SUMMARY OF FINDINGS

(PR)

The Pre-License Inspection (PLI) of this CAR-T Manufacturer was assigned per eNSpect Assignment #183399 and a CBER/OCBQ/DMPQ PLI Assignment for BLA STN# 125714/0, which is included in Attachment PR1. The inspection was conducted per Compliance Program Guide 7345.848, Inspection of Biological Products (PAC 41848A, Pre-License Inspection, Somatic Gene Therapy). The Quality System, Production System, Laboratory System, Materials System, Facilities & Equipment System, and the Packaging Labeling System were covered during the current inspection. System coverage included reviewing procedures, records, and training. The CMC Submission Assessment and the CBER/OCBQ/DMPQ Assessment are included in Attachments PR3 and PR4. All the inspection requests in Attachment PR1 were covered during the current inspection.

This site, Juno Therapeutics, Inc. a Celgene Company, 1522 217 Pl. SE, Bothell, WA. 98021 (FEI: 3011834594) manufactures Autologous CD8+/CD4+ T Cells Expressing Chimeric Antigen Receptor (CAR) per BLA STN#: 125714/0. The product is used for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma, intravenous infusion. These two components CD4 and CD8 are manufactured and filled separately, but the manufacturing process is the same. The product name is JCAR017® (liso-cel). Operations at this site include Drug Substance and Drug Product manufacturing, primary and secondary packaging, drug product release and stability testing, and Lentiviral Vector (b) (4) testing.

This was the first inspection of this site. No previous inspections have been conducted.

The current 10/7-16/2020 Pre-License Inspection (PLI) noted the following observations: there was failure to thoroughly review any unexplained discrepancies: DEV-2019-03442, reported a (b) (4) from the contract test lab, (b) (4) which conflicted with a negative result from the (b) (4) vendor, (b) (4), the vendor did not conduct any type of OOS investigation, the reliability of the CoA from the vendor supplying the (b) (4) and previous (b) (4) Lots were not established, and the clinical assessment did not include an evaluation of any potential AEs associated with (b) (4) used in (b) (4); Notice of Events (NOEs) were not classified as Deviations; (b) (4) (b) (4) and (b) (4) are inspected for leaks but the result is not documented in the concurrent batch record; deficiencies were noted in aseptic practice; the bacterial endotoxin test method, MET-000054, "Bacterial Endotoxin Test Method", fails to specify the minimum time required for (b) (4); MET-001013, "Appearance by Visual Inspection", was not followed in that reference standards were not (b) (4) assessment, and the test sample was not (b) (4) for a color assessment; and (b) (4) of inspected EM (b) (4) presented discrepant enumeration results. A six-item Form FDA 483, Inspectional Observations, was issued to the firm at the conclusion of the inspection.

No samples were collected and no refusals were encountered during the current inspection.

ADMINISTRATIVE DATA

(PR)

Inspected firm:	Juno Therapeutics Inc
Location:	1522 217th Pl SE Bothell, WA 98021-7617
Phone:	908-219-0751
FAX:	
Mailing address:	1522 217th Pl SE Bothell, WA 98021-7617
Email address:	Jeffrey.Masten@bms.com
Dates of inspection:	10/7/2020-10/9/2020, 10/13/2020-10/16/2020
Days in the facility:	7
Participants:	Prabhu P Raju, Investigator – OBPO, Team Biologics Branch/Division I Eileen A Liu, Investigator – OBPO, Team Biologics Branch/Division II

At the beginning of the inspection, Investigators Prabhu Raju and Eileen Liu presented our credentials and issued an FDA-482, Notice of Inspection, to Mr. Jeffrey L. Masten, Vice President, Quality Assurance. At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued to Mr. Snehal Patel, Vice President, Site Head, Bothell. This was a team inspection conducted by Prabhu P. Raju, Investigator, Investigator and Eileen Liu, Investigator, and the Authorship of EIR sections is indicated by initials (PR, EL).

The assignment information for BLA STN# 125714/0 is included in Attachment PR5. The applicant Juno Therapeutics, Inc., Product Description, Manufacturing site address information, and a process flow diagram is included in Attachment PR5.

HISTORY OF BUSINESS

(PR)

Juno Therapeutics, Inc. was launched in 2013 in collaboration with three leading cancer institutions (Fred Hutch Cancer Research Center, Memorial Sloan-Kettering Cancer Center, and Seattle Children's Institute). Juno Therapeutics subsequently was acquired by Celgene Corporation and Bristol-Meyers Squibb Company (BMS), in 2018 and 2019, respectively (see Exhibit PR1, page six). Two clinical products, JCAR017 (lisocabtagene maraleucel) and (b) (4) , are produced at the Juno Manufacturing Plant (JuMP), located at 1522 217th Place SE, Bothell, WA. 98021 (see Exhibit PR1, page 15). The Juno (Dexter) facility contains Development Labs, Research, Process, and Technical Development, Patient Operations and Regulatory Affairs and is located at 400 Dexter Ave N #1200 Seattle, WA 98109 (see Exhibit PR1, page 7). The Bristol Meyer Squibb (BMS) Headquarters address is 430 E. 29th Street, 14th Floor, New York, NY, 10016 (see Exhibit PR45, 1st paragraph).

The Juno Manufacturing Plant (JuMP) was introduced in 2016, serving its first clinical patient. JuMP operates (b) (4) . There are approximately (b) (4) personnel engaged in Quality, Production, Storage, and Distribution activities at the Juno Manufacturing Plant (JuMP). The Juno Manufacturing Plant (JuMP) has not been inspected by any Health Authorities and does not hold any commercial manufacturing authorizations issued by competent authorities. In 2018 Celgene acquired Juno Therapeutics, Inc. and in 2019 Bristol Myers Squibb acquired Celgene. An overview of the history of this site is included in Exhibit PR1, page six, and Exhibit PR45.

JCAR017 (lisocabtagene maraleucel) is a CD19 directed genetically modified autologous T cell immunotherapy and is a cell suspension for infusion. The strength/potency is 50-100 x 10^6 CAR Positive viable T Cells. JCAR017 is an intravenous infusion for treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies. (b) (4) is another clinical product that is manufactured at this site but was not subject of this PLI inspection (see Exhibit PR1, page 15).

Juno Therapeutics, Inc. has the following three locations in the greater Seattle area (see Exhibit PR1, page 7).

Juno Manufacturing Plant (JuMP) (This location) (FEI: 3011834594)

Juno Therapeutics, Inc.
1522 217th Place SE, Bothell, WA 98021
(Manufacturing Operations, Manufacturing Sciences and Technology, Site Supply Chain, Facilities and Engineering, Quality Assurance, Quality Control)
Hours of Operation (b) (4) days per year (b) (4) employees

JuMP NOW (FEI: 3011834594)

22026 20th Ave SE, Unit 102, Bothell, WA 98021

(Additional Warehouse Space, Manufacturing Sciences and Technology)
Hours of operation: (b) (4) days per year

(*This site was not inspected during the current inspection)

Juno (Dexter) (FEI: 3010932912)

Juno Therapeutics, Inc.
400 Dexter Ave N #1200, Seattle, WA 98109
(Patient operations, Supply Chain, Quality, Regulatory Affairs, Research, Process, Corporate HQ)
Hours operation: (b) (4) days per year
Total personnel: (b) (4)

The top officials at the site are Mr. Jeffrey L. Masten, Vice President, Head of Site Quality, and Mr. Snehal Patel, Vice President Site Head, of Bothell. All official correspondence should be sent to Mr. Masten at the firm's address. An organizational chart is included in Exhibit PR1, page 12 & 13.

There has been no previous compliance history with this facility. This was the initial PLI inspection of this site.

A list of manufacturers related to JCAR017 lentiviral vector (b) (4) manufacturing is listed in the table below and in Attachment PR3, pages 7-8. The (b) (4) vector is a nonreplicating, self-inactivated lentivirus, based on (b) (4)
The vector is manufactured at a contract manufacturing facility (b) (4) and the Vector (b) (4) is shipped to a contract manufacturing facility (b) (4) for formulation and fill into (b) (4) (supplied by (b) (4) The vector stability studies support a (b) (4) . The following facilities (CMC, page 34) are used for the manufacturing and testing of the (b) (4) vector (b) (4) and the JCAR017 lisocabtagene maraleucel DS and drug product (DP):

Site	Registration	Address	Function
(b) (4)			

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

Juno Therapeutics Inc. Manufacturing Plant	FEI: 3011834594 DUNS: 079941307	1522 217th Place SE Bothell, WA 98021 United States	Testing of (b) (4) • (b) (4) JCAR017 DS & DP Production
Juno Therapeutics Inc.	FEI:3010932912 DUNS: 079290042	400 Dexter Ave N, Suite 1200 Seattle, WA 98109 United States	Testing of (b) (4) • (b) (4) JCAR017 Corporate Quality functions.

(b) (4)

Information for FMD-145 Letter:

Mr. Jeffrey L. Masten
Vice President, Quality Assurance
jeffrey.masten@bms.com
Juno Therapeutics, Inc.
1522 217th Pl SE
Bothell, WA 98021

The hours of operation are (b) (4) days per year, and this site has (b) (4) employees. The firm's registration status is current.

INTERSTATE (I.S.) COMMERCE

(PR)

JCAR017 is not a licensed product and is distributed under the IND. (b) (4) is also manufactured at this site but was not the subject of this Pre-License Inspection (PLI). A list of JCAR017 lots that were distributed under the IND is included in Exhibit PR42. An example product label is included in Exhibit PR6.

JURISDICTION (PRODUCTS MANUFACTURED AND/OR DISTRIBUTED)

(PR)

Lisocabtagene maraleucel (referred to throughout this document as JCAR017) is composed of autologous CD8 and CD4 T cells that are genetically modified with a lentivirus vector (b) (4) encoding a chimeric antigen receptor (CAR) that specifically recognizes the CD19 protein present on (b) (4) tumor cells as well as normal B cells (see Attachment PR3, page three). Lisocabtagene maraleucel is manufactured from autologous leukapheresis material that is sequentially positively-selected for the CD8 and CD4 T cells, which are then activated, transduced, expanded and formulated as separate components. JCAR017 (Lisocabtagene maraleucel) is formulated at (b) (4) into an infusible cryopreservation solution (b) (4) Multiple Electrolytes Injection, Type I, (b) (4) human serum albumin (HSA), 75% CryoStor® CS10) and filled into 5 mL cryopreservation vials, 1-4 vials per component, and stored at ≤ -130°C. Lot release testing is conducted on each CD8 and CD4 component to determine product quality and infused sequentially (first CD8 then CD4) at a 1:1 ratio of CAR-positive T cells to provide a target dose of $100x10^6$ CAR-positive T cells (acceptable dose range $50x10^6$ – $110x10^6$ CAR positive T cells). The drug product is provided sterile and contains no preservatives other than cryopreservation medium. Product is shipped frozen in a dry liquid nitrogen shipper, with the product vials stored inside of a carton secured in a metal rack. The drug product is stored in vapor phase liquid nitrogen (≤ -130°C) until required, when it is thawed and infused within 2 hours (see Attachment PR3. CMC Assessment Document, page three, 1st paragraph for complete description).

JCAR017 is administered as a defined composition of CAR-positive viable T cells (consisting of CD8 and CD4 components). JCAR017 is a cell suspension for infusion. A single dose of JCAR017 contains 50 to 110 x 10^6 CAR-positive viable T cells consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components, with each component supplied separately in one or more single dose vials. The infusion volume is calculated based on the concentration cryopreserved drug product CAR-positive viable T cells. The volume may differ for each component infused (see Exhibit PR1, page 17, for Indication and Product Description).

The following facilities (see Attachment PR3, CMC Document, page 6) are used for the manufacturing and testing of the (b) (4) and the lisocabtagene maraleucel DS and drug product (DP):

- Juno Therapeutics, Manufacturing Plant (JuMP), 1522 217th Pl. SE Bothell, WA 98021 USA

(b) (4)

- Juno Therapeutics, 400 Dexter Ave N. Suite, 1200, Seattle, WA 98109 USA

PERSONS INTERVIEWED/INDIVIDUAL RESPONSBILITY

(PR)

Upon entrance to the facility, credentials and a Form FDA-482, Notice of inspection, was issued to Mr. Jeffrey Masten, Vice President Site Quality. Mr. Brett Johnston, Senior Director, Quality Operations, accompanied me during the inspection and provided information, coordinated interviews with the firm's personnel, and accompanied me on facility walk-throughs. He reports directly to Mr. Jeffrey Masten, Vice President, Site Quality. Mr. Masten is responsible for all quality operations at the site and reports to Ms. Maria Brown, VP, Global CT Quality, Bristol Meyers Squibb, New Jersey. Her address is listed below.

Maria Brown
Vice President Global Cell Therapy Quality
Bristol Myers Squibb
556 Morris Avenue
Building S11
Summit, NJ 07901

The Site Head is Mr. Snehal Patel, Vice President, Site Head, Bothell. Mr. Patel has ultimate responsibility for all operations at the site, and reports to Ms. Ann Lee, Head of Cell Therapy Development and Operations (CTDO). Her address is listed below.

Ann Lee
Senior Vice President and Head of Cell Therapy Development & Operations
Juno Therapeutics, Inc.
400 Dexter Avenue N.
Seattle, WA 98109

At the conclusion of the inspection, a Form-FDA483, Inspectional Observations, was issued to Mr. Patel.

Organizational Charts are included in Exhibit PR1, pages 9-13. A list of individuals were interviewed during the inspection is included in Exhibit PR4.

(EL)

Ms. Anne L. Shandy (Director, Quality Systems) assisted me throughout the inspection with document requests, interview arrangements, and coordination of facility tours. Additional Juno Manufacturing Plant (JuMP) key personnel, subject matter experts (SMEs), and associates who provided information, records, and accompanied me on facility tours are documented in this EIR and listed in **Exhibit EL-1**.

Opening meeting participants are listed below and collected in **Exhibit EL-2**.

Jeffrey L. Masten	VP and Quality Site Head
Snehal S. Patel	VP Global Manufacturing Network
Brian R. Christin	Director, Product Technical Stewardship, Cell Therapy Global MS&T
Mary F. Mallaney	Director, Early CMC Portfolio and Technical Writing
Anne L. Shandy	Director, Quality Systems
Michael C. Barlow	Associate Director, Manufacturing Operations

Bristol Myers Squibb™ (BMS) JuMP Bothell Site Leadership and Quality Leadership Team key personnel names, titles, hire dates, and job descriptions were collected and submitted in **Exhibit EL-3.** Examples of the firm's key leadership personnel include but are not limited to the following.

Jeffrey L. Masten – Vice President, Quality Site Head (Bothell)

- Hire date: October 23, 2017
- Responsible for the day-to-day operations of the JuMP Quality Assurance, Quality Systems, and Quality Control.

Snehal S. Patel – Vice President, Global Manufacturing Network

- Hire date: February 05, 2018
- Accountable for building, leading, and optimizing the operations of the global cell therapy manufacturing network.

Anne L. Shandy – Director, Quality Systems

- Hire date: June 03, 2019
- Responsible to lead the Quality System to ensure site level Quality Systems are appropriately designed, implemented, and measured for cGMP compliance and effectiveness.

Brett A. Johnston – Senior Director, Quality Assurance Operations

- Hire date: July 31, 2017
- Responsible for the day-to-day operations of the JuMP Quality Operations team, including but not limited to drug substance and product quality "on-the-floor" support to manufacturing operations, initiation and completion of in-process manufacturing and QC deviation investigations, and review and approval of site specific procedures and GMP documentation.

Quyen L. Huynh – Director, QC

- Hire date: March 09, 2015
- Responsible for overseeing cGMP cell based assays and raw material testing in order to ensure product safety; lead cross-functional teams in support of product development, and technology transfer.

Frances Browder – Director, QC

- Hire date: September 25, 2017
- Responsible to provide senior leadership of the QC Microbiology department; overseeing cGMP testing including environmental monitoring in order to ensure product safety; lead cross-functional teams in support of product development, technology transfer, and raw materials planning.

MANUFACTURING/DESIGN OPERATIONS

(PR)

The Juno Manufacturing Plant (JuMP) located in Bothell, WA, is a multi-product manufacturing site for cell therapy products (JCAR017 (b) (4) The JuMP facility will serve as a commercial launch facility for Juno Therapeutics, Inc (a Celgene Company) for manufacturing JCAR017 (lisocabtagene maraleucel) (see Attachment PR4, page 16). A complete description of all manufacturing operations at this site is described in the CMC Assessment document in Attachment PR3 and a summary is included in Attachment PR5, page two & three.

The Juno facility is a (b) (4) Building. Warehouse, QC Labs, Electrical Room, Offices, etc. are located on the (b) (4) and the manufacturing area is located on the (b) (4) (see floor diagram in Exhibit PR9, and Exhibit PR44). Leukapheresis material is the patient-specific starting cellular material for JCAR017 DS manufacturing. The leukapheresis material is collected at centers that have been qualified by Juno (see Exhibit PR3 for a list of approved collection centers). The collections are performed according to written procedures by staff that have education, training, and experience required to meet state and local requirements for this activity (see CMC Assessment Document, Attachment PR3, bottom of page 17). The firm indicated that this JuMP facility can produce (b) (4) lots, each composed of a CD8 and CD4 component, per week (see Attachment PR3, page 60, top of page).

The cGMP cell processing areas located with JuMP include cleanrooms and product support space that are serviced by dedicated HVAC systems. The cleanroom areas are designed for autologous cell therapy processing. The rooms are designed to meet ISO (b) (4) ISO (b) (4) classifications depending on the use of the room. There are local ISO (b) (4) biosafety cabinets (BSCs) within ISO (b) (4) rooms used for process steps that are exposed to the environment (open system operation) (see Attachment PR4, page 16 for additional description).

The cGMP cell processing areas on the (b) (4) is included in page 10, Attachment PR4.

A description of the JCAR017 manufacturing operations is included in Attachment PR4, page two, and is summarized in the following paragraphs. The JCAR017 (lisocabtagene maraleucel) drug product consists of two separate components, a cryopreserved CD8+ T cell suspension and a cryopreserved CD4+ T cell suspension of intravenous administration.

This drug product consists of autologous CD8+ (killer) and CD4+ (helper) T cells expressing CD19-specific chimeric antigen receptor (CAR). The independent manufacturing of CD8+ and CD4+ drug product components provides an ability to control the ratio of the CD8+ and CD4+ CAR+ T cells dosed and therefore reducing between-lot (i.e. patient) variability and biological activity.

The cryopreserved CD8+ and CD4+ T cell suspensions are individually formulated in a (b) (4) . Each CD4+ and CD8+ suspension is filled separately into cryogenic vials composed of (b) (4) (up to 4 vials per drug product component). The cryopreserved cell suspensions (CD8+ and CD4+ T cells) are stored at ≤ -130 °C in vapor phase of liquid nitrogen. Each drug product vial contains (b) (4) CAR+ viable T cells/mL. The cryo-stored cell product components are thawed just before patient administration at a target dose at the infusion site. The thawed cell should be administered within two hours of thaw. The thawed vial(s) are visually inspected for damage and leaks. Each cell suspension is drawn in a syringe (5 mL syringe for 4.6 mL suspension). The drawn suspension volume and syringe volume can change depending on dose requirements for administration. Syringes are not included in the product package.

Primary operations occur on the (b) (4) with (b) (4) occurring on the (b) (4) . The manufacturing steps are listed below and included in Exhibit PR1, page 23 (Floor Diagram listing process steps) and Exhibit PR9.

(b) (4)

Incoming material, including (b) (4) (see Attachment PR4, page 28, first 5 paragraphs). We observed (b) (4) on (b) (4). An example COC for a leukapheresis collection is included in Exhibit PR8. Approved collection sites are included in Exhibit PR3.

Critical equipment used for manufacturing JCAR017 includes (b) (4) (see Exhibit PR2, pages 2-5).

(b) (4) instrument (b) (4) including a (b) (4) (see Exhibit PR2, page six).

The (b) (4) is an (b) (4) used throughout the process (including (b) (4) and product formulation/fill). This (b) (4) (see Exhibit PR2, page four).

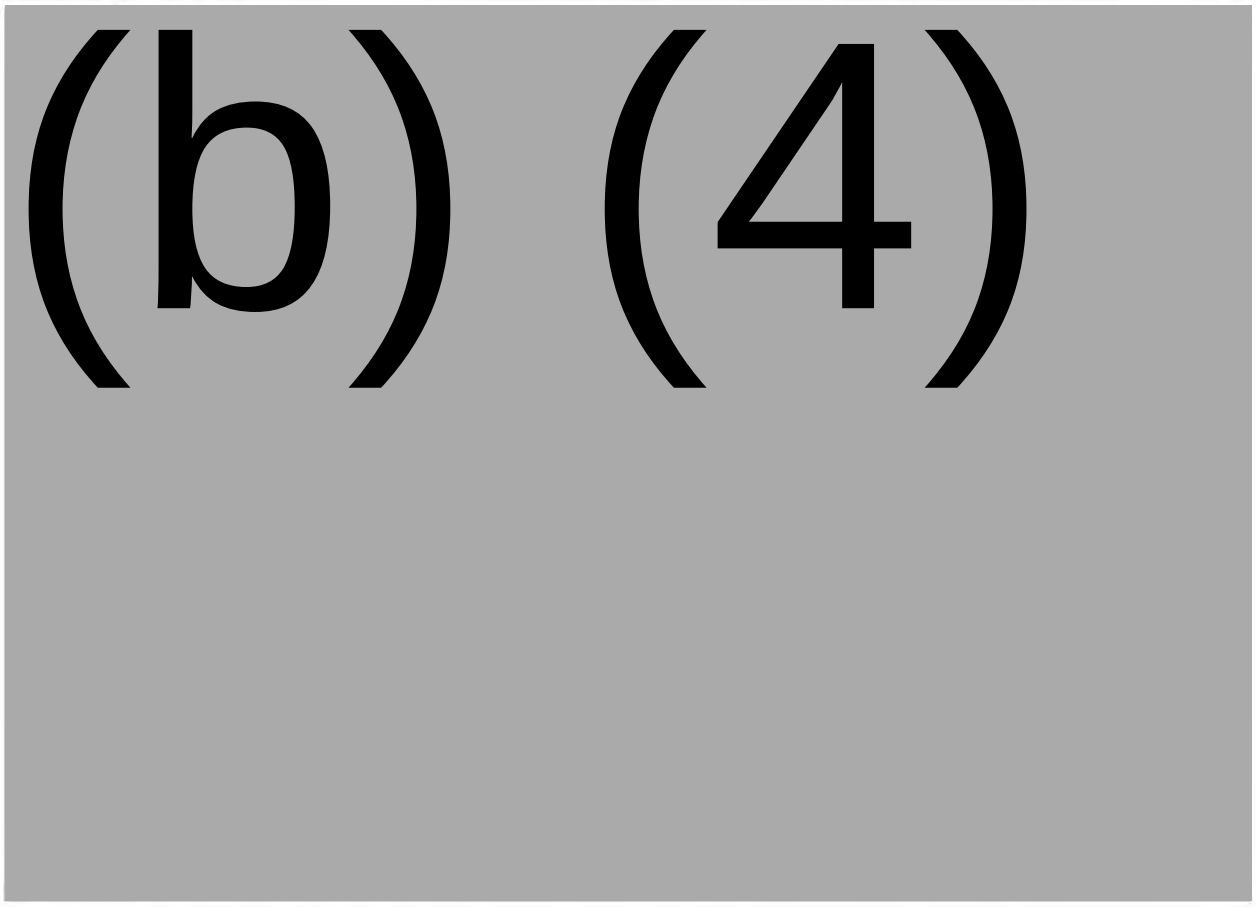
(b) (4). This functionally (b) (4) is based on (b) (4)

Common acronyms used to describe in-process material and finished drug product are included below.

(b) (4)

FDP-Formulated Drug Product
CDP-Cryopreserved Drug Product

The CAR-T manufacturing operations at this site are described in the following two flow diagrams and can be divided into drug substance and drug product. A chain of identity, the ability to link a patient to their autologous blood product from the time of leukapheresis collection through product administration is illustrated Exhibit PR1, page 19. The following flow diagram is included in the assignment email in Attachment PR5, page two. I (PR) verified the process flow diagram reflects current operations.



Description of the manufacturing process: As previously mentioned leukapheresis material is the patient-specific starting cellular material for JCAR017 DS manufacturing (see CMC Assessment

Document, Attachment PR3, bottom of page 17 and page 18 for a description of leukapheresis collection). The manufacturing process begins (b) (4) at the manufacturing facility. The first portion of the manufacturing process is intended to (b) (4) material for further manufacturing. A complete description of the manufacturing process is included in the CMC Assessment document included in Attachment PR3, pages 9-12, and is also described below.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

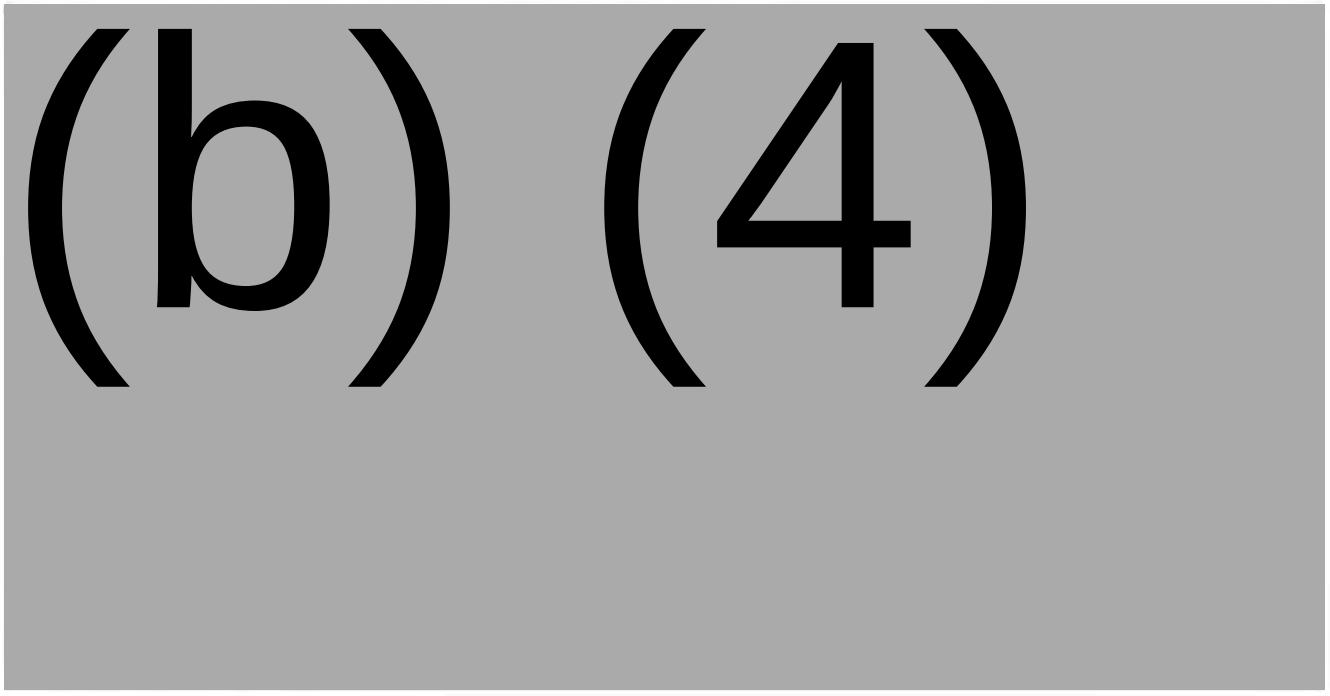
(b) (4)

Final Formulation is described in Attachment PR3, page 27 and page 28.

(b) (4)

Description of the manufacturing process: final formulation

(b) (4) DP with no intermediates or extended hold steps. The [redacted] Multiple Electrolytes Injection, Type 1, [redacted] human serum albumin (HAS), 75% CryStor® CS10). The [redacted] aliquoted into four 5 ml [redacted] cryovials. Filled final product vials are examined for appearance, then cryopreserved using a controlled rate freezer and stored at ≤ -130 °C in vapor phase liquid nitrogen until lot release testing is complete. The lot release testing results are used to determine the volume of each DP component required to meet the target dose. The number of 5 mL vials required for administration are packaged into the secondary packaging and the released product is then shipped in a liquid nitrogen Dewar to qualified treatment sites for administration to the patient (See Attachment PR3, page 5, CMC Assessment document). Further detail is described below (see Attachment PR3, page 27 & 28).



Chain of Identity (COI)

The Chain of Identity (COI) is the ability to link a patient to their autologous blood product from the time of the leukapheresis collection through product administration. Controls are implemented at every process step outlined below to prevent patient material mix-up and is illustrated in Exhibit PR1, page 19.

- Patient Enrollment→Apheresis Scheduling →Apheresis→Shipment to Manufacturing Site→Receive and QA Release for Processing→Manufacture→Test, Package, and Release for Shipment→Shipment to Infusion Site→Drug Product Infusion into Patient at Treatment Site

A complete description of the COI process is included in the CMC Assessment document in Attachment PR3, page 18, bottom paragraph. At every step in the treatment cycle, from leukapheresis

collection to Drug Product (DP) administration, COI is checked and verified prior to subsequent processing, which was observed throughout the inspection. When a patient is scheduled for leukapheresis collection, a patient specific JOIN, a unique alphanumeric sequence, is assigned. The JOIN is used as the basis for COI controls throughout production. Patient identifying information (PII) comprising of the patient's first name, last name, and date of birth (DOB), along with the JOIN are used to verify patient identity during patient collection and product infusion operation. The PLI Assignment, Attachment PR1, page 14 requested to observed how COI is maintained during packaging for shipping. I observed how COI is maintained and confirmed the Release for Infusion (RFI) records were correct.

Excipients used in the formulation of CD4 and CD8 DP are described in Attachment PR3, page 33. and are listed below.

- CryoStor CS10 (b) (4)
- Albumin (Human) 25% (b) (4)
- (b) (4) (Multiple Electrolytes Injection, Type 1), (b) (4)

A complete process flow description is also included in Exhibit PR2.

Inspectional Coverage

Six systems were covered during this inspection and the inspection was conducted per the Pre-License Inspection (PLI) CBER/OCBQ/DMPQ Assignment that is included in Attachment PR1. All the inspectional requests were covered with the exception of the support utilities section in Attachment PR1, page 14 (Support Utilities). System coverage included a review of records, procedures, and training.

Quality System

Organizational Charts and Quality Integrations

(EL)

I reviewed the following organizational charts from the opening meeting presentation showing relationship of quality (QA and QC), production, and management functions **(Exhibit EL-4, pages 8 to 13)**.

- Global Product Development and Supply
- Cell Therapy Development and Operations (CTDO) Organizational Structure
- CTDO Extended Leadership Team

- JuMP Site Leadership Team
- JuMP Quality Leadership Team

I additionally reviewed BMS quality integration plan with Ms. Heidi A. Davis (Sr. Director, Quality). Ms. Davis explained that transition was very much in the early stage of integration from Juno/Celgene to BMS. JuMP is going through risk assessment to prioritize system integration, and integration is estimated to complete in late 2022. I reviewed the following integration documents.

- QMS-OCD-IntgPlan (012881), effective 11/15/2019 which describes BMS day 1 Quality integration plan **(Exhibit EL-5)**.
- QMS-OCD-QMS Intg (012731), effective 07/10/2020 which describes (b) (4) BMS and (b) (4) Celgene Quality Management System (QMS) Integration Strategy and timeframe **(Exhibit EL-6)**.

I reviewed BMS QMS integration activities that have been completed as of 10/13/2020 **(Exhibit EL-7)**.

- STD-010028, entitled "Notification to Management", V1.0, effective 03/16/2020. This document summarizes (b) (4) Celgene's notification to management requirements for escalating potential events alignment with QMS-OCD-IntgPlan (012881).
- SOP-010879, entitled "BMS Quality Council Network QMS-SOP-11-1A Versions 3.0", V1.0, effective 06/26/2020. This SOP is to describe the enterprise-wide governance structure, process steps, and requirements to ensure the suitability and effectiveness of the BMS Quality System.
- SOP-010540, entitled "CTDO Quality Management Review", V2.0, effective 07/10/2020. This procedure defines the CTDO Manufacturing Site Quality Management Review process.
- QMS-SOP-11-5A (015655), entitled "Global GxP Data Integrity Procedure", pending effective date is 04/06/2021. This SOP is to provide the framework for implementation of data integrity requirements for GxP data.

Quality management documents update appeared adequate to reflect the current situation of BMS acquisition of Celgene and Celgene acquisition of Juno (POL-000031 is current so no update). No concern was noted.

Scale-out Capability and Capacity

(EL)

I discussed with Mr. Masten how JuMP will handle demand for increase in manufacturing after commercialization. Mr. Masten stated two clinical products, JCAR017 (for U.S., Europe, and Japan)

(b) (4) are produced at the JuMP. Currently, JuMP is receiving no more than leukapheresis units at each given time and is handling (b) (4) patient products per week with patients being the maximum for both clinical products. I asked Mr. Masten how training will be maintained as the workforce is increased to accommodate the expected JCAR017 scale-out process. Mr. Masten stated that for 2019 (from 12/31/2018 through 12/31/2019), there were a total of new hires at the JuMP. Similarly, for 2020 (from 12/31/2019 through 9/30/2020), there were a total of new hires at the JuMP. The firm's workforce is at capacity of about employees and does not anticipate hiring many new hires.

Mr. Masten stated the firm will likely set up (b) (4), to accommodate scale-out demand.

Walkthrough Inspection

(EL)

I conducted facility walkthrough inspections throughout the current inspection. Areas of inspection included the document control rooms (Rm (b) (4) Rm (b) (4) the manufacturing areas of leukapheresis receipt (Rm (b) (4), leukapheresis (b) (4), Rm (b) (4) (Rm (b) (4) drug product final fill (b) (4), Rm (b) (4) and all of the QC Laboratories. Deficiencies were noted and documented in **Observations # 4, 5, and 6** of this EIR.

(PR)

Assessment of the Quality System was two phased. The first phase included review of the Quality Control Unit (QC) and all of its approval duties and responsibility to review and approve all procedures related to production, quality control and quality assurance, and to ensure the procedures are adequate for their intended use. This also includes the associated record keeping systems. The second phase was to assess the data collected in order to identify quality problems that may be linked to other systems.

Procedures were reviewed and Attachment PR1, page five, states that specific Complaints, Adverse Events, and Recall SOPs were reviewed by CBER/OCBQ/DMPQ. SOPs already reviewed by CBER/OCBQ/DMPQ included the following: SOP-003187, Biological Deviation Reporting (BPDR), dated 25Feb2019, SOP-001136, Global Product Quality Complaint Handling Procedure, dated 19Feb2020, SOP CTDO Complaint Intake Process, dated 21May2020, SOP-001139, Global Product Recall Process, dated 17Jun2019, SOP-010699, Cell Therapy APR/PQR for Drug Products, dated 04June2020, and SOP-000047, Bothell JuMP Self-Inspection Procedure, dated 29Apr2020. The (b) (4) is used to

manage product quality complaints, deviations, OOSs, and CAPAs. A list of the firm's Quality SOPs is summarized in Exhibit PR5.

Follow up to the Deviations, CAPAs, and Change Controls, listed in Attachment PR2 were reviewed during the inspection, and no concerns were noted. I followed up on DCR 2019-10704 at the site, per request from CBER/OCBQ/DMPQ and noted no deficiencies with the implementation of this particular change control.

The firm's Quality Management SOP, POL-GMP-000031, was reviewed and describes the firm's Quality Management system. The Global Quality System Manual, QMAN-000002, dated 25Jun2019, defines the Quality Unit responsibilities for GMP functional management reviews and global GMP policies, internal communications, resource management, and quality planning. Key responsibilities for the Quality Unit concerning GMP functions included but were not limited to: internal audits, approving changes, authorizing written documents, approving specifications, approving batch records, checking the maintenance of equipment, ensuring that production records are evaluated, and ensuring products are stored according to appropriate documentation.

The Quality Audit and Self Inspection process was reviewed, and I confirmed internal audits are conducted on a routine basis (see request in Attachment PR1, page four, Internal Audits).

Quality system coverage included but was not limited to coverage sections below.

Adverse Events

(PR)

AEs are processed by the Juno Therapeutics, Inc. Seattle Dexter Corporate site. I reviewed a listing of AEs submitted under the IND from 1/1/20 to the present. I did review the firm's Adverse Event SOPs and noted some deficiencies which are discussed in the Objectionable Conditions/Discussion with Management section as a discussion item.

The current Adverse Event SOP, SOP-G-500, Adverse Event Case Processing Worldwide, dated 11Oct2020, does not include the following criteria for reporting post-marketing adverse experiences to FDA. Specifically,

a) There is no definition of what type of Adverse Event requires submission of a post market 15-Day "Alert Report" (i.e. Serious & Unexpected, whether foreign or domestic).

b) There is no description of what type of Adverse Events are submitted to FDA for Scientific literature & Post marketing Studies.

Additionally, SOP WP-USA-704, Global Drug Safety & Risk Management, dated 09October, 2020, does not include what types of Adverse Events are to be submitted in quarterly & annual periodic reports (i.e. all serious, expected, and nonserious adverse experiences).

Complaints

(PR)

The Complaint SOP, SOP-001136, Global Product Quality Complaint Handling Procedure, dated 19Feb2020, was reviewed and no concerns were noted. The Work Practice (WP) document, CTDO Complaint Intake Process, WP-010312, dated 21May2020, was also reviewed.

Five complaints were received that did not involve JCAR017 production and had to do with legibility of labels at the collection sites. Complaints are documented in the (b) (4) and are initially received by the Seattle Dexter Corporate site.

BPDRs

(PR)

I reviewed SOP-003187, Biological Product Deviation Reporting (BPDRs). JCAR017 was not a licensed commercial distributed product at the time of the inspection, and there were no BPDRs submitted.

Deviations

(PR)

Deviations were reviewed from Jan 1, 2019 to the present date. The Global Deviation Management SOP, SOP-001145, dated 07Jun2019, was reviewed and several deviations since Jan 1, 2019 were reviewed. The SOP has deviation classifications of Critical, Major, Minor, and Notice of Event (NOE). There were deficiencies noted with the NOE classification and DEV 2019-03442 (included in Exhibit PR10) which is discussed in the Objectionable Conditions/Discussion with Management section, FDA483 Observations #1 & #2. Deviations are documented in the (b) (4) system.

(EL)

Deficiency in EM Excursion Investigation is documented under the **Facilities and Equipment System** and also discussed in **Discussion Item #1**of this EIR. Review of OOSs of non-conformance Lots are documented under the **Production System**. Review of additional OOSs are documented in the **Laboratory System** of this EIR.

Deviation Trend Program

(EL)

SOP-001216, entitled "Deviation Trending Program", V3.0, effective 09/04/2020 identifies the activities and responsibilities for tracking, trending, and managing deviation data. I reviewed deviation trending. Trends are identified by the Quality Systems, deviations within identified trends are reviewed and confirmed by SMEs. Confirmed trends are assessed by cross-functional workstream teams to determine whether CAPAs or mitigation activities are needed to prevent recurrence. The results of trending activities are published in reports. I reviewed quarterly deviation trend reports for Q4 2019 and Q1 2020. I verified they included the elements of total number of deviation records, the list of identified deviation trends in the quarter, the trend workstream results, the summary of trend deviations closed within the quarter, and the reference to trend deviations initiated within the quarter. No concerns were noted.

Annual Product Reviews

(PR)

SOP-010699, Cell Therapy Global APR/PQR for Drug Products, dated 04June2020 was reviewed and no deficiencies were noted. I explained that actual APRs would be reviewed post-approval. There was a request in Attachment PR1, page five, that vector manufacturing and testing will be part of the APR, and I confirmed that Section 4.2 of SOP-010699 included this language.

CAPAs

(PR)

The Global CAPA SOP, SOP-001151, Global CAPA Management, dated 17Dec2018, was reviewed and several CAPAs in response to deviations were also reviewed. A list of CAPAs that were reviewed off-site by CBER/DMPQ during the inspection is listed in Attachment PR2. I reviewed a database of CAPAs and no concerns were noted.

Change Control

(PR)

Change Control SOP-002081, Global Change Management in (b) (4) was reviewed and specific changes referenced in Attachment PR2 (DMPQ List) were also reviewed. I also reviewed SOP-000028, Controlled Document Management Procedure, and SOP-002701, Document Change Management Process in CellDox, dated 20Aug2020.

Document Control

(EL)

On 10/14/2020 accompanied by Mr. Alford Terry (Manager, Doc Control), I conducted a walkthrough inspection of the document control Rm (b) (4) Rm (b) (4). Access to (b) (4) rooms is controlled and secured by (b) (4) . Clinical labels are printed in Rm (b) (4). Work station inspections and line clearance are performed before printing labels to ensure no other Juno Order Identification Number (JOIN) is present in the room. Currently, all document archives are being stored in Rm (b) (4). Issuance of labels and batch records will be done in Rm (b) (4) when JCAR017 becomes commercialized.

I reviewed SOP-000028, entitled "Controlled Document Management Procedure", V13.0, effective 04/10/2020. SOP-000028 describes the requirements, responsibilities, and process for managing controlled documents including how documents are developed, routed, and approved, maintained, released, and obsoleted. Stipulations also include that quality unit gives the final approval to changes.

I reviewed procedures, records, and documents used in manufacturing and quality controls. I verified they are current and effective. Firm's document control appears adequate. No concerns were noted.

Quality Agreement

(EL)

On 10/14/2020, I discussed (b) (4) Lentiviral Vector contract service providers (CSP) with Mr. Chris D. Knecht (Associate Director, Supplier Quality). Mr. Knecht confirms BMS has oversight of all the Vector CSPs. Key oversight actions include the following **(Exhibit EL-8)**.

- SOP-001491, entitled "Global Vendor Quality Management", V4.0 **(Exhibit EL-9)** states the Vendor Quality Manager (VQM) has the oversight of Vector CSPs including but not limited to:
    - Quality event oversight and approval
    - Quality performance monitoring (routine meetings)

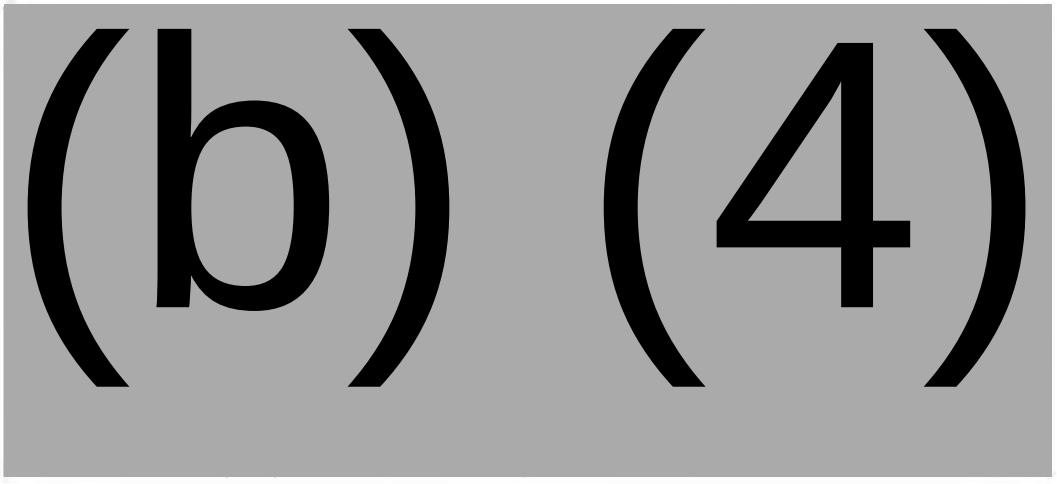
- Batch record/documentation review and vector lot release

- In alignment with SOP-001445, entitled "Global Quality Agreement Process", V10.0 **(Exhibit EL-10)**, all Vector CSPs have approved quality agreements to define roles and responsibilities. This is including but not limited to:
  - Changes, deviations, and OOS are communicated direct to BMS; final summaries are reviewed and approved by BMS.
  - Internal tracking deviations and OOS are opened per SOP-001145, entitled "Global Deviation Management", V10.0 or SOP-001146, entitled "Analytical Out of Specification and Aberrant/Out of Trend Result Investigations", V9.0.

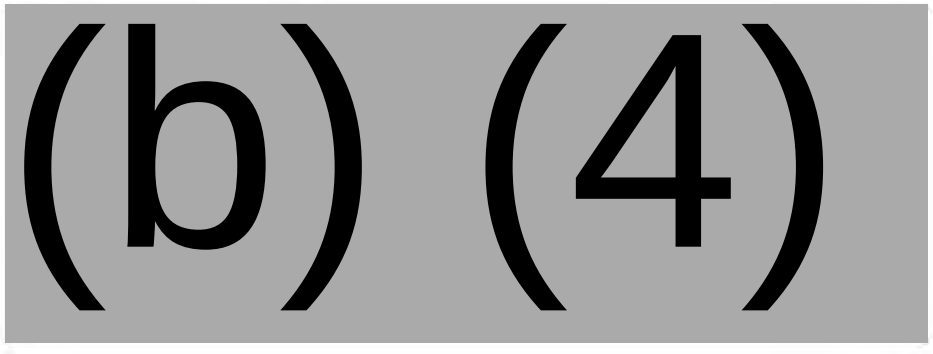
- 100% CSP batch record review is performed per SOP-010414, entitled "CTDO QA Release of Cell Bank, Plasmid and Vector Manufactured by Contracted Service Providers", V3.0.

Below is CSP (b) (4) lentiviral testing overview:

(b) (4)



(b) (4)



- (b) (4)
  - [redacted]
- (b) (4)
  - [redacted]
- Juno Therapeutics (BMS)
  - (b) (4)

Recall

(PR)

The recall procedure was reviewed and no deficiencies were noted. The firm has not recalled any JCAR017 product. SOP-001139, Global Product Recall Process, was reviewed and no concerns were noted. JCAR017 is not a licensed product and commercial distribution is currently under an IND.

Production System

(PR)

Production System coverage included a review of procedures, records and training. Manufacturing operations, previously described, were verified according to the CMC submission in Attachment PR3, page 9-13.

Observation of Operations

(PR)

We observed operations throughout the process and the specific items listed in the PLI Assignment included in Attachment PR1, pages 16-18. Incoming Leukapheresis Receipt (see CoA in Exhibit PR8). (b) (4) [redacted] Drug Product Formulation, Fill, and Cryopreservation. The JCAR017 Process Overview is included in Exhibit PR2, page 34, and it is an approximate (b) (4) process from Leukapheresis receipt to drug product, formulation, fill and cryopreservation.

Batch Records

(PR)

I reviewed example electronic batch records for all (b) (4) steps involved in manufacturing a JCAR017 FDP which consists of the CD8 and CD4 arms. Data was reviewed to be ALCOA (Attributable, Legible, Concurrent, Original, Accurate) in their eBR system. I reviewed SOP-000485, Electronic Batch Record Review, dated 01Jun2020, and the following example time frame controls were reviewed and verified. The (b) (4) from apheresis collection end time to the first (b) (4) , was verified in Batch Record for CR80-4C6H1F (JOIN) (b) (4) Lot, and after DSMO addition to the (b) (4) to start the freezing process for the Finished Drug Product (FDP) was verified. I reviewed the batch record review procedures, executed batch records, IPCs, CPPs, Release Specifications, and CQAs per the inspection request in Attachment PR1, page four and seven.

I reviewed data from 5 recent shipments of FDP to verify the temperature is maintained and the shipment occurred within the allowable time (see PLI Assignment Request, Attachment PR1, page seven, Shipping Validations). I reviewed production scheduling operations and Mr. Brett Johnston, Senior Director, Quality Assurance, said (b) (4) leukapheresis collections are processed (b) (4) with a maximum capacity of (b) (4) leukapheresis collections, since the COVID-19 pandemic outbreak in response to the PLI inspection request for production capacity in Attachment PR1, page nine. There was adequate controls to manufacture JCAR017 (b) (4) in production suites where both products can be handled in the (b) (4) , and (b) (4) . Scheduling processing time for batches was adequate and space was adequate for production operations (see PLI request in Attachment PR1, page nine).

Visual Inspection

(PR)

Visual Inspection procedures for Formulated Drug Product (FDP) were observed. (b) (4) , and operations were qualified/trained. I reviewed SOP-001347, Visual Inspection of JCAR017 Final Drug Product (FDP) vials and single use components of interest (b) (4) used to fill final drug product vials. This document describes the use of a visual inspection (b) (4) that are used to find material defects and specify how to proceed when defects are observed at the Juno Manufacturing Plant (JuMP).

I reviewed Visual Inspection Qualification, SOP-001466, dated 27Jul2020, and the Visual Inspection of JCAR017 Final Drug Product, SOP-001347, dated 24Ap2020, and example training reports. I also observed final visual inspection operations per the request in Attachment PR1, page ten (Visual Inspection Procedures).

Aseptic Process Simulation

(PR)

I reviewed Aseptic Process Simulation (APS) with Mr. Matt Morgan, Validation Engineer III. I reviewed the most recent Platform APS Summary Report – Q2 2020, 06June2020-14June2020. (b) (4) is used to simulate routine manufacturing process, including inputs, intermediates, and drug products. Simulated materials are submitted to Quality Control (QC) for (b) (4) testing. Each (b) (4) There has not been a (b) (4) failure for the (b) (4) that have been executed since 2017. A list of executed runs is included in Exhibit PR43, page six, and I reviewed the most recent run on (b) (4) and noted no deficiencies. I reviewed the PLI Assignment Request in Attachment PR1, page seven, Process Validation/PPQ and ReValidation Program, and noted no deficiencies.

An overview presentation is included in Exhibit PR43. Each APS represents each unit operation (b) (4) Final Product), Material and container closure systems, aseptic assemblies and connections, line clearance and changeover, shift changes and operator change-out, non-routine interventions/events. Maximum batch sizes are simulated, resulting in the longest process duration. Non-routine interventions used include, (see PLI Assignment Request, Attachment PR4, page 10), room capacity maximized during open aseptic operations, simulated spill in biosafety cabinet, and (b) (4) Worst case scenarios simulated are included in Table 1, page 8, of Aseptic Process Simulations (APS), SOP-001039, dated 27May2020.

The simulated unit operations for each run are listed in the Platform Comparison Risk Assessment Summary Report, and I reviewed the Q2, 2020 (Platform APS Process Flow) Simulated Unit Operations and the Platform APS Process Flow for simulated buffer, media, reagent preparations. No concerns were noted.

Non-routine procedures and worst case manipulations and unit operations are incorporated in APS runs. Non-routine interventions used in the APS include maximum room capacity, **simulated spill in BSC** and (b) (4) (which is outlined in SOP-001039, Aseptic Process Simulations (APS), dated 27May2020, Section 9.8).

All the unit operations illustrated in the manufacturing process flow diagram are included in the Aseptic Process Simulation (APS) (from (b) (4) product freezing). In the APSs, maximum surface area for product contact and shortened (b) (4) times are aimed. Procedures involving aseptic media and buffer preparations, handling steps to perform in process (b) (4), filling containers and introduction of new equipment, and highest number of sterile welding, connections and sampling as well as open manipulations in BSC are simulated. All in process containers and filling of (b) (4) vials were also incorporated in APS. In process (b) (4) until being processed further and therefore, there is no need to include those hold durations in APS as well as controlled rate freezing duration (a negative impact on

the ability of certain (b) (4) post-thaw) (see Attachment PR4, page 10, Middle paragraph, which was verified).

The overall processing time for each APS is dictated by the inclusion of the maximum number of routine manipulations identified. The simulation of the required manipulations, both open (performed in the ISO (b) (4) and closed (b) (4)) ensures that a worst case challenge to the process is demonstrated (Attachment PR4, page 10, bottom four paragraphs was verified). All containers along with (b) (4) vials (final containers), waste container and unused media are (b) (4)

DP Lot Release

(EL)

On 10/14/2020, I reviewed the DP lot release process. The following SOPs were reviewed with Mr. Thomas M. Blake (Associate Director, QA) and (b) (6) (Sr. Specialist, QA).

SOP-001376, entitled "JuMP Release for Infusion and Product Distribution", V2.0, effective 09/29/2020 describes the activities and documentation requirements for the Release for Infusion (RFI) of Cryopreserved Drug Product (CDP) prior to patient treatment **(Exhibit EL-11)**. I reviewed QC test data for RFI CoA (section 6.5) and requirements for RFI CoA generation (section 6.7). I also reviewed criteria for release, exception release, reject, and controlling of non-conforming lots. The SOP-001376 appeared adequate to ensure the maintenance of the COI/COC while RFI CoA was produced. SOP also appeared adequate to ensure the correct RFI document was generated and provided to the clinical site. No concerns were noted.

SOP-001377, entitled "JuMP Final Product Disposition", V2.0, effective 07/18/2020 describes the Final Disposition requirements for Cryopreserved Drug Product (CDP), when applicable (e.g. CDP with incomplete QC testing at the point of Release for Infusion) **(Exhibit EL-12)**. I reviewed final disposition requirements, QC test data documentation review, requirements for closures of lot associated deviations and/or excursions, and Material Review Board (MRB) process when DP failure occurs. SOP-001377 appeared adequate. No concerns were noted.

Non-conforming DP Lots

(EL)

On 10/15/2020, I reviewed non-conforming lots; (b) (4) (OOS-Safety) and (b) (4) (OOS-Identity, Viability, Purity, Strength) with Mr. Blake (Associate Director, QA) and (b) (6) (Sr. Specialist, QA).

Lot (b) (4) (the CD4 arm) failed to meet the drug product specification for endotoxin. The endotoxin result was (b) (4), which is above the acceptance of (b) (4). This lot was (b) (4) was placed into Rejected status in the (b) (4) on 01/27/2020 as FDA will not approve Exception Release for a safety related failure per MRB discussion and decision. The remaining cryopreserved CD4 material was successfully (b) (4) and met all release specifications. RFI of (b) (4) (the CD8 arm) and (b) (4) was completed on (b) (4). Investigation into rejection of Lot (b) (4) appeared adequate. No deficiency was noted.

Lot (b) (4) (the CD4 arm) failed to meet the drug product specifications for viability, purity, identity, and strength while (b) (4) (the CD8 arm) met all specifications. This lot was (b) (4) and it was a (b) (4) Patient material was suspected as the cause of failures. Lot (b) (4) was rejected and Lot (b) (4) was released by exception per MRB recommendation (there is little expected safety risk of administering the CD8+ drug product component only) and per FDA approval. Investigation into rejection of Lot (b) (4) appeared adequate. No deficiency was noted.

New Specification for Breyanzi ® Drug Product, US, Adult

(EL)

During the inspection, I was given SPC-001271, entitled "Specification: Breyanzi® Drug Product, US. Adult", V3.0, effective date pending. I was told by management Juno agrees with all CBER requests to tighten release specifications. SPC-001271, Version 3.0 contains revision of test methods and new acceptance criteria per CCR-2020-10589 and BLA IRs 12, 42, and 47. Release of Version3.0 is pending commercialization of the drug product. SPC-001271, V3.0 was collected and submitted in **Exhibit EL-13**. No concerns were noted.

DS Lot Release

(EL)

(b) (4) Lentiviral vector lot disposition was reviewed. The complete (b) (4) production is (b) (4) . Juno performs internal release on the (b) (4) per SOP-010414, entitled "CTDO QA

Release of (b) (4) and Vector Manufactured by Contracted Service Providers", V3.0. The firm's overview of (b) (4) Lentiviral vector lot disposition was also collected and submitted in **Exhibit EL-14**. Firm's DS lot release process was reviewed with no comments.

In-Process Controls of CD4 and CD8 (b) (4)

(EL)

On 10/09/2020, I discussed with (b) (6) (Principal Process Engineer, Manufacturing Science and Tech) on (b) (4) CD4 and CD8 (b) (4) check. I reviewed the Global Change Management # CCR-2020-10674 in response to IR #40 and IR #61 for addition of (b) (4) In-Process Control of (b) (4) and (b) (4) . (b) (6) stated the firm is committed to the Agency to implement changes in the U.S. commercial Breyanzi manufacturing process prior to commercial launch at JuMP. (b) (6) confirmed changes are currently in progress and the addition of (b) (4) In-Process Control of CD4 and CD8 (b) (4) check are on track to meet the implementation deadline on 10/31/2020. No concern was noted.

Drug Product Formulation and Final Fill Process

(EL)

On 10/08/2020, I observed the aseptic filling of DP Lot (b) (4) inside the ISC (b) (4) (b) (4) Rm (b) (4). It is to note that I did not get to see the (b) (4) . I observed the (b) (4) being placed in the ISC (b) (4) Next, I observed aseptic operator (b) (4) . The operator then aseptically (b) (4) This process was (b) (4) . I also observed the (b) (4) . I confirmed the (b) (4) were pre-labelled before filling. Deficiency in (b) (4) was documented in **Discussion Item #3** of this EIR. Objectionable observation in aseptic practice was documented in **Observation #4** of this EIR.

Stability Program

(EL)

STD-010019, entitled "Cell Therapy (CTDO) Stability Program Standard". V3.0, effective 05/01/2020 defines the standards and guidelines for the stability program within Cell Therapy

Development Operations (CTDO). I reviewed the firm's stability program for storage condition, testing frequency, selection of batches, container closure system, test panel and specification, evaluation, and stability commitment.

Currently, (b) (4) of stability vials of (b) (4) are being stored in-house at different locations. Specifically, stability samples in (b) (4) vials are being stored in Rm (b) (4) Stability samples in QC vials (b) (4) are being stored in Rm (b) (4) (QC Sample Management Room). The firm does not have dedicated stability chambers. Stability samples are being stored in the temperature they are required.

I selected Batch (b) (4) currently under stability. I tracked sample storage locations using the Laboratory Information Management System (LIMS). *To note, it was not feasible to pull samples out of the* (b) (4) *for verification, exposure to room temperature may affect sample integrity.* I verified stability samples were appropriately stored in the (b) (4). No deficiency was noted.

Product Retain Handling

(EL)

I reviewed the firm's Product Retain Handling. JuMP does not have dedicated DS or DP retain locations in-house. Retain sample handling is part of the routine sample management. For example, according to the CD4 CDP sample plan, (b) (4) QC aliquots of the CD4 Cryopreserved Drug Product (ThCDP) designated as QA Retain are being stored with the rest of the ThCDP QC vials. Similarly, according to the CD8 CDP sample plan, (b) (4) QC aliquots of the CD8 Cryopreserved Drug Product (TcCDP) designated as QA Retain are being stored with the rest of the TcCDP QC vials per routing sampling plans.

During the inspection, management provided me with a letter dated 10/30/2019, from Juno to the Director, Office of Tissues and Advanced Therapies CBER, requesting an exception to the sample retention requirements under 21 CFR 600.13 **(Exhibit EL-15)**. I was not given any information whether such request has been granted. The firm's retain handling was reviewed with no comments.

Aseptic Gowning Qualification

(EL)

SOP-001032, entitled "JuMP Aseptic Gowning Qualification Program", V4.0, effective 03/07/2020 defines the qualification, requalification, and disqualification processes for aseptic gowning in ISO (b) (4) rooms and ISO (b) (4) To pass initial qualification, the candidate must pass (b) (4)

(b) (4) out of a maximum of (b) (4) qualification monitoring events. Requalification is required every (b) (4) for active operators. If the candidate fails initial or requalification, the candidate must return to initial qualification. Qualified personnel will be disqualified if they are the subject of an adverse trend or the requalification results do not meet acceptance criteria. To regain qualification status, disqualified personnel will follow the initial qualification procedure outlined in the SOP.

I reviewed 2019 and 2020 aseptic/gowning qualification and requalification of aseptic operators (b) (6) I noted operator (b) (6) failed aseptic qualification but was requalified after repeating and passing (b) (4) re-tests.

I requested and was informed I could observe the aseptic gowning process in the morning of 10/16/2020. However, I was not told it was only a demonstration. On 10/16/2020, standing in the ISC (b) (4) Entry Corridor Rm (b) (4), I observed aseptic gowning demonstration performed by (b) (6) (Associate III, Manufacturing) and (b) (6) (Training Associate III, Manufacturing) inside the ISC (b) (4) Entry Airlock Rm (b) (4) (entrance to the (b) (4) Rm (b) (4). I told Mr. Masten I was unable to adequately evaluate the aseptic gowning process based on a demonstration. To sufficiently evaluate, I would have to observe an actual aseptic gowning that lead to the routine manufacturing of DS or DP. Mr. Masten acknowledged my concern.

During the demonstration, I observed aseptic operators using (b) (4) to sanitize sterile gloves and outer packaging of sterile garments. I was told by management (b) (4) is being used throughout the JuMP facility. However, the (b) (4) expiry has not been adequately established. Deficiency was noted. See **Discussion Item #5** of this EIR for further detail.

Additionally, I observed aseptic operators examining sterile garment packages for tears and damages before use. According to management, garments are (b) (4) . They are (b) (4) . I asked how they were able to detect minute tears or pin hole size damages that could not be easily seen by naked eyes. The firm had no comments to my question. The firm lacks assurance of sterile clean room garment package integrity. Concerns were noted.

Microbiological Contamination Controls

(EL)

Manufacturing flows: I conducted facility walkthrough inspections throughout the current audit. Areas of inspection included the manufacturing areas, QC Laboratories, and the document control rooms. I verified airflow, personnel, material, product, and waste flows appeared adequate. No concerns were noted.

Clean rooms pressure differentials: See **FACILITIES AND EQUIPMENT SYSTEM** of this EIR for further detail.

Segregation, labeling, and tracking procedures: I observed leukapheresis receipt (Rm (b) (4), leukapheresis (b) (4), Rm (b) (4) (Rm (b) (4), harvest and drug product final fill (b) (4), Rm (b) (4)), and all of the QC Laboratories. I verified segregation, labeling, and tracking procedures appeared being followed for microbiological contamination controls and for COI/COC. No concerns were noted.

Aseptic procedures and practice: Deficiencies of aseptic procedures and practice are documented in **Observation #4** and **Discussion Items #3 and #5** of this EIR.

Changeover/line clearance procedures: I observed leukapheresis receipt (Rm (b) (4). I verified changeover/line clearance were performed as specified in SOPs. No concerns were noted.

Aseptic gowning procedures: I was unable to adequately evaluate the aseptic gowning procedures because only a demonstration was arranged. Also, the firm lacks assurance for clean room sterile garment package integrity. Concerns were noted. See Aseptic Gowning Qualification section of this system for further detail.

Faculties & Equipment System

(PR)

Coverage of this system included verifying the appropriateness of buildings and facilities including maintenance, equipment qualification (installation and qualification), equipment calibration and preventive maintenance, cleaning and validation of cleaning processes as appropriate, prevention of cross contamination, extractable and leachable or other contaminants on product contact equipment causing deterioration or rendering product less suitable for intended use, and utilities that are not intended to be incorporated into the product such as HVAC, compressed gases, and steam/water systems. The PLI Assignment Requests in Attachment PR1, page 13-16, were reviewed, with exception of the Support Utilities listed in Attachment PR1, page 15.

Material & Personnel Flow

(PR)

SOP-000145, Cell Processing Facility Material and Personnel Flow, dated 08Jul2020, was reviewed for the definition of flow of personnel, equipment, materials, product, samples, and waste through the Cell Processing Facility (CPF), to minimize the risk of introducing or spreading contaminants, misplacing materials, and cross contaminating products. I observed material and personnel flow throughout the inspection and noted no deficiencies.

Computerized Systems

(PR)

Computerized Systems used in manufacturing/GMP operations include (also see Exhibit PR1, page 20) the following and are also described in the DMPQ Assessment Document in Attachment PR4 (page 29-30).

(b) (4)

The implementation of these systems was reviewed as per the PLI Assignment request in Attachment PR1, page 14, and COI Controls as specified on page 14 were reviewed throughout the inspection and no concerns were noted. The implementation and function of these systems was reviewed throughout the inspection.

Global Server Data Backup and Recovery with (b) (4) t per IT-WP-3006, dated 14Feb2020, was reviewed. Active files are kept with no time limit. When a file is deleted, it is kept in the backup system

for (b) (4) full backups are kept for (b) (4) . The (b) (4) suite is used to perform backups (b) (4) . Each backup is performed according to a defined set of schedules.

Alarm Logs

(PR)

SOP-000208, Equipment Monitoring System, dated 07Sep2019, was reviewed. The purpose of the procedure was to describe the monitoring, trending and alarming of equipment and areas that are subject to temperature and environmental control/monitoring. As per the request in Attachment PR1, page 13, (b) (4) Alarm log and example equipment alarm logs were reviewed.

(b) (4) Alarm logs were reviewed and documented and are potentially classified as NOEs or Deviations. The JuMP Alarm Response, SOP-000260, dated 27May2020, that describes alarm response for GMP Equipment was reviewed. I reviewed an example list of (b) (4) Alarms since 07Octo2020, and no critical alarms were noted.

Changeover/Line Clearance

(PR)

I reviewed the firm's change over procedure per SOP-000186, Changeover Procedure, dated 21Aug2020, which is included in Exhibit PR32. I reviewed the documentation in the electronic batch records, and the recipes. Changeover is done at end of process and line clearance is done at beginning and I verified steps were done in the eBR. Attachment PR1, page 4, specified reviewing Changeover and Line Clearance Procedures and this was conducted with no concerns noted.

Gowning Procedures

(PR)

Gowning Procedures were reviewed throughout my inspection walk-throughs and SOP-000131, Gowning Procedure at JuMP, dated 15Sep2020, was reviewed for adherence to gowning controls and practices within classified, and controlled non-classified areas. SOP-000131, dated 15Sep2020, Gowning Procedure at JuMP is included in Exhibit PR33. Gowning deficiencies were noted with aseptic gowning and are outlined in page 31 of this EIR, Aseptic Gowning.

BSC HVAC Qualification and BSC of units were reviewed.

(PR)

I reviewed example HVAC qualifications for BSCs, that were located in the facility and noted no concerns. I also reviewed SOP-000354, Certification of Cleanrooms, Controlled Areas, and Related HEPA Filters, dated 14Jul2020, which defines the minimum requirements for the certification of cleanrooms and associated terminal HEPA filters. I reviewed an example HEPA recertification of ISO (b) (4) Room (b) (4), which included airflows, airflow velocity, leak testing, and room air exchange rate. I also reviewed example recertification of an ISO (b) (4) BSC, which -is used in the (b) (4) of the individual (b) (4) (see Exhibit PR9, Floor Diagram) A CBER/OCBQ/DMPQ 704(a)(4) Records Request was for the review of (b) (4) BSC recertification reviews used for open manipulations: (b) (4). I reviewed that data and no concerns were noted.

Calibration/Maintenance/Calibration Logs

(PR)

SOP Calibration Program, SOP-000204, dated 27Apr2020, and the Preventive Maintenance Repair Program, SOP-000189, dated 26June2020, was reviewed and example logs for the critical equipment below was reviewed below (see request in Attachment PR1, page 16).

(b) (4)

I also reviewed SOP-000211, 27Jul2020, (b) (4) Operation and Maintenance. The (b) (4) is used to culture and expand activated T cells within Juno's Cell Therapy manufacturing processes. The purpose of the SOP was to describe procedures for general operation and maintenance of the (b) (4). There were no concerns noted for the firm's calibration and maintenance program.

Environmental Monitoring (EM) and Personnel Monitoring (PM) Program

(EL)

The JuMP conducts EM of ISO classified areas and PM of employees who work in designated ISO classifications. I reviewed the following relevant SOPs.

- SOP-000078, entitled "Environmental Monitoring Program", V19.0, effective 10/04/2020.
- SOP-000174, entitled "Environmental Monitoring in (b) (4) Areas", V6.0, effective 04/10/2020.
- SOP-000525, entitled "Environmental Monitoring Investigation Procedure", V8.0, effective 08/27/2020.

I reviewed EM/PM methods (viable air/surface, nonviable particulates), frequencies (b) (4) , locations (maps and descriptions) and acceptance criteria (alert and action limits).

My review revealed ISO (b) (4) a week EM frequency does not appear adequate. Each (b) (4) is equipped with an ISO (b) (4) where aseptic fillings of final DP are performed. Areas surrounding the critical ISO (b) (4) zone are classified as ISO (b) (4) The ISO (b) (4) classification also includes the (b) (4) I noted while ISO (b) (4) PM is performed for each lot of DP manufactured, the ISO (b) (4) routine EM (b) (4) are only monitored (b) (4) . ISO (b) (4) EM frequency does not appear adequate. To note, the JuMP manufactures multiple patient lots in the ISO (b) (4) Management explained that the ISO (b) (4) EM frequency was based on risk assessment.

EM Risk Assessment and Trending

(EL)

EM risk assessment: I reviewed the following reports with Ms. Kauser Hussain (Associate Director, QC).

- RPT-000584, entitled "Environmental Monitoring Gap Assessment and Risk Assessment Program", V5.0, effective 06/30/2020.
- RPT-001088, entitled "ISO (b) (4) Environmental Monitoring Risk Assessment Summary Report", V1.0, effective 02/12/2020 **(Exhibit EL-16)**.

My review revealed a preliminary hazard analysis (PrHA) tool was used and scores were assigned to determine levels of risk (Low, Med, High, Critical). However, Ms. Kauser could not adequately explain how the assigned scores in RPT-001088 section 9.3 Figure 9.1; (b) (4) points medium risk score, (b) (4) points high risk score, and (b) (4) point low risk score led to the ISO (b) (4) EM frequency being only (b) (4) (instead of (b) (4) **(Exhibit EL-16, page 11, Figure 9.1)**.

Ms. Kauser additionally stated the risk assessment was based on EM data collected from 2018 to June 2020. I requested to see EM qualification or validation data but was not provided with requested information at the conclusion of the inspection.

Ms. Kauser also stated that prior to 08/30/2019, the frequency for ISO7 EM was only (b) (4) After 08/30/2019, the frequency was increased to (b) (4) . Thus, the increase in frequency from (b) (4) beginning 08/30/2020 appeared to mean there was an increase in risk. However, Ms. Kauser explained the increase was not based on risk (negative data or trend), but the additional sampling made it more like continuous monitoring. This appeared to contradict firm's claim that EM frequency is based on risk assessment.

Ms. Kauser continued to explain that the ISO(b)(4) was considered medium risk because no open products were in the ISO(b)(4) rooms. She also stated an additional QC person performing sampling could have negative impact on product quality so it was decided not to increase EM frequency. I said to Ms. Kauser that adequately trained QC personnel collecting EM samples should not have posed a risk to product safety in the ISO(b)(4) area. The firm's risk assessment lacked adequate rationale in determining the ISO(b)(4) EM frequency to only (b) (4) considering the firm manufactures multiple drug product lots (b) (4)

EM trending: I reviewed with Ms. Tara K. Byerly (Manager, QC) the following quarterly EM trending.

- 2020 Q1 and Q2 – (b) (4)
- 2019 Q3 and Q4 – (b) (4)

I reviewed EM trending. No negative trending was observed in the (b) (4) ISO(b)(4) BSCs and the ISO(b)(4) surrounding areas despite isolates being recovered in these areas. The firm's EM trending was reviewed. My review was unremarkable.

Deficiency in PM

(EL)

During the manufacture walkthrough inspection, aseptic operators were observed spraying gloves with (b) (4) and handling multiple (b) (4) wipes immediately prior to PM sampling of gloves. Sanitizing gloves just prior to sampling is inappropriate because it can prevent recovery of microorganisms that were present during an aseptic manipulation. PM results for (b) (4) aseptic operators are unreliable. Objectionable observations were noted in PM. See **Observation #4** of this EIR for further details.

Deficiency in EM Excursion Investigation

(EL)

Deficiency in adverse mold trend investigation: I reviewed EM excursions and investigations. My review revealed multiple adverse mold trends in the JuMP being identified from 2018 to 2020. Specifically, a total of eight (8) deviation investigations and eight (8) CAPAs were initiated. My review also revealed CAPA effectiveness checks were inadequate in that CAPAs implementation have not been effective in preventing a recurrence of deviations. I collected the following summaries prepared by the firm.

- DEV-2019-02289 Cryopreservation Mold Adverse Trend **(Exhibit EL-17)**
- Overview of Mold **(Exhibit EL-18)**
- A compilation of mold recoveries corrective and preventative action **(Exhibit EL-19)**
- Mold Identification from ISO areas, 10/01/2020 to 09/30/2020 **(Exhibit EL-20)**
- Mold Excursion in (b) (4) **(Exhibit EL-21)**

Exhibit EL-18, **page 9** lists deviation numbers (of all eight (8) deviations), dates of occurrence, descriptions of the event, ISO locations of excursions, and related CAPA numbers. **Exhibit EL-18**, **page 7** is a facility heat map indicating where molds were recovered including colony counts between 10/2019 and 09/2020. Heat map shows the ISO (b) (4) Cryopreservation room had the most recoveries of (b) (4) counts and the ISO (b) (4) room had (b) (4) counts. Heat map also shows mold species had been recovered from the ISO (b) (4) outer corridors, the ISO (b) (4) inner corridors, several of the ISO (b) (4) Cell Expansion rooms, and lately from the ISO (b) (4) and one of the ISO (b) (4)

Exhibit EL-21 shows (b) (4) ISO (b) (4) ISO (b) (4) Environmental Monitoring Excursions (EME)

- (b) (4) : one (1) CFU (b) (4) was recovered from the abdomen of an aseptic operator working on media preparation in the ISO (b) (4)
- (b) (4) one (1) CFU (b) (4) was recovered from the abdomen of an aseptic operator during harvest in the ISO (b) (4)
- (b) (4) : one (1) CFU (b) (4) was recovered from the left glove of an aseptic operator during media preparation in the (b) (4) ISO (b) (4)

Exhibit EL-17, **page 3** DEV-2019-02289 summary lists contributing factors of adverse mold trends identified including,

- Hard to reach areas to clean
- Multiple water sources and standing water
- Equipment not suitable for cleaning (b) (4)
- Lack of pressure cascade to keep potential mold spores within Cryo

- (b) (4) airflow due to low air returns

It also lists significant facility changes required to address above factors,

- Close of CP and classify as CNC
- Add HEPA filtration
- Add low wall returns
- Increase air turnover rate

The topic of adverse mold trend was discussed with management throughout the current inspection. On 10/08/2020, Ms. Browder stated the required facility changes were at early discussion stage. The consideration was to downgrade the Cryopreservation Room to controlled not classified (CNC). As such, it would not be monitored but still be cleaned. I said to Ms. Browder that downgrading and cease monitoring the room would not make the adverse mold trend go away. The mold would still be there unless adequate corrective actions are implemented.

On 10/14/2020, Mr. Masten stated that the firm relied on standard procedures and controls to mitigate issues because it has proven to be sufficient to mitigate problems. Management repeatedly stated they believed both cleaning and CAPAs were effective. **Exhibit EL-19** contains a list of completed CAPAs, actions, impacts, and effectiveness. The observed adverse mold trend was also documented in **Discussion Item #1** of this EIR.

My review revealed CAPA effectiveness checks were inadequate in that CAPAs implementation have not been effective in preventing a recurrence of deviations. The latest mold adverse trend occurred in 08/2020. DEV-2020-02629 was initiated on 09/08/2020 to investigate the issue.

Deficiency in DEV-2020-02629 investigation: I reviewed DEV-2020-02629 **(Exhibit EL-22)**. In summary, the deviation was initiated on 09/08/2020 for EM adverse trend of mold identified in the ISC(b) (4) Room (b) (4) The (b) (4) Room is a specialized room for the preparation of supply sterile kits used during ISC(b) (4) batch related activities such as media preparation and Cell Therapy processing.

Exhibit EL-22, **Page 2**, under impact assessment, it documents this deviation is classified as minor because there is no product manipulation occurring in this room. I found prior deviation investigation inadequate in that it did not address potential product impact considering supply kits assembled in the (b) (4) Room are being used for ISC(b) (4) batch activities. Investigation did not trace kits packaged and later used for potential impact to product quality and safety. Also, no isolate identifications were included in the investigation to evaluate whether mold species were recurring or objectionable/pathogenic.

I was subsequently notified that DEV-2020-02629 will be re-opened to include evaluation of potential product impact for Lots utilizing impacted kits. Additionally, the firm initiated DCC-003807 to revise SOP-000525, Environmental Monitoring Investigation Procedure, to extend requirement for product

impact assessment and to include mold species identifications within investigation document **(Exhibit EL-23)**.

ISC (b) (4) Biosafety Cabinet (BSC) Certification

(EL)

I reviewed 2019 and 2020 (b) (4) ISC (b) (4) BSC (b) (4) and (b) (4) BSC (b) (4) (b) (4) certifications conducted by (b) (4) . I verified (b) (4) were evaluated and (b) (4) units had passed certification. No deficiencies were noted.

(b) (4) HEPA filter Certification

(EL)

I reviewed 2020 (b) (4) Rm (b) (4) Rm (b) (4) HEPA filters (b) (4) certifications conducted by (b) (4) . Each of the (b) (4) HEPA filters and the associated Entry and Exit Airlock each also has (b) (4) HEPA filter. I verified criteria were met for (b) (4) filter unit tested. No deficiencies were noted.

HVAC Trending, Alarm logs, and Excursions

(EL)

SOP-001300, entitled "Engineering Control of (b) (4) , V2.0, effective 07/13/2020 defines the requirements and responsibilities of the engineering control of (b) (4) within the GMP classified areas of the Cell Processing Facility (CPF).

The (b) (4) controls heating, ventilation, and air conditioning. The (b) (4) also continuously monitors critical utilities and provides alarm management. On 10/13/2020 and 10/15/2020, I discussed HVAC system with (b) (6) (Supervisor, Facilities). I reviewed HVAC trending and alarm logs of the (b) (4) from 02/2020 to 09/2020. I verified observed excursions were due to either planned maintenance or calibrations, except for one excursion occurring on 04/04/2020. On 04/04/2020, CPF's air handling system went down due to power outage, the system function was restored by the backup generator within 15 seconds. No deficiencies were noted.

I observed (b) (4) monitoring in real time. I asked (b) (6) to show me in real time the (b) (4) monitoring of the CPF on the screen in the conference room. I observed positive (b) (4) readings from the critical ISO (b) (4) to the lesser critical ISO (b) (4) areas, also from the ISO8 to ISO9 areas. The GMP classified areas (b) (4) appeared within acceptable range. I noted that the firm does not have an audible alarm to alert aseptic operators working in the (b) (4) when excursions occur. No objectionable deficiencies were noted.

Smoke Study

(EL)

On 10/09/2020, I discussed airflow/smoke studies with (b) (6) (Engineer III, Validation). I watched videos of (b) (4) smoke studies conducted under dynamic condition in 07/2020. I observed the (b) (4) final filling process being performed in the ISO (b) (4) critical zone by an aseptic operator. I also observed required operations being conducted in the surrounding ISO (b) (4) area by an aseptic verifier. I verified operations were adequately simulated. I also verified (b) (4) of smoke was maintained inside the ISO (b) (4) under dynamic condition (no turbulent airflow was observed). I further observed relative positive (b) (4) from the ISO (b) (4) Rm (b) (4) to the pass-through, to the ISO (b) (4) Exit Airlock Rm (b) (4), and to the ISO (b) (4) Entry Airlock Rm (b) (4). (b) (6) stated the air is single pass within an ISO classified rooms. No deficiencies were noted.

To note, management stated this is the first time (b) (4) *studies were being conducted in the JuMP CPF. The frequency, reporting, and approval process are under evaluation.*

Facilities Cleaning / Sanitation / Decontamination

(EL)

I reviewed and discussed facilities cleaning with management throughout the current audit. I reviewed disinfectant efficacy testing protocol and final report with (b) (6) (Sr. Specialist, QC). I noted the firm has not established the efficacy for disinfectant (b) (4) used in the cleaning of the (b) (4) Room floor. The (b) (4) disinfectant efficacy study in use was conducted in Celgene (b) (4) New Jersey site, located at 556 Morris Ave, Building (b) (4), Summit, NJ 07901. The firm lacks study to show that (b) (4) is effective on JuMP facility surface. See **Discussion Item #2** for further details. Deficiency was noted.

I reviewed with (b) (6) (Supervisor, Manufacturing) SOP-000183, entitled "Cell Processing Facility Cleaning and Sanitization". V14.0, effective 05/31/2020. SOP-000183 provides guidance on the facility cleaning and sanitization (C&S) program. I reviewed cleaning logbooks used

in the ISO (b)(4) ISO (b)(4) and ISO (b)(4) manufacturing areas, I verified appropriate disinfectants and disinfectant rotation were used as specified in written SOP.

I reviewed SOP-000186, entitled "Changeover Procedure", V14.0, effective 08/21/2020. I observed line clearance and changeover of leukapheresis receipt. I verified cleaning had occurred (b) (4) receipt (line clearance) and (b) (4) processing (changeover) as specified in the SOP.

I asked how cleaning was performed if concurrent manufacturing operations were occurring (as per changeover SOP) (b) (6) (Specialist, Manufacturing) explained that efforts were being made to ensure manufacturing schedules allow for adequate cleaning between lots. Also, visual and physical barriers were set up to allow for adequate cleaning if concurrent manufacturing operations were occurring. I observed manufacture operations on 10/09/2020, I verified there were demarcation lines on the floor to (b) (4) the (b) (4) workstations in the leukapheresis receipt Rm (b) (4). I also verified there (b) (4) workstations in the leukapheresis (b) (4) Rm (b) (4)

I selected and reviewed cleaning logbooks used in the ISO (b)(4) ISO (b) (4) ISO (b)(4) manufacturing areas (LOG-20-502, LOG-20-480, and LOG-20-385, respectively). I verified the (b) (4) cleaning and sanitization occurred as specified in the SOP. No deficiencies were noted.

On 10/16/2020, during the walkthrough inspection of the (b) (4), I inspected the Janitor's closet located in Rm (b) (4). I observed several buckets used for the double-bucket mopping system being stored in Rm (b) (4). I was told by Mr. Donald M. Ane (Sr. Manager, Manufacturing) these buckets were shared for the cleaning of all manufacturing areas, including the ISO classified clean rooms (ISO (b) (4) and the CNC area such as the (b) (4) room. Concerns were noted for not having dedicated cleaning buckets for ISO classified clean rooms.

ISO (b)(4) Biosafety Cabinet (BSC) Cleaning and Sanitization (C&S)

(EL)

SOP-000129, entitled "Biological Safety Cabinet Operations and Maintenance, (b)(4), V10.0, effective 08/21/2020 stipulates the operation, maintenance, cleaning, and sanitization of ISO (b)(4) BSCs used for the open operation of (b) (4) and for the DP final fills.

On 10/13/2020, I reviewed with (b) (6) BSC line clearance, changeover, and cleaning. I reviewed procedures for line clearance (b) (4) cleaning and sanitization (C&S) using (b) (4). I also reviewed procedures for changeover (b) (4) C&S using (b) (4) followed by (b) (4). I further reviewed the (b) (4), and C&S of the BSC. I selected and reviewed (b) (4) BSC cleaning logs, I verified cleaning had been performed as specified in the SOP. No deficiencies were noted.

I noted SOP- 000129, V10.0 is silent regarding the C&S of the (b) (4) use and in case of spills. (b) (6) explained that section 8.4.1.7 of the SOP states to avoid (b) (4) C&S agents directly (b) (4) . As far as she knew no spills had occurred and the (b) (4) has never been cleaned. Concerns were noted for the lack of written procedure for the (b) (4) C&S during both routine use and in case of biohazard spills to prevent contamination of DP.

Biological Waste Decontamination and Disposal

(EL)

I reviewed firm's biological waste decontamination and disposal. In summary, biological waste generated in the cleanroom areas are moved via exit pass-throughs and exit airlocks into the exit corridor and out of the facility through the dedicated waste exit airlock. Biohazardous waste is collected in dedicated, labeled receptacles with bio hazard bags, and later collected by a contractor for incineration and offsite disposal. No concerns were noted.

I reviewed firm's biological spills containment plan described in section 10.7 of the SOP-000118, entitled "Emergency Plan-JuMP", V5.0, effective 06/18/2020. Section 10.7 instructs how to contain, clean, and dispose of spills occurred from an employee, in ISC (b) (4) ISC (b) (4), in centrifuges, and in nonclassified area (including labs). Procedure appeared adequate. No concerns were noted.

Laboratory System

(EL)

QC Laboratories Overview

I conducted walkthrough inspections of the QC Laboratories located on the (b) (4) floor. The "Quality Control Overview" presentation was collected and submitted in **Exhibit EL-24**. QC laboratories and tests conducted in each room are described as follow.

- Sample Management (Room (b) (4)
  - Sample receiving and storage
- Analytical Chemistry (Room (b) (4))
  - Appearance by Visual Inspection (General Parameter)
  - Raw Material Testing

- Cell Biology (Room (b) (4)
  - (b) (4) (General Parameter)
  - (b) (4) (Purity)
  - (b) (4) (Potency)

- (b) (4) (Room (b) (4)
  - (b) (4) (Purity, Identity, Strength)

- (b) (4) (Rooms (b) (4)
  - (b) (4) (Safety)
  - Mycoplasma Detection (Safety)

- Microbiology (Rooms (b) (4))
  - Endotoxin (Safety, Rooms (b) (4)
  - Sterility (Safety, Room (b) (4)
  - Environmental Monitoring (Room (b) (4)

Validation of Analytical Test Methods

(EL)

I briefly reviewed the verification or validation of the following analytical test methods. No other method validations were reviewed.

JCAR017 Bacterial Endotoxin Test Method (TM-0054): The level of endotoxin present in the JCAR017 cryopreserved drug product (CDP) (b) (4), TcCDP and ThCDP) was assessed using (b) (4) method as described in (b) (4) I briefly reviewed the method verification protocol PTC-0197, V00 and the method verification report RPT-0396, V01. Assay specificity, accuracy, repeatability, and ruggedness were established using (b) (4) lots of representative JCAR017 CDP CD4 and CD8 arms, (b) (4) types of reagents (b) (4) and (b) (4) operators performing multiple repeats on different days. A final product (b) (4) that overcame inhibition or enhancement was selected for JCAR017. No concerns were noted.

I additionally reviewed MET-000054, "Bacterial Endotoxin Test Method", V8.0. and inspected critical assay accessories during the laboratory walkthrough inspections. Deficiencies were noted and documented in **Discussion Item # 6** of this EIR. Specifically, (b) (4) are being used to store test samples. Endotoxin can adhere to (b) (4) to give false negative test results. Also, (b) (4) are being used for samples and (b) (4) The presence of beta glucan in the (b) (4) can lead to false positive test results.

Additionally, MET-000054, V8.0 failed to specify the minimum time required for adequate (b) (4) to ensure the release of endotoxins. Objectionable observation was noted. See **Observation #5a** of this EIR for further details.

Sterility Test Method Validation of JACR017 Using the (b) (4) : I reviewed method validation report RPT-001776, V1.0. (b) (4) sterility test method suitability was performed using (b) (4) CDP product lots, challenge compendial organisms (including in-house isolates), target (b) (4) inoculum and tested in (b) (4) in the presence of CDP. Test results showed the (b) (4) sterility method detected a wide range of microorganisms without inhibition by JCAR017. No concerns were noted.

I reviewed SOP-001244, (b) (4) Procedure for JCAR 017", V5.0. I also observed an actual inoculation during the manufacture walkthrough inspection. Deficiency was noted in that written procedure was not followed for JCAR017 DP inoculation; wet (b) (4) on the (b) (4) was not allowed to dry. Wet (b) (4) can introduce contamination to test samples. Deficiency was documented in **Discussion Item #3** of this EIR.

Sample Management in Quality Control (QC)

(EL)

SOP-000069, entitled "Quality Control Sample Management", V11.0, effective 06/26/2020 stipulates the processes required to ensure custody, identity, and integrity of samples received, processed, distributed, and stored by the QC group. On 10/07/2020, I conducted a walkthrough inspection of the Sample Management Room (b) (4) accessed) located in the QC Laboratories. I verified samples delivered to this room were received and logged into the LIMS and were stored/locked under required temperatures. I selected sample submission sheets and checked for the physical samples against paper requests. I verified samples with the correct barcode identification and quantities were being stored in the designated temperature as documented in the submission sheets and also in LIMS. No concerns were noted in QC sample management.

During a walkthrough inspection of the Sample Management Room, I noted EM samples were kept in a (b) (4) on a laboratory (b) (4) awaiting delivery to the QC Laboratory for incubation. I reviewed EM plates submission logbook and found at times EM plates were kept at (b) (4) in the Sample Management Room for more than (b) (4) before incubation begins. Firm's work instruction allows incubation of EM samples within (b) (4) of sampling. However, there is no study to demonstrate the (b) (4) time does not affect microbial recovery. Deficiency was noted. See **Discussion Item #4** of this EIR for further details.

Sample Receipt and Testing Procedures

(EL)

Each QC Laboratory is equipped with [redacted] to receive samples delivered by Sample Management. I observed execution of the following assays which are used as lot release tests. I also watched for maintenance of the COI throughout QC testing.

JCAR017 [redacted] test is a high complexity [redacted] assay involving multiple test steps and requiring the use of different reagents, accessories, and instruments. On 10/13/2020, I observed execution of part of the day [redacted] DP samples and [redacted] sample in the Cell Biology Laboratory located in Room [redacted]. I observed all test sample vials had printed barcode labels. I also observed accessories such as [redacted] I watched the analyst performing [redacted] I observed the analyst verifying vial IDs and Lot IDs before each transfer. Good laboratory technique and practice appeared to be observed in maintaining COI throughout the QC testing. No concerns were noted.

JCAR017 [redacted] *(MET-000115, V13.0)*: This immunophenotyping test also is a high complexity assay that demands good laboratory techniques and proficiency in operating the [redacted]. On 10/13/2020, I observed part of the [redacted] assay being performed for [redacted] JCAR017 DP samples and [redacted] sample in the [redacted] Laboratory located in Room [redacted]. I interviewed the analyst regarding the sample receipt process. I was told after delivering test samples to the laboratory, the sample manager stood by to witness receipt into LIMS by the laboratory personnel before departure. I watched the analyst making [redacted]. I observed samples and accessories were all labelled and I observed the analyst verifying sample IDs before each transfer or pipetting. Good laboratory technique and practice appeared to be observed in maintain COI throughout the QC testing. No concerns were noted.

On 10/15/2020, in the Analytical Chemistry Laboratory (Room [redacted], I observed data analysis of the samples assayed on 10/13/2020. I observed the analyst [redacted] to obtain viable [redacted] by following MET-000115, entitled "JCAR017 [redacted], section 10.10 Data Analysis. I was told analyzed data will be reviewed by a second qualified person and the analysis software has audit trail to ensure sample COI and data integrity. No concerns were noted.

Appearance by Visual Inspection (MET-001013, V6.0): On 10/13/2020, I observed [redacted] DP lots clarity and color assessments in the Analytical Chemistry Rm [redacted]. Appearance by Visual Inspection is a final DP release test. Written procedures were not followed in performing the assessment. Objectionable observation was noted. See **Observation #5b** of this EIR for further details.

Microbial Enumeration of EM Plates (SOP-000229, V6.0): To note, this is not a release test. Microbial enumeration is to count and record Colony Forming Unit (CFU) on EM or bioburden (b) (4). On 10/07/2020 in the Environmental Monitoring Laboratory Rm (b) (4), I randomly selected and inspected EM plates that had been enumerated, counts verified by a (b) (4), and results recorded in LIMS (b) (4). I found CFUs were not accurately enumerated by either the original analyst and (b) (4). Objectionable observation was noted. See **Observation #6** of this EIR for further details.

Sample Mix-up OOS Deviation Investigations

(EL)

On 10/13/2020, I discussed with Mr. Adam F. Barrios (Manger, QC) the following OOS deviations due to sample mix-up.

- DEV-2019-01581 was discovered on 07/10/2019 when the results for the (b) (4) CD4 and CD8 in-process samples associated with Lot (b) (4) were not as expected. Sample switch during plating was suspected.
- DEV-2019-01669 was discovered on 07/17/2019 for suspected sample mix-up for CD4 and CD8 (b) (4) results.
- DEV-2019-02125 was discovered on 08/21/2019 for suspected sample mix-up for (b) (4) Helper Cell Cryopreserved Drug Product (b) (4) results.

As a result, CAPA 2019-00855 was initiated to address COI issues which required the re-training for all analysts and resulted in the creation of WIN-001133, entitled "Sample Preparation for (b) (4). WIN-001133 includes enhanced instruction and color photos to enable better understanding of the assay setup.

Regarding the (b) (4) sample mix-up, Mr. Barrios said he observed the (b) (4) operations and interviewed analysts to identify opportunities for sample mix-up. Similarly, WIN-001146, V1.0 was created to account for intermediate storage of processed material within the PCR Laboratory.

Corrective actions appeared effective, Mr. Barrios stated there has not been any OOS results due to sample mix-ups.

(b) (4)

(EL)

(b) (4) Measurements are either performed in the manufacture areas or in the QC Laboratories. Specifically, all samples tested in the manufacture areas are from (b) (4)

preparations while samples tested in the QC Laboratories can be from either (b) (4) preparation. For example, in the QC Laboratories, CD8 Cryopreserved Drug Product (TcCDP) (b) (4) are tested as follow.

- (b) (4) preparation is tested per MET-000026, (b) (4)
- (b) (4) preparation is tested per MET-000107, JCAR017 (b) (4)
- (b) (4) preparation is tested per MET-000115, JCAR017 (b) (4) to determine (b) (4) assay.

A list containing complete (b) (4) measurements performed in the commercial (b) (4) process, including information such as sample types, sample preparation (b) (4) test location (MFG or QC), procedure/method used, and testing purpose, was collected and submitted in **Exhibit EL-25**.

QC Equipment Qualification, Calibration and Maintenance

(EL)

I reviewed the following equipment/instrument qualification, calibration, or preventive maintenance (PM) performed from 01/2019 to date.

(b) (4): is used for the release testing of (b) (4) for Purity, Identity, Strength. There are a total of four (b) (4) instruments in the (b) (4) laboratory; (b) (4) are in use and the (b) (4) is under qualification.

(b) (4)

I reviewed the Work History and maintenance logbook for each instrument. I verified the (b) (4) verification (b) (4), (b) (4) maintenance (i.e., (b) (4) (i.e., (b) (4) user access review/PM, (b) (4) vendor PM, and (b) (4) user access review were performed as specified in SOP-000166, entitled " Operation and Maintenance (b) (4) ", V7.0. No deficiencies were noted.

I reviewed unplanned (b) (4) maintenance. I verified unplanned maintenance was recorded in the Work History and documented as "On Demand" events. I further verified the date and description of events and the subsequent repair appeared to be appropriately recorded. For example, I confirmed (b) (4) out of service "on demand" event and the replacement of new unit from (b) (4) were documented in the Work History. No deficiencies were noted.

(b) (4) are used for the release testing of bacterial endotoxin (safety). I reviewed Work History and Work Details of each instrument. I verified test parameters such as absorbance, alignment, accuracy, repeatability, OD validation, system test, and temperature uniformity were within acceptance criteria. I verified the (b) (4) maintenance (by QC) and the (b) (4) PM (by vendor (b) (4)) were performed as specified in SOP-000375, entitled "Operation and Maintenance for the Endotoxin (b) (4) ", V4.0. No deficiencies were noted.

(b) (4) Readers are used for the release testing of JACR017 (b) (4) . I reviewed Work History and Work Details of each instrument. I verified test parameters such as performance test, database maintenance, instrument/sensors cleaning, optics, filters and apertures cleaning, temperature & humidity sensors electronic check, mechanics test, and post-PM performance test were performed during the (b) (4) vendor PM. I also verified the (b) (4) maintenance were performed as specified in SOP-000462, entitled "Operation and Maintenance of (b) (4) ", V2.0. No deficiencies were noted.

(b) (4) is used for the release testing (safety) of (b) (4) . I reviewed Work History and Work Details of (b) (4) . I verified the (b) (4) maintenance (instrument self-test and cleaning), (b) (4) PM (qualification verification), and (b) (4) PM (b) (4) validation) were performed as specified in SOP-001259, entitled "Operation and Maintenance (b) (4) Instrument", V2.0. No deficiencies were noted.

(b) (4) is used for the release testing (safety) of Mycoplasma (b) (4) . I reviewed Work History and Work Details (b) (4) I verified test parameters such as optics maintenance, (b) (4) maintenance, and (b) (4) calibration including the (b) (4) calibrations were performed during the (b) (4) vendor PM. I also verified the (b) (4) PM were performed according to SOP-001258, entitled "Quality Control Operation and Maintenance of the (b) (4) Instrument", V2.0. No deficiencies were noted.

Analytical OOS/OOT investigations and Retest Procedures

(EL)

SOP-001146, entitled "Analytical Out of Specification and Aberrant/Out of Trend Results Investigations", V9.0, effective 06/13/2019 describes the global process for investigating Out of specification (OOS) and aberrant/Out of Trend (OOT) analytical test results.

Retest is not allowed unless deemed acceptable following the full investigation phases specified in the SOP. In summary, a laboratory checklist is filled out followed by Phase I investigation. Repeat testing is allowed if OOS/OOT result is caused by a laboratory error. If the OOS/OOT result is not caused by a laboratory error, proceed to Phase II full-scale investigation and CAPA determination. No concerns were noted for firm's OOS/OOT investigation procedures.

Addition Deviations and OOS Deviations Reviewed

(EL)

I reviewed the following deviations and related CAPAs.

- DEV-2019-03239: OOS (b) (4)) result for (b) (4) tested by MET-000115
- DEV-2020-01600: Cryopreserved Drug Product (CDP) (b) (4) OOS (b) (4) for Lot (b) (4)
- DEV-2020-00864: OOS (b) (4)) result for (b) (4) tested by MET-000115
- DEV-2020-00132: CDP (b) (4) OOS (b) (4) for Lot # (b) (4)
- DEV-2020-00751: CDP CD4 Identity and Strength OOS (CD3+CAR+ cells not detected, (b) (4) CD3+CAR+ cells/mL) for Lot # (b) (4)
- DEV-2019-03381: Atypical Color of (b) (4) found during Incoming Visual Inspection of Juno lot (b) (4)
- DEV-2020-00892: Atypical Color of (b) (4) found during Incoming Visual Inspection of Juno Lot (b) (4)
- DEV-2019-01997: Conditionally Released (b) (4) used in the Manufacturing of (b) (4) Lot# (b) (4)
- DEV-2020-00255: Conditional Release of (b) (4)
- DEV-2020-00262: Conditional Release (b) (4) Lot (b) (4)
- DEV-2020-00783: Environmental Excursion During Filling of (b) (4) Lot# (b) (4)

- DEV-2020-00890: End of (b) (4) for (b) (4); DOM (b) (4) showed low level (b) (4)

Deviation investigations appeared adequate. No concerns were noted.

To note: On 10/07/2020, I observed what appeared to be a contaminated in-process sample (b) (4) *, identified as "*(b) (4) *being delivered to the QC laboratory. DEV-2020-02969 was initiated.* (b) (5), (b) (7)(E)

Materials System

(PR)

Raw materials used in the JCAR017 manufacturing process are purchased from Juno approved suppliers and identified, tested, and released prior to use. Raw materials are qualified either by in-house testing by Juno, or at contract testing laboratories, or accepted based on suppliers certification documentation. Raw material specifications list parameters and associated tests in addition to minimal identity (visual or other method) testing required by ICH GMP for Pharmaceutical Ingredients. Compendial materials are tested to the referenced compendia. For non-compendial materials, tests are defined by a material's composition, function, and point of use in the manufacturing process. The DMPQ Assessment references personnel, incoming materials, product, and waste flow in Attachment PR4, page 27, and no concerns were noted from the DMPQ Assessment. I reviewed SOP-001048, Raw Material Qualification and Classification, dated 26Sep2019, SOP-000200, Apheresis Receipt and Inspection, dated 17Jun2020, SOP-001149, Raw Material Retain Program, dated 09Dec2019, and SOP-000220, Visual Inspection of Incoming Material, dated 27Apr2020, and noted no deficiencies with these procedures.

(b) (4), See Exhibit PR44, page one). (b) (4). Documentation is reviewed and additional testing is performed by Juno as specified. (b) (4)

The Warehouse was inspected for appropriate segregation of materials, and identification of quarantined and rejected items. Incoming sampling, and testing operations were also reviewed. I reviewed warehousing operations with Mr. David Chu, Senior Manager, Supply Chain, on 10/7/20 and observed various ambient and temperature controlled storage areas. No concerns were noted.

I reviewed the incoming inspection, records, and CoAs for the following materials (as referenced in Attachment PR1, page 11).

Multiple Electrolytes Injection Type I (excipient)
Albumin (Human) Solution (25% Albumin) (excipient)
CryoStor CS10 (excipient)
(b) (4) CD4 (b) (4) (selection)
(b) (4) CD8 (b) (4) (selection)
(b) (4)
(b) (4)

I reviewed an example Lentiviral Vector, Lot (b) (4) Receipt Lot file and an example Syringe, Graduated, Disposable, 5 mL receipt lot file. (b) (4) Sampling procedures for visual inspection for syringes was reviewed. There is no sampling or testing for the Lentiviral vector at this site.

I reviewed BOM-001026, JCAR017 Bill of Materials-Manufacturing, dated 19Jul2019, which list the materials used in the JCAR017 process and SOP-001148, Raw Material Certification and (b) (4) Testing (see Exhibit PR25). I also reviewed QC Sampling Procedures with Mr. Tom Chui, Warehouse Manager, on 10/15/2020. I reviewed retain storage of raw materials at (b) (4) with Mr. David Chew, Warehouse Manager., and SOP-001149, Raw Material Retain Program.

Packaging & Labeling System

(PR)

JCAR017 Packaging and Shipping

JCAR017 Product Packaging and Shipping, WIN-000043, dated 11Sep2020, was reviewed, and I observed this operation on Tuesday, October 13, 2020. I observed Chain of Identity (COI) and Chain of Custody (COC) control.

I observed packaging and labeling operations ("Pack Out") as per the SOP and followed up on the PLI BLA 125714/0 Inspection Assignment request in Attachment PR1, page 10, and confirmed the information in the CMC Assessment Document (see Attachment PR3 page 58). I confirmed that the DP was maintained in a frozen state through the COI check, packaging, and shipping. There was ample space for more than one lot to be packaged.

A (b) (4) is used to move CDP (Cryopreserved Drug Product) from the LN2 storage area to the Packout Area (see floor diagram, page 2, Exhibit PR1, Step 9). SOP-000152, Dewar Packaging and Shipping procedure, dated 18Sep2020, was also reviewed and no deficiencies were noted. I reviewed an example completed packaging record for Lot (b) (4) and no deficiencies were noted.

TRAINING

(EL)

I reviewed firm's training procedure SOP-000168, entitled "CTDO GxP Training Program", V11.0, effective 09/11/2020 with Ms. Ciandra R. Barber (Sr. Manager, GMP Training) and (b) (6) (Sr. Specialist, Training). SOP-000168 outlines training responsibilities, general requirements, curricula creation, and training effectiveness evaluation.

I additionally reviewed cGMP training curriculum; SCORM-001003, entitled "SCORM JuMP GMP Annual Training 2020", V1.0 for which the curriculum includes GMP Introduction, Good Manufacturing Practice, Quality Systems, Aseptic Manufacturing, Case Studies, and Knowledge Check/Conclusion. I verified topics on data integrity were included in the curriculum. I additionally reviewed annual cGMP training records for the last two years of selected personnel. I selected three (3) training records from each QA, QC, manufacturing, Facility Management, and IT department. My review revealed annual training records were up to date for selected personnel. No deficiencies were noted.

I asked Mr. Masten how training will be maintained as the workforce is increased to accommodate the expected JCAR017 scale-out process. Mr. Masten stated that for 2019 (from 12/31/2018 through 12/31/2019), there were a total of (b) (4) new hires at JuMP. Similarly, for 2020 (from 12/31/2019 through 9/30/2020), there were a total of (b) (4) new hires at the JuMP. The firm's workforce is at capacity and does not anticipate hiring many new hires.

I additionally reviewed employee (Dis)Qualification, trainer (De)Authorization per WIN-001057, entitled "Employee Qualification and Trainer Authorization", V2.0, effective 01/03/2020. WIN-001057, section 7.1 stipulates to utilize FRM-001212 to qualify personnel on training items without having to attend or complete the training (for personnel with sufficient knowledge/subject matter expertise). The same form is used to disqualify personnel. Specifically, rationale and justification must be provided by management on FRM-001212 to qualify or disqualify employees. No concerns were noted.

I selected and reviewed task specific training records. I reviewed aseptic qualification and aseptic gowning of four (4) manufacturing operators. I noted one of the operators failed aseptic qualification. Following procedures, he was requalified after repeating and passing three (3) re-tests. During the

walkthrough inspection, I observed firm's employees did not always follow written SOP in conducting analytical procedures. Training does not appear effective. Objectionable observations were noted. See **Observations # 4, 5b,** and **6** of this EIR for further details.

MANUFACTURING CODES

(PR)

Lot numbers are assigned to each manufacturing component including the leukapheresis product, CD4+/CD8+ cryopreserved intermediates, and CD4+/CD8+ drug products. The lot numbering structure consists of two parts. The first is a patient-specific 10 character randomized alphanumeric sequence (JOIN) that is shared across process components for a patient collection and is a completely random number. The second is an alphabetic suffix (lot suffix) appended to the JOIN to denote the various production components (i.e. leukapheresis product, intermediate, drug product). An example lot code is included below, and a Lot Numbering Overview is included in Exhibit PR41.

A891-783XC A

JOIN CODE = A891-783XC

Suffix (A) = Leukapheresis Product

VOLUNTARY CORRECTIONS

There was no previous FDA inspection at this site. This was the first inspection at this site.

OBJECTIONABLE CONDITIONS AND DISCUSSION WITH MANAGEMENT

(PR)

The format of this Objectionable Conditions/Discussion with Management section is presented as the FDA-483 item in bold form, background supporting data and relevant evidence which includes a detailed discussion of the observation and relevance, and the firm's comments, if any. If no supporting Exhibits are referenced, the supporting information is limited to the investigator's review, interviews, and discussion thereof. Any reference to the "firm" means the firm's individuals. All comments under "Discussion with Management" sections under each FDA-483 item are comments made by the firm during the issuance of the FDA-483, Inspectional Observations, during the FDA closeout meeting on

10/16/2020. The Form FDA-483, Inspectional Observations, was issued to Mr. Snehal Patel, Vice President, Site Head Bothell, and in the presence of the following individuals:

Mr. Jeffrey L. Masten, VP and Quality Site Head
Mr. Brett A. Johnston, Senior Director, Quality Assurance
Ms. Mary F. Mallaney, Director, Early CMC Portfolio and Technical Writing
Ms. Anne L. Shandy, Director, Quality Systems

I read the following statement to the firm during the closeout meeting, which is included in the header of the Form FDA-483, Inspectional Observations. "This document lists observations made by the FDA Representative(s) during the inspection of your facility, they are inspectional observations and do not represent a final agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above, if you have any questions, please contact FDA at the phone number and address above."

The objectionable conditions documented on the Form FDA-483, Inspectional Observations, are described below.

1.There is a failure to thoroughly review any unexplained discrepancy, the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has been already distributed. Specifically,

DEV-2019-03442 (Critical Classification), created on 10Dec2019, reported a (b) (4) positive result for (b) (4) Juno Lot (b) (4). The contract laboratory performed (b) (4) for (b) (4) Juno Lot (b) (4) that is part of the Vendor Parent Lot (b) (4) (corresponding to Juno Lots (b) (4) The contract laboratory's result was "Fail" for the specification of (b) (4)." The sample exhibited a positive reaction when (b) (4). The Certificate of Analysis (CoA) provided by the Vendor for Lot (b) (4) states that (b) (4) Testing was performed per (b) (4) and that no (b) (4) was detected. All product lots using (b) (4) Juno Lot (b) (4), the only lot utilized in the manufacturing process, were subsequently rejected. DEV-2019-03442 Root Cause Analysis, Final Impact Analysis, and Corrective Actions were deficient for the following reasons.

(PR)

Supporting Evidence, Background, and Discussion:

The CBER/OTAT Product Office raised the following concern for follow up during the current inspection (see Attachment PR6).

(b) (4) used in the CAR T cell manufacturing process is tested for (b) (4) by the supplier (b) (4), see Exhibit PR15). The material qualification for (b) (4) by Juno does not include a retest (this is usually acceptable). Juno tested an (b) (4) lot (Juno lot (b) (4), manufacturer lot (b) (4) for (b) (4) at (b) (4) testing has (b) (4). The (b) (4) lot failed for (b) (4) testing at (b) (4). This is in contrast to the lot passing testing for (b) (4) as evidenced on the (b) (4), see Exhibit PR18. The deviation, DEV-2019-03442, dated 10DEC2019 (see Exhibit PR10) details a discussion with (b) (4), but no further action associated with (b) (4). Juno decided to change to (b) (4) as this process should (b) (4).

Mr. Johnston told me that no in process lots were released to patients and a lot trace assessment is included in Exhibit PR13. Of note, Juno had started to use the affected (b) (4) lot in JCAR017 manufacturing and multiple JCAR017 lots were affected, but no finished drug product from the affected (b) (4) Vendor Lot (b) (4) was released/distributed (see Exhibit PR12, page five, Exhibit PR10, page nine, Impact statement at bottom of the page, and page seven, 2nd paragraph). (b) (4) statement is included in Exhibit PR14, and states the ubiquitous nature of (b) (4) and how (b) (4) will destroy (b) (4) and (b) (4) (see Exhibit PR14, page one, 3rd paragraph). The change, DCR-2019-10831, from (b) (4) to (b) (4), approved December 20, 2020, is included in Exhibit PR22. This change was in direct response from another investigation during the same time period where several lots of (b) (4) became contaminated due to (b) (4) (see Exhibit PR34, DEV 2019-03089, Microbial Contamination Trend). (b) (4) in-process product lots of JCAR017 were affected during the 12Nov2019-23Nov2019 time period (see Exhibit PR34, page two). Mr. Johnston stated that change from (b) (4) was the correction for this Deviation, DEV 2019-03089, and DEV 2019-03442.

The following were the concerns from CBER/OTAT that I followed up on during the current inspection (see Attachment PR6, Concerns Section).

1. The deviation report and CAPA are insufficient. The deviation does not indicate if Juno evaluated the reason for the testing discrepancy, if they reviewed the (b) (4) testing method and validation, or if they plan to institute increased confirmatory testing. At this time, there is no confirmation that (b) (4) testing is sufficient to support use of future material. Additional concerns include what steps have they taken to confirm (b) (4) assertations about the effectiveness of (b) (4) to (b) (4).

2. Due to the autologous nature of the drug product, it is not clear why they began to use the (b) (4) lot prior confirmatory testing. True it is not required for material qualification, but patient treatment was affected; at risk manufacturing is not acceptable for autologous products. Additionally, we would like to understand the patient impact of this decision and what

decision making was involved in deciding to terminate autologous drug product manufacturing.

The firms' investigation for DEV-2019-03442 is included in Exhibit PR10 and the Executive Summary is in Exhibit PR20. I explained to Mr. Brett A. Johnston, Senior Director, Quality Assurance, and Mr. Matthew C. Whitaker, Manager, Quality Assurance that this investigation was not thorough enough, and there should have been more of an assessment of the (b) (4) vendor, (b) (4) (b) (4), and why they got a negative result for (b) (4). The Certificate of Analysis showing the negative result is included in Exhibit PR18. The Quality Agreement between Juno and (b) (4) is included in Exhibit PR21. The following are areas where DEV-2019-03442 could have been more thorough.

a) The reliability of CoA from the vendor supplying (b) (4) Lots was not established and therefore the quality of previously supplied (b) (4) lots, which were released based on the vendor CoA (b) (4) negative results, was not determined.

The reliability of the COA from (b) (4). (see Exhibit PR18) was questionable since (b) (4), the contract test lab, tested (b) (4) lot for (b) (4), as positive (see Exhibit PR11, page one) and (b) (4) test was negative. I asked Mr. Matthew C. Whittaker, Manager Quality Assurance, if retains from previous (b) (4) lots tested by (b) (4) were tested to see if the results matched. I explained there should have been more of an investigation to previous (b) (4) lots shipped from (b) (4). to see if the negative results were valid. Their method may not be sensitive enough for low levels of (b) (4)

(b) (4) had a statement about the ubiquitous nature of (b) (4). They seemed to be saying that random positives were going to occur and they were not going investigate their positive result for (b) (4) Parent Lot (b) (4). I explained that reliability of CoA from the vendor, (b) (4), for (b) (4) needed to be reestablished.

b) A clinical impact analysis was requested to understand the potential clinical risk of (b) (4) exposure to patients treated with JCAR017 where (b) (4) was used in the (b) (4). The clinical impact analysis stated there was no known transmission of (b) (4) to humans. The clinical impact analysis did not include an assessment of adverse events for patients treated with JCAR017 where (b) (4) was used in the (b) (4)

The clinical impact analysis is included in Exhibit PR19. The clinical impact analysis stated there was no known transmission of (b) (4) to humans. The clinical impact analysis did not include an assessment of adverse events for patients treated with JCAR017 where (b) (4) was used in the (b) (4) There were hundreds of AEs that were submitted since Jan 1, 2020, under the IND, but DEV-2019-03442 did not include an assessment of adverse events for patients treated for JCAR017 where (b) (4) lot was used in (b) (4). I explained to Mr. Whitaker, Manager Quality Assurance, that this assessment should have been included in Dev-2019-03442.

Since the reliability of (b) (4) test results for (b) (4) for lots manufactured prior to the + Vendor Lot (b) (4), was not established, and the (b) (4) test method may not have picked up positive (b) (4) results, a review of AEs for any potential link to (b) (4), should have been conducted and included in DEV-2019-03442 (Critical Classification), created on 10Dec2019.

c) A CAPA with Effectiveness Checks, per SOP-001151, Global CAPA Management, dated 17Dec2018, was not opened specifically for DEV-2019-03442, to address the inconsistency between the OOS results from the contract testing lab for Juno Lot (b) (4) (Vendor Lot (b) (4)) and the vendor CoA negative (b) (4) results. CAPA effectiveness checks were not conducted for the implemented corrections involving the (b) (4), for the purpose of (b) (4), and the cleaning of QC/Microbiology locations where (b) (4) Juno Lot (b) (4) was used.

DEV-2019-03442, dated 10 DEC 2019 is included in Exhibit PR10. On page 10 of Exhibit PR10 it indicates that a CAPA was not initiated for this deviation. Mr. Johnston, Senior Director, Quality Assurance, said that the corrections were in the deviation so a CAPA was not initiated. I explained that per SOP-001151, Global CAPA Management, dated 17Dec2018, a CAPA as defined on Exhibit PR24, page three, Section 3.9, should have been initiated. I explained that their contract testing lab, (b) (4), had produced a positive result for the (b) (4) Vendor Lot (b) (4) (see (b) (4) CoA, Exhibit PR11, page one, Result-Fail), and the vendor (b) (4) had produced a negative result for (b) (4) (see Exhibit PR18, page one, (b) (4) Not Detected). The Executive Summary for DEV-2019-03442, is included in Exhibit PR20 and the summary of the corrections listed, including the replacement of (b) (4), for the purpose of (b) (4), and the cleaning of QC/Microbiology locations where (b) (4) Juno Lot (b) (4) was used. I explained that these corrections listed in the Executive Summary (see Exhibit PR20, page two, Corrective Actions) should have been part of a formal CAPA and the corrections, in the form of effectiveness checks, should also have been included as part of the CAPA.

d) The contract test lab, that reported the positive (b) (4) result, conducted an OOS Investigation (Record ID: (b) (4), dated 07NOV2019) and concluded that the assay controls performed as expected and the assay is valid. The (b) (4) assay for (b) (4) was positive from the contract laboratory that tested (b) (4) Lot (b) (4), and negative from the vendor that supplied (b) (4) Lot (b) (4). DEV-2019-03442 did not include an OOS investigation conducted by the (b) (4) vendor (b) (4) as per Attachment C (GMP (b) (4) Investigations) of the Global Deviation SOP, SOP-001145, dated 07Jun2019, to determine if their assay produced a valid result, and the assay controls performed as expected.

As mentioned previously, the contract test lab, (b) (4), that reported the positive (b) (4) result, conducted an OOS Investigation (Record ID: (b) (4), dated 07NOV2019) and concluded that the assay controls performed as expected and the assay is valid. This

conclusion is included in Exhibit PR11, page four, Investigation Summary. I explained to Mr. Johnston that the (b) (4) Vendor, (b) (4) ., see Exhibit PR14, page one, had a (b) (4) statement that (b) (4) is ubiquitous in (b) (4), and (b) (4) was found to be the most effective and least damaging virus inactivation method. The last page of Exhibit PR14, Exhibit PR10, page eight,

bottom sentence, and page nine, top of page, stated since the (b) (4) results obtained by (b) (4) for Vendor Lot (b) (4) were within Specification (Not Detected), no further investigation by vendor will be conducted. I explained that an OOS investigation, similar to the one (b) (4) conducted, which is included in Exhibit PR11, page 4-6, should have been conducted by (b) (4)

Discussion with Management: The firm voiced no objection to this FDA483 Inspection Observation.

2. Written records of investigations into unexplained discrepancies, the failure of a batch or any of its components to meet specifications, do not always include the appropriate conclusions and follow-up. The following Notice of Events (NOEs) were not classified as Deviations.

(PR)

Supporting Evidence, Background, and Discussion:

I reviewed several lists, electronic and hard copy, of Deviations throughout the inspection and noted that Deviations can be classified as Critical, Major, Minor, or Notice of Event (NOE). The firm's Deviation Classification procedure is outlined in Exhibit PR27. On page three of this overview, it states that for NOEs, a root cause investigation was not conducted. I reviewed this process with (b) (6) , Sr. Specialist, Quality System Compliance. I also reviewed the firm's Global Deviation Management SOP, SOP-0001145, dated 07Jun2019, which is included in Exhibit PR23. On page three of this procedure a Deviation is defined as "An event that is determined to be a failure, non-conformance or departure from approved procedures…..which may affect the safety, quality, identity, purity, or potency of product, have regulatory implications and/or an impact on a critical system". I explained that deviations classified as "NOE Only" do not meet the definition of a deviation, even though this SOP as the least critical risk deviation classification as "NOE Only".

The Global Deviation procedure, SOP-001145, dated 07Jun2019, is included in Exhibit PR23, and the Deviation Severity Classifications are defined on page four of Exhibit PR23. A NOE deviation is defined as an event having no impact on materials or product, process, systems or equipment, the root cause of the event is known and does not require any additional investigation and the deviation is not considered a repeat occurrence. I explained to the firm's management that they should not be classifying "NOE Only" events as "NOE Only" deviations since the NOE Only definition on page four of Exhibit PR23 would not make these types of events deviations. I explained that the critical, major, and minor deviation definitions outlined in page four of Exhibit PR23 are correct deviation definitions and the NOEs described in this FDA483 observation should have classified as minor, major, or critical deviations, and not "NOE Only" deviations.

Mr. Brett Johnston, Senior Director, Quality Operations, stated that for the following examples these deviations were classified NOE Only (see page four, Exhibit PR23), since the root cause of the event was known. I told him that I believed the root cause for the deviations listed below were not truly known which is why a root cause analysis should have been conducted as defined in the Global

Deviation Management SOP, SOP-001145, dated 07Jun2019, Exhibit PR23, page five. On this page, Root Cause and Root Cause Analysis is defined as a wide range of approaches, tools, and techniques used to uncover causes of problems.

The Attachment B, Internal Celgene Deviation Event Decision Tree (see Exhibit PR23, page 21), states several criteria when a Deviation Record should be initiated in (b) (4). The following meet the Attachment B criteria of "unexplained and unexpected discrepancy", and the following NOE deviations should have been classified as Critical, Major, or Minor deviations and not "NOE" deviations. Classification as a NOE deviation means a root cause analysis and corrective action does not have to be conducted.

a) **DEV-2020-02527, dated August 29, 2020, NOE Classification, reported Suspected Contamination of CMAT (b) (4) during Cryopreservation of Lot (b) (4). The Deviation was classified NOE only since there was no impact to product. The CD8 Cryopreserved Material (CMAT) (b) (4), Lot (b) (4), had a (b) (4) appearance. CMAT typically has a clear appearance. SOP-000236, Microbial Contamination Response, dated 02Apr2020, requires a deviation be initiated in the event of suspected contamination.**

DEV-2020-02527, dated August 29, 2020, NOE Classification, reported Suspected Contamination of CMAT (b) (4) during Cryopreservation of Lot (b) (4). This deviation is included in Exhibit PR28. The CD8 Cryopreserved Material (CMAT) (b) (4) Lot (b) (4), had a (b) (4) appearance (see Exhibit PR28, page one, top paragraph). On August 29, 2020 in Cryopreservation Room (b) (4), a Manufacturing Associate and a Manufacturing Technician observed that the CD8 Cryopreserved Material (CMAT) (b) (4) for Lot (b) (4) had a (b) (4) appearance. CMAT typically has a clear appearance and the (b) (4) appearance was abnormal for CMAT (see Exhibit PR28, page one, Description of Problem Sections, (b) (4), top of page).

In the Immediate Actions Section (see Exhibit PR28, page one, bottom of page) a contamination response was initiated per SOP-000236, v6.0 Microbial Contamination Response (included in Exhibit PR31). Page one of Exhibit PR31, SOP-000236, Section 3.4. states to ensure that the contamination investigation is completed in accordance with Celgene SOP-001145, which is the Global Deviation Management SOP. I reviewed SOP-001145, Global Deviation Management, dated 07Jun2019, Attachment B, Internal Celgene Deviation Event Decision Tree, (Exhibit PR23, page 21), and one of the decision questions states if this event was an unexpected or unexplained discrepancy which would make this event a critical, major, or minor deviation and not a NOE deviation. I explained that this event fits that classification and the Decision Tree states if the answer to this question is a "Yes", initiate a Deviation Record in (b) (4) (see Exhibit PR23, page 21).

On page two of Exhibit PR28 (Impact Assessment at the bottom of the page) it states that the cause was determined to be Methods/Procedure and SOP-000236 requires a deviation to be initiated in the event of a suspected contamination, however the investigation confirmed that the abnormal (b) (4) appearance observed in the CMAT was not the result of microbial contamination. One of the reasons this Event was classified as an NOE deviation was the cause was known at the time of the event (see

Exhibit PR28, page two, bottom of page). This was not the case since they did not know whether the contamination was microbial or not, which is why you initiate a minor, major, or critical deviation and initiate a contamination investigation to determine the root cause. Exhibit PR27, Deviation Severity Classification Strategy, page three, states that for NOE deviations a Root Cause Investigation is not conducted, but in this case it seems like one was conducted to determine that the contamination was not microbial, which would upgrade this event classification to a critical, major, or minor deviation. However, the root cause for this contamination should be documented, which it wasn't since this was classified as an "NOE" (see Exhibit PR27, page three) deviation, and root cause investigations are not conducted for NOE deviations. Also, the decision tree in Exhibit PR27, page four, the "Yes" decisions would seemingly make this event a Critical, Major or Minor Deviation.

Mr. Brett Johnston, Senior Director. Quality Operations, and (b) (6), Sr. Specialist, Quality System Compliance, stated that since the root cause was known in this instance, it was not Classified as NOE deviation, however at the time of the discovery of the potential contamination, the root cause was unknown. DEV-2020-02527, page two, Impact Assessment section, states that the cause was determined to be Methods/Procedure-Other, which was not known at the time of the occurrence and was seemingly determined after a "root cause" investigation, which would mean according to Exhibit PR27, page three, that DEV-2020-02527, was a critical, major, or minor deviation.

b) DEV-2020-02599, dated September 4, 2020, NOE Classification, reported QC (b) (4) Pipette (b) (4) Found to be Out of Process Tolerance During On Demand Calibration. This Event was classified NOE only since there was no impact to product quality. However, the Description section of this deviation stated the potential impact from out of tolerance pipettes would result in invalid test results and failure to meet assay and sample acceptance criteria. Approximately (b) (4) JCAR017 lots had invalid test results and were identified as lots that were potentially affected by the pipettes out of tolerance failure.

DEV-2020-02599, dated September 4, 2020, NOE Classification, reported QC (b) (4) Pipette (b) (4) Found to be Out of Process Tolerance During On Demand Calibration. This deviation is included in Exhibit PR29. The Detailed Description of this Event is included in Exhibit PR29, page one. It states that a LIMS query was performed for lots performed using (b) (4) pipette from the last calibration due date to the date the pipette was taken out of service (03June2020 to17Aug2020). The query returned (b) (4) lots and showed that no MET-000030 and MET-000122 assays were performed during this time frame (see Exhibit PR29, page one, Detailed Description Section, 6th paragraph). The next paragraph states the potential impact from out of tolerance pipettes would result in invalid test results and failure to meet assay and sample acceptance

criteria. (b) (4) lots listed in Exhibit PR29, page 2-5, were identified as having invalid test results and are identified as lots that are impacted by the pipettes out of tolerance failure.

I reviewed SOP-001145, Global Deviation Management, dated 07Jun2019, Attachment B, Internal Celgene Deviation Event Decision Tree, (Exhibit PR23, page 21). As in the previous example, I reviewed Attachment B, Internal Celgene Deviation Event Decision Tree, and one of the decision questions states if this event was an unexpected or unexplained discrepancy, and was there a batch or batch component specification failure. I explained that this event fits that classification and the Decision Tree states if the answer to this question is a "Yes", initiate a Deviation Record in (b) (4) (see Exhibit PR23, page 21, Attachment B). Exhibit PR27, Deviation Severity Classification Strategy, page three, states that for NOE deviations a Root Cause Investigation is not conducted, but in this case it seems like one was conducted to say the root cause was "equipment malfunction due to not passing calibration" (see Exhibit PR29, page six, Impact Assessment, Item 2) which would make this classification a "Deviation" (see Exhibit PR27, page three). However, the root cause, for why the pipette was out of calibration, should be documented, which it wasn't since this event was classified as an "NOE" deviation (see Exhibit PR27, page three and Exhibit PR29, page six, top of page), and root cause investigations are not conducted for NOE deviation. I explained to Mr. Johnston that saying "equipment malfunction due to not passing calibration" is the root cause is not adequate. The root cause is what caused the equipment not passing calibration.

The QA Assessment described in Exhibit PR29, page six, top of page, states that this deviation is NOE only since there is no impact to product quality, the direct cause of the event was known at the time of the event discovery (Equipment Malfunction due to not passing calibration), however the cause is being investigated by trend investigation DEV-2020-01860, and this was also a repeat event. I mentioned to Mr. Brett Johnston, Senior Director. Quality Operations, that these statements would make this deviation a "Critical, Major, or Minor" deviation and not a "Notice of Event" deviation according to Exhibit PR23, page 21, Attachment B).

Exhibit PR27, Deviation Severity Classification Strategy, page three, states that for NOE classified deviations a Root Cause Investigation is not conducted, and in this case it was being conducted which would make this event a Minor, Major, or Critical Deviation. Also, the decision tree in Exhibit PR27, page four, the "Yes" decision triggers would apply for this deviation and seemingly make this event a Critical, Major or Minor Deviation.

c) DEV-2020-02726, dated September 17, 2020, NOE Classification, reported Operators inadvertently (b) (4) instead of Viral Vector during (b) (4) for Lot (b) (4) The cause was determined to be Personnel Inattention and DEV-2020-02726 was classified NOE-only. Management counseling of the manufacturing operators was completed but a CAPA, per SOP-00151 (Global CAPA Management, dated 17Dec2018), with Effectiveness Checks for the management counseling corrective action was not implemented.

DEV-2020-02726, dated September 17, 2020, "NOE Classification", reported Operators inadvertently (b) (4) instead of Viral Vector during (b) (4) for Lot (b) (4) . This deviation is

included in Exhibit PR30, and the top of the first page has the title description, and the Detailed Description. The Detailed Description states on 16Sep2020 the Manufacturing (MFG) Associate (b) (4) and (b) (4) were performing the (b) (4) of lot (b) (4) in room (b) (4) per MIR_JCAR017_CDP_EBR. Recipe version 13. After (b) (4) of the Viral Vector (b) (4) notice that the (b) (4) on the Viral Vector was (b) (4).

As in the previous examples, I reviewed SOP-001145, Global Deviation Management, dated 07Jun2019, Attachment B, Internal Celgene Deviation Event Decision Tree, (Exhibit PR23, page 21) and one of the decision questions states if this event was an unexpected or unexplained discrepancy, and also if there was a batch or batch component specification failure. I explained that this event fits that classification and the Decision Tree states if the answer to this question is a "Yes" initiate a Deviation Record in (b) (4) (see Exhibit PR23, page 21).

The justification for stating this deviation is NOE only is included in Exhibit PR30, page two, Initial Impact Assessment. The Initial Impact Assessment stated that there is no impact to safety, quality, identity, potency and purity of products, the six month historical review of similar events revealed that this is not a repeat occurrence, and the cause was determined to be Personnel Inattention, there this event is considered NOE-only.

Mr. Brett Johnston, Senior Director, Quality Operations, stated that like in the previous examples, this deviation was classified NOE Only (see page four, Exhibit PR23, for NOE definition), since the root cause was known. I explained that the QA Impact Assessment (see Exhibit PR30, page two), stated that root cause was determined to be Personnel Inattention, therefore this event was considered NOE only, was not the root cause. There should have been a root cause analysis as defined in the Global Deviation Management SOP, SOP-001145, dated 07Jun2019. See Exhibit PR23, page five, Root Cause and Root Cause Analysis definition: a wide range of approaches, tools, and techniques used to uncover causes of problems. The root cause analysis should have been conducted to determine what caused the Personnel Inattention (i.e., was it lack of training, failure to follow SOP, etc.).

I told him that I believed the root cause for the deviations listed above were not truly known which is why a root cause analysis should have been conducted as defined in the Global Deviation Management SOP, SOP-001145, dated 07Jun2019, (see Exhibit PR23, page five, Root Cause and Root Cause Analysis definition: a wide range of approaches, tools, and techniques used to uncover causes of problems)

Discussion with Management: The firm voiced no objection to this FDA483 Inspection Observation.

3. The written procedure for Manufacturing Material Visual Inspection, SOP-000512, dated 20Jun2020, defines the method used to inspect raw, intermediate, and Formulated Drug Product (FDP) materials for foreign particulates and defects, and applies to the visual inspection of GMP materials used throughout the manufacturing process. SOP-000512 does not specify when in the manufacturing process CD8 and CD4 intermediate materials, CMAT and AMAT, and their immediate containers are inspected for leaks. Specifically,

(PR)

Supporting Evidence, Background, and Discussion:

SOP-000512, dated 20Jun2020, is included in Exhibit PR26 and defines the method used to inspect raw, intermediate, and Formulated Drug Product (FDP) materials for foreign particulates and defects, and applies to the visual inspection of GMP materials used throughout the manufacturing process. During the inspection I reviewed this procedure with Mr. Brett Johnston, Senior Director. Quality Operations, and I showed page one of Exhibit PR26, Purpose Section, and it specified inspecting raw material, intermediate, and Formulated Drug Product (FDP) materials for foreign particulates and defects, but not specifically for leaks. Mr. Johnston said that SOP-000512 applies to inspecting for leaks. I showed him page four of Exhibit PR26 and I wanted to know what intermediate products and at what stages were specifically inspected for leaks. Mr. Johnston said that SOP-000512 is also used for inspecting for leaks. When I was reviewing example electronic batch records with (b) (6) , Supervisor, Manufacturing, he mentioned that at the CMAT (Cryopreserved Material) stage and the AMAT (Activated Material) stage the in-process material, was inspected for leaks per SOP-000512. I reviewed the process flow in Exhibit PR2, page, seven through ten, with Mr. Johnston, and there are several in-process materials such as CMAT (Cryopreserved Material) (CMAT) (see Exhibit PR2, page 8) and AMAT (Activated Material) that are described and serve as background information for this observation.

a) Intermediate CD8 and CD4 Cryopreserved Material (CMAT) contained in (b) (4) are inspected for leaks upon (b) (4) , but the inspection is not documented concurrently in the applicable section of the (b) (4) electronic batch record.

A diagram of (b) (4) is included in Exhibit PR40, page one. I also reviewed (b) (4) Electronic Batch Records with (b) (6) Supervisor, Manufacturing, The (b) (4) operations where the process of (b) (4) being received is described in Exhibit PR2, page 8.

Intermediate CD8 and CD4 Cryopreserved Material (CMAT) contained in (b) (4) are inspected for leaks upon (b) (4) Suites. I observed this operation during the inspection for an in-process CMAT lot. I reviewed this exact step for a previously manufactured CMAT in-process lot, Lot (b) (4) , and the eBR section, see Exhibit PR36, page one, documents the (b) (4) of the CMAT material in the (b) (4) (Suite (b) (4)) and a visual inspection for leaks is conducted but not documented. The eBR included in Exhibit PR46 also documents the (b) (4) of the CMAT in-process material, but there was no check for leaks.

b) Intermediate CD8 and CD8 Activated Material (AMAT) contained in (b) (4) are inspected for leaks upon (b) (4) , but the inspection is not documented concurrently in the applicable section of the (b) (4) electronic batch record.

A diagram of the (b) (4) Bag that contains the Activated Material (AMAT) is included in Exhibit PR40, page two. The Activation process that produces AMAT is described in Exhibit PR2, page 8. I also reviewed (b) (4) Electronic Batch Records with (b) (6), Supervisor, Manufacturing,

Intermediate CD8 and CD4 Cryopreserved Material (AMAT) contained in (b) (4) are inspected for leaks upon receipt in the Activation/Transduction Suites. I reviewed this exact step for a previously manufactured AMAT in-process lot, Lot (b) (4) and the eBR section, see Exhibit PR36, page three, documents the (b) (4) of the AMAT material in the (b) (4) Suite (Suite (b) (4) and a visual inspection for leaks is apparently conducted after (b) (4), but is not documented in the applicable eBR section (see Exhibit PR36, page three).

Mr. Johnston showed me Exhibit PR38, which is a presentation of CMAT (b) (4) leak awareness, and Exhibit PR37, JCAR017 Process Overview-Material Inspection. I explained that I was aware of specific points in the manufacturing process where in-process material was inspected for leaks and being documented concurrently in the electronic batch record, which is why I raised the concerns in FDA 483 Observation 3a & 3b. I had observed inspection for leaks at the CMAT stage and the AMAT stage, but the inspection was not documented concurrently in the electronic batch record.

Discussion with Management: The firm voiced no objection to this Form FDA-483, Inspectional Observations.

4. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established or followed. Specifically,

On 10/08/2020, we observed the aseptic filling of drug product (DP) Lot (b) (4) in the (b) (4), Rm (b) (4). We observed the following deficient aseptic practice.

a) We observed an aseptic verifier (b) (4) his gloves with (b) (4) before performing personnel monitoring (PM) of his gloves. SOP-000567, entitled "ISO (b) (4) Environmental Monitoring and ISO (b) (4) Personnel Monitoring", V10.0, section 15.2 states (b) (4).

b) We also observed an aseptic operator performing viable surface monitoring of the (b) (4). For each sample collected, the operator (b) (4). After completing the surface monitoring, he proceeded to perform PM of his gloves. SOP-000567, entitled "ISO (b) (4) Environmental Monitoring and ISO (b) (4) Personnel Monitoring", V10.0, section 13.6 states (b) (4).

(EL)

Supporting Evidence, Background, and Discussion:

This item was discussed with (b) (6) (Supervisor, Manufacturing) during the manufacture walkthrough inspection and with Mr. Jeffrey L. Masten (VP and Quality Site Head) in the conference room.

On 10/08/2020, while standing in the Exit Corridor Rm (b) (4), through a glass window I observed the aseptic filling of DP Lot (b) (4) inside the ISO (b) (4) in the (b) (4) , Rm (b) (4). At the conclusion of the aseptic final fills, I observed aseptic verifier (b) (6) (b) (4) his gloved hands with (b) (4) prior to reaching into the ISO (b) (4) to perform left and right gloved finger dabs using (b) (4) . To note, the firm's written procedure prohibits (b) (4) . Specifically, SOP-000567, entitled "ISO (b) (4) Environmental Monitoring and ISO (b) (4) Personnel Monitoring", V10.0, effective 06/20/2020, section 15.2 states do (b) (4) **(Exhibit EL-26, page 18)**. (b) (4) is for assessing the risk to processes and products. (b) (4) ; is inappropriate because it can prevent recovery of microorganisms that were present during an aseptic manipulation. Management acknowledged this observation. DEV-2020-03108 was initiated to address the observed deficient practice.

a) On 10/08/2020, I also observed aseptic operator (b) (6) performing PM of gloves after completing the aseptic fills. At the conclusion of the aseptic fills, I observed operator DQ conduct viable surface monitoring inside the (b) (4). A total of (b) (4) surfaces; (b) (4) , were sampled. For each sample collected, operator (b) (4) with (b) (4) After completing all the (b) (4) monitoring, he then proceeded to perform PM of his gloves using (b) (4). It is to note that DQ had handled multiple (b) (4) prior to performing PM. Similarly, using (b) (4) prior to sampling is inappropriate because it can prevent recovery of microorganisms that were present during an aseptic manipulation. Firm's written procedure also prohibits such practice. Specifically, SOP-000567, V10.0, section 13.6 states (b) (4) **(Exhibit EL-26, page 17)**. Management acknowledged this observation.

I additionally reviewed operators (b) (4) training records. Records show both had completed training in aseptic operations. However, training did not appear effective due to observed deficient practices.

Discussion with Management: The firm voiced no objection to this FDA-483 item during the close-out of the inspection.

5. Laboratory controls do not include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity. Specifically,

a) MET-000054, entitled "Bacterial Endotoxin Test Method", V8.0 is deficient in that it fails to specify the minimum time required for the adequate (b) (4) .

On 10/13/2020, we observed (b) (4) **DP lots** (b) (4) **and color assessments in the Analytical Chemistry Rm** (b) (4)**. We observed the analyst did not** (b) (4) **reference standards for** (b) (4) **assessment, she also did not** (b) (4) **test sample for color assessment. MET-001013, entitled "Appearance by Visual Inspection", V6.0, section 11.6 states** (b) (4) **. Additionally, section 11.7.1 states to** (b) (4)

(EL)

Supporting Evidence, Background, and Discussion:

This item was discussed with Ms. Tara K. Byerly (Manager, QC).

a) Bacterial endotoxin test is used for DP release. I discussed MET-000054, V8.0 with (b) (6) . Section 11.3 of the method provides requirement to (b) (4) endotoxin or (b) (4) endotoxin **(Exhibit EL-27, page 12)**. Additionally, section 12.9 of the method stipulates to prepare (b) (4) **(Exhibit EL-27, page 15)**. While the (b) (4) preparations have been established, my review revealed MET-000054, V8.0 is silent regarding the requirement for (b) (4) of (b) (4) to ensure the release of endotoxins that may have adhered to the surface of the containers, thus can result in low endotoxin recovery or give false negative test results. On 10/13/2020, I interviewed QC associate (b) (6) QC Associate II) in the Microbiology Laboratory Room (b) (4). I asked associate (b) (6) that in practice how he (b) (4) for endotoxin testing. Associate NT replied that he (b) (4) The firm has no study to show (b) (4) provides adequate (b) (4)

Management acknowledged my concern. CAPA-2020-01059 was initiated to address the observed deficiency.

The following item was discussed with Ms. Quyen L. Huynh (Director, QC Operations) and Ms. Anne L. Shandy (Director, Quality Systems) in the laboratory, and with (b) (6) (Associate

III, QC) in the conference room.

b) Appearance test is used for DP release. It is to determine the clarity and the degree of coloration in finished DP. I discussed MET-001013, entitled "Appearance by Visual Inspection", V6.0, effective 09/21/2020 with (b) (6).

On 10/13/2020, in the Analytical Chemistry Laboratory, Rm (b) (4), I observed (b) (6), Associate II, QC) performing the appearance testing for (b) (4) DP lots. I observed associate did not (b) (4) the reference standards (b) (4) as required by section 11.6 of the MET-001013. Instead, I observed her (b) (4) and comparing individual test sample to each of the (b) (4) reference standards (b) (4) of the visual inspection (b) (4) for (b) (4) assessment **(Exhibit EL-28, page 7)**.

I also observed associate (b) (6) did not (b) (4) test samples when comparing an individual sample to each reference standard as required by section 11.7.1 of MET-001013, V6.0 for color assessment. Instead, associate (b) (6) (b) (4) each test sample and standard (b) (4), and proceeded with her visual inspection. It was only when I commented on the procedure stipulated (b) (4) associate (b) (6) began to (b) (4) both the sample and standard before visual inspection **(Exhibit EL-28, page 8)**.

I reviewed associate (b) (6) training record. Record shows she is qualified in Appearance by Visual Inspection. Training did not appear effective due to observed deficient practice.

Exhibit EL-29 is the Electronic Laboratory Notebook data sheets containing color and clarity assessment results of the (b) (4) DP lots.

Management acknowledged my concerns. DEV-2020-03113 was initiated to address the observed deficiencies.

Discussion with Management: The firm voiced no objection to this FDA-483 item during the close-out of the inspection.

6. Deviations from written test procedures are not justified to assure compliance with established specifications and standards.

On 10/07/2020 in the Environmental Monitoring Laboratory Rm (b) (4), we randomly selected and inspected EM plates that had been enumerated, counts verified by a second verifier, and results recorded in LIMS earlier the same day. We observed (b) (4) of the inspected EM plates showed discrepant enumeration results. The observed discrepancies were confirmed by the firm's management.

(EL)

Supporting Evidence, Background, and Discussion:

This item was discussed with Ms. Frances Browder (Director, QC Microbiology) and Ms. Tara K. Byerly (Manager, QC).

On 10/07/2020, I conducted a walkthrough inspection of the QC Laboratories. In the Environmental Monitoring Laboratory located in Rm (b) (4), I observed stacks of EM plates sitting on the laboratory bench. I was told EM plates colony forming units (CFU) had been enumerated by (b) (6), Associate, QC) earlier the same day. A second verifier; (b) (6), Associate, QC) had just finished verifying all original enumerations and the results had been recorded in LIMS.

I randomly selected and examined EM plates. My examination revealed discrepant colony counts in (b) (4) of the plates. I showed associate (b) (6) the (b) (4) plates. He performed enumerations again and confirmed the observed discrepancies. Ms. Browder herself also performed enumerations and confirmed the discrepant results.

I additionally reviewed associates (b) (6) training in microbial enumerations. Training records show both had completed training in colony counting. However, training did not appear effective in that both (b) (6) did not correctly enumerate colony growth in (b) (4) of the examined EM plates.

I informed management that regardless of ISO classifications, and like all other QC test results, EM viable colony recoveries should be accurately enumerated, adequately verified, and appropriately reported to assure data integrity. Firm's management acknowledged my concern. DEV-2020-02989 was opened during the current audit to address the observed deficiency.

Exhibit EL-30 is a Table prepared by the firm which details the discrepant EM results. The Table contains information of sample ID, sample location, ISO classification, sample type, previous colony count, and actual colony count.

The EM discrepancies are summarized below.

- The firm recorded (b) (4) for sample (b) (4) was observed by a FDA investigator.
- The firm recorded (b) (4) for sample (b) (4) were observed by a FDA investigator.
- The firm recorded (b) (4) for sample (b) (4) were observed by a FDA investigator.
- The firm recorded (b) (4) for sample (b) (4) were observed by a FDA investigator.
- The firm recorded (b) (4) for sample (b) (4) were observed by a FDA investigator.
- The firm recorded (b) (4) for sample (b) (4) were observed

by a FDA investigator.

- The firm recorded (b) (4) for sample (b) (4) were observed by a FDA investigator.
- The firm recorded (b) (4) for sample (b) (4) CFUs were observed by a FDA investigator.

Discussion with Management: The firm voiced no objection to this FDA-483 item during the close-out of the inspection.

GENERAL DISCUSSION WITH MANAGEMENT

On 10/16/2020, the following deficiencies were discussed with the firm's individuals but were not listed on the Form FDA-483, Inspectional Observations. Deficiencies were discussed in the presence of the following individuals.

Mr. Jeffrey L. Masten, VP and Quality Site Head
Mr. Snehal Patel, Vice President, Site Head Bothell
Mr. Brett A. Johnston, Senior Director, Quality Assurance
Ms. Mary F. Mallaney, Director, Early CMC Portfolio and Technical Writing
Ms. Anne L. Shandy, Director, Quality Systems

(PR)

1. I discussed with the firm's management that current Adverse Event SOP, SOP-G-500, Adverse Event Case Processing Worldwide, dated 11Oct 2020, does not include the following criteria for reporting post-marketing adverse experiences to FDA. Specifically,

a) There is no definition of what type of Adverse Event requires submission of a post market 15-Day "Alert Report" (i.e. Serious & Unexpected, whether foreign or domestic).

b) There is no description of what type of Adverse Events are submitted to FDA for Scientific literature & Post marketing Studies.

Additionally, SOP WP-USA-704, Global Drug Safety & Risk Management, dated 09October, 2020, does not include what types of Adverse Events are to be submitted in quarterly & annual periodic reports (i.e. all serious, expected, and nonserious adverse experiences).

(EL)

1. Your firm's Quality Assurance (QA) did not fulfill its responsibility to fully review corrective actions in response to adverse mold trends. Specifically, from 2018 to 2020, adverse mold trends of the Juno Manufacturing Plant (JuMP) have been observed. As a result, a total of eight (8) deviation investigations and eight (8) CAPAs were initiated. Your CAPA effectiveness checks were inadequate in that CAPAs implementation have not been effective in preventing a recurrence of deviations.

2. SOP-000183, entitled "Cell Processing Facility Cleaning and Sanitization", V14.0, effective 05/31/2020 instructs to use (b) (4) to clean the (b) (4) . However, your firm has not sufficiently established the efficacy of disinfectant (b) (4) currently being used in the (b) (4) cleaning of the (b) (4) . The (b) (4) disinfectant efficacy study in use was conducted in Celgene S12 New Jersey site. Your firm lacks a study to show that (b) (4) is effective on your facility surfaces. Management acknowledged the observed deficiency. I was told by Mr. Masten the (b) (4) disinfectant efficacy study specific to JuMP is anticipated to begin in January 2021.

3. Written procedure was not followed. On 10/08/2020, an aseptic operator was observed to cover the (b) (4) with a (b) (4) . The operator later removed the wipe, did not allow the (b) (4) to dry, then proceeded to (b) (4) DP into the (b) (4) . SOP-001244, entitled (b) (4) Procedure for JCAR017", V5.0, effective 05/28/2020, section 8.6.1 states to (b) (4) **(Exhibit EL-31, page 5)**. Wet (b) (4) can introduce contamination to test samples. Management acknowledged my concern. DEV-2020-03100 was opened during the current audit to address the observed deficiency.

4. WIN-000149, entitled "QC Microbiology Sample Submission and (b) (4) , V7.0 allows (b) (4) samples within (b) (4) of the first (b) (4) being closed in a session **(Exhibit EL-32, page 3, section 8.4)**. However, your firm lacks hold time study to demonstrate that the (b) (4) hours hold time does not affect microbial recovery of EM samples. A Logbook summary prepared by the firm showing prolonged (b) (4) storage was collected and submitted in **Exhibit EL-33**. Management acknowledged my concern. For immediate action, Document Change (DCC-003813) has been initiated to reduce hold time from (b) (4) . The firm also commits to conduct hold time study at the Bothell facility.

5. The (b) (4) expiry has not been established. (b) (4) are being used throughout the JuMP. SOP-000129, entitled "Biological Safety Cabinet Operation and Maintenance, (b) (4) ", V10.0, effective 08/21/2020, section 8.2.3 Table 2 specifies (b) (4) being the open container expiry for (b) (4) **(Exhibit EL-34, page 4)**. The assigned (b) (4) expiration is not supported by a study to demonstrate that under normal use, the (b) (4) sterility can be maintained until or beyond the end of (b) (4) expiry.

6. Accessories for the Endotoxin assay are not suitable for their intended use. Specifically, (b) (4) are being used to store test samples. Endotoxin can adhere to (b) (4) to give false negative test results. Additionally, (b) (4) are being used for samples and (b) (4). The presence of (b) (4) in the (b) (4) can lead to false positive test results. Management acknowledged my concerns. CAPA-2020-01059 was initiated during the current audit to address the observed deficiencies.

The firm committed to sending a written response in 15 Working Days to FDA, and had no objections to any of the Form FDA-483, Inspectional Observations, or the general discussion items.

REFUSALS

No refusals were encountered.

ADDITIONAL INFORMATION

There are no vaccination or testing requirements for this site. FMD-57 was followed throughout the inspection, and masks were worn at all times due to the COVID-19 Pandemic.

SAMPLES COLLECTED

No Samples were collected.

ATTACHMENTS

Form FDA-482, Notice of Inspection

Form FDA-483, Inspectional Observations

Attachment PR1	Modified PLI Plan for JuMP BLA125714, (22 pages)
Attachment PR2	ORA_CBER List of Deviations CAPAs and Change Controls-JUMP, (2 pages)
Attachment PR3	CMC Review Document, (52 pages)
Attachment PR4	BLA125714-DMPQ Summary for JuMP Mfg Site [for ORA], (29 pages)
Attachment PR5	Assignment Info Email, dated September 24, 2020, (3 pages)
Attachment PR6	CBER/OTAT Follow-up Request, (1 page)

EXHIBITS COLLECTED

PR1	JuMP Company Overview_JCAR017 lisocabtagene maraleucel Overview, (40 pages)
PR2	JCAR017 Process Overview, (12 pages)
PR3	Approved Vendor List, Clinical Sites Approved for Leukapheresis, (9 pages)

PR4 Participant List Inspection, (9 pages)
PR5 List of Quality SOPs, (1page)
PR6 JCAR017 vial label, (1 page)
PR7 Electronic Batch Record Review, SOP-000485, dated 01Jun2020 (12 pages)
PR8 Example Collection Site Material COC, (1 page)
PR9 JuMP Manufacturing Floor Diagram (b) (4) Floor, (1page)
PR10 DEV-2019-03442 Summary, (14 pages)
PR11 (b) (4) . CoA and Test Result Analysis, (6 pages)
PR12 Containment Area Release Memo, DEV-2019-03442, date 20DEC19, (6 pages)
PR13 QC Micro Lab Response to (b) (4) in Raw Material, dated 15Jan2020, (4 pages)
PR14 (b) (4) Statement on (b) (4), DEV-2019-03442, (10 pages)
PR15 (b) (4) Specifications, dated 31July2020, (11 pages)
PR16 (b) (4) Test Method for (b) (4) Testing, (5 pages)
PR17 (b) (4) testing summary, (2 pages)
PR18 (b) (4) COA for (b) (4)) Lot (b) (4) , (6 pages)
PR19 DEV-2019-03442 Attachment 9. (b) (4) Clinical Impact Analysis, (1 page)
PR20 DEV-2019-03442 Attachment 10. (b) (4) Executive Summary, (2 pages)
PR21 Quality Agreement between Celgene/Juno and (b) (4) , (16 pages)
PR22 DCR-2019-10831 Overview, (23 pages)
PR23 Global Deviation Management SOP-001145, dated 07Jun2019, (20 pages)
PR24 SOP 001151, Global CAPA Management, dated 17Dec2018, (20 pages)
PR25 Raw Materia Certification and (b) (4) Testing, SOP1148, dated 20June2020, (7 pages)
PR26 Manufacturing Material Visual Inspection SOP000512, dated 20Jun2020 , (17 pages)
PR27 Deviation Severity Classification Strategy Overview, (5 pages)
PR28 DEV-2020-02527 Summary, (4 pages)
PR29 DEV-2020-02599 Overview, (8 pages)
PR30 DEV-2020-02726 Overview, (4 pages)
PR31 SOP-000236 Microbial Contamination Response, 02April2020, (11 pages0
PR32 Changeover Procedure, SOP-000186, dated 21Aug2020, (10 pages)
PR33 Gowning Procedure at JuMP, SOP-000131, dated 15Sep2020, (16 pages)
PR34 JCAR017 Microbial Contamination DEV-2019-03089 Trend Summary, (10 pages)
PR35 (b) (4) Contamination Customer Report for DEV-2019 -03089, (10 pages)
PR36 Electronic Batch Record Printouts, where Visual Inspection (b) (4) in-process material was conducted, (4 pages)
PR37 JCAR017 Process Overview, Material Inspection, (5 pages)
PR38 CMAT (b) (4) Leak Awareness Presentation, (9 pages)
PR39 DEV-20200-0300 (b) (4) Leak Trend Investigation Overview, (12 pages)
PR40 (b) (4) (CMAT) and (b) (4) (AMAT) Diagrams, (3 pages)
PR41 Lot Numbering Overview Description, (1 page)
PR42 Lot Distribution List, (4 pages)
PR43 Aseptic Process Simulation(APS) Presentation, (8 pages)
PR44 Juno Floor Diagram (b) (4) Floor), (2 pages)
PR45 History of Business Summary, (1 page)

PR46 JCAR017 eBR CMAT Receipt, (2 pages)

EXHIBITS COLLECTED

Exhibit	Description	Pages
EL-1	Participant List of People Interviewed by Eileen Liu	5
EL-2	Opening Meeting Participants	1
EL-3	BMS JuMP Bothell Site Leadership and Quality Leadership Team	8
EL-4	Opening Meeting Presentation	40
EL-5	QMS-OCD-IntgPlan (012881), effective 11/15/2019	14
EL-6	QMS-OCD-QMS Intg (012731), effective 07/10/2020	12
EL-7	BMS QMS Integration Activities Completed "To Date" 10/13/2020	55
EL-8	Contract Services Provider (CSP) Oversight for Viral Vector	6
EL-9	SOP-001491, entitled "Global Vendor Quality Management", V4.0	9
EL-10	SOP-001445, entitled "Global Quality Agreement Process", V10.0	10
EL-11	SOP-001376, entitled "JuMP Release for Infusion and Product Distribution", V2.0, effective 09/29/2020	14
EL-12	SOP-001377, entitled "JuMP Final Product Disposition", V2.0, effective 07/18/2020	8
EL-13	SPC-001271, entitled "Specification: Breyanzi® Drug Product, US. Adult", V3.0, effective date pending	11
EL-14	Overview: (b) (4) Lentiviral Vector Lot Disposition	7
EL-15	Request for Exception from the Sample Retention Plan	1
EL-16	RPT-001088, entitled "ISO(b) (4) Environmental Monitoring Risk Assessment Summary Report", V1.0, effective 02/12/2020	17
EL-17	DEV-2019-02289 Cryopreservation Mold Adverse Trend	6
EL-18	Overview of Mold	13
EL-19	A Compilation of Mold Recoveries Corrective and Preventative Action	7
EL-20	Mold Identification from ISO Areas, 10/01/2019 to 09/30/2020	6
EL-21	Mold Excursion in OORs	4
EL-22	DEV-2020-02629	8
EL-23	Facility Mold Control Strategy	4
EL-24	Quality Control Overview Presentation	8
EL-25	(b) (4) Measurement Performed	2

EL-26	SOP-000567, entitled "ISO (b) (4) Environmental Monitoring and ISO (b) (4) Personnel Monitoring", V10.0, effective 06/20/2020	32
EL-27	MET-000054, entitled "Bacterial Endotoxin Test Method", V8.0, effective 07/13/2020	31
EL-28	MET-001013, entitled "Appearance by Visual Inspection", V6.0, effective 09/21/2020	12

EL-29	(b) (4) DP Lots tested for Color and Clarity Assessment	3
EL-30	EM Enumeration Discrepancy Table	1
EL-31	SOP-001244, entitled "(b) (4) Procedure for JCAR017", V5.0, effective 05/28/2020	13
EL-32	WIN-000149, entitled "QC Microbiology Sample Submission and (b) (4), V7.0	7
EL-33	EM Plate Submission and (b) (4) Details	1
EL-34	SOP-000129, entitled "Biological Safety Cabinet Operation and Maintenance, (b) (4) V10.0, effective 08/21/2020	26

x Prabhu P. Raju -S

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Prabhu P. Raju
Investigator

x Eileen A. Liu -S

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Eileen Liu
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