

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125813/0

Obecabtagene autoleucel (Obe-cel)

Kula N. Jha, Ph.D., Biological Reviewer, MRB1/DMPQ

1. **BLA#:** STN 125813/0

2. **APPLICANT NAME AND LICENSE NUMBER**

Autolus Inc., License No. (2339)

3. **PRODUCT NAME/PRODUCT TYPE**

Non-Proprietary/Proper/USAN: Obecabtagene autoleucel (Obe-cel)

Proprietary Name: AUCATZYL

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

- a. Pharmacological category: A gene therapy cellular product consisting of autologous enriched T cells that are *ex vivo* genetically engineered with (b) (4), the lentiviral vector (LVV), to express a novel CD19CAT-41BB ζ antigen receptor (CAT CAR)
- b. Dosage form: Cell suspension (dispersion)
- c. Strength/Potency: 410x10⁶/mL CAR-positive viable T cells
- d. Route of administration: Intravenous injection (I.V.)
- e. Indication(s): Treatment of adult patients (18 years and over) with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukemia (ALL)

5. **MAJOR MILESTONES**

Filing Meeting: January 08, 2024

Mid-cycle Meeting: May 15, 2024

Late-cycle Meeting: August 02, 2024

PDUFA Action Date: November 16, 2024

6. **DMPQ CMC/FACILITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Kula N. Jha, Ph.D., OCBQ/DMPQ/MRB1	3.2.S Drug Substance (CD19 CAR-positive T cells), 3.2.S Drug Substance (b) (4) LVV), 3.2.P Drug Product, 3.2.A.1 Facilities and Equipment

7. **SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/Status
Nov 17, 2023	STN 125813/0.0	Original BLA submission
Dec 18, 2023	STN 125813/0.4	Information to plan for the pre-license inspection (PLI) of Autolus Limited (henceforth referred to as The Nucleus), the drug substance (DS) and drug product (DP) manufacturing facility located at Stevenage, UK Response to DMPQ information request (IR) # 1 (Reviewed)

DMPQ review memo BLA 125813/0

Date Received	Submission	Comments/Status
Feb 09, 2024	STN 125813/0.18	Additional clarification on the production schedule and other PLI related information Response to DMPQ IR # 2 (Reviewed)
Feb 26, 2024	STN 125813/0.22	Information on environmental monitoring (EM), utility systems, facility cleaning, and microbial hold-time study for in-house prepared media and buffers at Autolus Limited Response to DMPQ IR # 3 (Reviewed)
Feb 12, 2024	STN 125813/0.30	Information on (b) (4) validation, container closure integrity testing (CCIT) of (b) (4) LVV (b) (4), and sterility of (b) (4) used in the production of the (b) (4) LVV at (b) (4) Response to DMPQ IR # 4 (Reviewed)
May 14, 2024	STN 125813/0.35	Response to FDA Form 483 observations during the PLI performed in April 2024 (Reviewed)
Jun 04, 2024	STN 125813/0.38	Additional information on CCIT validation for (b) (4) Freezing Bags used for the storage and transport of obe-cel Response to DMPQ IR # 5 (Reviewed)
Jul 12, 2024	STN 125813/0.43	Commitment to execute a new CCIT study for obe-cel freezing bags using (b) (4) Analysis Follow-up response to DMPQ IR # 5 (Reviewed)
Jul 30, 2024	STN 125813/0.46	Clarification of Autolus' response to the FDA Form 483 observations; Requalification summary report for CO ₂ supply testing in Cleanroom (b) (4) at Autolus Limited Response to DMPQ IR # 8 (Reviewed)
Jul 31, 2024	STN 125813/0.47	Draft protocol for the proposed CCIT study on obe-cel freezing bags Follow-up response to DMPQ IR # 6 (Reviewed)
Aug 8, 2024	STN 125813/0.48	Additional information on media fill program for (b) (4) LVV manufacturing at (b) (4) Response to IR # 9 (Reviewed)
Aug 09, 2024	STN 125813/0.51	Draft protocols for the supplemental (b) (4) validation and CCIT study for (b) (4) LVV at (b) (4) and follow-up information on CCIT of obe-cel freezing bags Response to IR # 8 (Reviewed)
Aug 13, 2024	STN 125813/0.52	Annual qualification summary report and qualification summary report for repeat testing for clean compressed air (CCA) at Autolus Limited Follow-up response to IR # 3 and 4 (Reviewed)

Date Received	Submission	Comments/Status
Aug 30, 2024	STN 125813/0.57	Draft protocols for (b) (4) LVV (b) (4) CCIT validation and testing; commitment for a new CCIT study Follow-up response to IR # 7 (Reviewed)
Sep 03, 2024	STN 125813/0.59	Qualification reports for (b) (4) (including (b) (4) , risk assessment of process gas sampling and location Response to IR # 8 (Reviewed)
Sep 03, 2024	STN 125813/0.60	(b) (4) validation report (b) (4) testing only) for the manufacture of (b) (4) LVV at (b) (4) Follow-up response to IR # 7 (Reviewed)
Sep 12, 2024	STN 125813/0.65	Viral disinfectant efficacy study assessment at Autolus Limited Follow-up response to IR # 8 (Reviewed)
Sep 13, 2024	STN 125813/0.66	Qualification summary report for (b) (4) used for (b) (4) LVV production at (b) (4) Response to IR # 10 (Reviewed)
Sep 13, 2024	STN 125813/0.68	Obe-cel (b) (4) freezing bags CCIT study report Follow-up response to DMPQ IR # 6 (Reviewed)
Sep 27, 2024	STN 125813/0.72	Obe-cel (b) (4) freezing bags CCIT validation report and autoclaves loads qualification (b) (4) Response to DMPQ IR # 11 (Reviewed)
Sep 30, 2024	STN 125813/0.73	(b) (4)) for the manufacture of (b) (4) LVV at (b) (4) Follow-up response to IR # 7 (Reviewed)

8. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Autolus Inc., the applicant, submitted Biologics License Application (BLA) STN 125813/0 to support the licensure of obe-cel (AUCATZYL), a gene therapy cellular product consisting of autologous T cells that are genetically modified *ex-vivo* with a lentiviral vector (LVV), (b) (4) , to express a CD19 chimeric antigen receptor (CAR). AUCATZYL was developed as a CAR-T cell therapy for the treatment of adult patients (18 years and over) with relapsed or refractory (r/r) B cell precursor acute lymphoblastic leukemia (ALL). The dosage form of the drug product (DP) is a cell suspension (dispersion) to be administered as an I.V.

The container closure system (CCS) for AUCATZYL is (b) (4) freezing bag which consists of an (b) (4) with a corresponding overwrap bag. (b) (4) freezing bags are FDA 510K cleared (b) (4)). Determination of which bag size is dependent on total number of cells per bag.

The Division of Manufacturing and Product Quality (DMPQ) reviewed and evaluated the drug substance (DS) and DP manufacturing processes and facilities proposed for the manufacture of AUCATZYL. This review memo includes summaries and assessments of the DS and DP manufacturing processes and quality attributes, and an overview of the manufacturing facilities information including utilities, cross-contamination controls, and equipment qualification and cleaning and sterilization processes.

CBER performed a pre-license inspection (PLI) of Autolus Limited (referred to as The Nucleus) (FEI # 3015674982) located at Marshgate, Stevenage, UK, for AUCATZYL. Autolus Limited is the AUCATZYL DS (CD19 CAR-positive T cells) and DP (obe-cel) manufacturing site, and the PLI was classified voluntary action indicated (VAI).

Following evaluations of the compliance histories and experience with proposed responsibilities, a PLI was waived for the (b) (4) [REDACTED] which is a contract manufacturing site for the manufacture, release/stability testing, and labeling and packaging of (b) (4) LVV. The basis for the inspection waiver of the (b) (4) [REDACTED] facility is documented in a separate inspection waiver memo dated April 16, 2024.

Based on the information submitted to BLA 125813/0 and in conjunction with the PLI of Autolus Limited, approval is recommended. One Postmarketing Commitment is also noted.

B. RECOMMENDATION

I. APPROVAL

Based on the information provided in the original application and amendments, DMPQ recommends the approval of obe-cel (AUCATZYL).

The following is a Postmarketing Commitment (PMC) from DMPQ:

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

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Kula N. Jha, CMC/Facility Reviewer, CBER/OCBQ/DMPQ/MRB1	Concur	
Kathleen R. Jones, Acting Team Lead/Branch Chief, CBER/OCBQ/DMPQ/MRB1	Concur	
Carolyn A. Renshaw, Division Director, CBER/OCBQ/DMPQ	Concur	

Table of Contents

3.2.S DRUG SUBSTANCE (b) (4)	7
3.2.S.2 Manufacture	7
3.2.S.2.1 Manufacturer(s)	7
3.2.S.2.2 Description of Manufacturing Process and Process Controls	7
3.2.S.2.4 Controls of Critical Steps and Intermediates	8
3.2.S.2.5 Process Validation and/or Evaluation	9
3.2.S.4 Control of Drug Substance	16
3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)	16
3.2.S.4.2 and 3.2.S.4.3 Analytical Procedures and Validation of Analytical Procedures	16
3.2.S.4.4 Batch Analyses	16
3.2.S.6 Container Closure System	17
3.2.S.7 Stability	19
3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data	19
3.2.S DRUG SUBSTANCE [CD19 CAR-positive T cells]	19
3.2.S.2 Manufacture	20
3.2.S.2.1 Manufacturer(s)	20
3.2.S.2.2 Description of Manufacturing Process and Process Controls	20
3.2.S.2.3 Control of Materials	21
3.2.S.2.4 Controls of Critical Steps and Intermediates	23
3.2.S.2.5 Process Validation and/or Evaluation	23
3.2.S.4 Control of Drug Substance	23
3.2.S.4.1 Specification(s), 3.2.S.4.2 Analytical Procedures, 3.2.S.4.3 Validation of Analytical Procedures, 3.2.S.4.4 Batch Analysis, and 3.2.S.4.5 Justification of Specification(s)	24
3.2.S.6 Container Closure System	24
3.2.S.7 Stability	24
3.2.S.7.1 Stability Summary and Conclusions, 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment, and 3.2.S.7.3 Stability Data	24
3.2.P DRUG PRODUCT (Obe-cel)	24
3.2.P.1 Description and Composition of the Drug Product	24
3.2.P.2.5 Microbiological Attributes	24
3.2.P.3 Manufacture	26
3.2.P.3.1 Manufacturer(s)	26
3.2.P.3.3 Description of Manufacturing Process	27
3.2.P.3.4 Controls of Critical Steps and Intermediates	27
3.2.P.3.5 Process Validation and/or Evaluation	27
3.2.P.5 Control of Drug Product	31
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)	31
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	31
3.2.P.5.4 Batch Analyses	31
3.2.P.7 Container Closure System	32
3.2.P.8 Stability	33

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data 33
3.2.A APPENDICES 33
3.2.A.1 Facilities and Equipment – (b) (4) 35
3.2.A.1 Facilities and Equipment – Autolus Limited 49

Module 3

3.2.S DRUG SUBSTANCE (b) (4)

[Redacted]

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

16 pages determined to be not releasable: (b)(4)

(b) (4)

[Redacted text block]

3.2.P DRUG PRODUCT (Obe-cel)

3.2.P.1 Description and Composition of the Drug Product

The obe-cel final DP is formulated as a cell suspension (dispersion) for I.V. infusion. The DP is cryopreserved in a medium containing (b) (4) PBS/EDTA buffer, (b) (4), human serum albumin (HSA) and dimethyl sulfoxide (DMSO).

The formulated obe-cel (10 million CD19 CAR-positive viable T cells/mL) is filled into the (b) (4) freezing bags. The target dose of 410 million CD19 CAR-positive viable T cells is filled in three different bags to enable the split dosing regimen (10, 100 and 300 million cells, respectively). The fill volume based on the number of CD19 CAR-positive T cells are variable based on the (b) (4) and (b) (4) in each lot of obe-cel. The filled bags are individually packed in metal cassettes, stored in the liquid nitrogen at $\leq -150^{\circ}\text{C}$, and supplied in a liquid nitrogen dry vapor shipper.

3.2.P.2.5 Microbiological Attributes

The obe-cel DP is tested for endotoxin (detection by (b) (4) and sterility (b) (4) at the time of release and/or during the stability studies to verify the sterility assurance of the product.

Additionally, sterility testing was performed for the following components used in the manufacture of obe-cel:

- (b) (4)

(b) (4) freezing bag ((b) (4)) used as the primary CCS for obe-cel consists of a freezing bag with ports and a corresponding overwrap bag. The freezing bags from the supplier are received as (b) (4) bags; the sterilization process was validated to achieve a sterility assurance level (b) (4)

Container closure integrity for the DP was evaluated in two parts: (b) (4) of the DP inside the bag.

Physical stress study was conducted as per (b) (4) standards according to the (b) (4) test procedure to confirm the integrity of the freezing bags under the following the worst-case conditions:

- (b) (4)

Results from the physical stress testing complied with the requirements of (b) (4) for collapsible plastic containers for the storage of human blood components. Additionally, post-shipment container closure integrity was also assessed using the (b) (4) test procedure, and the results demonstrated that the freezing bags maintain physical integrity during transportation.

For the sterility assurance, CCIT studies were performed for the obe-cel freezing bags using a (b) (4) test method. The CCIT test method was developed and validated in accordance with (b) (4) bag configurations. The method development, validation, and final testing were performed by (b) (4) located in (b) (4), and the applicant submitted the CCIT method validation report in Amendment STN 125813/0.72.

For the method validation, obe-cel (b) (4) filled freezing bags were shipped from Autolus Limited to the testing site in (b) (4), whereas the freezing bags with (b) (4) were filled with the (b) (4) at the testing site. All acceptance criteria were met for each of the test units, demonstrating method suitability for the use in routine CCIT of the obe-cel freezing

bags. Based on the method validation study, the limit of detection (i.e., minimum defect size in the (b) (4)) for (b) (4) bags were determined as (b) (4) respectively, in nominal diameter.

The final CCIT was performed using the validated (b) (4) test method on obe-cel formulation-filled freezing bags following the proposed commercial manufacturing process. (b) (4)

(b) (4)
All test units met the acceptance criteria i.e., (b) (4)

(b) (4) The applicant submitted the summary report in Amendment STN 125813/0.68.

CCIT was also validated for (b) (4)

(b) (4) The freezing bags were shown to be intact, and no (b) (4) was observed.

Reviewer's comment: Testing and acceptance criteria for sterility (no growth) and endotoxin (b) (4) for the DP release and/or stability specifications appear acceptable. CCIT testing is done to ensure sterility of the product during storage and shipping. Originally the sponsor submitted a CCIT study using (b) (4) method, however it was not clear if it was done in accordance with (b) (4), since the study did not include a representative positive control with intended defects, nor did the method include (b) (4). However, in response to an IR from the Agency, a new CCIT study was performed for the obe-cel freezing bags using a validated (b) (4) method in accordance with the (b) (4). Based on the assessment of results from the method validation and final testing, the CCIT appears acceptable and supportive of sterility assurance of the obe-cel filled in the (b) (4) freezing bags.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The DS and DP are manufactured at Autolus Limited located in Stevenage, United Kingdom (FEI: 3015674982).

Reviewer's comment: Please see Section 3.2.A.1 for a complete list of the DS/DP manufacturing and testing facilities.

3.2.P.3.3 Description of Manufacturing Process

CD19 CAR-positive T cells DS produced (b) (4) step are formulated to produce the final DP.

The obe-cel DP manufacturing process consists of the following two steps:

- Formulation and final fill
- Cryopreservation and storage

(b) (4)

The cell suspension is then (b) (4) with the cryopreservation buffer (b) (4) containing DMSO and HSA) to reach the final DP concentration of 10×10^6 cells/mL, (b) (4) HSA, and 7.5% DMSO. The formulated DP (target dose of 410×10^6 cells) is filled in three different freezing bags (b) (4) (10 - 20 mL) and (b) (4) (30 - 70 mL)] to enable a split dose regimen. The fill volumes and number of CD19 CAR-positive T cells are variable depending on the (b) (4) and viable cell concentration. The filling operations are performed using a (b) (4) in Grade (b) (4) area. The filled DP bags are visually inspected, labeled, and overwrapped before they are frozen in a (b) (4) cryopreserved in liquid nitrogen at $\leq -150^\circ\text{C}$.

No reprocessing steps are permitted in the obe-cel manufacturing process. The final DP is transported frozen at $\leq -150^\circ\text{C}$ in a validated liquid nitrogen shipper.

3.2.P.3.4 Controls of Critical Steps and Intermediates

No microbiological product attributes are included in the pre-determined CPP and IPC tests performed during the obe-cel manufacturing process. However, the prepared media and buffers were subjected to hold time studies which included microbiological safety testing.

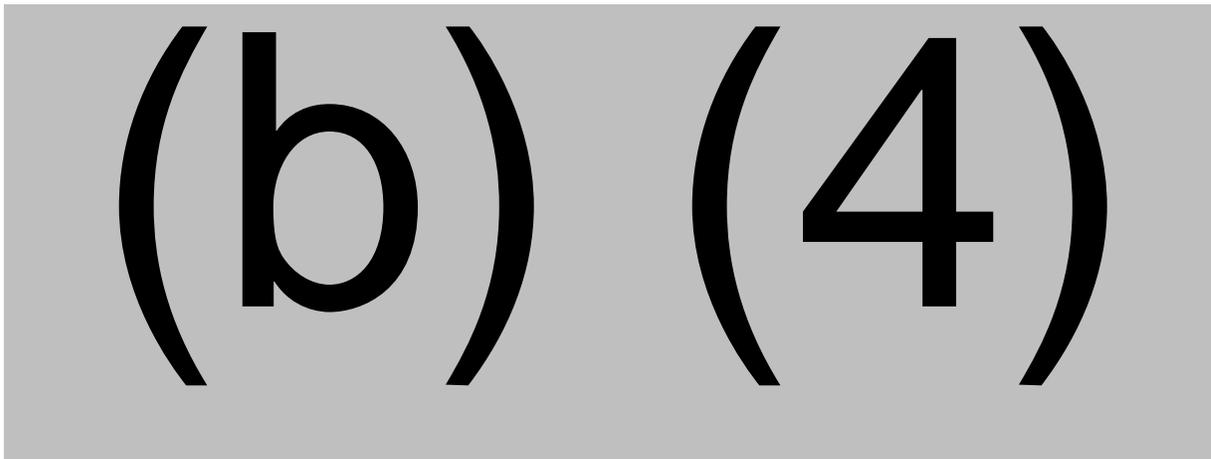
Reviewer's comment: Please see the assessment in 3.2.S.2.3 Control of Materials above.

3.2.P.3.5 Process Validation and/or Evaluation

PPQ

The obe-cel commercial manufacturing process validation included (b) (4) PPQ runs using (b) (4) lots of (b) (4) LVV. Each PPQ run was initiated with a single healthy donor leukapheresis starting material resulting in a single lot of the obe-cel DP. To perform product comparability study, healthy donor leukapheresis starting material for each PPQ run was split into two parts for producing one PPQ DP lot at each site - Autolus Limited and Cell and Gene Therapy Catapult Manufacturing Center (CGTC-MC).

A summary of the PPQ lots manufactured at the Autolus Limited, Stevenage site is given below:



The CPPs and IPCs in the validation studies did not include microbiological testing. Results for all (b) (4) PPQ lots met the pre-determined acceptance criteria of the microbiological release specification i.e., endotoxin (b) (4) and sterility (no growth).

Routine environmental monitoring (EM) was performed during the manufacture of the PPQ lots, and no excursions to the established acceptance criteria were observed.

Reviewer's comment: *The PPQ appears acceptable. All the PPQ batches met the microbial (endotoxin and sterility) acceptance criteria, and the results from the EM as well were compliant to the established acceptance criteria. The microbial data from the PPQ, along with the APS as described below, appear to support the aseptic process at Autolus Limited. Assessment of non-microbial product quality attributes, CPPs and IPCs for the obe-cel PPQ runs, the extended characterization, capacity challenge study, chain of identity/chain of custody, and extractables/leachables evaluation are deferred to OTP.*

Aseptic Process Simulation

APS studies were performed to evaluate sterility assurance during the manufacture of the obe-cel at Autolus Limited. The APS design included a risk assessment of the manufacturing process and covered the following unit operations:

- (b) (4) [Redacted]

1 page determined to be not releasable: (b)(4)

(b) (4)

Shipping Validation

The obe-cel DP is transported at $\leq -150^{\circ}\text{C}$ by a qualified shipper from Autolus Limited site, either directly to the US treatment site or to a site in the US for temporary storage.

The shipping validation included the following scenarios:

- (b) (4)

(b) (4)

(b) (4)

(b) (4)



3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

The obe-cel DP is tested at release and stability for sterility (no growth) and at release for endotoxin (b) (4)

Reviewer's comment: Testing for the microbial product quality attributes and their acceptance criteria included in the release and stability specifications appears to be acceptable. Justifications provided for the acceptance criterion for the level of endotoxin in obe-cel DP appears acceptable considering the maximum volume (b) (4) and duration of infusion as well as recommended endotoxin threshold dose (b) (4) for IV administration in an average (b) (4) adult). Assessment of release and stability specifications and their acceptance criteria is deferred to OTP.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Reviewer's comment: Sterility (b) (4) and endotoxin (detection by (b) (4) release testing is performed on the DP. Assessment of method validation testing for endotoxin and sterility for the obe-cel DP release/stability is deferred to DBSQC. For CCIT, please see the assessment in Section 3.2.P.2.5 Microbial Attributes. Assessment of method validations for the other product quality attributes is deferred to OTP.

3.2.P.5.4 Batch Analyses

Batch analysis of the obe-cel DP manufactured at Autolus Limited following the commercial manufacturing process (process (b) (4) included the PPQ and site comparability batches (n (b) (4) stability batches (n (b) (4) technology transfer batches (n = (b) (4), and batches manufactured for capacity challenge study and shipping validation (n = (b) (4).

Sterility and endotoxin test results for the batches manufactured at Autolus Limited following the commercial manufacturing process, process (b) (4) complied with the release specifications for endotoxin (b) (4) and sterility (no growth).

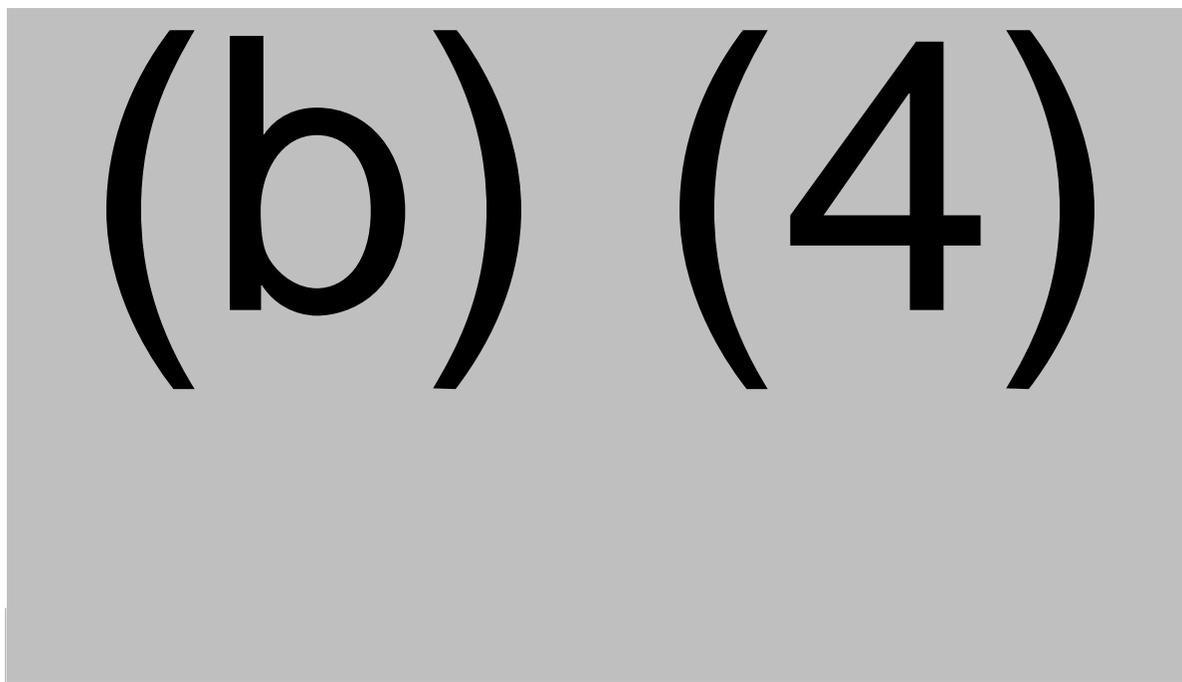
Reviewer's comment: Results from all obe-cel DP batches manufactured at Autolus Limited met the microbial acceptance criteria, and the batch analysis appears acceptable. Review of batches from a product quality perspective is deferred to OTP.

3.2.P.7 Container Closure System

The obe-cel DP is filled in the (b) (4) freezing bags (primary CCS) in a closed process following which the bags are sealed off and overwrapped with corresponding overwrap bags. The (b) (4) freezing bags are 510K cleared (# (b) (4) in the US. (b) (4) the freezing bag (including tubing and ports) and overwrap bags are made of (b) (4). Depending on the volume to be filled, two sizes of freezing bags are used for the obe-cel DP - (b) (4) for 10 - 20 mL DP and (b) (4) for 30 - 70 mL DP.

The overwrapped bag is inserted into a secondary container closure (metal cassette) with a felt insert for (b) (4) and without a felt insert for (b) (4) bag. The metal cassette with the obe-cel DP is held in liquid nitrogen storage and transferred into a liquid nitrogen dry vapor cryoshipper for transportation. For shipping, up to four obe-cel (b) (4) bags, individually packed in cassettes, are inserted in one (b) (4). The loaded (b) (4) is placed into a cryoshipper and transported to the treatment center.

A summary of the CCS components for obe-cel DP is provided in the following table:



Each lot of the (b) (4) freezing bags is tested by the supplier for include sterility (b) (4) pass), sterilization by (b) (4) ; pass)], and endotoxin (b) (4) (b) (4) Additionally, incoming material were tested in-house by (b) (4) and visual particulates test by (b) (4) (b) (4) practically free of visible particles).

The applicant provided drawings of the components of the primary, secondary, and tertiary container closure system in *Section 3.2.P.7 Container Closure System*.

Reviewer's comment: *The obe-cel DP CCS appears acceptable and suitable to protect the sterile DP from microbial ingress during the storage (for information see the Section 3.2.P.8 Stability) and transport. Please see the assessment of CCIT in Section 3.2.P.2.5 Microbiological Attributes above.*

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Obe-cel DP is stored at $\leq -150^{\circ}\text{C}$ until thawed for administration in patient. The stability studies were performed using the DP filled in the proposed commercial CCS ((b) (4) freezing bags) stored under the long-term storage conditions of $\leq -150^{\circ}\text{C}$.

The stability program included more than (b) (4) obe-cel DP lots including (b) (4) PPQ lots. A summary of the stability studies to support the shelf-life of six months for obe-cel is provided in Table 1 in *Section 3.2.P.8.1 Stability Summary and Conclusion*. All supportive and registrational stability data were provided in Table 1 - 8 in *Section 3.2.P.8.3 (Stability Data)*.

The stability protocol included testing for sterility by (b) (4) method at the time release and 6-month time points. Based on the available data available, results from all the obe-cel lots met the acceptance criteria for sterility (negative) at all tested timepoints.

Reviewer's comment: *Information provided on the stability studies for the obe-cel DP manufactured at Autolus Limited appears acceptable. Results from the stability studies met the acceptance criteria for sterility. From a microbial safety perspective, the proposed shelf-life of six months appears acceptable for obe-cel. Assessment of other product quality attributes during the stability studies is deferred to the OTP.*

3.2.A APPENDICES

Facility Table:

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
<p>Facility: Autolus Limited (referred to as The Nucleus) Marshgate, Stevenage, Hertfordshire, United Kingdom SG1 1FR FEI # 3015674982</p> <p>DS (CD19 CAR-positive T cells) and DP (obe-cel) manufacture, release and stability testing; labeling and packaging, and storage (b) (4) and obe-cel)</p>	<p>Inspection</p>	<p>Yes</p>	<p>Yes</p>	<p>April 2024 PLI CBER/OCBQ VAI</p>
<p>Facility: (b) (4) [Redacted]</p> <p>Lentiviral vector (b) (4) manufacturing, release and stability testing, labeling and packaging, and storage</p>	<p>Waiver</p>	<p>Yes</p>	<p>Yes</p>	<p>(b) (4) PLI CBER/OCBQ VAI</p>
<p>Facility: (b) (4) .</p>	<p>Not Required</p>	<p>No</p>	<p>Yes</p>	<p>(b) (4) Surveillance</p>

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
<p>(b) (4)</p> <p>Lentiviral vector (b) (4) release testing (b) (4)</p>				<p>ORA/OBPO NAI</p>

FDA Establishment Identifier (FEI); Pre-License Inspection (PLI); Office of Compliance and Biologics Quality (OCBQ); Office of Regulatory Affairs (ORA); Office of Biological Products Operations (OBPO); Voluntary Action Indicated (VAI); No Action Indicated (NAI)

3.2.A.1 Facilities and Equipment – (b) (4)

(b) (4)

(b) (4)

13 pages determined to be not releasable: (b)(4)

(b) (4)

[Redacted text block]

[Redacted text block]

3.2.A.1 Facilities and Equipment – Autolus Limited

1. Site overview

Autolus Limited is a manufacturing facility for autologous CAR-T cell therapy products. This facility is comprised of a (b) (4)

. An overview of the facility layouts and drawings were provided in *Section 3.2.A.1 Facility and Equipment - CD19 CAR-Positive T cells - Autolus Ltd.*(b) (4)

[Redacted text block]

Reviewer's comment: Information provided on the manufacturing suites and other areas in the Autolus Limited facility appear acceptable. The obe-cel DS and DP manufacturing areas' EM qualification and ability to meet pre-determined requirements is assessed in Environmental Monitoring (EM) and Qualification section below.

2. Contamination and cross-contamination control

Contamination control strategy for the Autolus Limited facility considers multiple elements such as design of facilities/utilities, personnel, raw materials controls, cleaning and disinfection, equipment, and microbial controls. Each of such elements included the following aspects:

- Monitoring controls (personnel, in-process, materials, environmental, utility, and pest)
- Validation of controls (personnel qualification/requalification, process qualification/lifecycle, analytical qualification/lifecycle, facility, utilities, and equipment qualification/requalification)
- Contamination controls (personnel training, hygiene and gowning, process design, raw materials and consumables, equipment design, cleaning and disinfection, and facility and utility design)

The facility flows for the personnel, materials, product, and wastes were designed to reduce the contamination and cross contamination risks.

Contamination controls and segregation procedures:

Potential product contamination is controlled by use of closed systems during manufacturing, controlled air flow from dedicated heating, ventilation, and air conditioning (HVAC) systems, pressure differential zones, air locks, gowning, and defined flows for the raw materials, product, equipment, personnel, and wastes. Media preparation and closed cell manufacturing processing are performed in a Grade (b) (4) at rest and (b) (4) in-operation) areas. The direction of air flow in the facility is maintained from an area of higher classification to that of lower classification. The continuity of the operation of systems and equipment (in case of power failure) is supported by generators and uninterrupted power supply.

Gowning and personnel flow:

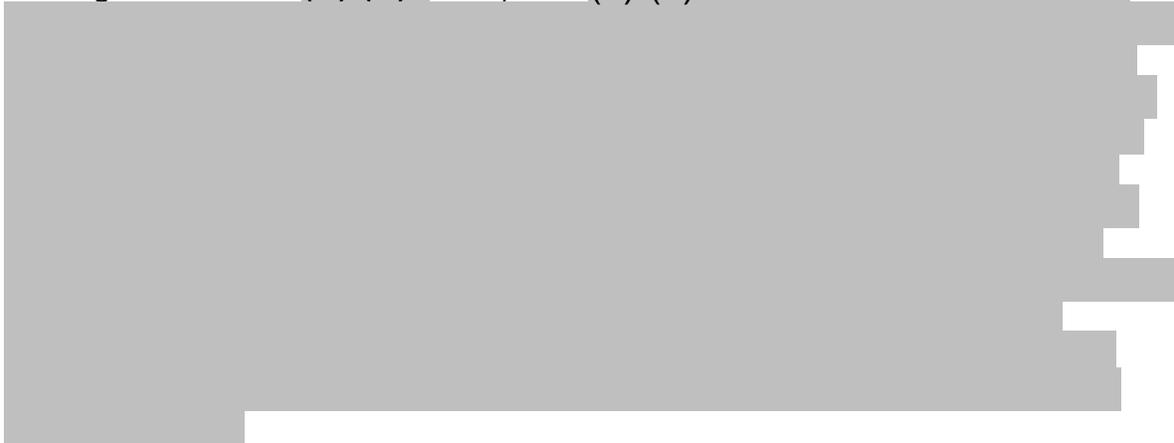
Autolus Limited has written procedures for gowning and personnel flow. Personnel must complete the training requirements and comply with the established gowning procedures while accessing the manufacturing areas. The facility design ensures that the personnel entry (clean gowns) and exit (dirty gowns) are segregated to reduce the risk of contamination.

Reviewer's comment: The Autolus Limited facility design and contamination/cross-contamination controls appear acceptable as the facility utilizes pressure cascades, single-use disposable materials, designated flows for raw materials, product, equipment, personnel, and waste, and appropriate segregation practices.

3. Facility Flows

The manufacturing area floor plan and flow diagrams for personnel, materials, product, and wastes for the Autolus Limited were provided in the BLA.

All materials including raw materials, biological materials (e.g., leukapheresis starting material and (b) (4) LVV), and (b) (4)



All waste generated in the manufacturing areas are categorized as hazardous wastes and disposed according to the established waste disposal procedures. Where possible, movement of waste is designed to be separate from materials and personnel flows. Liquid waste generated in QC laboratories is deactivated with suitable chemical disinfectant before moving the waste to the staging area.

Reviewer's comment: *The facility flows schematics provided for the obe-cel manufacturing areas in the Autolus Limited facility are unidirectional. Flow patterns do not appear to present unnecessary challenges that could potentially introduce contaminants during manufacturing. The contamination control measures implemented for the material flow within the facility include (b) (4)*



The facility flows for raw materials, waste, personnel, and product appear acceptable.

4. Utilities

HVAC system/EM

Each cleanroom is served by a dedicated HVAC system with defined pressure cascades including personnel airlock (PAL) and material airlock (MAL) pressure 'Hills'. The applicant provided the HVAC zoning and pressure differential schematics for (b) (4) of the facility. For Grade (b) (4) areas, the HVAC systems are full fresh air systems and all air handling units (AHUs) have (b) (4) high efficiency particulate air (HEPA) filters for supply air. The HVAC system is suitable for microbial decontamination of the cleanrooms using (b) (4) fumigation. The HVAC design criteria during commissioning and qualification of

cleanrooms included the temperature, humidity, room pressure, air change rate and recovery. Installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ) were performed for Cleanroom^{(b) (4)} and HVAC systems under as built (b) (4) at-rest (b) (4) and in-operation (b) (4) conditions following the (b) (4) requirements. EM performance qualification (EMPQ) studies were performed in the media/materials preparation room and Cleanroom^{(b) (4)} under dynamic condition. (b) (4) PQ runs encompassing different shifts and activities were conducted, and the EM sampling locations were determined based on the internal environmental risk assessment as per PDA Technical Report No. 13 Revised 2022 (TR 13). Results from the EMPQ studies met the acceptance criteria for both non-viable and viable monitoring, and the EMPQ acceptance criteria for both non-viable particulates and viable complied with EU GMP Grade^{(b) (4)} and (b) (4) in-operation state. Temperature and humidity excursions observed in the PQ runs were investigated and determined to have a low risk to the Cleanroom^{(b) (4)} activities or environment. Based on the EMPQ studies the maximum occupancy for Cleanroom^{(b) (4)} the media preparation room, and the material preparation room were determined as (b) (4) operators, respectively. The HVAC systems are controlled by the site Building Management System (BMS), and re-qualified (b) (4)

Additional information on the EM qualification of the Cleanroom^{(b) (4)} and media preparation room was provided in Amendment STN 12813/0.22. For the EM qualification studies, only one replicate was used for the 'as built' state, whereas (b) (4) replicates each were used for the at-rest and in-operation states. Samples for non-viable particulates were collected for all the three states (as built, at-rest, and in-operation), whereas samples for viable particulates were collected only during in-operation state. Summaries of the environmental conditions for Cleanroom^{(b) (4)} and media preparation areas were provided in Table 1 and Table 2, respectively, of Amendment STN 125813/0.22. Sampling type, sampling locations, and acceptance criteria for routine EM were identical to EMPQ for all Grade (b) (4) areas. All the EM results met the acceptance criteria which were identical to those for EMPQ.

Reviewer's comment: *The environmental monitoring program appears appropriate for activities performed in the manufacturing areas. The action limits appear to be consistent with (b) (4) and EU GMP Grade (b) (4) in-operation state standards. The environmental monitoring program appears acceptable. The EM program was also reviewed during the April 2023 PLI.*

Process Gases (Clean Compressed Air and Carbon Dioxide Gas)

Clean compressed air (CCA) and Carbon dioxide (CO₂) gas are product contact utilities. CCA is used in the (b) (4)

(b) (4)

. Compressed air is generated by

(b) (4)

A risk assessment was performed to determine sampling points and frequencies for a routine monitoring program for the process gases used in the manufacture of obe-cel. In Amendment STN 125813/0.59, the applicant provided a summary of the routine monitoring activities, which included the frequency of testing of each point of use, location of the points of use, the tests to be performed including viable particulates, and acceptance criteria (e.g., alert and action limits). Based on the risk assessment, the sampling frequencies were determined as (b) (4) for all high risk POU locations and (b) (4) for end of line POU. The action limits for viable (no growth) and non-viable (b) (4) for the routine EM were set in accordance with (b) (4)

The process gases (CCA and CO₂) quality tests were performed according to (b) (4)

The test results from the qualification/re-qualification studies met the qualification criteria. All deviations were either resolved and closed or approved corrective and preventive actions (CAPA) were put in place for resolution.

Liquid Nitrogen

Liquid nitrogen is a non-product contact utility used for the storage and transport of obe-cel in cryogenic tanks and (b) (4) filling in the warehouse.

Reviewer's comment: Results from the qualification/requalification studies of the product-contact utilities (CCA and CO₂ gas) met the acceptance criteria, but some deviations were observed which subsequently were either resolved and closed or an approved CAPA were put in place for their satisfactory resolution. Based on the risk assessment performed by the applicant, the frequency of testing of each POU, locations of the points of use, the quality tests to be performed, and acceptance criteria appear to be acceptable. Validation testing was performed by (b) (4) from each POU and routine monitoring was not being performed. In amendment STN 1259813/0.46, the applicant committed to initiate a CAPA to perform a routine monitoring program of CCA and CO₂ with increased frequency in which the gas samples will be collected routinely from the POU positions following a risk-based assessment and tested for viable and non-viable particles. Subsequently, the applicant submitted (b) (4) qualification report for CO₂ testing (Amendment STN

125813/0.46) and (b) (4) qualification summary report as well as qualification summary report for repeat testing for CCA (Amendment STN 125813/0.52) in Cleanroom (b) (4). As both CCA and CO₂ gas are (b) (4), and there have been no sterility failures, this appears acceptable to ensure suitability of these critical utilities to support the controlled manufacturing process for obe-cel. As utility trending data are assessed during routine surveillance inspections, and inspectional follow-up is not being recommended. The liquid nitrogen system was subjected to commissioning only and no OQ was performed, and this appears acceptable as it is not a product-contact utility. This will be followed up during the next surveillance inspection as it was an inspectional observation. See the EIR for more details.

5. Computer Systems

The computer systems utilized in the manufacture and testing of obe-cel in the Autolus Limited facility include the following:

- Computerized Maintenance Management System (CMMS)
- Laboratory Information Management System (LIMS)
- (b) (4)
- Operational Technology (OT) Networks
- Labelling Software
- Enterprise Resource Planning (ERP)
- Document Management System (DMS) and Quality Management System (QMS)
- Environmental Monitoring System (EMS)
- Process Control System (PCS)

The computer systems were subjected to risk assessment and verified with respect to data integrity and electronic records and electronic signatures (ERES). Validations were performed and the systems are maintained in accordance with the FDA guidance. IQ/OQ/PQ qualifications of the computer systems were completed, and the results met all the acceptance criteria. Validation summary reports for the computer systems were provided in *Section 3.2.R Regional Information*.

Reviewer's comments: *Computer systems used in the manufacture and testing of obe-cel appears acceptable as they were validated following the FDA guidance and all requirements were met in the IQ/OQ/PQ studies. Additionally, 21 CFR Part 11 of several computer systems were checked during the PLI of Autolus Limited, and no concerns were noted.*

6. Equipment

No multi-use product-contact equipment are used in the obe-cel manufacturing process. Materials that are product-contact are single-use, disposable, and supplied sterile. Therefore, no equipment cleaning validation was performed. All equipment is product-dedicated, qualified, and subjected to IQ/OQ/PQ and periodic maintenance. Most of the obe-cel manufacturing operations are carried out using closed systems that employ single-use consumables such as bags and tubing sets. Nevertheless, the obe-cel manufacturing process also involves some open processing steps (e.g.,

(b) (4) performed within (b) (4) (Grade ^{(b) (4)} environment). A list of the key equipment used in the manufacture of obe-cel is provided in Table 7 of *Section 3.2.A.1 Facilities and Equipment*.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

5 pages determined to be not releasable: (b)(4)