

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125785/0 and 125787/0

CASGEVY (exagamglogene autotemcel)

Greg Price, Ph. D., Lead Consumer Safety Officer, OCBQ/DMPQ/MRB3

Carl Perez, Consumer Safety Officer, OCBQ/DMPQ/MRB3

1. **BLA#:** STN 125785/0 and 125787/0

2. **APPLICANT NAME AND LICENSE NUMBER**

Vertex Pharmaceuticals, Inc., License #: 2279

3. **PRODUCT NAME/PRODUCT TYPE**

USAN: exagamglogene autotemcel (exa-cel)

Proprietary name: CASGEVY

Other names: CTX001

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

a. Pharmacological category: autologous CD34+ human Hematopoietic Stem and Progenitor cells (hHSPCs) modified by CRISPR-Cas9-mediated gene editing.

b. Dosage form: suspension

c. Strength/potency: ≥ 3 million CD34+ cells per kg of patient weight

d. Route of administration: intravenous

e. Indications

STN 125785/0: Treatment of transfusion dependent β -thalassemia (TDT)

STN 125787/0: Treatment of sickle cell disease (SCD)

5. **MAJOR MILESTONES**

Filing Meeting:	STN 125785/0: May 11, 2023 STN 125787/0: May 18, 2023
Mid-Cycle Meeting:	STN 125785/0: September 28, 2023 STN 125787/0: July 31, 2023
Pre-License Inspections (PLIs):	(b) (4)
Late-Cycle Meeting:	STN 125785/0: December 14, 2023 STN 125787/0: October 19, 2023
Action Due Date:	STN 125785/0: March 30, 2024 STN 125787/0: December 8, 2023

Note: STN 125787/0 received Priority Review designation; STN 125785/0 received Standard Review designation.

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

Reviewer/Affiliation	Section/Subject Matter
Greg Price, OCBQ/DMPQ/MRB3	Drug Substance, Drug Product, Facilities and CMC Reviewer, Lead Inspector (b) (4) (b) (4)

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Date Received	Submission(s)	Comments/Status
September 8, 2023	Amendments STN 125785/0.45, 125787/0.53	(b) (4) responses to Form FDA 483 observations found during PLI
September 15, 2023	Amendments STN 125785/0.49, 125787/0.56 CMC IR #7	IR response to provide additional information on DP visual inspection
September 22, 2023	Amendments STN 125785/0.55, 125787/0.61	(b) (4) responses to Form FDA 483 observations found during PLI
September 22, 2023	Amendments STN 125785/0.56, 125787/0.62	(b) (4) responses to Form FDA 483 observations found during PLI
October 3, 2023	Amendments STN 125785/0.59, 125787/0.67	(b) (4) confirmation of completion of defined CAPAs to FDA 483 observations found during PLI
October 11, 2023	Amendments STN 125785/0.62, 125787/0.70	IR response to provide additional (b) (4) manufacturing equipment information
October 30, 2023	Amendments STN 125785/0.66, 125787/0.74 CMC IR #9	IR response to provide additional (b) (4) and (b) (4) (b) (4) stability data

8. REFERENCED REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	No review is required, information pertinent to container closure is provided in the BLA
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	No review is required, information pertinent to container closure is provided in the BLA
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	No DMPQ review required

BLA 125785/0 and 125787/0 DMPQ Review Memo (CASGEVY)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	No review is required, information pertinent to container closure is provided in the BLA
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	No DMPQ review required
MF (b) (4)	(b) (4)	(b) (4)	Yes	No DMPQ review required
MF (b) (4)	(b) (4)	(b) (4)	Yes	No DMPQ review required
MF (b) (4)	(b) (4)	(b) (4)	Yes	No DMPQ review required
MF (b) (4)	(b) (4)	(b) (4)	Yes	No DMPQ review required
MF (b) (4)	(b) (4)	(b) (4)	Yes	No DMPQ review required
MF (b) (4)	(b) (4)	(b) (4) Vial	Yes	No review is required, information pertinent to container closure is provided in the BLA
STN (b) (4)	(b) (4)	Elastomeric Formulations, Coatings and Films	Yes	No review is required, information pertinent to container closure is provided in the BLA

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
STN (b) (4)	(b) (4)	(b) (4)	Yes	No DMPQ review required

9. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Vertex Pharmaceutical, Inc. (Vertex) is requesting approval for CASGEVY (exagamglogene autotemcel, or exa-cel), autologous CD34+ human Hematopoietic Stem and Progenitor cells (hHSPCs) modified by CRISPR-Cas9-mediated gene editing and suspended in (b) (4) cryopreservation solution containing 5% dimethyl sulfoxide (DMSO). Exa-cel is indicated for the treatment of transfusion dependent β -thalassemia (TDT) and sickle cell disease (SCD). Vertex submitted two BLAs under two separate STNs for each indication (STN 125785/0 for TDT, and STN 125787/0 for SCD). The CMC and facility information of Module 3 is identical for both BLA submissions, which was confirmed by Vertex in the information request (IR) response in Amendments STN 125785/0.3 and STN 125787/0.3. The reviews of the CMC, facility and equipment information of STN 125785/0 and STN 125787/0 are covered in this memo.

Exa-cel is an autologous product consisting of CRISPR-Cas9 mediated gene edited CD34+ hHSPCs. Cas9 and SPY101 are combined to form the ribonucleoprotein (RNP) complex, which enters the cell via electroporation. Once inside the cell, Cas9 is directed by SPY101 to cleave both strands of the target cellular DNA which results in the key gene editing event and the formation of Exa-cel drug product (DP). Cas9 and SPY101 are gene editing reagents and not considered as true drug substances (DS). For ease of review, the Agency requested Vertex to submit the Cas9 and SPY101 CMC information in separate Module 3 DS sections at the Vertex pre-BLA meeting on August 9, 2022 (CRMTS #14208). The Cas9 and SPY101 CMC information are reviewed in separate DS sections in this memo.

The (b) (4) is manufactured at (b) (4)
 (b) (4) Cas9 (b) (4) is manufactured at (b) (4)
 (b) (4) of the SPY101
 and Cas9 (b) (4) are performed at (b) (4)
 (b) (4) located in (b) (4) PLIs of
 the (b) (4) and (b) (4) facilities were performed on (b) (4) and (b) (4)
 (b) (4) respectively. No Form FDA 483 was issued at the conclusion of the
 (b) (4) PLI, which was classified as No Action Indicated (NAI). At the conclusion of

the (b) (4) PLI, a Form FDA 483 was issued on (b) (4) with two inspectional observations, which the firm responded to on August 11, 2023. A review of (b) (4) responses is documented in a separate 483 response review memo, with all inspectional 483 observations being adequately resolved resulting in a Voluntary Action Indicated (VAI) inspection classification. In lieu of a pre-license inspection (PLI) at (b) (4) a review of requested manufacturing site records under Section 704(a)(4) was performed and the compliance of the facility was found adequate. The (b) (4) CMC and facility information provided in the submissions appears acceptable.

The manufacture, labeling, packaging, and storage of Exa-cel DP are performed at two sites: (b) (4) located in (b) (4) and (b) (4) located in (b) (4). PLIs of the (b) (4) and (b) (4) facilities were performed on (b) (4) and (b) (4) respectively. At the conclusion of the (b) (4) PLI, a Form FDA 483 was issued on (b) (4), with two inspectional observations, which the firm responded to on August 18, 2023. A review of (b) (4) responses is documented in a separate 483 response review memo. All inspectional 483 observations were adequately resolved, and the (b) (4) PLI was classified as VAI. At the conclusion of the (b) (4) PLI, a Form FDA 483 was issued on (b) (4) 2023, with seven inspectional observations, which the firm responded to on September 8, 2023. A review of (b) (4) responses is documented in a separate 483 response review memo, with all inspectional 483 observations adequately resolved resulting in a VAI inspection classification. The (b) (4) and (b) (4) CMC and facility information provided in the submissions appears acceptable.

The following (b) (4) facilities are contract testing laboratories performing release and/or stability testing of exa-cel DP (b) (4) (b) (4)

(b) (4)

All (b) (4) facilities have either an acceptable FDA-inspection history and/or an acceptable recent inspection performed by a foreign regulatory authority with whom the Agency has a cooperative arrangement covered under the Mutual Recognition

Agreement (MRA). For these reasons, the decision was made to waive PLIs for all above (b) (4) testing facilities.

B. RECOMMENDATION

I. APPROVAL

Based on the information provided, approval is recommended.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Greg Price, Ph. D., Lead CSO OCBQ/DMPQ/MRB3	Concur	
Carl Perez, CSO OCBQ/DMPQ/MRB3	Concur	
CDR Donald Ertel, Branch Chief OCBQ/DMPQ/MRB3	Concur	
Carolyn Renshaw, Division Director OCBQ/DMPQ	Concur	

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Module 3

3.2.S DRUG SUBSTANCE (Cas9)

(b) (4)

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

(b) (4)

3.2.P DRUG PRODUCT

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

Exa-cel consists of autologous CD34+ human Hematopoietic Stem and Progenitor cells (hHSPCs) modified by CRISPR-Cas9-mediated gene editing and suspended in (b) (4) Cryopreservation solution containing 5% dimethyl sulfoxide (DMSO).

Exa-cel is a single dose consisting of at least 3 million CD34+ cells per kg of patient weight, suspended in (b) (4) cryopreservation medium containing 5% DMSO at approximately $4 - 13 \times 10^6$ cells/mL. Edited cells from more than one vial and more than one lot may be used to provide a complete patient dose through intravenous administration.

Exa-cel is packaged in 20 mL (b) (4) Vials at 1.5 - 20 mL per vial in liquid nitrogen vapor ($\leq 135^\circ\text{C}$). The vials will be clearly labeled for autologous use only and linked to the recipient using a unique identifier for each subject.

3.2.P.2.4 Container Closure System

The primary container closure selected for Exa-cel DP (DP) is a sterile, single-use 20 mL (b) (4) Vials (vial) from (b) (4). The vial is composed of (b) (4) for the body, which is known for shock resistance, barrier properties and transparency. The stopper is composed of (b) (4) (b) (4) a proprietary material for (b) (4). Both (b) (4) and (b) (4) are known for having a low leachables profile.

The 20 mL vial is a ready-to-fill vial and is used for cryopreservation, storage, and transport of the Exa-cel DP to the Authorized Treatment Centers (ATCs) and has been demonstrated to maintain robust container closure under the conditions of freezing, storage, and transport. The vials are pre-sterilized and consist of a pre-assembled (vial body, stopper, top ring, and cap) system. Vial filling is accomplished using a specifically designed needle inserted through the stopper followed by (b) (4)-sealing of the needle puncture of the stopper.

CCIT was performed on vials filled to various volumes with (b) (4) cryoprotectant which is used to formulate the DP. The vials were frozen and stored at NMT -135°C in LN2 according to Exa-cel manufacturing procedures. (b) (4) separate CCI studies were performed using (b) (4) (b) (4) (b) (4) methods.

(b) (4) tested (b) (4) sizes of the (b) (4) vials (b) (4) 20 mL). The (b) (4) mL and (b) (4) mL vials are used for sample collection and storage as well as stability samples. The 20 mL DP vials were filled with (b) (4) mL, (b) (4) mL, and (b) (4) (b) (4) mL fill volumes of (b) (4). All testing was performed using positive control samples with the limit of defect detection for the (b) (4) and (b) (4) mL (b) (4) vials of (b) (4) and (b) (4) for the 20 mL DP vials. All testing of filled vials passed acceptance criteria and no loss of CCIT was noted for any vials.

The (b) (4) method was an additional test to demonstrate adequate CCI of the 20mL DP vials. Vials filled at the (b) (4) fill volumes were used and tested following 10 months of storage time at NMT -135°C in LN2. The limit of detection for this method is (b) (4). The vials were (b) (4) (b) (4) (b) (4). All positive controls demonstrated (b) (4) and none of the sample vials were positive for (b) (4).

3.2.P.2.5 Microbiological Attributes

Exa-cel DP consists of live gene-edited cells and is manufactured under aseptic conditions and stored in sterile cryopreserved medium because DP cannot be terminally sterilized. Sterility is maintained by using verified, pre-sterilized raw materials and components, maintaining appropriate aseptic controls during manufacturing and packaging. In-process controls during Exa-cel manufacturing include testing for (b) (4).

(b) (4) Additionally, the release testing of drug product includes compendial testing for sterility, mycoplasma, and endotoxin to ensure safety of the product prior to use.

Exa-cel DP is packaged in 20 mL ready-to-fill (b) (4) for cryopreservation, storage, and transport to the Authorized Treatment Centers (ATCs). The vial and stopper are molded in Grade (b) (4) rooms and the vials are sterilized by (b) (4) by the vendor and are pyrogen-free.

Reviewer's Assessment: The CCIT testing has demonstrated the (b) (4) vials remain integral following freeze thaw at the storage conditions of NMT -135°C in LN2. The (b) (4) vials are pre-sterilized by the manufacturer and additional sterility testing of every vial batch is performed at (b) (4) and (b) (4) prior to usage. We defer review of extractable and leachables to OTP. The information provided appears acceptable.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Refer to section 3.2.A.1 for a complete list of all manufacturing facilities.

3.2.P.3.3 Description of Manufacturing Process

Exa-cel manufacturing steps are listed below along with any CPPs or IPCs for each step if applicable.

(b) (4)

Visual Inspection

DP appearance is evaluated by visual inspection (VI) in (b) (4)

evaluated independently (b) (4)

by (b) (4) qualified VI operators. DP vials meeting the acceptance criteria are reported as: translucent cell suspension, practically free of visible foreign particles. VI operators are qualified by (b) (4) and training with a challenge vial kit, with requalification (b) (4)

The DP vial is

Overall Reviewer's Assessment of Section 3.2.P.3.3:

- The manufacturing steps along with any CPP and IPC were provided. Sterility is measured (b) (4). Additionally, the (b) (4) (b) (4) is tested for sterility along with the final DP. The information provided appears acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

This section is deferred to OTP.

3.2.P.3.5 Process Validation and/or Evaluation

(b) (4)

4 pages have been determined to be not releasable: (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)

Sterility, endotoxin, and mycoplasma testing are part of the product safety specifications. Bacterial endotoxin (b) (4) and sterility are measured as part of the final DP release specifications. Bacterial endotoxin is measured using the (b) (4) (b) (4). Sterility testing is performed with (b) (4) methods according to (b) (4). The sterility acceptance criterion is specified as “no growth”.

Reviewer’s Assessment: These are (b) (4) tests. We defer review of the mycoplasma, sterility, and endotoxin test methods to DBSQC.

3.2.P.5.4 Batch Analyses

To date, there have been no sterility, endotoxin, or mycoplasma release testing failures for any of the PPQ batches manufactured at (b) (4) or (b) (4).

Overall Reviewer’s Assessment of Sections 3.2.P.5.4

- ☐ The information provided appears acceptable.

3.2.P.7 Container Closure System

Exa-cel DP is filled and stored in 20 mL Ready-to-Fill (b) (4). The (b) (4) (b) (4) vial body and the (b) (4) stoppers are pre-assembled and sterilized prior to DP fill. The (b) (4) vials are manually filled in a Grade (b) (4) by piercing the stopper with a filling needle, and then the puncture hole is sealed using a (b) (4) system.

The vial body and stopper are molded in a Class (b) (4) environment and immediately assembled in full in an (b) (4) manufacturing process. Vials are then packed and sterilized by (b) (4). A manufacturer's Certificate of Conformity (COC) is issued for each vial lot. The vial and stopper formulations do not contain materials of animal origin as stated in the COC. There is no contact between the seal (top ring and cap) and the exa-cel DP. Sterility and endotoxin are re-tested by either (b) (4) or (b) (4) for each shipment of the closed vials to ensure safety prior to filling.

Overall Reviewer's Assessment of Section 3.2.P.7:

- The (b) (4) vials used for exa-cel DP are pre-assembled and sterilized prior to use. Sterility and endotoxin are re-tested on each shipment to ensure safety. The dimensions of the vial, stopper and cap were provided. The information appears acceptable.

3.2.P.8 Stability

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

HD lots of Exa-cel DP have been used for stability testing to ensure patients are dosed with the maximum number of cells. Supportive stability studies of Exa-cel DP held in vapor phase liquid nitrogen (≤ -135 °C) for (b) (4) months have demonstrated DP stability. Some registrational lots have 12 months of stability data, and the PPQ lots manufactured at both (b) (4) and (b) (4) have 3 months of stability data to date. Sterility and endotoxin are measured with some of the stability lots, and to date, there have been no sterility failures or endotoxin excursions (b) (4).

Overall Reviewer's Assessment of Section 3.2.P.8.1:

- To date, there have been no sterility or endotoxin test failures. The data appears acceptable from prevention of microbial contamination perspectives.

3.2.A APPENDICES

There are (b) (4) separate facilities involved in the manufacture exa-cel critical DS components and DP. The review of each facility is described in the sections below. The facilities table listing all facilities involved in the manufacture, packaging, testing, and storage is provided in the facilities table below:

Facilities Involved in Exa-cel Manufacture:

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
<p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4) DP (Exa-cel) manufacturing, labeling, release, and stability testing (except potency, on-target editing, sterility, mycoplasma), packaging, and storage.</p>	Inspection	Yes	Yes	ORA Last inspection (b) (4) NAI
<p>(b) (4)</p> <p>(b) (4) /DP (Exa-cel) release and stability testing (except potency, on target editing, sterility, mycoplasma).</p>	Inspection	Yes	Yes	<p>No FDA inspection history</p> <p>Last international inspection: (b) (4) (b) (4)</p>

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
(b) (4) [REDACTED] [REDACTED] (b) (4) (Cas9) (b) (4) manufacturing, labeling, packaging, (b) (4) [REDACTED]	Inspection	Yes	Yes	No FDA inspection history (b) (4) certificate: (b) (4)
(b) (4) [REDACTED] [REDACTED] (b) (4) (b) (4) (Cas9 and SPY101) (b) (4) [REDACTED] labeling, and packaging.	Inspection	Yes	Yes	ORA Last inspection (b) (4) VAI (b) (4) certificate: (b) (4)
(b) (4) [REDACTED] [REDACTED] (b) (4) (SPY101) (b) (4) manufacturing, labeling, packaging, (b) (4) [REDACTED]	Inspection- 704(a)(4) Records Request in lieu of	Yes	Yes	ORA/OPQO 704(a)(4) records request (b) (4) ORA Last inspection (b) (4) : NAI
(b) (4) [REDACTED] [REDACTED] DP (Exa-cel) release testing (mycoplasma).	Waiver	Yes	Yes	ORA Last inspection (b) (4) VAI

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
(b) (4) DP (Exa-cel) release and stability testing (sterility).	Waiver	Yes	Yes	ORA Last inspection (b) (4) NAI
(b) (4) DP (Exa-cel) release and stability testing (on-target editing). (b) (4) (SPY101) (b) (4)	Waiver	Yes	Yes	No FDA inspection history Last international inspection: (b) (4)
(b) (4) DP (Exa-cel) release and stability testing (b) (4) potency).	Waiver	Yes	Yes	MRA Inspection Review of (b) (4) inspection performed in (b) (4) ORA OPQO Work Activity completed (b) (4) VAI
(b) (4) (b) (4) DP (Exa-cel) release (sterility and mycoplasma) and stability (sterility) testing.	Waiver	Yes	Yes	ORA Last inspection (b) (4) VAI

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Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
(b) (4) (b) (4) DP (Exa-cel) release and stability testing (sterility).	Waiver	Yes	Yes	ORA Last inspection (b) (4) VAI
(b) (4) (b) (4) (Cas9 and SPY101) (b) (4)	Not required	No	Yes	ORA Last inspection (b) (4) VAI
(b) (4) (b) (4) (b) (4) (SPY101) (b) (4)	Not required	No	Yes	ORA Last inspection (b) (4) NAI
(b) (4) (b) (4) (b) (4) (SPY101) (b) (4)	Not required	No	Yes	ORA Last inspection (b) (4) VAI

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
(b) (4)	Not required	No	Yes	ORA Last inspection (b) (4) VAI
(b) (4)				
(b) (4) (SPY101) (b) (4)				
(b) (4) (SPY101) (b) (4)				
(b) (4)	Not required	No	No	FDA Last inspection: (b) (4) (b) (4) certificate: (b) (4)
(b) (4)				
(b) (4)				
(b) (4) (Cas9) (b) (4)				
(b) (4)				

(b) (4) **Cas9 Manufacture)**
(b) (4)

(b) (4)

Reviewer Assessment: The (b) (4) facility is dedicated to the manufacture of Cas9^{(b) (4)} and appears to have the appropriate measures in place to mitigate the risk of cross-contamination.

Heating, Ventilation and Air Conditioning (HVAC)

(b) (4) air handling unit (AHU) supplies the air for the following classified cleanrooms at (b) (4)

(b) (4)

A requalification of the HVAC system was completed in (b) (4) which consisted of the following:

(b) (4)

All acceptance criteria were met, except for one action limit exceedance of a (b) (4) (b) (4). After the completion of an investigation, an improvement to the personnel flow procedure was implemented. Requalification of the HVAC is performed (b) (4).

Reviewer Assessment: Air flow and differential pressure cascade diagrams were provided, which show room air flow and pressure differentials from higher to lower cleanroom class. The most recent requalification of the HVAC system was reviewed during the (b) (4) PLI and appears acceptable and demonstrates it can adequately maintain the (b) (4) and (b) (4) environments. The exceedance observed in the EMPQ during requalification was determined to be due to the presence of (b) (4) people in the airlock performing gowning activity (worst-case). A CAPA was implemented to limit airlock occupancy to a (b) (4) person maximum. The information provided appears acceptable.

Clean Utilities

(b) (4)

Reviewer Assessment: All clean utilities underwent initial qualification, which were summarized in the submission. In addition to the (b) (4) air monitoring trend data from the last (b) (4) months, the most recent clean utility qualifications were reviewed during the (b) (4) PLI and can be referenced in the site's Establishment Inspection Report (EIR). The information provided appears acceptable.

Environmental Monitoring

The (b) (4) program includes at-rest and in-operation monitoring at regularly scheduled intervals. At-rest monitoring occurs (b) (4) for classified areas and (b) (4) for CNC areas. In-operation monitoring occurs for all process steps for every batch manufactured and can be reduced or extended on a process and risk-based basis. In-operation monitoring of the CNC areas is performed (b) (4) in the pre-processing room. EM monitoring includes (b) (4) nonviable particulate counts, and (b) (4). In-operation nonviable particulate counts and (b) (4) cover the entire process duration at sampling sites placed at locations based on risk. In addition, personnel monitoring is performed on the gloves of all personnel involved in manufacturing activities performed in the (b) (4) of the process. Nonviable and viable EM alert and action limits are summarized in the tables below. In the event of an excursion of an EM action limit, a deviation report is initiated,

and an investigation is performed. EM trending reports are prepared and reviewed
(b) (4)

(b) (4)

Reviewer Assessment: A facility diagram of the cleanroom EM sampling locations was provided. The EM limits align with (b) (4). In addition, EM trending data from the previous (b) (4) months were reviewed during the (b) (4) PLI. The information provided appears acceptable.

Facility Cleaning

There are (b) (4) different types of cleanroom cleanings performed at (b) (4)

(b) (4)

(b) (4)

Reviewer Assessment: *The disinfectant efficacy study was reviewed during the (b) (4) (b) (4) PLI and appears acceptable. In addition, a personnel, material, and waste flow diagram were provided and appears acceptable. The facility cleaning program appears acceptable.*

Equipment

The Cas9 (b) (4) major manufacturing equipment used at (b) (4) is summarized in the following table.

(b) (4)

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(b) (4)

Reviewer Assessment: The cleaning program of product-contact equipment appears acceptable in the removal of (b) (4). The most recent cleaning validations for the product contact production equipment listed above, including all cleaning parameters and limits, were reviewed during the (b) (4) PLI and appear acceptable. In addition, the manual cleaning procedures were reviewed and appear acceptable.

Computer Systems

The (b) (4) is used for the monitoring of the room environmental conditions (temperature, (b) (4) differential pressure, Grade (b) (4) (b) (4) Grade (b) (4) humidity, monitored not controlled) of the cleanroom areas and temperature-controlled equipment at (b) (4). The system was validated in an initial IQ, OQ, PQ prior to use and receives a periodic system review in addition to requalification and system updates.

Reviewer Assessment: The (b) (4) system and the most recent (b) (4) requalification were reviewed during the (b) (4) and appears acceptable.

(b) (4) SPY101 Manufacture)
(b) (4)

(b) (4)

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

Reviewer Assessment

The HVAC system appears to be adequate in controlling the cleanroom environments at (b) (4) based upon the EM program and recent 2022 data. Viable and non-viable environmental monitoring programs are in place with adequate stringency based on (b) (4) and ISO (b) (4) standards. The information provided appears acceptable.

Equipment Qualifications

All equipment used to manufacture the bulk (b) (4) has been qualified. The SPY101 major manufacturing equipment along with OQ/PQ testing is listed below:

(b) (4)

(b) (4)

Reviewer Assessment

All SPY101 manufacturing equipment has undergone qualification studies. An IR was submitted to obtain additional information regarding the (b) (4) qualifications (eCTD # 60, 10/11/2023). All (b) (4) systems were qualified for (b) (4) (b) (4) All (b) (4) systems used in SPY101 manufacture appear to be in a qualified state. The PQ for the (b) (4) used (b) (4) performed using the (b) (4) program. (b) (4)

(b) (4) could not be more than (b) (4) All data met acceptance criteria. The data provided appears acceptable.

Equipment Cleaning

(b) (4)

Reviewer Assessment

Most of the product contact equipment used to manufacture SPY101 is (b) (4)
(b) (4) Some equipment such as the (b) (4)
(b) (4) is (b) (4) To assess the cleaning parameters
performed on these (b) (4) pieces of equipment, and IR was submitted (eCTD # 60,
10/11/2023). (b) (4) conducted a risk assessment for (b) (4)
(b) (4) determined that SPY101 is not the worst-case
soil and therefore the current cleaning validations in place encompass SPY101. For
product changeover, a cleaning verification is performed that measures (b) (4)
As SPY101 is
not the worst-case soil and cleaning verifications are performed for product
changeovers, the information provided appears acceptable.

Contamination Control

(b) (4)

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

(b) (4)

Reviewer Assessment

The manufacture of SPY101 is a (b) (4)

The recent EM monitoring data was reviewed for the (b) (4) 704(a) records review, and no negative trends were noted, and the cleaning program appears to adequately control the clean room environments. The information provided appears adequate.

Utilities

(b) (4)

All testing passed acceptance criteria.

Reviewer Assessment

The recent (b) (4) monitoring data from the previous (b) (4) was reviewed for the (b) (4) 704(a) records review, and no negative trends were

noted; these utilities appear to be in a state of control. The information provided here appears adequate.

Computer Systems

The following computer systems are used at (b) (4)

- document management system
- change control management
- controlling production machines
- controlling downstream systems
- controlling the air conditioning
- controlling QC equipment
- data back-up and archiving
- inventory management

All systems are validated in accordance with the requirements of 21 CFR Part 11 and the recommendation of GAMP^{(b) (4)} (Good Automated Manufacturing Practice). The following qualification activities are conducted during computer systems validation:

- Creation of a User Requirement Specification
- Creation of a Design Specification Document
- DQ, IQ, OQ, PQ

Every (b) (4) (b) (4) issues a report on each computer system with an assessment of the validation status.

Reviewer Assessment

The computer systems at (b) (4) were validated in accordance with 21 CFR Part 11 requirements and are all in a validated state. The information provided appears acceptable.

(b) (4)

Cas9 and SPY101 Manufacture)

(b)

(4)

(b) (4)

Reviewer Assessment: Personnel flow, material/waste flow and the (b) (4) room pressure diagrams were provided and appear acceptable. The flows were confirmed during the (b) (4) PLI.

(b) (4)

Reviewer Assessment: *Diagrams of room classifications and pressure differentials were reviewed and appear acceptable. The EMPQ, which was also reviewed during PLI, demonstrated the HVAC functions properly to adequately to maintain the cleanroom classification in accordance with (b) (4) [REDACTED]. The information provided appears acceptable.*

Clean Utilities

Clean utility systems used for the (b) (4) of Cas9 and SPY101 at (b) (4) include (b) (4). No (b) (4) are used in the manufacturing process for (b) (4) Cas9 and SPY101.

(b) (4)

Reviewers Assessment: The (b) (4) test frequencies and acceptance criteria, which aligns with (b) (4) and are comparable to (b) (4) appear acceptable. The (b) (4) test data and trending reports from the previous (b) (4) were reviewed during the (b) (4) PLI and appear acceptable.

Environmental Monitoring

An environmental monitoring (EM) program is in place at (b) (4) to ensure non-viable and viable particulates remain within the specified limits within the cleanrooms. Non-viable air particulates are monitored (b) (4) within the Grade (b) (4) and surrounding Grade (b) (4) areas. (b) (4) (b) (4) Viable (active air sampling) and non-viable air particulate counts are monitored (b) (4) in Grade (b) (4) and (b) (4) production rooms. Surface monitoring is performed (b) (4) in Grade (b) (4) and (b) (4) production rooms. Personnel monitoring is performed (b) (4) and includes (b) (4) (b) (4) sampling locations. Recovered organisms are isolated and identified, with results trended in an (b) (4) report. Non-viable particulate EM limits follow the (b) (4) (b) (4) and (b) (4) requirements. Viable EM limits are summarized in the table below.

(b) (4)

(b) (4)

Reviewer Assessment: Non-viable EM limits align with (b) (4) (b) (4) provided non-viable and viable EM sampling location diagrams of the (b) (4) and Grade (b) (4) fill room (3.2.A. Appendices, (b) (4) Figures 13 and 14). In addition, EM sample locations were noted during the observation of fill operations during the PLI and appear to be placed accordingly based on risk. EM trend data from the previous (b) (4) (b) (4) were reviewed during the (b) (4) PLI and appear acceptable.

Facility Cleaning

All manufacturing rooms are cleaned and sanitized based on the established procedures defining cleaning frequencies and cleaning agents. The cleaning frequencies are as follows:

(b) (4)

Reviewers Assessment: The facility cleaning program and the disinfectant efficacy study, which was reviewed during the (b) (4) PLI, appear acceptable. The

disinfectants used to clean the facility appear suitable and effective in the removal of residues and organisms from all surfaces found in the cleanrooms.

Equipment

The major production equipment used for (b) (4) Cas9 and SPY101 are summarized in the following table.

(b) (4)

Reviewer Assessment: (b) (4) provided a table summary of the initial and most recent qualifications of all major equipment (3.2.A. Appendices, (b) (4) Table 20). In addition, the most recent requalification reports for all major equipment were reviewed during the (b) (4) PLI. All major equipment were successfully requalified, and all deviations adequately investigated and resolved, with no impact to the requalification. The information provided appears acceptable.

Sterilization by (b) (4)

(b) (4)

Reviewer Assessment: The sterilization method by (b) (4) for sterilizing product-contact materials at (b) (4) appears acceptable. The most recent requalification of the (b) (4) including (b) (4) was reviewed during the (b) (4) PLI and appears acceptable.

Equipment Cleaning

All major production equipment does not have direct product contact and is cleaned manually at regular frequency according to the respective SOP.

Reviewer Assessment: The manual cleaning procedures and the training of personnel performing equipment cleaning were reviewed during the (b) (4) PLI and appear acceptable to adequately clean equipment manually.

Computer Systems

(b) (4)

Reviewer Assessment: The online monitoring system appears to adequately monitor the environmental conditions of the manufacturing areas. The system was evaluated during the (b) (4) PLI and appears acceptable.

Contamination Control

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

Reviewer Assessment: The (b) (4) facility appears to have the appropriate measures in place to mitigate the risk of cross-contamination.

Aseptic Processing Validation

(b) (4)

(b) (4) (Exa-cel Manufacture)
(b) (4) is a contract development manufacturing facility (CDMO) located in (b) (4) (b) (4) manufactures the Exa-cel DP. The (b) (4) production area has separate, segregated and self-contained processing suites. Product and environmental safety, product segregation and integrity are assured in part through the utilization of separate heating, ventilation, and air conditioning (HVAC) systems for each processing suite and support area, room pressure differentials,

interlocking doors, personnel gowning, training to written procedures and control of personal access.

DMPQ conducted a pre-license inspection of (b) (4) from (b) (4) and determined it to be acceptable to manufacture Exa-cel DP.

Description of Manufacturing Areas

Exa-cel is produced in dedicated production suites, which include dedicated equipment. Changeover / line clearance occurs when changing from one production run to the next of different batches.

Changeover activities at (b) (4) include equipment cleaning and sanitization, ensuring removal of materials and supplies from the cleanroom from prior batches of Exa-cel, removal of product specific equipment (if applicable), and cleaning of all room and common equipment surfaces. Personnel flow within the manufacturing facility is (b) (4) and designed to maintain cleanliness to ensure compliance with requirements of the process area's product segregation and the security and integrity of the product. Access is by authorization and is controlled via (b) (4). Personnel flow, access, and frequency and duration of access are intentionally minimized to control and ensure environmental standards.

Clean Room Design

Exa-cel at (b) (4) is manufactured in one of (b) (4) dedicated Grade (b) (4) suites (b) (4). The cleanroom supply, distribution and filtration of air is regulated for the control of airborne and surface particulates to meet the appropriate cleanliness level via the use of ceiling terminal HEPA filters. The cleanrooms have low wall returns to recirculate air as applicable. The manufacturing suites consist of separate rooms dedicated to the functional activities of starting material processing, formulation, and fill and finish. The cleanroom suites and gowning areas are designed to control airborne and surface particulates via utilization of airlocks and interlocking doors to control air pressurization balance, and flow of materials and personnel. The core production areas have been designed for the separate, simultaneous production of product lots for multiple clients. Exa-cel suites are designed to meet (b) (4) standards (e.g., ISO (b) (4) Grade (b) (4) ISO (b) (4) / Grade (b) (4) ISO (b) (4) / Grade (b) (4) and ISO (b) (4) / Grade (b) (4)). Aseptic manufacturing operations are performed under ISO (b) (4) / Grade (b) (4) environmental conditions with the use of Class (b) (4) Type (b) (4). The (b) (4) are certified for (b) (4) to provide safety for the operator and product as well as for particulate content per (b) (4). The (b) (4) are designed with (b) (4).

(b) (4) cleanroom areas use a differential pressure cascade from higher classification to lower classification in the controlled classified processing areas. Room temperature and differential pressures are continuously monitored and alarmed by a Building Monitoring System (BMS).

Reviewer Assessment

Flow diagrams were provided for the cleanrooms at (b) (4) and reviewed. Clean room design allows for (b) (4) flow patterns and all Exa-cel manufacturing rooms have designated personnel and material airlocks. For aseptic manufacturing operations, the Grade (b) (4) are within a Grade (b) (4) background. The Exa-cel manufacturing rooms were reviewed during the (b) (4) PLI. The information provided appears acceptable.

Facility Cleaning

Cleaning and sanitation are performed using a (b) (4) system for (b) (4) and is scheduled at various frequencies based on area classification and risk (b) (4) (b) (4). Cleaning frequencies and scheduling are established based on the type of activity and the amount of traffic occurring in each specific area. Levels (L) delineate cleaning and sanitation activities:

(b) (4)

All disinfection agents have been qualified through disinfectant efficacy (DE) studies. All product contact items used in the manufacturing process are pre-sterilized single-use only items that do not require processing prior to use. Cleaning and sanitization of (b) (4) (b) (4) and other non-product contact equipment is performed on a routine basis per established wipe-down procedures using chemical agents such as (b) (4).

Reviewer Assessment

The frequency of cleaning and cleaning agents were provided, and the DE studies were reviewed during the (b) (4) PLI conducted in (b) (4). The (b) (4) EM monitoring trends for years (b) (4) through (b) (4) were also reviewed during the PLI which demonstrated a state of environmental control highlighting adequate cleaning and disinfection. Taken as a whole, the facility cleaning appears acceptable.

HVAC and Environmental Monitoring and Performance Qualification (EMPQ)

The HVAC system is comprised of mechanical Air Handling Units (AHU) and Roof Top Units (RTU) that provide (b) (4) (b) (4) air to the manufacturing clean rooms. The air is further controlled by (b) (4) (b) (4) to manage the air supply, return and exhaust volumes to achieve the desired room pressures and air pressure cascade. Room pressures and air pressure cascade diagrams were provided and demonstrated air pressure cascades from rooms of greater criticality to less stringently controlled rooms of lower classification.

All air supplied to cleanrooms goes through terminal HEPA filters for particle and contamination control. The HVAC system supply is approximately (b) (4) recirculation and (b) (4) fresh air. The HVAC system was installed and commissioned in accordance with an approved Installation Operational Qualification (IOQ) and Commissioning protocol. The executed IOQ protocol was designed to ensure the HVAC system was

installed and operates in compliance with design intent and user requirements. Testing was done to capture activities for balancing room air change verification, HEPA installation/ certification, and room certification. These qualifications confirmed that the manufacturing suites and support area air handling systems met conditions per (b) (4) (b) (4)

The facility design and contamination control features for the manufacturing area were challenged by performing an EMPQ. The EMPQ qualification activities were implemented in (b) (4) phases:

(b) (4)

Under static conditions monitoring of Grade (b) (4) areas was conducted to demonstrate the rooms/areas meet their classification. Under dynamic conditions mimicking operational activities, monitoring of Grade (b) (4) areas was conducted to demonstrate the rooms/areas meet their classification.

Upon completion of the approved EMPQ protocol, routine monitoring sampling sites were determined, and routine environmental monitoring commenced.

For execution of the EMPQ study, the cleanroom suites and ancillary areas were (b) (4)

(b) (4)

The EMPQ was performed in the (b) (4) Exa-cell manufacturing suites (b) (4). The EMPQ data collected verified that the Grade (b) (4) environment within each suite can support the Grade (b) (4) environment (within the (b) (4)) where aseptic manufacturing is performed. A total of (b) (4) non-viable samples, (b) (4) Viable Air samples, and (b) (4) Surface Viable samples were evaluated for each suite and included in a sampling plan. There were no exceptions noted. The protocols were executed in (b) (4) phases as specified below, and the resulting data met all acceptance criteria. Phase will be executed under routine manufacturing conditions and summarized within approximately (b) (4) of monitoring.

(b) (4)

(b) (4) executed a risk assessment to determine sampling site selections for Phase (b) (4) of the (b) (4) EMPQ protocols. Sampling included total non-viable particulate (NVP) counts, viable air counts, and surface viable counts.

Reviewer Assessment

The HVAC system was qualified and EMPQ demonstrated that it performs adequately to maintain cleanroom environments to the predetermined levels. (b) (4) levels also passed the stringent acceptance criteria for all rooms. The EMPQ was performed under both static and dynamic conditions with no deviations provided. The HVAC systems and EMPQ were also reviewed during the (b) (4) PLI conducted in (b) (4) along with the DE studies. The information provided appears acceptable.

Environmental Monitoring

An EM program is in place at (b) (4) to establish the manufacturing environment is consistently maintained according to standards. EM is performed during each batch of Exa-cel manufactured. Sampling includes surface (b) (4) viable airborne particulates, non-viable airborne particulate, and personnel testing. The testing limits based on room classification are listed below.

(b) (4)

Reviewer Assessment

Viable and non-viable environmental monitoring programs are in place with adequate stringency based on the FDA guidance document “Guidance for Industry Sterile Drug Products Produced by Aseptic Processing —Current Good Manufacturing Practice”. The information provided appears acceptable.

Utilities

WFI

(b) (4) grade sterile WFI is purchased and used for cleaning activities and is not manufactured on site.

Process Gases

(b) (4) uses Liquid Nitrogen (LN₂), (b) (4) LN₂ is used for freezing and storage of the Exa-cel DP and is supplied to the facility in (b) (4) (b) (4) LN₂ system for distribution. The (b) (4) LN₂ system is fed from a bulk tank located at the rear of the building. (b) (4) is supplied to the facility in portable cylinders. There are (b) (4) distribution piping systems within the facility to distribute this gas.

(b) (4)

(b) (4)

Reviewer Assessment

The clean utilities used at (b) (4) are purchased and not manufactured on site. The LN₂ systems and (b) (4) distribution systems were qualified for use and determined to be acceptable. The information provided appears acceptable.

Major Manufacturing Equipment Qualifications

Equipment used in the manufacturing and testing of (b) (4) and drug product are assessed through a qualification protocol to ensure the equipment is acceptable for its intended use. A continuing qualification program is in place to ensure that qualified equipment, controlled temperature units, and utilities continue to function in a qualified

state after initial qualification. Continuing qualification frequencies are determined through a risk-based approach and documented in the respective validation documents.

(b) (4) Filling System Qualification

(b) (4)

(b) (4)

MaxCyte Electroporator Qualification

(b) (4)

■ (b) (4)

■ (b) (4)

(b) (4)

CliniMACS Prodigy Qualification

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

Liquid Nitrogen Cryostorage Tank Qualification

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer Assessment

All major exa-cel equipment has been qualified. The equipment qualifications were also reviewed during the (b) (4) PLI conducted in (b) (4) The information provided appears acceptable.

Computer Systems

The validation of computerized systems follows a lifecycle and risk-based approach per

the organization Computerized System Validation procedure. BMS, Document Management Systems and Regulatory Asset Management Systems have been implemented and validated to support commercial operations.

The BMS controls and monitors the heating, cooling, ventilation, and pressure of the classified areas required to ensure the respective area(s) is operating as designed. The system monitors various pieces of equipment located in the clean suite and provides set points and alarms to alert the appropriate personnel of excursions that occur. The system maintains an audit trail of the alarms, who acknowledged them, as well as the reason for the alarm. The BMS performs the following functions:

- Control and monitor (b) (4) conditions (temperature, pressure differential, humidity)
- Control and monitor equipment operation and status
- Provide local and remote alarming capabilities
- Capture and store historical trend, alarm, and audit trail data
- Provide the capability to report on historical BMS data
- The BMS was qualified through an IQ/OQ approach.

Reviewer Assessment

The computer systems were reviewed during the (b) (4) PLI conducted in (b) (4) and determined to be acceptable.

Contamination Control

The contamination control strategy at (b) (4) includes the following elements:

(b) (4)

Multi-Product Considerations

Batches are manufactured in Exa-cel-dedicated production suites for any operations where open manipulations may occur. Manufacturing steps that occur in common

areas, for example, Visual Inspection Room (for drug product visual inspection), (b) (4)

are performed with the following controls in place:

- Visual inspection

(b) (4)

Cross-Contamination Controls

The combined design of the facility layout, HVAC system, and the controlled area classifications minimize any cross contamination through, but not limited to the following controls:

- The utilization of dedicated AHUs and FFUs
- Air quality classifications – specified, controlled, and validated
- Pressure differentials in the processing/production areas – monitored via BMS
- The physical separation of each of the process suites – each with unidirectional flow
- Airlocks and interlocking doors
- Procedurally mandated behaviors through employee training, to include aseptic techniques, gowning qualifications and controls, cleaning, and sanitation controls
- (b) (4) controlled access to the manufacturing and support areas
- Limiting and minimizing manufacturing area access, frequency, activities, and number of personnel in processing rooms
- Isolated and dedicated active pass-thru areas for material transport, including cleaning procedures for the pass-throughs

Aseptic Process Simulations (APS)

All APS involve high and medium risk interventions encountered during Exa-cel manufacturing operations. Additionally, all APS includes a representative number of

low-risk manipulations to ensure media is in contact with material surfaces used during routine manufacture. Intervention criticality was identified by risk assessment.

The APS protocols are required to be executed in (b) (4) for new processes, to restart processes following an extended shutdown period (b) (4) from the last date of harvest), major process changes that necessitate changes to the APS protocol, adverse trends for final product sterility, or to support Process Validation for commercialization.

(b) (4) consecutive successful executions must be performed in these cases.

Subsequent routine APS is performed every (b) (4)

(b) (4)

As a result of these deviations the APS was re-executed.

Reviewer Assessment

The re-executed APS runs were reviewed during the (b) (4) PLI conducted in (b) (4) (b) (4) and the data demonstrated no APS failures following (b) (4) APS runs in each manufacturing suite (b) (4) suggesting the CAPA implementation was successful. Additionally, all previous APS runs performed in (b) (4) passed acceptance criteria. The information provided here and reviewed during the (b) (4) PLI appears acceptable.

(b) (4) (Exa-cel Manufacture)

(b) (4) is a CDMO located in (b) (4) manufacturing exa-cel DP. The (b) (4) campus consists of (b) (4) separate facilities: (b) (4) (b) (4) Exa-cel is manufactured in (b) (4) while exa-cel testing is performed in the (b) (4) located in Building (b) (4) is not involved in the commercial manufacture of Exa-cel. No licensed commercial products are currently manufactured by (b) (4) and the (b) (4) facility is currently dedicated to the manufacture of exa-cel. A PLI of (b) (4) was performed by DMPQ from (b) (4) which resulted in a satisfactory outcome.

The (b) (4) facility is a (b) (4)-story modular building containing approximately (b) (4) of space. The (b) (4) floor contains the manufacturing rooms, warehouse and material release rooms, while the (b) (4) floor contains office and storage spaces. There are (b) (4) Grade (b) (4) cleanrooms (b) (4) and (b) (4) Grade (b) (4) processing rooms (b) (4) supporting the Grade (b) (4) cleanrooms. There are (b) (4) Grade (b) (4) in each of the Grade (b) (4) cleanrooms for aseptic open processes. Each Grade (b) (4) cleanroom has (b) (4) separate personnel airlocks and passthrough hatches to allow (b) (4) flow of personnel and materials, respectively. (b) (4) (b) (4) passthrough hatches allow decontamination of materials for transfer into the graded areas. Grade (b) (4) cleanrooms (b) (4) and Grade (b) (4) processing room will be used for exa-cel manufacturing at (b) (4)

DMPQ conducted a PLI of (b) (4) from (b) (4) and determined it to be acceptable for the manufacture Exa-cel DP.

Reviewer Assessment: Material, personnel, waste and product flow diagrams of the (b) (4) facility were provided and appear acceptable.

Heating, Ventilation and Air Conditioning

The HVAC system for the (b) (4) facility consists of filter fan units (FFU) in each room supplying HEPA-filtered air. The number of FFUs that are fitted into each room is based on the size and grade of the room. Each FFU is controlled by the BMS, which also controls the room temperature and humidity. Terminal HEPA filters are located with

each FFU. Each room is supplied with (b) (4) fresh air and (b) (4) recycled air. The (b) (4) environmental monitoring system monitors room temperature and differential pressure. Humidity is controlled by the BMS. The HVAC system and facility undergo requalification and maintenance every (b) (4) during the routine facility shutdown. Qualification of the HVAC system consists of:

(b) (4)

An initial qualification of the facility was performed, which consisted of EMPQ, APS and technical transfer activities. After a deep clean of the facility, (b) (4) performed full EM sampling of the facility at-rest. After a facility clean, (b) (4) of mock manufacturing activities simulating routine use of the Grade (b) (4) areas, followed by cleaning and post-clean EM were performed. An APS was performed to validate the sterile manufacturing capability of the (b) (4) facility. Technical transfer of the exa-cel manufacturing process and support activities was completed after successful completion of the EMPQ and APS.

Reviewer Assessment: *The most recent facility and HVAC system requalification performed in (b) (4) were reviewed during the (b) (4) PLI. All acceptance criteria were met, and all deviations raised during qualification were adequately investigated and closed and determined to have no impact to the requalification. The HVAC system appears to adequately maintain cleanroom classifications in accordance with (b) (4). The information provided appears acceptable.*

Clean Utilities

(b) (4) does not generate any water for use in the exa-cel manufacturing process. Potable water for general building use (e.g., kitchen, restroom) is supplied by the municipality. All water (WFI and water for irrigation) for use in the cleanroom is procured from an approved supplier. Water for irrigation is used in the (b) (4) and in (b) (4) for the cleanroom (b) (4). WFI is used to perform the (b) (4) (b) (4) test.

The only process gas used in (b) (4) related to the manufacture of exa-cel is (b) (4) which is used in the (b) (4) are stored in an exterior cage. (b) (4) are obtained from an approved supplier and are tested prior to use, with a (b) (4) at each point of use. The

gas distribution lines of (b) (4) were initially qualified and receives maintenance at the defined intervals.

Environmental Monitoring

Classification of the cleanroom areas at (b) (4) follow (b) (4) and (b) (4) regulations. Routine EM includes air viable (active and passive) and non-viable particulate counts, surface sampling and personnel. Generally, at-rest monitoring occurs every (b) (4) for all classified areas. Continuous non-viable particulate counts and (b) (4) are performed for all manufacturing activities taking place in the Grade (b) (4). In addition, continuous non-viable particulate counts and active viable air samples are collected in the surrounding Grade (b) (4) room during all manufacturing processes. All personnel working inside the Grade (b) (4) and Grade (b) (4) environment are monitored at the end of the process.

(b) (4) has defined alert and action limits, with EM excursion response procedures. All microbial growth recovered from the Grade (b) (4) or Grade (b) (4) classified areas are submitted for identification testing. Microbial growth recovered from all other classified areas are submitted for identification testing when the action level is exceeded. EM result trending is performed (b) (4) and (b) (4).

Reviewer Assessment: Tables summarizing EM alert and action limits, and EM sampling location diagrams of (b) (4) were provided and appear acceptable. EM trend data from the previous (b) (4) were reviewed during PLI and appear to demonstrate adequate non-viable particulate and microbial control of the cleanrooms.

Facility Cleaning

All manufacturing rooms are cleaned and sanitized based on the established procedures defining cleaning frequencies and cleaning agents. The cleaning frequencies for all classified areas at (b) (4) are (b) (4), (b) (4), and (b) (4). Sterile cleaning agents are used in the Grade (b) (4) Grade (b) (4) areas. Cleaning agents used in (b) (4) include:

(b) (4)

(b) (4)

Reviewer Assessment: *The EM trending data from the previous (b) (4) were reviewed during the PLI, which shows adequate viable and non-viable control within the manufacturing areas. The cleaning frequencies and disinfectant study, which were also reviewed during PLI, appears suitable and effective in the removal of residues and organisms from all surfaces found in the cleanrooms.*

Equipment

All major equipment used in the manufacture of exa-cel were initially qualified for use, with routine requalification and maintenance at the appropriate time intervals. All product contact materials used with production equipment are ready-to-use, disposable consumables that are received sterilized from a qualified supplier. The major production equipment used to manufacture exa-cel at (b) (4) are summarized in the table below.

(b) (4)

(b) (4)

CliniMACS Prodigy

The CliniMACS Prodigy (Prodigy) is used for the separation, enrichment, and expansion of target cell populations of Peripheral Blood Mononuclear Cells (PBMC) in the manufacture of exa-cel. IOQ of the Prodigy verified the proper installation and set-up of the system software and function settings, which was performed by the manufacturer,

(b) (4) Unit functions such as the (b) (4)

(b) (4) were tested. The PQ of the Prodigy was completed during the technical transfer of the exa-cel manufacturing process and support activities to (b) (4). The technical transfer protocol included the release criteria for the exa-cel batches manufactured, which comprised the acceptance criteria for PQ. (b) (4) PQ runs were performed, with (b) (4) manufactured for each run. All acceptance criteria were met with one minor deviation observed, which was investigated and appropriately addressed. The Prodigy is requalified (b) (4).

(b) (4)

Liquid nitrogen (LN2) cryostorage tank

The LN2 tanks provide frozen storage for vialled exa-cel DP in vapor phase liquid nitrogen. After a vendor performed IOQ, a PQ was performed consisting of a

(b) (4). All acceptance criteria were met, with two minor deviations observed and appropriately addressed. The LN2 tanks are recalibrated (b) (4).

(b) (4) vial filler

The (b) (4) vial filler is used to fill and seal (b) (4) vials using a (b) (4) syringe and (b) (4) (b) (4) respectively. After the vendor-performed IOQ, a PQ was performed in conjunction with the technical transfer of the exa-cel manufacturing process and support activities to (b) (4). The exa-cel batches manufactured during the technical transfer were filled using the (b) (4) vial filler. All acceptance criteria were met, with no major deviations observed during the qualification of the (b) (4) vial fillers, which are requalified (b) (4).

MaxCyte Electroporator

The MaxCyte Electroporator is the device used to allow gene-editing components to pass into the target cells by electroporation. IOQ included installation and equipment set-up activities, which were performed by the vendor. PQ of the electroporator was included during the technical transfer of the exa-cel manufacturing process to (b) (4). All exa-cel batches manufactured during PQ met the release criteria. The PQ met all acceptance criteria, with one planned deviation observed and appropriately addressed. The electroporator is requalified (b) (4).

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

requalification for all major production equipment listed above were reviewed during the (b) (4) PLI conducted (b) (4) The information provided appears acceptable.

Computer Systems

The major computer systems utilized at (b) (4) are:

(b) (4)

Reviewer Assessment: All computer systems were validated according to the EC Guide to GMP, Annex (b) (4) and with the requirements of GAMP. The computer systems were reviewed during PLI and appear to be validated and acceptable.

Contamination Control

(b) (4) has the following design and procedural controls in place to minimize the risk of microbial contamination.

(b) (4)

Reviewer Assessment: The (b) (4) facility appears to have the appropriate measures in place to mitigate the risk of cross-contamination.

Aseptic Processing Validation

(b) (4) performed an APS to verify the open process steps of the Exa-cel manufacturing process are aseptic and contamination controls are adequate. An initial qualification, consisting of (b) (4) APS runs that covered all routine open and closed manufacturing process manipulations, was performed, with (b) (4) APS performed

every (b) (4) thereafter to confirm the adequacy of the contamination controls. (b) (4) (b) (4) purchased from a qualified vendor and verified by the QC Laboratory to promote microbial growth, was used in place of the product and reagents. Worst-case conditions were used, which were considered to be the maximum number of routine and non-routine open aseptic manipulations. Routine EM sampling was performed during the execution of the APS, including personnel monitoring. (b) (4) DP vials were filled for each APS run, which is greater than the number of DP vials filled in a commercial lot (b) (4) vials). After the completion of the simulated manufacturing process, (b) (4) vials were (b) (4) The acceptance criteria of an APS are (b) (4) (b) (4) In addition, all EM sampling collected during the APS resulting in an excursion must be adequately investigated and addressed per the protocol. A summary of the APS is provided in the table below.

(b) (4)

Reviewer Assessment: All APS runs met the acceptance criteria. During the (b) (4) PLI, the most recent APS (b) (4) performed (b) (4) in (b) (4) was reviewed. All (b) (4) vials resulted in (b) (4). In addition, all EM excursions and deviations were adequately investigated and addressed, with no impact to the APS. The information provided appears acceptable.

Overall Reviewer's Assessment of Section 3.2.A.1:

- ❑ The (b) (4) facility information provided with the submission appears acceptable. During the PLI of the (b) (4) facility performed from (b) (4) 2023, the quality systems, facilities and equipment, materials and QC laboratories were reviewed and determined to be acceptable for the manufacture of Cas9 (b) (4).
- ❑ The manufacture of (b) (4) SPY101 at (b) (4) is a (b) (4) -controlled process. The facility has been recently inspected by the (b) (4) and the report reviewed by ORA with an acceptable outcome of VAI. Additionally, we performed a 704(a)(4) Records Review of the (b) (4) facility for this submission which appears acceptable. Overall, the (b) (4) facility appears to be in a qualified state.
- ❑ The (b) (4) facility information provided with the submission appears acceptable. A PLI of (b) (4) was performed (b) (4). The quality systems, facilities and equipment, materials and QC laboratories were reviewed and determined to be satisfactory for the manufacture of (b) (4) Cas9 and SPY101.
- ❑ A recent PLI in support of exa-cel DP manufacture at (b) (4) was conducted by the FDA from (b) (4). (b) (4) quality systems, exa-cel manufacturing, facilities, and QC laboratories were reviewed and determined to be acceptable for manufacturing exa-cel. The information provided with this submission was reviewed and appears acceptable.
- ❑ The (b) (4) facility information provided with the submission appears acceptable. In addition, a PLI of (b) (4) was performed from (b) (4). The quality systems, facilities and equipment, materials and QC laboratories were reviewed and determined to be satisfactory for the manufacture of Exa-cel.

3.2.R Regional Information (USA)

❑ **Executed Batch Records**

The review of executed batch records is deferred to OTP.

❑ **Combination Products**

N/A. Exa-cel is not a combination product.

❑ **Comparability Protocols**

No comparability protocols under DMPQ purview were submitted under STN 125785/0 and STN 125787/0.