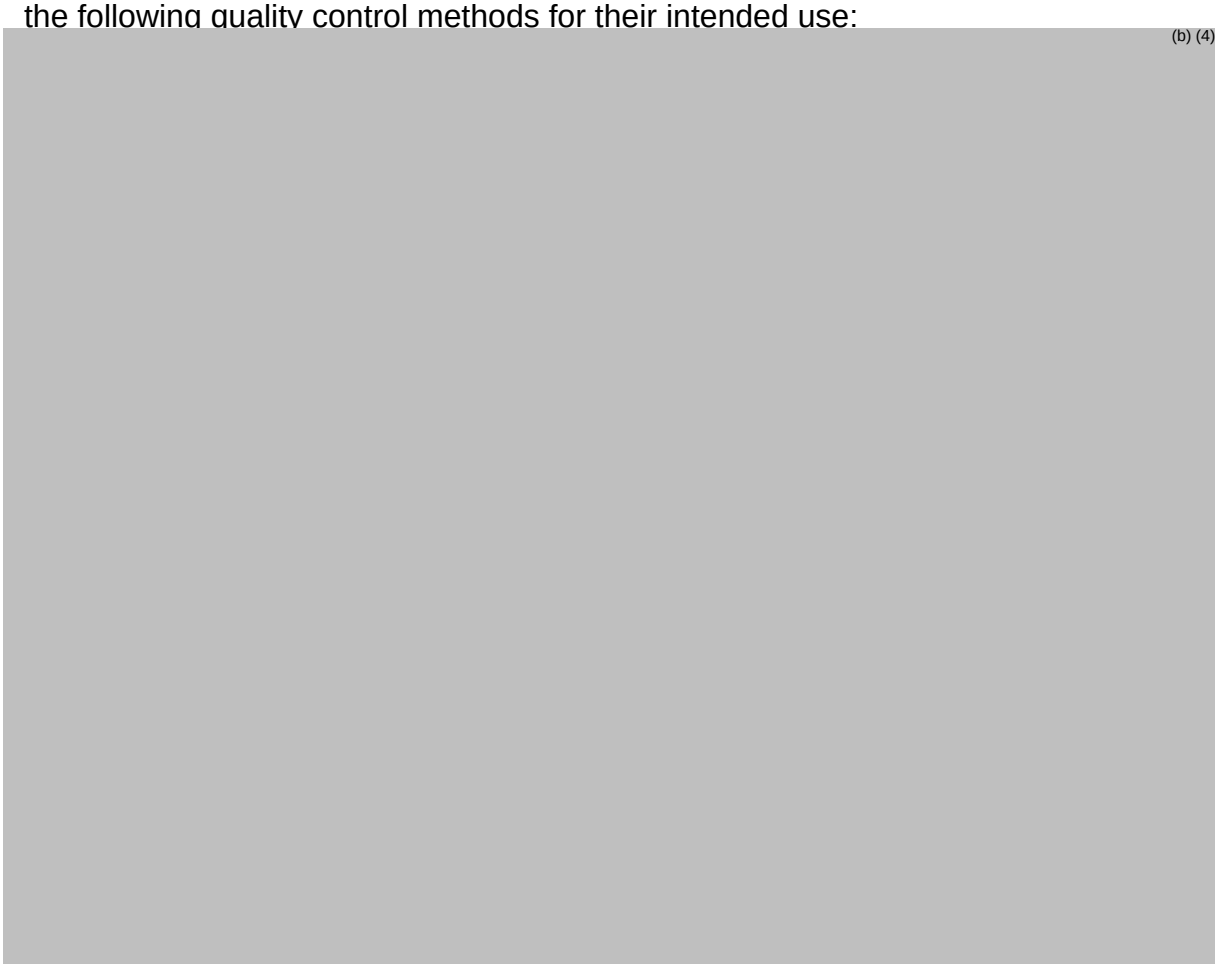
3. Reference is made to information and data provided during the pre-license inspection (PLI) at Akeso BioPharma Co., Ltd. (FEI 3017057933; Zhongshan, China), and in response to the Agency's information requests (IRs) dated February 24, 2022, April 12, 2022, May 12, 2022, and September 27, 2023, concerning 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 (DS) 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).

4. Reference is made to information provided in the original submission and in response to the Agency's IRs dated April 12, 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.

5. 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)

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.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[3]

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

6. Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide**."

FACILITY INSPECTIONS

Following the pre-license inspection (PLI) of Akeso Biopharma, Co., Ltd., Guangdong, China (FEI 3017057933), the DS and DP 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.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

7. Describe in detail any significant changes or findings in the safety profile.

8. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
   - Present tabulations of the new safety data combined with the original application data.
   - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

9. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

10. Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

11. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

12. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

13. Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

14. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Ashley Lane, Senior Regulatory Health Project Manager, at Ashley.Lane@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Paul Kluetz, MD
Supervisory Associate Director (acting)
Office of Oncologic Diseases Office of New Drugs
Center for Drug Evaluation and Research

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/

PAUL G KLUETZ
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