Our STN: BL 125813/0

BLA APPROVAL
November 8, 2024

Autolus Inc.
Attention: Nirav Patel
15810 Gaither Drive, Suite 230
Gaithersburg, MD 20877

Dear Nirav Patel:

Please refer to your Biologics License Application (BLA) received November 17, 2023, submitted under section 351(a) of the Public Health Service Act (PHS Act) for obecabtagene autoleucel.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2339 to Autolus Inc., Gaithersburg, Maryland, under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. This license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product obecabtagene autoleucel, which is indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

The review of this product was associated with the following National Clinical Trial (NCT) number: 04404660.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture obecabtagene autoleucel at your Autolus Limited facility located at Marshgate, Stevenage, Hertfordshire SG1, 1FR, United Kingdom. The (b) (4) lentiviral vector will be manufactured at (b) (4) located at (b) (4). You may label your product with the proprietary name AUCATZYL and market it in infusion bags containing 10 to 300 $\times 10^6$ chimeric antigen receptor (CAR)-positive cells frozen in 10 to 70 mL of solution. A total recommended dose of 410×10^6 CD19 CAR-positive viable T cells is filled into 3 to 5 infusion bags.

ADVISORY COMMITTEE

We did not refer your application to the Cellular, Tissue, and Gene Therapies Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

DATING PERIOD

The dating period for obecabtagene autoleucel shall be 6 months from the date of manufacture when stored at ≤-150˚C. The date of manufacture shall be defined as the date of final formulation of the drug product. The dating period for the (b) (4) lentiviral vector shall be (b) (4) from the date of manufacture when stored at (b) (4)

FDA LOT RELEASE

You are not currently required to submit samples or protocols of future lots of obecabtagene autoleucel to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, electronically through the eBPDR web application or at the address below. Links for the instructions on completing the electronic form (eBPDR) may be found on CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of obecabtagene autoleucel, or in the manufacturing facilities.

LABELING

Under 21 CFR 201.57(c)(18), patient labeling must be referenced in section 17 PATIENT COUNSELING INFORMATION. Patient labeling must be available and may either be reprinted immediately following the full prescribing information of the package insert or accompany the prescription product labeling.

We hereby approve the draft content of labeling including: Package Insert and Medication Guide submitted under amendment 94, dated November 7, 2024 and the draft package and container labels submitted under amendment 76, dated October 2, 2024 and amendment 82, dated October 16, 2024.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the: Package Insert and Medication Guide submitted on November 7, 2024. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

PACKAGE AND CONTAINER LABELS

Please electronically submit final printed package and container labels identical to the package submitted on October 16, 2024 and container labels submitted on October 2, 2024, according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

All final labeling should be submitted as Product Correspondence to this BLA, STN BL 125813 at the time of use and include implementation information on Form FDA 356h.

ADVERTISING AND PROMOTIONAL LABELING

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. In addition to the reporting requirements in 21 CFR 600.80, you must submit adverse experience reports for secondary malignancies as 15-day expedited reports to the FDA Adverse Event Reporting System (FAERS). For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format — Postmarketing Safety Reports* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports and FDA's Adverse Event reporting System website at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at https://www.fda.gov/vaccines-blood-biologics/lot-release/lot-distribution-database-ldd.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and

effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pediatric patients under 1 year of age because the necessary studies are impossible or highly impracticable. This is because of the rarity pediatric patients ages < 1 year with relapsed of refractory B cell malignancies.

We are deferring submission of your pediatric study for the ages of 1 to <17 years because the product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.28 and section 505B(a)(4)(C) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an "**Annual Status Report of Postmarketing Study Requirement/Commitments**" and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. This required study is listed below:

1. Conduct a molecularly targeted pediatric cancer investigation to evaluate dosing, pharmacokinetics, safety and antitumor activity of obecabtagene autoleucel following lymphodepletion with fludarabine and cyclophosphamide in patients 1 year to less than 17 years of age who have relapsed refractory (r/r) B-cell acute lymphoblastic leukemia and r/r aggressive mature B-cell non-Hodgkin lymphoma.

   Final Protocol Submission: Completed

   Study Completion: September 2027

   Final Report Submission: March 2028

Submit final study reports to this BLA STN BL 125813. In order for your PREA PMR to be considered fulfilled, you must submit and receive approval of either an efficacy or a labeling supplement. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated as:

- **Required Pediatric Assessment**

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to identify a serious risk of secondary malignancies associated with the use of obecabtagene autoleucel.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following study:

2. A post-marketing, prospective, multi-center, observational study to assess and characterize the risk of secondary malignancies, and the long-term safety following treatment with obecabtagene autoleucel (Study AUTO1-LT2). The study will include at least 500 adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia; each enrolled patient will be followed for 15 years after product administration.

We acknowledge the timetable you submitted on February 22, 2024, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: December 16, 2024

Study Completion Date: June 30, 2044

Final Report Submission: June 30, 2045

Please submit the protocol to your IND 19534, with a cross-reference letter to this BLA, STN BL 125813 explaining that this protocol was submitted to the IND. Please refer to the sequential number for each study/clinical trial and the submission number as shown in this letter.

Please submit final study reports to the BLA. If the information in the final study report supports a change in the label, the final study report must be submitted as a supplement to this BLA, STN BL 125813. For administrative purposes, all submissions related to this postmarketing study required under section 505(o) must be submitted to this BLA and be clearly designated as:

- **Required Postmarketing Correspondence under Section 505(o)**

- **Required Postmarketing Final Report under Section 505(o)**
- **Supplement contains Required Postmarketing Final Report under Section 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

You must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing requirement;
- the original milestone schedule for the requirement;
- the revised milestone schedule for the requirement, if appropriate;
- the current status of the requirement (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status for the study or clinical trial. The explanation should include how the study is progressing in reference to the original projected schedule, including, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm.

We will consider the submission of your annual report under section 506B of the FDCA and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in section 505(o) and 21 CFR 601.70. We remind you that to comply with section 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to periodically report on the status of studies or clinical trials required under section 505(o) may be a violation of FDCA section 505(o)(3)(E)(ii) and could result in regulatory action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitments as described in your letters of October 25, 2024 amendment# 86, October 31, 2024 amendment# 91, and November 4, 2024 amendment# 92, as outlined below:

3. Autolus Inc. commits to conducting an additional product-specific requalification of the LVV adventitious agents test using a sample withdrawn from the (b) (4) . The final qualification study report will be submitted as a Postmarketing Commitment by March 31, 2025.

   Final Study Report Submission: March 31, 2025

4. Autolus Inc. commits to providing a supplemental assay validation of the obe-cel (b) (4) assay, which evaluates the accuracy and linearity of the (b) (4) assay at (b) (4) CD19 CAR frequencies. The final study report will be submitted as a PMC by May 31, 2025

   Final Study Report Submission: May 31, 2025

5. Autolus Inc. commits to establishing a procedure for (b) (4) between “in-use” and “new” lots of the (b) (4) antibody lots used for the (b) (4) (obe-cel) release assays. The protocol used for analytical bridging will be submitted by June 30, 2025.

   Protocol Submission: June 30, 2025

6. Autolus Inc. commits to providing a reassessment of the acceptance criterion for the (b) (4) assay following the manufacture of (b) (4) additional lots of commercial (b) (4) vector.

   Final study report submission: December 31, 2025

7. Autolus Inc. commits to providing a supplemental validation study report evaluating the robustness of the (b) (4) assay performed as part of the (b) (4) release test.

   Final study report submission: March 31, 2025

8. Autolus Inc. commits to execute a new container closure integrity testing (CCIT) study for the (b) (4) LVV (b) (4) using a validated (b) (4) analysis method and a positive control with an established sensitivity [i.e., minimum critical leak defect (size) that can be reliably detected] in accordance

with (b) (4) The final study report will be submitted as a Postmarketing Commitment - Final Study Report by December 31, 2024.

Final Study Report Submission: December 31, 2024

9. Autolus Inc. commits to evaluating specificity and accuracy (b) (4) LVV purified final product at a concentration within the range of the assay to determine assay interference caused by the presence of LVV in the formulation matrix.

   Final Validation Study Report Submission: June 30, 2025

10. Autolus Inc. commits to evaluating specificity and accuracy (b) (4) LVV purified final product at a concentration within the range of the assay to demonstrate any assay interference caused by the presence of LVV in the formulation matrix.

    Final Validation Study Report Submission: June 30, 2025

11. Autolus Inc. commits to evaluating specificity and accuracy (b) (4) LVV purified final product at a concentration within the range of the assay to demonstrate any assay interference caused by the presence of LVV in the formulation matrix.

    Final Validation Study Report Submission: June 30, 2025

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125813. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**

- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

Sincerely,

Melissa J. Mendoza, JD
Director
Office of Compliance
and Biologics Quality
Center for Biologics
Evaluation and Research

'Lola Fashoyin-Aje, MD, MPH
Director
Office of Clinical Evaluation
Office of Therapeutic Products
Center for Biologics
Evaluation and Researc