

CBER CMC BLA Review Memorandum

BLA STN 125714/0

lisocabtagene maraleucel

BREYANZI

Reviewer/Title/Affiliation

Rabia Ballica, PhD, Reviewer, CBER/OCBQ/DMPQ

1. **BLA#:** STN 125714/ 0

2. **APPLICANT NAME AND LICENSE NUMBER**

Juno Therapeutics, Inc., a Celgene Company

3. **PRODUCT NAME/PRODUCT TYPE**

Non-Proprietary/Proper/USAN: lisocabtagene maraleucel

Proprietary Name: BREYANZI

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

a. Pharmacological category: Cell

b. Dosage form: Cell Suspension for Infusion

c. Strength/Potency [the concentration of drug product, type of potency assay(s)]
Target 100 x 10e6 CAR-positive viable T cells

d. Route of administration: Intravenous Infusion

Indication(s): Treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least 2 prior therapies.

5. **MAJOR MILESTONES**

Rolling BLA; CMC section received December 18, 2019

Filing Meeting February 01, 2020

Major Amendment April 15, 2020

Mid-cycle meeting July 18, 2020

Late-cycle meeting September 01, 2020

Inspection conducted-Juno (JuMP) site: October 07-16, 2020

Inspection conducted-(b) (4) site: Pre-license inspection (PLI) could not be performed during BLA review cycle due to COVID-19 public health emergency with the infection rates in local area.

Inspection conducted-(b) (4) site: Inspection waived

PDUFA Date: November 16, 2020

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Rabia Ballica, PhD CBER/OCBQ/DMPQ/Branch I	3. Quality 3.2.S Drug Substance (as per CBER *SOPP 8401.4) 3.2.P. Drug Product (as per CBER *SOPP 8401.4) 3.2.A.1. Facilities and Equipment (as per CBER *SOPP 8401.4)

*SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications, New Drug Applications and Supplements
Version 2.0, Effective Date: March 19, 2019

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No ¹)
N/A	N/A	N/A

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
12/18/2019	STN 125714/0.2	Module 3. Quality Submission
02/07/2020	STN 125714/0.8	Module 3. Quality Amendment on (b) (4) manufacturing at (b) (4) facility
02/26/2020	STN 125714/0.13	Module 3. Quality CAR-T cell manufacturing at Juno facility
02/28/2020	STN 125714/0.14	Module 3. Quality (b) (4) manufacturing at (b) (4) facility
03/09/2020	STN 125714/0.16	Module 3. Quality (b) (4) manufacturing at (b) (4) facility
03/26/2020	STN 125714/0.22	Module 3. Quality CAR-T cell manufacturing at Juno facility and (b) (4) manufacturing at (b) (4) facility
04/07/2020	STN 125714/0.26	Module 3. Quality (b) (4) manufacturing at (b) (4) facility
04/27/2020	STN 125714/0.34	Module 3. Quality CAR-T cell manufacturing at Juno facility and (b) (4) manufacturing at (b) (4) facility

Date Received	Submission	Comments/ Status
06/19/2020	STN 125714/0.53	Module 3. Quality Amendment in response to the pre-inspection records request for Juno (JuMP) manufacturing facility (as per 704(a)(4))
06/29/2020	STN 125714/0.54	Module 3. Quality Amendment in response to the pre-inspection records request for (b) (4) manufacturing facility (as per 704(a)(4))
07/17/2020	STN 125714/0.36	Module 3. Quality CAR-T cell manufacturing at Juno facility and (b) (4) manufacturing at (b) (4) facility
07/21/2020	STN 125714/0.57	Module 3. Quality CAR-T cell manufacturing at Juno facility
10/05/2020	STN 125714/0.74	Module 3. Quality Amendment in response to the second round of the pre-inspection records request for Juno (JuMP) manufacturing facility (as per 704(a)(4))
10/07/2020	STN 125714/0.77	Module 3. Quality Amendment in response to the second round of the pre-inspection records request for (b) (4) manufacturing facility (as per 704(a)(4))

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
BLA 125714/0	Juno Therapeutics, Inc.	N/A	N/A	Module 3. Quality
CBER Master File (b) (4)	(b) (4)	(b) (4) Closed System Cryogenic Vial	Yes	Information pertinent to container closure is provided in the BLA
CBER Master File (b) (4)	(b) (4)	(b) (4) Cell and Gene Therapy Facility	Yes	Information pertinent to (b) (4) Gene Therapy Facility

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The reviewed and evaluated information under DMPQ purview (as per CBER SOPP 8404.1) appears acceptable. All the identified deficiencies were addressed with the amendments in response to information requests. The review of the records provided in response to the pre-inspection records requests (as per 704(a)(4)) was also performed and this review was documented in a separate memo (records review memo) for each of the inspection sites (b) (4) JuMP). However, due to the ongoing COVID-19 pandemic restrictions, all of the pre-license inspections have not been completed yet. The outcome of the inspections and its impact on the BLA review will be documented in an addendum memo.

The pre-license inspection of JuMP facility located in Bothell, WA was conducted for the manufacture of lisocabtagene maraleucel product from October 7 – October 16, 2020 by the local ORA investigators and a FDA Form 483 was issued with 6 observations. The classification and final outcome for this inspection was not decided or readily available ahead of the ADD (Approval Due Date).

The pre- license inspection of (b) (4) facility located in (b) (4) has not been inspected yet for the manufacture of the (b) (4). The

inspection could not be performed during the review cycle of the BLA due to the COVID-19 situation in the local area.

The inspection of (b) (4) site where the (b) (4) vector is manufactured (fill/finish) was waived based on the previous CBER inspection history and the information provided in the original BLA submission and its amendments (refer to the inspection waiver memo).

A. RECOMMENDATION

A final recommendation cannot be determined yet until the inspections have been completed. A recommendation will be noted in the addendum memo(s) once the impact to the BLA can be assessed from the 483 observations, if any, noted during the pre-license inspections.

I. APPROVAL

II. COMPLETE RESPONSE (CR)

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Rabia Ballica, PhD CBER/OCBQ/DMPQ/BI	Concur	
Carolyn Renshaw, Branch Chief OCBQ/DMPQ/BI	Concur	

Review of CTD
Table of Contents**Module 3**

Tables, diagrams and figures included in this memo are copied directly from the submission (unless otherwise is noted).

3.2.S DRUG SUBSTANCE²**3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties**

Deferred to the Product Office.

3.2.S.2 Manufacture**3.2.S.2.1 Manufacturer(s)**

Table. Manufacturing and Testing Facilities (not copied directly from the submission)

Facility	Responsibilities	Inspection History
Juno Therapeutics Inc. 1522 217th Pl. SE Bothell, WA 98021, USA FEI: 3011834594; DUNS: 079941307	-Drug Substance (DS) and Drug Product (DP) Manufacturing -Primary and Secondary Packaging -DP Release and Stability Testing -Lentiviral Vector DP (b) (4)	ORA pre-license inspection (PLI) October 7-16, 2020 (inspection classification not available at the time of ADD due to timing of the inspection in the review cycle)
(b) (4) FEI: (b) (4) DUNS: (b) (4)	(b) (4)	CBER PLI (postponed due to COVID-19 pandemic)

² For a drug product containing more than one drug substance, the information requested for section "S" should be provided in its entirety for each drug substance.

3.2.S.2.2 Description of Manufacturing Process

Drug Substance - (b) (4) Lentiviral Vector Manufacturing Processes

The JCAR017 CAR construct is delivered via a lentiviral vector (b) (4), which was designed to consistently deliver the CAR construct to T cells for stable integration into the genome. This viral vector is designed to be replication incompetent. (b) (4) is manufactured at (b) (4) contract manufacturing facility, (b) (4) is manufactured at (b) (4) contract manufacturing facility in (b) (4).

1) (b) (4) manufacturing process

(b) (4) is manufactured using a (b) (4)



2) (b) (4) manufacturing process

The (b) (4) manufacturing process consists of (b) (4)



(b) (4)

Drug Substance – JCAR017 (lisocabtagene maraleucel) Manufacturing Process

Drug substance (DS) and drug product (DP) are manufactured using single use product contact equipment at Juno's (JuMP) manufacturing site located in Bothell, WA.

1) Drug substance manufacturing

Patient leukapheresis product is collected at the clinical site and then shipped using a qualified shipper to the manufacturing facility for CAR-T cell manufacturing. T cells are purified (b) (4)

(b) (4)

(b) (4)

(b) (4)

the drug product components, CD4+ and CD8+ as described in section 3.2.P.3.3.

2) **Drug product manufacturing**: Also refer to section 3.2.P.3.3 in this memo.

The (b) (4)

the cryopreservative CS10 using (b) (4) CS10 is added to achieve a final CS10 concentration of 75%.

Formulated drug product (b) (4) drug product cryopreservation vials (5 ml) using syringes. Filled vials (closed system primary packaging system) are frozen using a controlled rate freezer. The CD4+ and CD8+ drug components are cryo-stored and shipped in a qualified liquid nitrogen (LN2) shipper to clinical site to be administered to the patient.

□ **Manufacturing process steps**

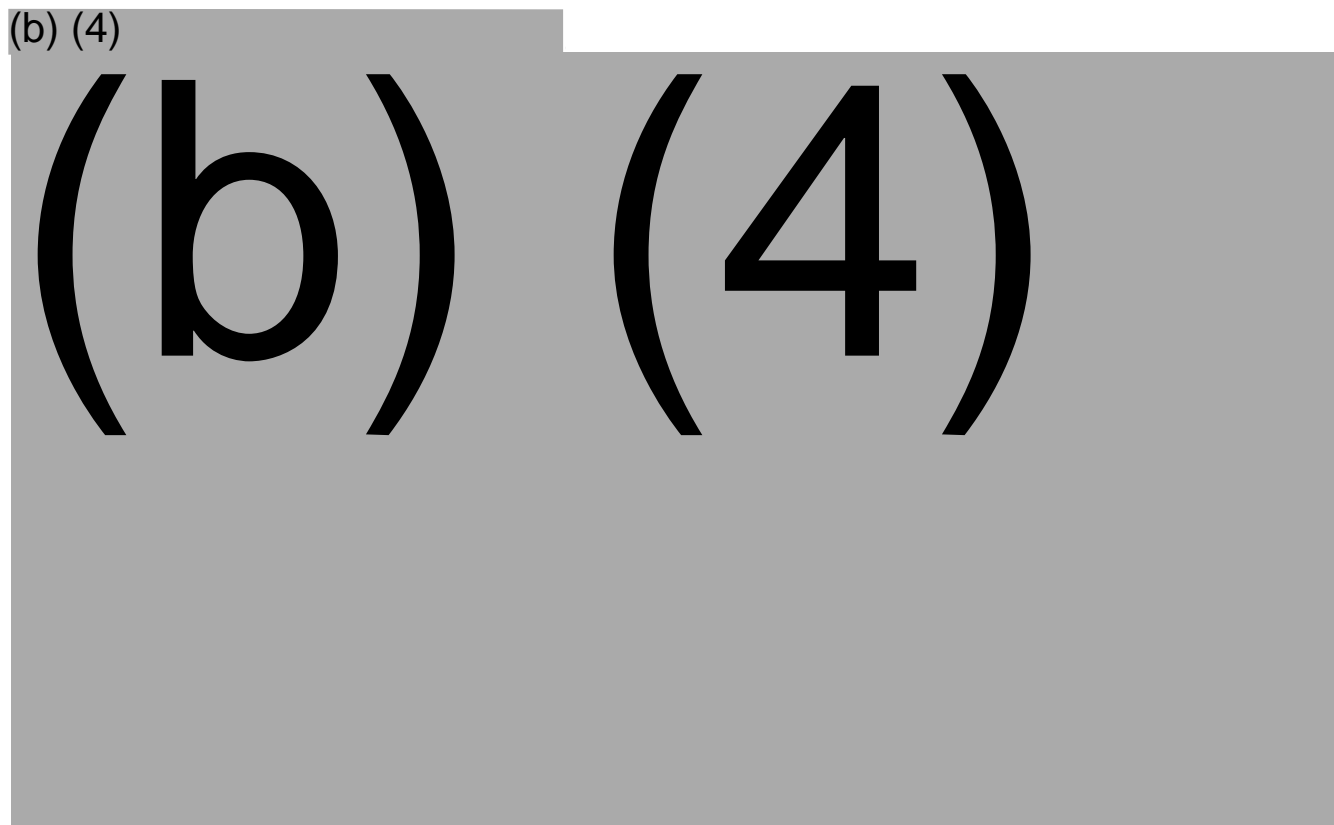
Drug Substance - (b) (4) Lentiviral Vector Manufacturing Process Steps

The manufacturing process steps for (b) (4), which are described in section above, are illustrated in the manufacturing process flow diagram below along with in process controls and critical process parameters (3.2.S.2. Manufacture).

JCAR017 (lisocabtagene maraleucel) Manufacturing Process Steps

The following JCAR017 process overview illustrates DS and DP manufacturing steps process steps (copied directly from the presentation given during the JuMP PLI inspection).

(b) (4)

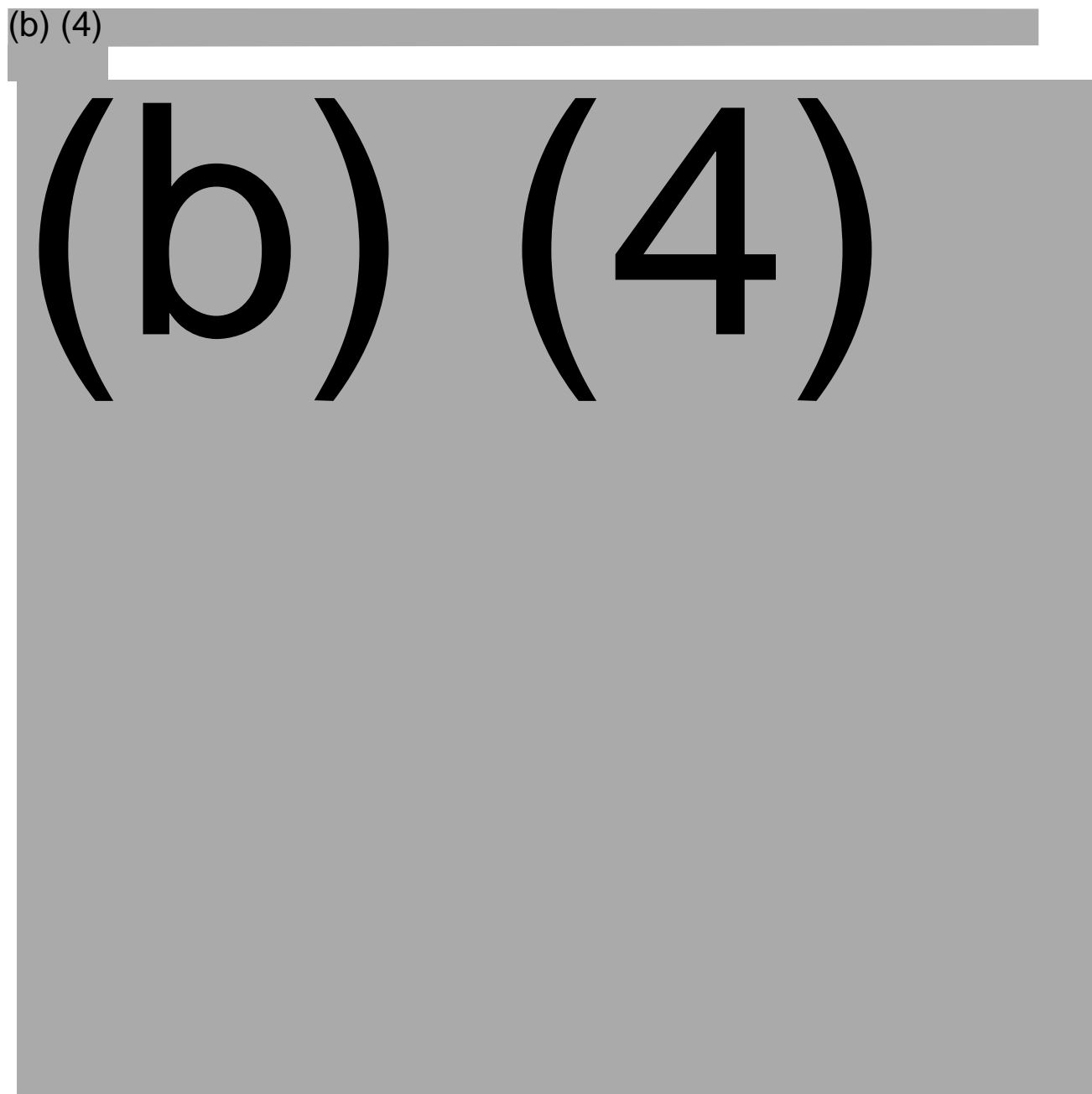
**1) Drug substance manufacturing process steps**

JCAR017 (lisocabtagene maraleucel) consists of (b) (4)



The following manufacturing process flow diagram illustrates the DS manufacturing steps along with in process controls and critical process parameters (3.2.S.2. Manufacture).

(b) (4)



- 2) **Drug product manufacturing process steps**: Also refer to section 3.2.P within this memo.

The following manufacturing steps described earlier in this section are illustrated along with in process controls and critical process parameters in the following diagram.

(b) (4)

(b) (4)

❑ **Batch Numbering, Pooling and Scale Definition**

Defer to Product Office. Refer to the PO CMC review memo.

❑ **Storage and Shipping**

(b) (4) shipping and storage:

(b) (4) are stored at (b) (4). The shipping validation for (b) (4) supports the shipping conditions at temperatures of (b) (4) from time of pack out completion (e.g., shipper closure) on dry ice under the real-world shipping conditions. The shipping validation for (b) (4) supports the shipping conditions at temperatures of (b) (4) from time of pack out completion (e.g., shipper closure) on dry ice under the real-world shipping conditions. For the shipping validations, refer to section 3.2.S.2.5.

JCAR017 shipping and storage:

JCAR017 (lisocabtagene maraleucel) drug product consists of CD8+ and CD4+ components, each is independently cryopreserved in (b) (4) at $\leq -130^{\circ}\text{C}$ in vapor phase of liquid nitrogen. (b) (4)

(b) (4) For the shipping validations, refer to sections 3.2.S.2.5. and 3.2.P.3.5 in this memo.

3.2.S.2.3 Control of Materials

□ Control of Raw Materials NOT of Biological Origin

For detailed information on the controls of single use materials, refer to sections 3.2.a.1 “Facilities and Equipment”, 3.2.S.6, 3.2.P.7, 3.2.S.2.5 and 3.2.P.3.5.

(b) (4)

(b) (4)

(b) (4)

Single use containers and product contact equipment were purchased from the qualified vendors and qualified in house through aseptic process simulations (APSS), equipment qualifications and process characterization studies (where applicable).

The (b) (4) were accepted based on the certificate of analysis (COA). For detailed information on the single use materials used in the (b) (4)

(b) (4) manufacturing, refer to 3.2.a.1 “Facilities and Equipment” for (b) (4) facilities and sections 3.2.S.6, 3.2.S.2.5 and 3.2.P.3.5.

For the information on the (b) (4) for the single use materials and the control of the (b) (4) used in the (b) (4) manufacturing, refer to the Product Office (PO) CMC review memo.

Control of materials for JCAR017 manufacturing (single use materials):

Single use bags, vials and product contact equipment were purchased from the qualified vendors and qualified in house through aseptic process simulations (APSs), equipment qualifications and process characterization studies (where applicable).

Single use materials are accepted based on the qualified supplier’s/manufacture’s certification documentation and visually inspected as per:

-SOP-000220 “Visual Inspection of Incoming Material” (Version 8.0, Effective Date 27 Apr 2020) that was provided in the **June 19th Amendment** in response to the pre-inspection records request, and

-SOP-000512 “Manufacturing Material Visual Inspection” (Version 5.0, Effective Date 20 Jun 2020) that was provided in the **October 5th Amendment** in response to the second round of the pre-inspection records request.

SOP-000512 applies to the inspection of raw, intermediate, and formulated drug product (FDP) materials for foreign particulates and defects.

SOP-000112 Receipt and Control of Incoming Materials is used for the receipt and release of materials for use in manufacturing and testing at the JuMP warehouse.

(b) (4)

“Container Closure Integrity

Testing (b) (4)” (Version 1.0, Effective Date 05 Nov 2019) that was provided in the **October 5th Amendment** in response to the second round of the pre-inspection records request. Additionally, for in house visual inspection of (b) (4)

. This record was also provided in the **October 5th Amendment**.

SOP-001347 Visual Inspection of JCAR017 Final Drug Product (Version 2.0, Effective date 24 Apr 2020) that was provided in the **June 19th Amendment** is used for the pre-use visual inspection of the drug product vials. (b) (4) vials (the final product vials) is integrity tested and visually inspected.

For the information on the extractables/leachables for the single use materials and the control of the formulated media, reagents and buffers used in the JCAR017 manufacturing, refer to the Product Office (PO) CMC review memo.

❑ **Control of Raw Materials of Biological Origin**

Deferred to the Product Office. Refer to the PO CMC review memo.

❑ **Control of Starting (i.e., Source) Material(s)**

Deferred to the Product Office. Refer to the PO CMC review memo.

(b) (4) site.

(b) (4) on Leukophersis product is performed for the presence of microorganisms at JuMP (Juno) manufacturing site.

❑ **Generation of the (b) (4)**

Deferred to the Product Office. Refer to the PO CMC review memo.

❑ **Cell Banking System - Generation, Characterization, and Testing**

Deferred to the Product Office. Refer to the PO CMC review memo.

❑ **Master and Working (b) (4)**

Deferred to the Product Office. Refer to the PO CMC review memo.

Overall Reviewer's Assessment of Section 3.2.S.2.3:

- ❑ The information on the controls of single use materials used in the (b) (4) and JCAR017 manufacturing that were submitted in the original BLA submission and amendments is adequate. The reviewed information was confirmed for the single use materials used at Juno manufacturing site during the pre-inspection inspection of this site and will be confirmed during the pre-license inspection of (b) (4).
- ❑ Starting materials are tested for the presence of microorganisms at (b) (4) Juno.

3.2.S.2.4 Controls of Critical Steps and Intermediates

Controls of Critical Steps and Intermediates for (b) (4)

Critical process parameters (CPPs) are monitored and controlled as summarized in the following tables (3.2.S.2. Manufacture). (b) (4) manufacturing process flow diagram, CPPs and tests, refer to Figure in section 3.2.S.2.2.

Container closure integrity tests listed above (b) (4)

(b) (4) and described in SOP "RPT-001752 Container Closure Integrity Testing and (b) (4)", (Version 1.0, Effective Date 05 Nov 2019. Those SOPs were reviewed and found acceptable. For additional information, refer to the record review memo for Juno (JuMP) manufacturing site.

Overall Reviewer's Assessment of Section 3.2.S.2.4:

- From the DMPQ review standpoint, the information provided is acceptable as submitted in the original BLA submission and amendments (submitted in response to the BLA review associated information requests and pre-inspection records requests).
- 483 observation item #3 was issued for the lack of a (b) (4) during manufacturing, because there was no instruction on the batch records to perform in process (b) (4). Refer to the FDA Form 483 for the JuMP pre-license inspection - conducted from October 7-16, 2020. Note the firm's response to the 483 observations will be reviewed when received and the outcome and its impact on the BLA review will be documented in an addendum memo.


3.2.S.2.5 Process Validation and/or Evaluation

- DMPQ review and evaluation of facility design, and equipment and utility qualification are documented in 3.2.A.1.

Process Performance Qualification (PPQ)

- For detailed information on PPQ designs and associated results, refer to the product office memo. As summarized below, results for PPQ lots manufactured at (b) (4) met in process and release specifications for endotoxin and sterility and quality attributes (under the PO purview). For PPQ lots manufactured at Juno, refer to section 3.2.P. within this memo.



(b) (4)



(b) (4)



(b) (4)







3) PPQ for Cell Product

Refer to section 3.2.P.3.5 in this memo.

**Aseptic Process Validation (APS)
for (b) (4) Manufacturing**

(b) (4)



(b) (4)

(b) (4)

APS Validation for JCAR017 Drug Substance

Refer to the 3.2.P.3.5 section within this memo.

Amendments Reviewed for APS Conducted at (b) (4)

1) January 16th Amendment (b) (4)

The firm provides an update for the facility modifications discussed at the October 29th and November 19th (2019) teleconferences. For the inspection readiness that was discussed during those 2019 teleconferences, the table below provides a list of the items and a status update for those completed by 31 December 2019:

- (b) (4)

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Leukapheresis Product (Starting Material) - Storage and Shipping

(b) (4) components are not stored and shipped. But, starting material Leukapheresis product is shipped from the collection site to Juno manufacturing site. The validation of this shipping is summarized below:

(b) (4)

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.S.2.5:

- ❑ The information under DMPQ purview is acceptable.
- ❑ Deficiencies were identified and associated amendments in response to information requests for deficiencies were reviewed and evaluated. As documented above, all the deficiencies were addressed and there are no outstanding review issues. However, issues could be identified during the (b) (4) inspection which could impact the review outcome.



3.2.S.2.6 Manufacturing Process Development

- For detailed information on the manufacturing process development, refer to the PO CMC memo.

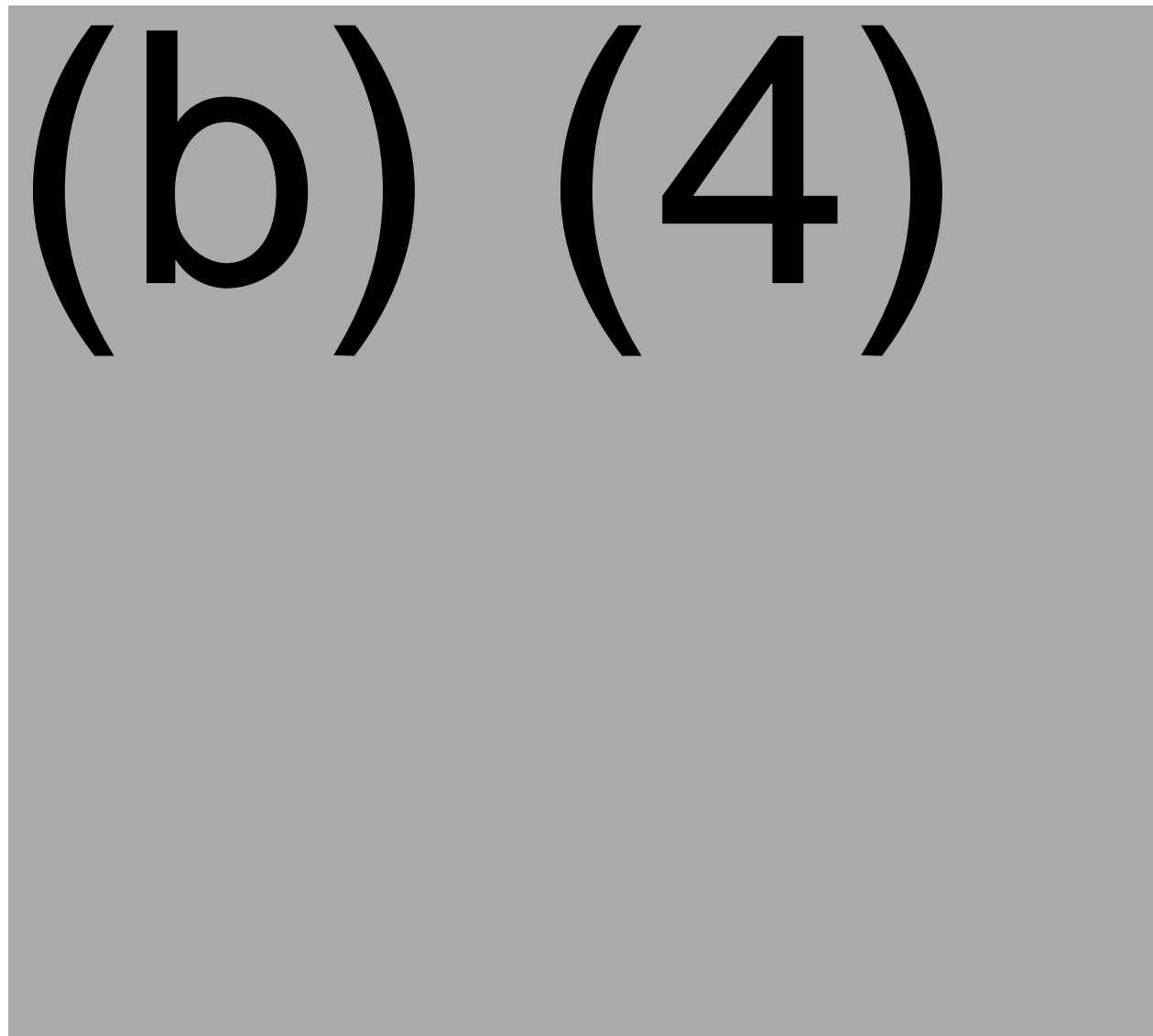
(b) (4)

(b) (4)

(b) (4)



(b) (4)



2) CAR-T Cell Product Manufacturing Process Development

Refer to section 3.2.P.2.6 within this memo.

Overall Reviewer's Assessment of Section 3.2.S.2.6:

- ☐ The information provided (under DMPQ purview) is acceptable as submitted.

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and Other Characteristics

Deferred to the Product Office. Refer to the PO CMC review memo.

3.2.S.3.2 Impurities

Deferred to the Product Office. Refer to the PO CMC review memo.

Overall Reviewer's Assessment of Sections 3.2.S.3.1 and 3.2.S.3.2

- The assessment of the information provided is deferred to the Product Office

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)

- Detailed information on specifications and associated justifications, refer to the PO CMC memo.

Release specifications for (b) (4) under DMPQ purview are sterility (no growth) and endotoxin (b) (4).

In-process testing for (b) (4) is described in section 3.2.S.2.4 Controls of Critical Steps and Intermediates within this memo.

For release and in process specifications for CAR-T cell DS and DP, refer to 3.2.P section within this memo.

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Sections 3.2.S.4.1 and 3.2.S.4.5:

- ❑ The information provided (under DMPQ purview) is acceptable as submitted.
- ❑ Release testing under DMPQ purview is adequate: Sterility testing is performed on (b) (4) are also performed at release.

3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures
Deferred to the Product Office. Refer to the PO CMC review memo.

Overall Reviewer's Assessment of Sections 3.2.S.4.2 and 3.2.S.4.3:

- ❑ The assessment as to whether validation is adequately performed to assure that methods are suitable for their intended purpose is deferred to the Product Office.

3.2.S.4.4 Batch Analyses

- Detailed information on batch analysis, refer to the PO CMC review memo.

(b) (4) **Manufacturing History**

Table. (b) (4) Lot History (b) (4)

(b) (4)

(b) (4) batch analysis data on the following lots manufactured at (b) (4) was provided in the batch analysis section for (b) (4)

Engineering/Development Lots were (b) (4)

PAD lots in that testing per specification is not required for development or engineering runs.

GMP lots were (b) (4)

All those lots met the release specifications for (b) (4).

Overall Reviewer's Assessment of Section 3.2.S.4.4:

- ☐ The information provided (under DMPQ purview) is acceptable as submitted.

3.2.S.5 Reference Standards or Materials

Deferred to the Product Office. Refer to the PO CNC review memo.

Overall Reviewer's Assessment of Section 3.2.S.5:

- ☐ The assessment as to whether the information provided is acceptable as submitted is deferred to the Product Office.

3.2.S.6 Container Closure System

- E&L studies and data as it pertains to safety and product quality is deferred to the Product Office.
- Shipping validation were included in section 3.2.S.2.5 Process Validation within this memo.

1) (b) (4) **Container Closure System**

The primary container closure system for the (b) (4) consists of a (b) (4)

(b) (4)

(b) (4)

(b) (4)

There are other SOPs that apply to the visual inspection of materials:

- 1) SOP-001347, Visual Inspection of JCAR017 Final Drug Product (Version 2.0, Effective date 24 Apr 2020) that applies to the visual inspection of the drug product vials (provided in the **June 19th Amendment**).
- 2) SOP-000220, Visual Inspection of Incoming Material (Version 8.0, Effective date 27 Apr 2020) that applies to incoming materials received at Juno (provided in the **June 19th Amendment**).

Overall Reviewer's Assessment of Section 3.2.S.6:

- The information provided (under DMPQ purview) appeared acceptable. The pre-inspection records provided additional information on the quality control of the single use materials, particularly the (b) (4) used for the storage of in process selected (b) (4) as described above. There are no outstanding review issues.
- Note, a Form FDA 483 issued for the inspection of JuMP facility had 6 observation items and one of them (observation #3) was related to the visual inspection of the (b) (4). The response to the 483 observations will be reviewed when received.

3.2.S.7 Stability**3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data****(b) (4) Lentiviral Vector Stability**

(b) (4) are stored at (b) (4)

Stability studies have been conducted at the recommended storage condition of (b) (4) and at the stressed temperature conditions to assess the shelf life of (b) (4). The table below lists the lots were placed on stability.

(b) (4)

(b) (4)

For the additional time point data, refer to the PO CMC memo. Note the expiry date (b) (4) falls into 2021.

Table. Stability Protocol for (b) (4)

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

Cell Product Stability

For CAR-T Cell Stability, refer to section 3.2.P.7 in this memo.

3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment

The firm provided a post-approval commitment statement. The results of the ongoing stability studies (listed in the table above) will be submitted in annual report to the BLA file. For additional information, refer to the PO CMC memo.

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

- ❑ The information provided (under DMPQ purview) is acceptable as submitted. As per the stability protocol, sterility testing is performed at (b) (4) and CCIT is performed at the months of (b) (4), which is acceptable. Sterility results at release met the acceptance criteria at release ((b) (4) and CCIT data is not available yet.
- ❑ The evaluation of the (b) (4) lentiviral vector stability protocol and available data is deferred to the Product Office.

3.2.P DRUG PRODUCT³

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

The JCAR017 (lisocabtagene maraleucel) drug product consists of two separate components, a cryopreserved CD8+ T cell suspension and a cryopreserved CD4+ T cell suspension for intravenous administration. The cryopreserved CD8+ and CD4+ T cell suspensions are individually formulated (b) (4). Each CD4+ and CD8+ suspension is filled separately into cryogenic vials composed (b) (4) (4 vials per drug product component). The extractable volume is 4.6 ml from 5 ml fill volume.

³ For a Drug Product with more than one dosage form, the information on each dosage form should be provided in a separate "P" section, as appropriate.

Table. Target Concentration of Constituents per Drug Product Container

Constituent	Quality Standard/ Grade	Function	Target Concentration (Cryopreservation vial)
CAR+ viable T Cells	In-house	Active	(b) (4) CAR+ viable T cells/mL ^a
Cryostor® CS10 (containing (b) (4) DMSO)	In-house	(b) (4)	75% [v/v] ^b
Multiple Electrolytes Injection, Type I	(b) (4)	(b) (4)	(b) (4) [v/v]
Albumin (Human) Solution (25% Albumin)	(b) (4)	(b) (4)	(b) (4) [v/v] ^c

^aExtractable volume: 4.6 mL per vial^bFinal DMSO concentration in drug product is 7.5%.^cFinal Albumin concentration in drug product is (b) (4). DMSO = dimethylsulfoxide; v/v = volume per volume

For information on allowable component dose volume calculations, refer to the PO CMC memo.

The planned commercial drug product vial configuration consists of a cryopreservation vial with a 5 mL fill volume, that includes a 0.4 mL excess to permit a 4.6 mL maximum extractable volume.

The accuracy and precision of extracting and delivering specific volumes of the JCAR017 drug product was assessed using a 20-gauge needle and a syringe size typical of commercial use (1 mL, 3 mL and 5 mL (b) (4) syringes).

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The JCAR017 (lisocabtagene maraleucel) drug substance (b) (4), which are processed further to manufacture the drug product without storage (refer to the manufacturing process flow diagrams in this memo).

3.2.P.2.1.2 Excipients

Table. Excipients Used in JCAR017 Drug Product

Excipient	Function	Final Concentration	Quality Standard/ Grade
Cryostor® CS10 (containing (b) (4) % DMSO)	(b) (4)	75% [v/v] ^a	In-house
Multiple Electrolytes Injection, Type I	(b) (4)	(b) (4) [v/v]	(b) (4)
Albumin (Human) Solution (25% Albumin)	(b) (4)	(b) (4) [v/v] ^b	(b) (4)

^aFinal DMSO concentration in drug product is 7.5%

^bFinal Albumin concentration in drug product is (b) (4) DMSO: dimethylsulfoxide; v/v: volume per volume

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Deferred to the Product Office. Refer to the PO CMC memo.

3.2.P.2.2.2 Overages

The JCAR017 drug product does not contain any overages.

3.2.P.2.2.3 Physicochemical and Biological Properties

Deferred to the Product Office. Refer to the PO CMC review memo.

3.2.P.2.3 Manufacturing Process Development

- For detailed information on the manufacturing process development, refer to the PO CMC memo.
- The following table lists pre- commercial and proposed drug product manufacturing process versions.

(b) (4)

(b) (4)

(b) (4)

3.2.P.2.4 Container Closure System

- Review and evaluation of E&L studies and data as it pertains to safety and product quality is deferred to the Product Office.

Container Closure Systems for CART- Drug Product (primary and secondary)

Primary Packaging System

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 four 5ml (b) (4) cryogenic vials per drug product component). The cryopreserved cell suspensions (CD8+ and CD4+ T cells) are stored at $\leq -130^{\circ}\text{C}$ in vapor phase of liquid nitrogen. Each drug

product component vial contains (b) (4) CAR+ viable T cells/mL. The cryo-stored cell product components are thawed just before the patient administration at a target dose at the infusion site. The thawed cells should be administered within 2 hours of the thaw. The four thawed vial(s) are visually inspected for damage or leaks. The each cell suspension is drawn in a syringe (5ml syringe). The drawn suspension volume (extractable volume 4.6 ml for 5 ml filled volume) and syringe volume can change depending on dose requirements for administration. Syringes are not included in the product package.

(b) (4)

(b) (4) container closure system (b) (4) illustrated in the figure above is designed as a closed system for the cryogenic closed system storage (b) (4)

The primary packaging material used for JCAR017 (lisocabtagene maraleucel) drug product is a 5 mL cryogenic vial with three independent ports:

- A vent port with a tube and microbial filter plug: Allows pressure equalization during product fill/withdraw
- A loading port with a tube and Luer fitting: Used during the drug product filling procedure
- A retrieval port with a foil-covered conical septum: At time of administration, the foil cover is removed and the retrieval port is used for withdrawing the drug product from the vial.

Table. Primary Container Closure Description

Component	Description	Sterilization Method	Manufacturer
Vial	5 mL; containing vent port, loading port, and retrieval port, (b) (4)	(b) (4)	(b) (4)

A 100% visual inspection of the vials is conducted by the manufacturer ((b) (4)) Incoming inspection is also performed in accordance with qualified procedures following an AQL sampling plan for critical, major, and minor defects upon receipt as per ANSI/ASQ Z1.4. The visual inspection SOPs used at Juno were provided in the response to IR# 7 in the **April 27th Amendment** and in the **June 19th and October 5th Amendments** in response to the pre-inspection records requests. The following visual inspection SOPs that were provided in these amendments were reviewed.

SOP-001347, Visual Inspection of JCAR017 Final Drug Product (Version 2.0, Effective date 24 Apr 2020) that applies to the visual inspection of the drug product vials (provided in the **June 19th Amendment**).

SOP-000512 Manufacturing Material Visual Inspection (Version 5.0, Effective Date 20 Jun 2020), refer to the pre-inspection records review for Juno (JuMP). This SOP was provided in the **October 5th amendment**.

Table. Manufacturer Vial Specifications, 5 mL

Component	Attribute	Specification	Test Method
5 mL cryogenic vial	Type	Cryogenic vial, nominal volume 4.6 mL	Visual Inspection
	Appearance	No visible particulates	Visual Inspection
	Dimensions ^a	In accordance with size-specific drawing ^b	N/A, (b) (4)
	Material	(b) (4)	(b) (4)
	Material Quality ^a	(b) (4)	(b) (4)
Vent port	Type	Tube and microbial filter	Visual Inspection
	Appearance	No visible particulates	Visual Inspection
	Dimensions ^a	In accordance with size-specific drawing ^b	N/A, (b) (4)
	Material	Tube: (b) (4) Filter plug: (b) (4)	Tube: N/A, (b) (4)
	Material Quality ^a	Complies with current (b) (4)	(b) (4)

^aTests: Dimensions and Material Quality can be omitted if the supplier of the primary packaging material is qualified and certifies compliance with the requirements.

^bA drawing of the cryogenic vial with containing vent, loading and retrieval ports is provided preceding this table

Table: Manufacturer Vial Specifications, 5 mL (Continued)

Component	Attribute	Specification	Test Method
Loading port	Type	Tube and Luer fitting	Visual Inspection
	Appearance	No visible particulates	Visual Inspection
	Dimensions ^a	In accordance with size-specific drawing	(b) (4)
	Material	Tube: (b) (4) female luer lock: (b) (4) Closed male luer cap: (b) (4)	(b) (4)
	Material Quality ^a	Complies with current (b) (4) standards	(b) (4)
Retrieval port	Type	(b) (4)	Visual Inspection
	Appearance	No visible particulates	Visual Inspection
	Dimensions ^a	In accordance with size-specific drawing	N/A, (b) (4)
	Material	Cover: Aluminum and polypropylene (b) (4)	(b) (4)
	Material Quality ^a	Complies with current (b) (4) standards	(b) (4)

^aTests: Dimensions and Material Quality can be omitted if the supplier of the primary packaging material is qualified and certifies compliance with the requirements.

^bA drawing of the cryogenic vial with containing vent, loading and retrieval ports is provided preceding this table.

The cell product component is filled into (b) (4) vial through its loading port using a syringe. This filling operation in the (b) (4) was observed and evaluated during the pre-license inspection conducted from October 7-16, 2020. For additional information on the filling operations, refer to the EIR for JuMP facility.

Information on the validation of the container closure integrity testing, sterilization process, shelf life and tests used, biocompatibility and quality system is provided in MF-(b) (4). The validation of the (b) (4) vial sterilization process and container closure test methods (b) (4) was reviewed and no objectionable issues noted.

A copy of COA/ certificate of testing for the primary packaging system was requested and the response was submitted with the March 26th Amendment (refer to the firm

response to the IR#7 in this amendment). The information in this COA is summarized below:

COA for the (b) (4) vials (cryogenic storage container with the vial body made of (b) (4) and tubing made of (b) (4) materials) contains the following test, inspection and results:

(b) (4)

(b) (4)

manufacturer.

In response to the IR#7, the firm also provided in house quality controls for the (b) (4) vials (DP primary packaging) in the March 26th Amendment.

In house quality controls:

- (b) (4) is an approved supplier. This vendor is subjected to an audit by the Sponsor's quality unit, which included an assessment of the manufacturing process sterility assurance program. A quality agreement is in place between the Sponsor and the supplier.
- Upon receipt of a new lot, the final drug product primary packaging is visually inspected by the quality control unit following an (b) (4). As part of vendor qualification, (b) (4) lots were tested for bacterial endotoxins with an acceptance criterion of (b) (4). All lots passed. With each receipt, the quality control unit reviews the supplier's Certificate of Conformance, verifying all required supplier testing has been performed and meets specification. This testing includes verification that the lot has been sterilized by (b) (4). The supplier's sterilization validation followed Method (b) (4) according to (b) (4).

Based on the discussions during the June 26th internal meeting with DMPQ management for this BLA (DMPQ Branch Chief indicated there was no additional need for sterility verification for (b) (4) vials because of the sterility assurances described above), sterility verification testing on the incoming vials was not requested because the sterilization method is validated and the vendor is qualified and audited as described in house controls above. Also note that the reviewer (Rabia Ballica) reviewed the (b) (4)

sterilization validation for the (b) (4) vials provided in the cross-referenced MF-(b) (4) and found no issues. This sterilization validation was performed according to (b) (4)

Endotoxin is tested in house as quality control verification testing. An acceptance criterion of (b) (4) /device is used even though COA has an acceptance criterion of (b) (4) but acceptable:

According to the FDA guidance, the endotoxin limit for general medical devices is (b) (4) unless the device is in contact with cerebrospinal fluid, where the limit is (b) (4). These limits are consistent with those from (b) (4) Medical Devices—Bacterial Endotoxin and Pyrogen Tests. The required endotoxin (EU) dose for parenterals is (b) (4)

Note for medical devices, using the extraction volume recommendations, the limit is (b) (4) /device for products that directly or indirectly contact the cardiovascular system and lymphatic system.

Secondary Packaging System

Secondary packaging material used for the shipping of JCAR017 drug product consists of (b) (4) chipboard cartons holding up to four vials each. The two chipboard cartons, labeled either CD8+ or CD4+ are placed into a cryogenic storage box. The entire payload is then loaded into a liquid nitrogen dry vapor shipper (LN2 Shipper) with adequate absorbent material able to absorb the full volume of the final drug product shipped. The use purpose of the adsorbent material was questioned with an information request (IR#6.2 and IR#6.3) and the response to this request was provided in the **March 26th Amendment**. The response that is summarized below was acceptable:

The absorbent material is included inside the cryogenic storage box along with the drug product primary containers as a precautionary containment measure in the unlikely event the primary packaging sustains gross damage during transit that results in a product leak. In the event of a leak, the absorbent material would contain the leak and serve as a safety measure for handling at the infusion site. Vials are inspected upon receipt at the infusion site and should not be used in the event of gross damage. There have been no instances of observed primary packaging leakage or breakage post-shipment during any clinical trial shipments (b) (4) shipments).

The amount of absorbent material was selected to ensure capability to absorb the maximum volume of drug product included in a shipment. The selected absorbent material size (3" x 4") has a maximum absorbent volume of (b) (4). Each cryogenic storage box contains a maximum of 8 cryopreservation vials (up to 4 vials per drug product component), each vial has a maximum fill volume of 5 mL (40 mL total).

Figure 10. Secondary Packaging – Chipboard Box

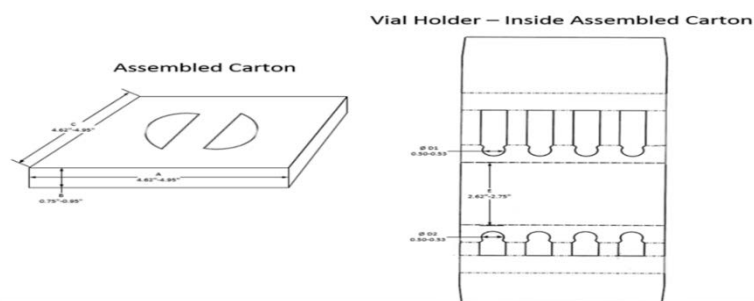
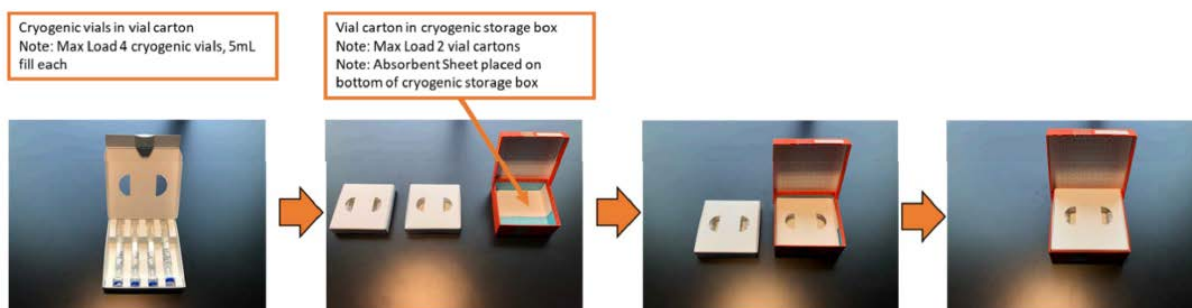


Figure 11. Secondary Packaging – Cryogenic Storage Box



Figure 12. Secondary packaging configuration¹ (copied directly from the March 26th Amendment)



¹ Packaging pictured is representative of clinical packaging materials. The commercial packaging may vary visually from the figure above and will reflect secondary commercial packaging as agreed upon with the FDA.

Container Closure Integrity of Primary Packaging

The firm indicates in Section 3.2.P.2.5 that the vial is compatible with the drug product formulation as demonstrated by the extractable/leachable studies presented in this section and the stability studies reported in Section 3.2.P.8.1 Stability Summary and

Conclusions [CD8+]. The evaluation of the information on E/Ls is deferred to the product office reviewers.

Pre-use container closure integrity testing (CCIT) on the primary packaging

As part of vendor release testing, all vials are (b) (4). Tested according to (b) (4) with internal acceptance criteria. This pre-use container closure integrity testing aligns with (b) (4) and (b) (4).

In-use container closure integrity testing

The container closure integrity testing by (b) (4). Then, the sealed containers were cryopreserved followed by storage at $\leq -130^{\circ}\text{C}$ for durations up to (b) (4), and shipment to a testing facility within an LN2 shipping container.


(b) (4)

(b) (4)

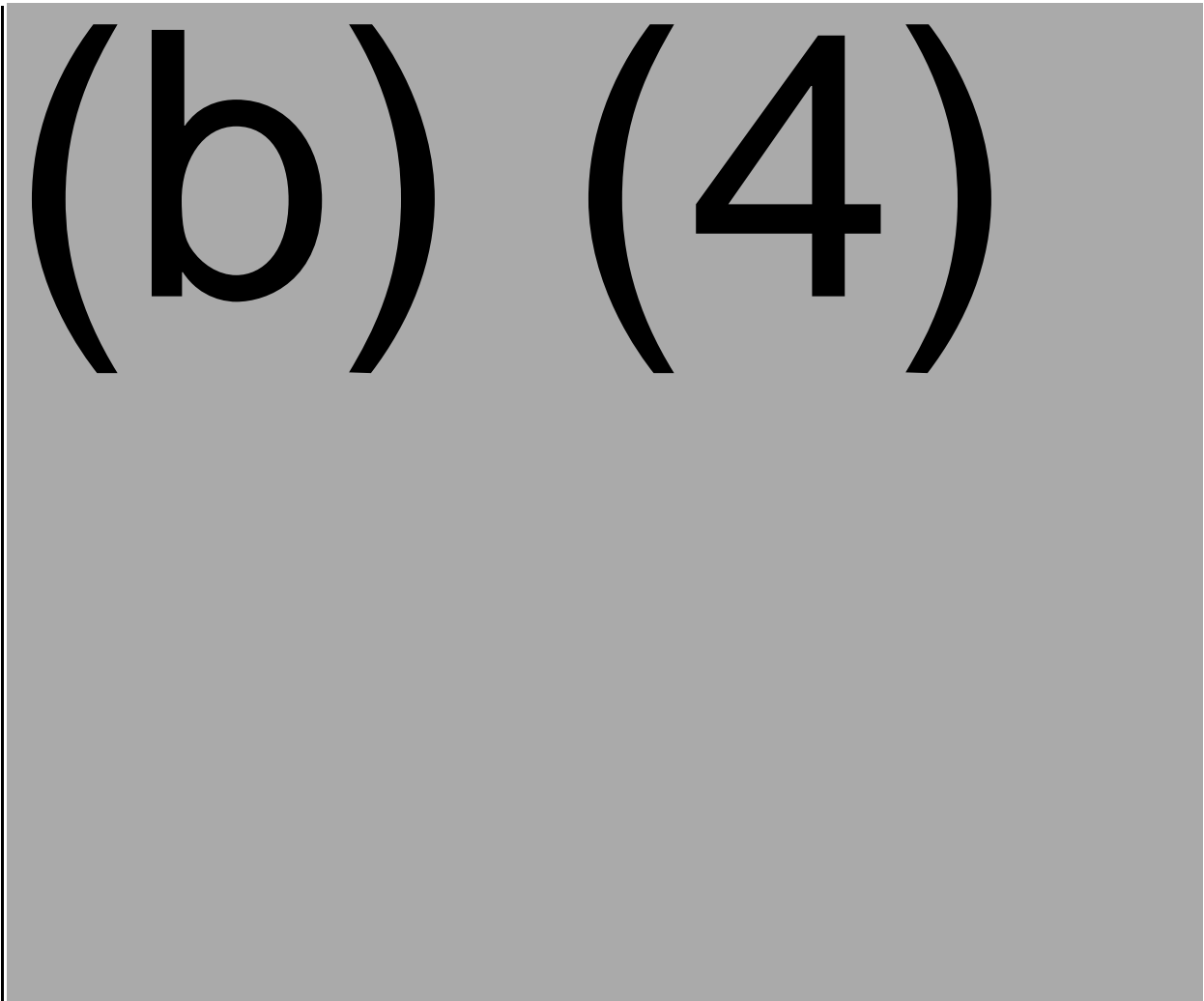
The following testing conditions (that were provided in the July 17th Amendment in response to IR# 1.2) were used for the (b) (4) on the cryo-stored and shipped (b) (4) vials:

Note that the limit of detection (LOD) was determined using (b) (4)

(b) (4)

The text "(b) (4)" is followed by three horizontal bars of varying lengths, indicating redacted content. The first bar is the longest, followed by a shorter one, and then another bar of similar length.

(b) (4)

A large rectangular area of the page is completely redacted, indicated by a large gray block. The text "(b) (4)" is written in large, bold letters at the top left of this redacted area.

Reviewer assessment of the information provided in the April 27th and July 17th Amendments for the container closure integrity testing:

The firm provided the validation reports in the **April 27th Amendment** for the integrity test methods used for (b) (4) containers. These containers were considered as rigid containers like (b) (4) vials and worst-case

vials for suitability testing. Therefore, the suitability of the integrity test methods, (b) (4) tests, were first determined with these (b) (4) vial types and then these integrity test methods were validated for the (b) (4) vials. The firm provided the validation results for the integrity testing on (b) (4) vials in the tables above (results from the MF and Juno study).

3.2.P.2.5 Microbiological Attributes

The JCAR017 (lisocabtagene maraleucel) drug product is composed of two individually formulated components, CD4+ and CD8+ and each component is manufactured using aseptic processing. The sterility of these drug components is ensured by the following microbiological controls:

- Raw materials used in the drug product manufacturing process are confirmed to be sterile prior to use in drug product manufacture.
- Container closure integrity (CCI) has been demonstrated in (b) (4) cryopreservation vials using (b) (4)
- Packaging materials are suitable for sterile cell therapy products.
- All JCAR017 drug product lots are tested for the presence of microbial contaminants

These controls are also summarized in the table below along with acceptance criteria.

Table. Microbiological Controls

Step/Materials	Control	Acceptance Criteria
Leukapheresis (b) (4)	In process (b) (4)	(b) (4)
Final cell product (DP)	Sterility testing (b) (4) >	No Growth
DP Container Closure System	Verification of container closure integrity for (b) (4) cryostorage and shipping	Pass
Raw materials	Sterility verification prior to use	No Growth
Final cell product (DP)	Endotoxin testing by (b) (4)	(b) (4)
Cell culture	(b) (4)	Not detected

(b) (4) for Leukapheresis product is qualified with respect to time period and temperature by evaluating (b) (4) and other quality attributes, but not for sterility (refer to subsection 5.6 of Section 3.2.P.3 in the original BLA submission).

Aseptic processing was validated with initial (b) (4) runs and then (b) (4) validation runs are performed for (b) (4) areas.

February 26th Amendment Review for Microbial Containment:

A teleconference call was held on 06 Dec 2019 to notify FDA for the (b) (4) contamination issue. FDA requested a follow-up call in 2 weeks and a summary of the deviation and change, investigation, root cause analysis, and CAPAs be submitted to support this BLA submission. This amendment was submitted in response to this request and contains the final investigation report for the deviation, DEV-2019-03089 opened for the contamination incidents. From 12NOV19 to 23NOV19, a total of (b) (4)

contaminated with bacterial microorganisms at the Juno manufacturing facility (JuMP). An extensive investigation and root cause analysis was conducted. It was concluded that the contamination was resulted from the (b) (4)

was followed up for the effectiveness and no contamination was observed. This amendment was also reviewed by the Product Office (PO) and refer to the PO CMC review memo.

3.2.P.2.6 Compatibility

Deferred to the Product Office. Refer to the PO CMC review memo.

Overall Reviewer's Assessment of Section 3.2.P.2:

- ☐ As summarized above, the information provided in the original BLA and amendments submitted in response to DMPQ information request is acceptable and there are no outstanding review issues.

☐

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Table. Facility Table – Manufacturing and Testing Facilities (not copied directly from the submission)

DS: Drug Substance; DP: Drug Product; PLI: Pre-License Inspection;
CMO: Contract Manufacturing/Testing Organization

Facility, Address and FEI and DUNS Numbers	Responsibilities	Inspection History
Juno Therapeutics Inc. (JUMP) 1522 217th Pl. SE Bothell, WA 98021, US FEI: 3011834594; DUNS: 079941307	DS and DP Manufacturing -Primary and Secondary Packaging -DP Release and Stability Testing -Lentiviral Vector DP (b) (4)	ORA PLI (October 7-16, 2020)
Juno Therapeutics Inc. 400 Dexter Ave N, Suite 1200 Seattle, WA 98109, US FEI: 3010932912; DUNS: 079290042	(b) (4)	N/A
(b) (4)	(b) (4)	N/A
(b) (4)	(b) (4)	N/A

3.2.P.3.2 Batch Formula

Table. Batch Formula for CD8+ Drug Product Component

Component	Quality Standard	Concentration	Amount per Batch
CD3+ CAR+ T Cells	In-house ^a	(b) (4) CAR+ viable T cells/mL	(b) (4) CAR+ viable T cells
CryoStor [®] CS10 (contains (b) (4) DMSO)	In-house ^b	75% [v/v] ^c	(b) (4)
Multiple Electrolytes Injection, Type 1	(b) (4)	(b) (4) [v/v]	(b) (4)
Albumin (Human) Solution (25% Albumin)	(b) (4) .	(b) (4) [v/v] ^d	(b) (4)

DMSO: dimethylsulfoxide; v/v: volume per volume

^a See Section 3.2.P.5.1 Specifications [CD8+] for the lot release specifications of JCAR017^b See Section 3.2.P.4.1 Specifications (b) (4) , CD8+] for the CryoStor[®] CS10 specification^c Final DMSO concentration in the drug product is 7.5%^d Final albumin concentration in the drug product is (b) (4)**Table.** Batch Formula for CD4+ Drug Product Component

Component	Quality Standard	Concentration	Amount per Batch
CD3+ CAR+ T Cells	In-house ^a	(b) (4) CAR+ viable T cells/mL	(b) (4) CAR+ viable T cells
CryoStor [®] CS10 (contains (b) (4) DMSO)	In-house ^b	75% [v/v] ^c	(b) (4)
Multiple Electrolytes Injection, Type 1	(b) (4)	(b) (4) [v/v]	(b) (4)
Albumin (Human) Solution (25% Albumin)	(b) (4) .	(b) (4) [v/v] ^d	(b) (4)

DMSO: dimethylsulfoxide; v/v: volume per volume

^a See Section 3.2.P.5.1 Specifications [CD4+] for the lot release specifications of JCAR017^b See Section 3.2.P.4.1 Specifications (b) (4) , CD8+] for the CryoStor[®] CS10 specification^c Final DMSO concentration in the drug product is 7.5%^d Final albumin concentration in the drug product is (b) (4)**Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:**

- ☐ The information provided is acceptable as submitted.
- ☐ The assessment of Sections 3.2.P.3.1 and 3.2.P.3.2 is deferred to the Product Office.

3.2.P.3.3 Description of Manufacturing Process

CAR-T Drug Product Manufacturing:

(b) (4)

(b) (4)

The drug substance product is (b) (4)

Formulated drug product is (b) (4) and is filled into drug product cryopreservation vials (5 ml) using syringes. Filled vials (closed system primary packaging system) are frozen using a (b) (4). The CD4+ and CD8+ drug components are cryo-stored and shipped in a qualified liquid nitrogen (LN2) shipper to clinical site to be administered to the patient.

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

- ☐ The information provided is acceptable as submitted.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Controls of critical steps and intermediates for CD8+ DP component manufacturing is the same as those of CD4+ DP component manufacturing. Therefore, the information is given in this section only for CD8+ component. There is no storage for intermediates such as harvest (continuous manufacturing process).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Table. Formulation, Fill, and Cryopreservation: Non-Critical Process Parameters

Non-Critical Process Parameter	Units	Target
CryoStor [®] CS10 Concentration in Drug Product	% v/v	75
Concentration of Multiple Electrolytes Injection, Type 1 in Drug Product	% v/v	(b) (4)
Concentration of Albumin (Human), 25% Solution in Drug Product	% v/v	(b) (4)
Number of Cryopreserved Drug Product Vials Filled	vials	4
Cryopreservation Vial Fill Volume (extractable volume + allowable excess volume)	mL	5.0
Cryopreserved Drug Product Storage Temperature	°C	≤ -130

(b) (4)

(b) (4)

For microbiological controls, refer to section 3.2.P.2.5 Microbiological Attributes within this memo.

The drug product manufacturing process does not allow for reprocessing of any unit operations.

Overall Reviewer's Assessment of Section 3.2.P.3.4:

- The information provided is acceptable as submitted.

3.2.P.3.5 Process Validation and/or Evaluation**Aseptic Process Validation/Aseptic Process Simulation**

Aseptic processing was initially validated with (b) (4) Aseptic Process Simulation (APS) runs and then is re-validated (b) (4). Results met the acceptance criteria as summarized in the table below.

The microbial growth medium used is (b) (4)

(provided in the **March 26th Amendment** in response to IR# 5.3).

(b) (4)

The batch record (a paper copy) for the November 2019 APS (BTH.MFG.187-SR-11.01. Summary Report of Platform APS - Q4 2019) was provided in the **June 19th Amendment** in response to the first round of pre-inspection records request (record request item 3.4) and reviewed. As per this batch record, all containers and waste container along with (b) (4) and EM was performed. Results for EM and (b) (4) met “No Growth” acceptance criterion. Also, the firm performed (b) (4) testing and met the acceptance criteria (promoted the (b) (4). In addition to all (b) (4) rooms, Day 0 Suite workstations (b) (4) CER were included in November 2019th APS which verifies the list in the table for the cleanrooms used in APS re-validation runs (provided in the **October 5th Amendment**) and the list provided in the **March 26th Amendment**.

Note the APS protocols summarized in this section and recently executed APS run (APS re-qualification executed in May, 2020) were also reviewed and evaluated during the pre-license inspection of the JuMP manufacturing site (conducted from Oct 7-16, 2020). For additional information on this evaluation, refer to the EIR for this inspection.

Drug Product Shipping Validation

The cryopreserved drug product (DP) is shipped from the manufacturing facility to the infusion site in a temperature-controlled liquid nitrogen dry vapor shipper (LN2 Shipper).

As per the **August 4th Amendment** in response to the PO information request (IR#3), the real time shipping routes were described in the table below for the JCAR017 drug product.

Evaluation of the information on the actual CART- drug product shipped using the qualified shipper described above is deferred to the Product Office.

Process Performance Qualification (PPQ)

Evaluation of PPQ design for DS and DP manufacturing processes and PPQ lots is deferred to the product office reviewers.

(b) (4) leukapheresis products were pre-designated as PPQ batches
(b) (4) The PPQ design included (b) (4) runs, with each (b) (4) run generating (b) (4) drug product lots. Each lot consisted of (b) (4) CD8+ drug product component and (b) (4) CD4+ drug product component (refer to Figure below), for a total of (b) (4) drug products (b) (4) drug product components) within the PPQ design.

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

[REDACTED]

[REDACTED] vials for leaks and damages at the infusion site are included in the labeling procedures.


In conclusion, the post-filling (b) (4) is acceptable because the (b) (4) is not a sterile barrier. Note the retrieval port itself (b) (4) constitutes the primary boundary of the container, integral to the container closure integrity of the system. Note this (b) (4) was also questioned by the Product Office for the labeling procedures. For additional information on the evaluation of the Product Office, refer to the PO CMC review memo.

Validation of Temperature Rate Controlled Freezing Process


The controlled rate freezing profile is used for cryopreservation of (b) (4) final cell product components in vials. The cryopreserved CD8+ and CD4+

cell components are stored in the vapor phase of liquid nitrogen (LN2) freezer at temperatures $\leq -130^{\circ}\text{C}$.





(b) (4)



(b) (4)



(b) (4)



Chain of Identity (COI) and Chain of Custody (COC)

A comprehensive chain of identity (COI) control strategy, consisting of electronic systems and procedural controls, have been established to prevent product and sample mix up during production in a multi-product facility (*refer to the review of 3.2.a.1*). Computer systems are validated (*refer to the review of 3.2.a.1*). The all COI checkpoints throughout production is evaluated and provided in the table below.

(b) (4)

(b) (4)

(b) (4))

(b) (4)

(b) (4)

For the detailed information on chain of identity physical and procedural controls, and relevant validated computer systems, refer to section 3.2.a.1 Facilities and Equipment-JuMP within this memo

Overall Reviewer's Assessment of Section 3.2.P.3.5:

- ❑ The information provided in the original BLA submission and amendments is acceptable. The deficiencies were identified and addressed in the amendments in response to associated information requests. There are no outstanding review issues.

3.2.P.4 Control of Excipients**3.2.P.4.1 Specifications**

Deferred to the Product Office. Refer to the PO CMC review memo.

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

Deferred to the Product Office. Refer to the PO CMC review memo.

3.2.P.4.4 Justification of Specifications

Deferred to the Product Office. Refer to the PO CMC review memo.

3.2.P.4.5 Excipients of Human or Animal Origin

Deferred to the Product Office. Refer to the PO CMC review memo.

3.2.P.4.6 Novel Excipient

Deferred to the Product Office. Refer to the PO CMC review memo.

Overall Reviewer's Assessment of Section 3.2.P.4:

- ❑ The assessment as to whether the information provided is acceptable is deferred to the Product Office.

3.2.P.5 Control of Drug Product**3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)**

Drug Product Specifications:**Table.** Specifications for JCAR017 (lisocabtagene maraleucel) CD8+ Drug Product Component

Quality Parameter	Attribute	Analytical Test	Release Acceptance Criteria	Stability Acceptance Criteria
Appearance	Color	Appearance	Colorless to Yellow or Brownish-Yellow, (b) (4)	Colorless to Yellow or Brownish-Yellow, (b) (4)
	Clarity		Slightly-Opaque (b) (4)	Slightly-Opaque (b) (4)
Identity	Identity	(b) (4)	(b) (4)	NA
Purity	(b) (4)	(b) (4)	(b) (4)	NA
Purity	(b) (4)	(b) (4)	(b) (4)	NA
	(b) (4)		(b) (4)	NA
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Strength	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Safety	(b) (4)	(b) (4)	(b) (4)	NA
Safety	Sterility	Sterility	No Growth	No Growth
Safety	Mycoplasma	Mycoplasma	Not Detected	NA
Safety	Endotoxin	Endotoxin	(b) (4)	NA

Note release acceptance criteria microbial attributes under DMPQ purview are acceptable. The evaluation of the rest of quality attributes and acceptance criteria is deferred to the product office.

Table. Specification for JCAR017 Drug Product (CD8+ and CD4+ DP Components)

Quality Parameter	Attribute	Analytical Test	Release Acceptance Criteria	Stability Acceptance Criteria
Strength ^a	(b) (4)	Calculation	(b) (4)	NA

(b) (4)

^bStrength of JCAR017 DP dose NA = not applicable

All drug product testing is completed prior to product disposition. Quality Assurance reviews all manufacturing batch records, approves the reported Quality Control results, and ensures the lot met all specification acceptance criteria before the product is dispositioned. Any deviations observed are assessed for impact to product quality prior to product disposition.

- Review and Evaluation of approaches and data used to establish the acceptance criteria, including statistical analysis, if any, and other factors (e.g. manufacturing process capability, clinical experience with current or related products, stability during shelf life) is deferred to the Product Office.
- Review and Evaluation of changes in release specifications during product development (e.g., tightening or shifting of acceptance criteria, replacing a method) compared to those used for licensure, if different is deferred to the Product Office.
- A general conclusion whether control strategy using combined control approaches (e.g., in-process testing, release and stability testing) is appropriate to assure drug product quality is deferred to the Product Office.

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

- The information provided is acceptable as submitted. The release specifications under DMPQ purview are adequate (sterility and endotoxin testing along with their acceptance criteria).

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

Deferred to the Product Office. Refer to the PO CMC review memo.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

- ❑ The assessment as to whether the information provided is acceptable as submitted is deferred to the Product Office.

3.2.P.5.4 Batch Analyses

The firm provided a list of the lots manufactured using process versions (b) (4) between Oct 2016 and Nov, 2018 at JuMP site (b) (4) lots).

The batch analysis data presented in this section contains part numbers (b) (4) that are representative of different process versions and manufacturing sites used throughout clinical development. (b) (4) represents process (b) (4) represents process (b) (4) represents process (b) (4). All of which were manufactured at JuMP. (b) (4) represents process (b) (4) in which the cryopreserved material was manufactured at (b) (4) and the drug product was manufactured at JuMP.

Review and evaluation of all the lots manufactured using the (b) (4) processes (b) (4) lots) are deferred to the PO reviewers. Sterility, mycoplasma and endotoxin results for the lots listed in this section met the acceptance criteria ("no growth" acceptance criterion for sterility and "Not Detected" for mycoplasma), except for the (b) (4) contaminated lots which reviewed by the Product Office in depth. Also note the endotoxin acceptance criterion was evolved as process version changed. For example, for the proposed commercial process (b) (4) while it is (b) (4) per dose for the (b) (4). For the batch analysis data for the lots, refer to section 3.2.P.5 of the original BLA submission.

3.2.P.5.5 Characterization of Impurities

Deferred to the Product Office. Refer to the PO CMC memo.

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

- ❑ The assessment of Provide your assessment as to whether the information provided in this section is deferred to the Product Office.

3.2.P.6 Reference Standards or Materials

Deferred to the Product Office. Refer to the PO CMC review memo.

3.2.P.7 Container Closure System

For the information under DMPQ purview, refer to section 3.2.P.2.4 Container Closure System within this memo.

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

- The information provided in the original BLA submission and amendments on the container closure system (primary and secondary packaging systems) is acceptable and there are no outstanding review issues.

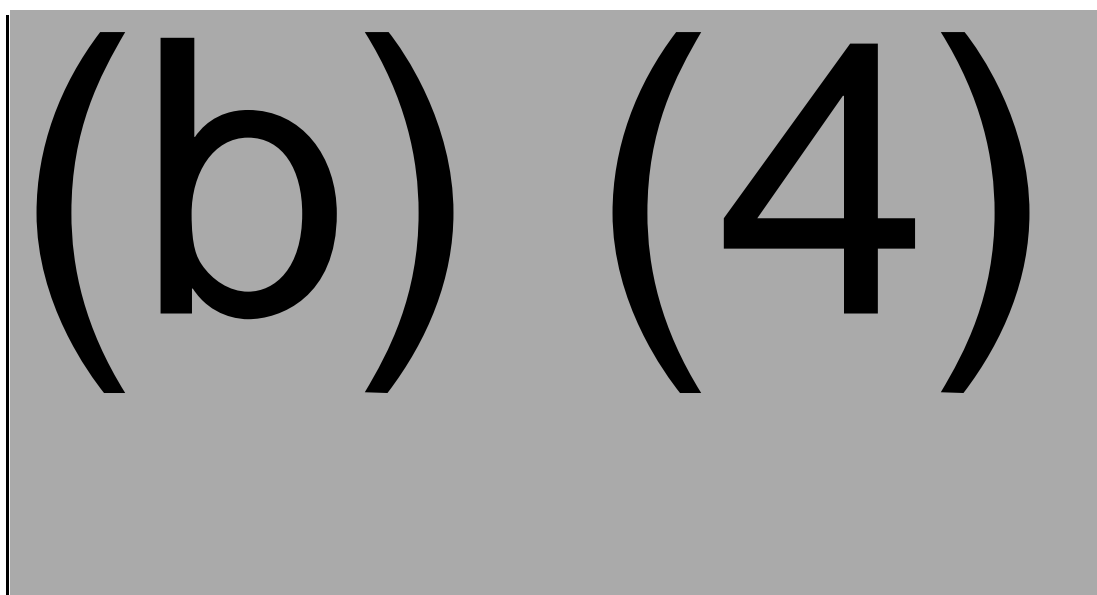
3.2.P.8 Stability**3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data**

JCAR017 (Lisocabtagene maraleucel) drug product consists of CD8+ and CD4+ components, each independently cryopreserved in (b) (4) containers at $\leq -130^{\circ}\text{C}$ in vapor phase of liquid nitrogen.

Long-term stability studies were performed to support the product shelf life for the JCAR017 CD8+ drug product component. The drug product batches used in primary and supportive stability studies are representative of the commercial process. All batches were manufactured at scale in the proposed commercial manufacturing site (JuMP), using the same controlled rate freezing process, and were filled into the same container as the commercial product. Most studies used leukapheresis material from (b) (4) as a starting material,

For new stability lots, sterility results for the time points indicated in the table below (protocol table) are not available yet.

Table. Stability Protocol of CD8+ Drug Product (Supportive Stability Batches (CAR+ Dosing))



Note the drug product (CD4+ and CD8+ drug product) is tested for sterility prior to cryo-freezing for release lots to be administered to the patient and stability lots. If sterility

testing on stability and patient lots does not meet “No Growth” criterion, lots are rejected.

The stability protocol in the table above will be updated to the proposed stability attributes and acceptance criteria in Section 3.2.P.5.1 Specification [CD8+] upon approval.

All the stability lots were filled in (b) (4) vials (5ml that is described in section 3.2.P.2.4). The available results met the acceptance criteria. Sterility testing is performed on (b) (4) and the sterility data at the time points listed in the table above for the stability protocol are not available yet (in 3.2.P.8.3 Stability Data).

Note the protocol for the ongoing stability studies do not have CCIT testing, but sterility testing will be performed at release and expiry along with the interim time points months (b) (4). Also note that the integrity of the cryostored (b) (4) vials were demonstrated using the (b) (4) testing performed on the (b) (4) cryo-stored vials as documented in this memo.

For detailed information on the stability studies, refer to the PO CMC memo.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

For detailed information on the post-approval stability commitment, refer to the PO CMC memo.

Post-approval commitment statement is provided as follow (copied from the BLA submission):

“The long-term stability program will continue as per the protocol in Section 3.2.P.8.1 Stability Summary and Conclusions [CD8+] and the data will be provided via the annual report. There is no post approval stability protocol or commitment for drug product stability batches because stability data generated to date has demonstrated successful cryopreservation and no practical impact throughout long-term storage.

The shelf life of JCAR017 drug product component (b) (4) additional stability data, which remains within specification as described in Section 3.2.P.5.1 Specification [CD8+], becomes available”

Overall Reviewer’s Assessment of Section 3.2.P.8:

- ☐ I agree with the proposed shelf-life and storage conditions. Sterility testing is performed at release and expiry (b) (4) as well as at the interim time points of (b) (4) months.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Manufacturing Facilities

lisocabtagene maraleucel drug substance and drug product is manufactured, filled, and labeled at Juno Therapeutics Inc., 1522 217th Pl. SE Bothell, WA 98021, USA.

Table. Manufacturing Facilities Table for lisocabtagene maraleucel.
(not copied directly from the BLA submission)

Name/Address	FEI Number And DUNS number	Responsibilities	Inspection/waiver	Justification /Results
Juno Therapeutics Inc. 1522 217th Pl. SE Bothell, WA 98021, USA	FEI: 3011834594; DUNS: 079941307	-DS and DP Manufacturing -Primary and Secondary Packaging -DP Release and Stability Testing -Lentiviral Vector DP (b) (4) (b) (4)	Pre-License Inspection	ORA October 7-16, 2020 (classification was not available at time of ADD due to timing of the inspection in the review cycle)
(b) (4) (b) (4)	FEI: (b) (4) DUNS: (b) (4)	(b) (4) (b) (4) (b) (4) (b) (4) (b) (4)	Pre-License Inspection	CBER Pending (postponed due to COVID-19 pandemic)
(b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)	FEI: (b) (4) DUNS: (b) (4)	(b) (4) (b) (4)	Waived	CBER DMPQ PAI (b) (4) (VAI)

ORA conducted a pre-license inspection (PLI) of Juno Therapeutics Inc, Bothell PA, from October 7 - 16, 2020 for drug substance and drug product manufacturing. At the conclusion of this inspection, a Form FDA 483 was issued. The official assessment and classification for this inspection would not be available at the time of ADD (approval due date).

CBER performed a pre-approval inspection of the (b) (4) location from (b) (4) as part of PAS STN (b) (4). All inspectional issues were resolved and the inspection was classified as VAI.

Pre-license inspection of (b) (4) is pending.

3.2.a.1. Facilities and Equipment for (b) (4) Lentiviral Vector Manufacturing

(critical component for lisocabtagene maraleucel manufacturing)

1) (b) (4) Lentiviral Vector Manufacturing Facility and Equipment - (b) (4)

(b) (4)

Facilities and Equipment (3.2.a.1-Juno/JuMP)

The Juno Manufacturing Plant (JuMP) located in Bothell, WA, is a multi-product manufacturing site for cell therapy products that are in clinical development. The JuMP facility also serves as a commercial launch facility for Juno Therapeutics, Inc., a Celgene company (Juno) for manufacturing JCAR017 (lisocabtagene maraleucel).

Note JuMP facility was inspected from October 7-October 16, 2020. For additional information on the facility and 5 systems (quality, production, materials and laboratory controls, facility and equipment and packaging and labeling), refer to EIR for this pre-license inspection.

The following table lists two clinical products which are currently manufactured at JuMP facility. Note both the products are cell therapy products that are genetically engineered using the same type of viral vectors, lentiviral vectors.

Table. Products manufactured at JuMP

Name	Type	Description	Development Phase	Company
Lisocabtagene maraleucel	Chimeric Antigen Receptor (CAR) T-cell Therapy	Autologous CD4+ and CD8+ T cells expressing a CD19-specific CAR.	Clinical	Juno Therapeutics
(b) (4)				

Risk management controls at the multi-product manufacturing facility were provided.

Critical operational controls are:

- Chain of identity (COI) and chain of custody (COC)
- Microbial Contamination Control
- Segregation (campaign, concurrent) and Changeover

In the original BLA submission, the following information is provided on new product and process introduction:

New products and/or processes introduced into the JuMP facility are evaluated to ensure they are in accordance with the approved standard operating procedure (SOP). Prior to the introduction, an assessment evaluating the following elements and criteria is undertaken:

-Materials, (including new raw materials), qualification, specification, and release testing requirements; vendor qualification.

- Facilities, including qualification state, microbial contamination control, and cleaning assessments.
- Equipment, including qualification state.
- Chain of identity, including in-process labels.
- Documentation, including SOPs, batch records, and bill of materials.
- Product-specific criteria, including analytical methods, in-process product specifications and final product specifications, final product labels, and secondary packaging (e.g., cartons, etc.).

Risk management strategies implemented to prevent mix-ups and cross-contamination of different patient lots between the same and two different products (Lisocabtagene maraleucel (JCAR017) and (b) (4) manufactured at JuMP was provided in the **October 5th Amendment** in response to the second round of the records request (record request item #1) and the provide information was summarized below:

*Introduction of a new product into the JuMP facility is governed by **SOP-001564**, JuMP New Product Introduction. This procedure ensures that risks associated with introducing new products, new viral vector or other critical materials, and major process changes are properly assessed prior to introduction into the JuMP facility.*

Risk management strategies employed to prevent mix-ups and cross contamination at JuMP include defining the flow of materials within the facility, the use of campaigned rooms and workstations, and specific Chain of Identity (COI) and Chain of Custody (COC) procedural controls within the manufacturing batch records (MBR).

The flow of product, materials, equipment, documents and personnel in the facility are unidirectional and governed by SOP-000145, Cell Processing Facility Material and Process Flow, and DWG-001002, Juno Manufacturing Facility Map.

*Patient material is processed in campaigned rooms and workstations within the cell process facility at JuMP. **SOP-000186**, Changeover Procedure (version 14.0, 21 Aug 2020), governs the creation and release of campaigned workstations within the facility through line clearance and changeover processes. As per the procedures described in SOP-000186, manufacturing ensures campaigned areas are dedicated to (b) (4) at a time and performs and documents line clearance and changeover activities. Quality assurance verifies line clearance and changeover activities and documentation. The following definitions are provided in this SOP -000186 (version 14.0, 21 Aug 2020):*

Campaigned room is defined as “A room in the Cell Processing Facility that is temporarily dedicated to processing materials for (b) (4)

Campaigned workstation is defined as “A workspace (within a room) and/or piece of equipment that is temporarily dedicated to (b) (4) (processing performed using non-human starting material such as APS, culture media, buffers, solutions). Note closed system manufacturing occurs in workstations.

Changeover is defined as “An inspection and cleaning of a campaigned room or workstation after processing. Changeover ensures that documents, materials, and waste associated with the processed lot are removed, and releases the campaigned room or workstation”.

Line Clearance is defined as “An inspection and cleaning of a campaigned room or workstation confirming that the area is clear of materials/documents from another lot prior to processing”.

As per this latest version of SOP-000186, campaigned rooms and campaigned workstations are listed below:

Campaigned rooms:

- (b) (4) (as applicable)

Campaigned workstations:

- (b) (4)

During specific manufacturing operations occurring in a campaigned room or workstation, additional cross contamination controls are specified within the manufacturing batch record (MBR) and SOP. Examples of these controls include chain

of identity barcode scanning of product, materials and other instructions to prevent cross contamination and mix-ups.

The COI and COC controls are in place from leukapheresis receipt through production, storage, testing, release, and distribution to ensure that the identity of each patient lot is tracked, patient lots are not accidentally exchanged with cellular material from another subject, and control is maintained over the location and access to patient lots. Throughout the manufacturing process, COI is checked and verified before allowing subsequent processing. As COI checks are performed, COC information is recorded allowing the tracking and tracing of all parties handling the product.

*In the **October 5th Amendment**, the information on how Juno handle manufacturing limits were also provided upon request. Capacity limits are qualified through the execution of PTC-001120, Run Rate Execution Protocol (“Run Rate Execution Protocol from (b) (4)”, Version 3.0, Effective Date 12 Sep 2020). Upon successful completion of the protocol, capacity limits are implemented through the change control process. The established capacity limits are managed by the scheduling and cell logistics team and site supply chain. If the site receives patient material that is in excess of the approved capacity, such as could be caused by incoming material transportation delays, the (b) (4) process (T cell selection) will be completed and the cryopreserved material held until there is available processing capacity for downstream operations. The maximum facility capacity of (b) (4) patients per week was reported in the August 4th Amendment in response to the PO IR. (b) (4) patients capacity represents a limit on the cumulative production of both lisocabtagene maraleucel (b) (4) such that the total number of patients within a week (sum of both products) will not exceed (b) (4)*

As per the text book definitions, campaigned based manufacturing means only (b) (4) at a time will be manufactured. During campaigned based manufacturing, one or more lots of the same product can be manufactured concurrently (in parallel) or in sequence/series (in other words manufacturing a series of batches of the same product in sequence in a given period of time). Juno does not make distinctions between concurrent and campaigned manufacturing at JuMP facility, but it appears that concurrent manufacturing occurs because campaigned based manufacturing is not defined for the same product. It was also indicated in the original BLA submission that the facility design and operation strategy include to allow for:

- Concurrent manufacturing of autologous cell therapies for multiple subjects: This is supported by:
Use of single use product contact equipment and storage containers and APS validated closed systems for unit operations, APS validated open manipulations in BSCs, automated processes (e.g., cell washing and formulation, cell

separation and cell expansion in a (b) (4) use of validated electronic systems (b) (4) for chain of identity (COI) and chain of custody (COC) of subject cells and materials, changeover procedures in place, and appropriate manufacturing room and workstation designs, procedures in place for segregation, labeling and tracking, gowning and manufacturing flows.

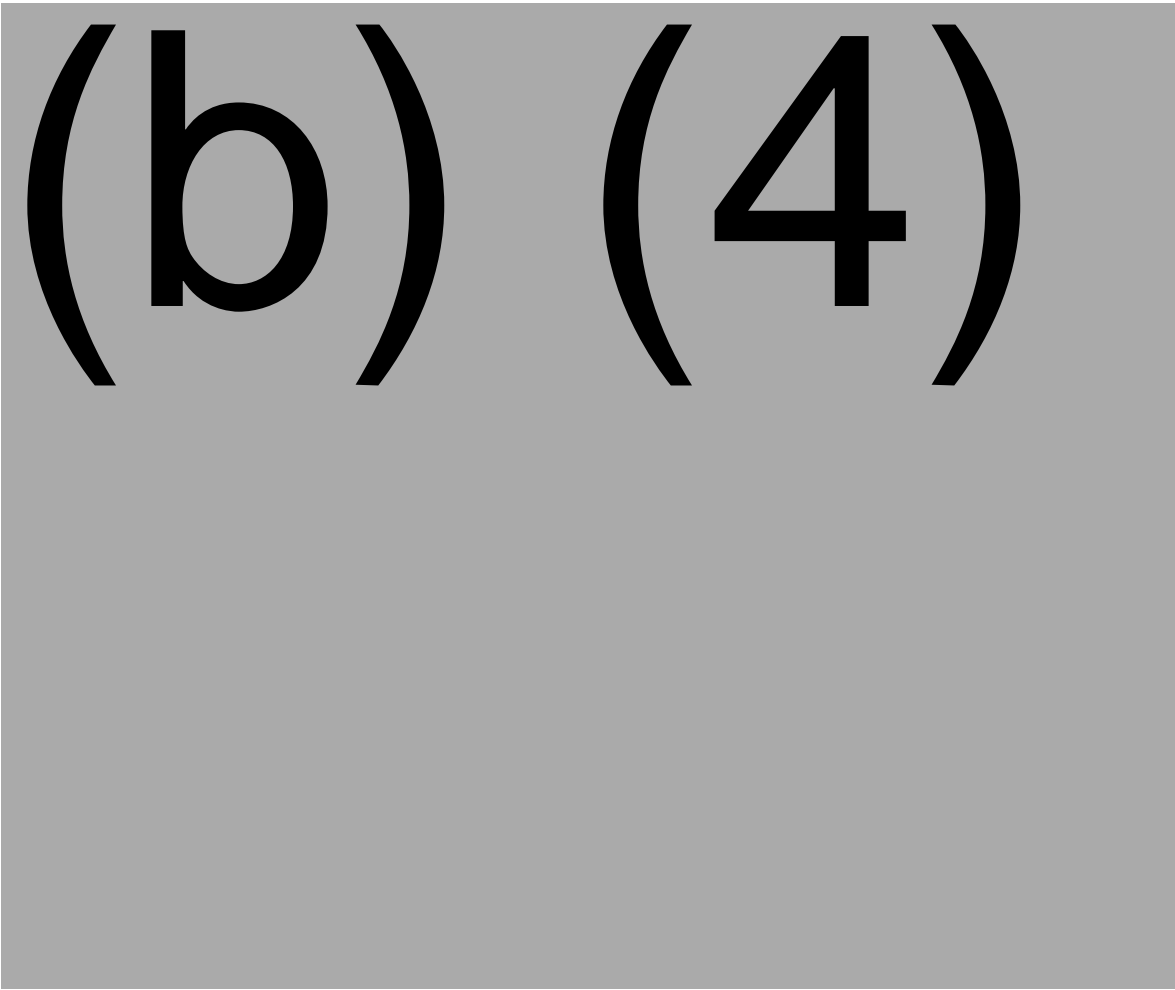
- The use of different types of viral vectors
- Manufacture of cell therapies that are licensed and in clinical trials

The reviewer agrees with that the facility design (as described in this section) and containment procedures (described in this section) support concurrent manufacturing.

Based on the definitions above, regardless of what product manufactured (concurrent or campaigned based), room (s) and workstation (s) are temporarily dedicated to processing materials for (b) (4), which is called as campaigned based areas. Note changeover procedures are in place between the campaigns and all the unit operations are carried out in closed systems, except for (b) (4) located in open operation rooms where open product filling operation is performed. Also note procedural controls for concurrent and campaigned based manufacturing was recommended to be followed up during the pre-license inspection of the JuMP facility by ORA (refer to EIR for the pre-license inspection of JuMP from October 7- October16, 2020).

Juno facility is a (b) (4). Warehouse, QC labs, Electrical room, Offices etc. are located on the (b) (4) and manufacturing area is located on the (b) (4). A layout for the (b) (4), a diagram for AHUs (refer to the figure below) and unidirectional flow diagrams for personnel, product, vector, waste and materials are provided in the submission.

(b) (4)



As you can tell from the diagram above, each manufacturing core has its own dedicated (b) (4) and entry corridor (b) (4) which is a good assurance for microbial and viral containment.

The rooms are designed to meet (b) (4) classifications depending on the use of the room. There are local (b) (4) used for process steps that are exposed to the environment (open system operations).

(b) (4)

(b) (4)

In the March 26th Amendment in response to IR#1.1, Juno provided information on air exchange rates and pressure differentials for (b) (4) areas:

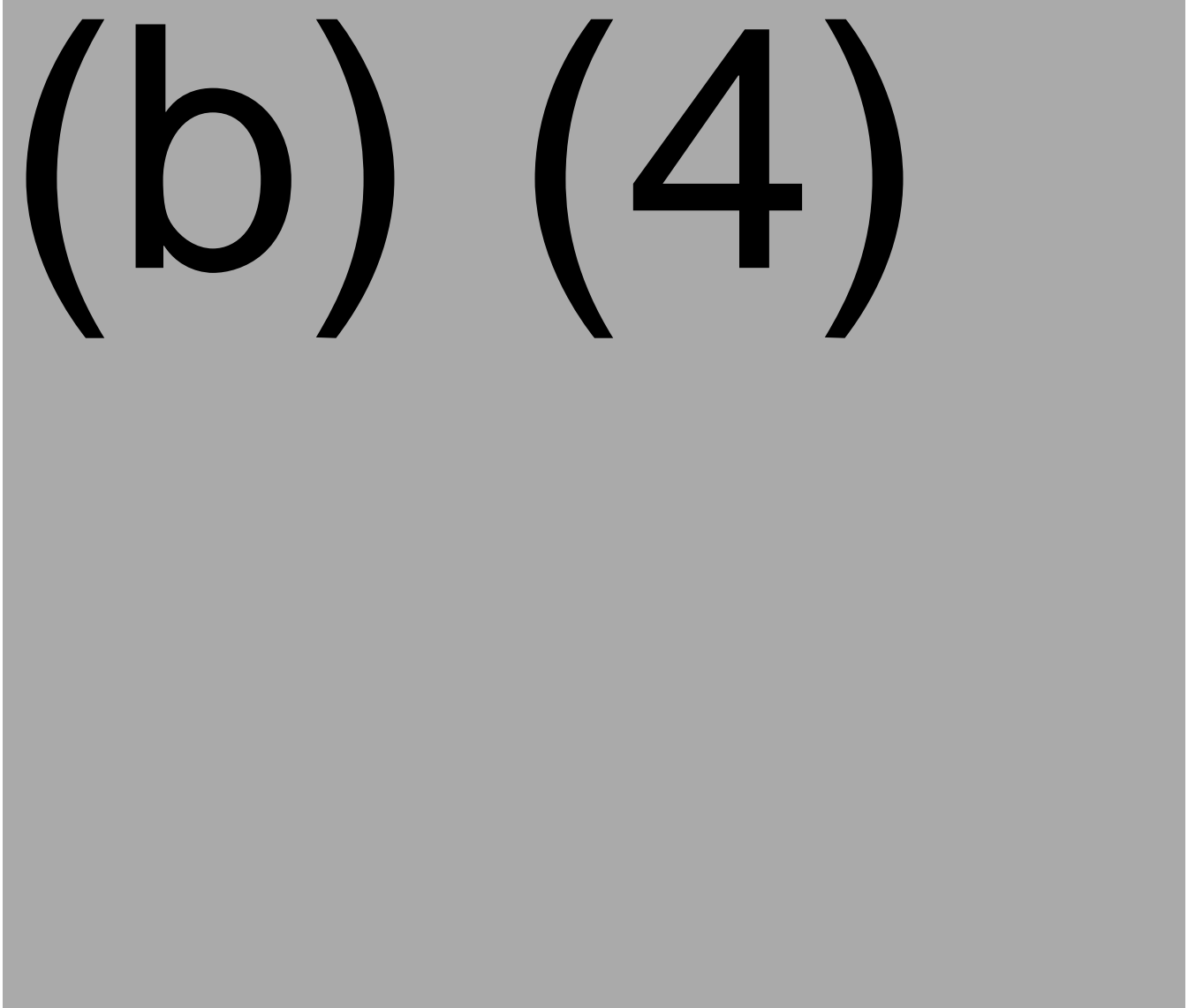
Air exchange rates for (b) (4) areas are provided in the table below. Pressure differentials for (b) (4) classified areas (b) (4) are provided in the figure below.

Table. Minimum Room Air Exchange Rate (RAER) Requirements in Air Changes per Hour (ACH) for ISO Classified Areas in the Cell Processing Facility (CPF).

(b) (4)

Air exchange rates are adequate.

(b) (4)

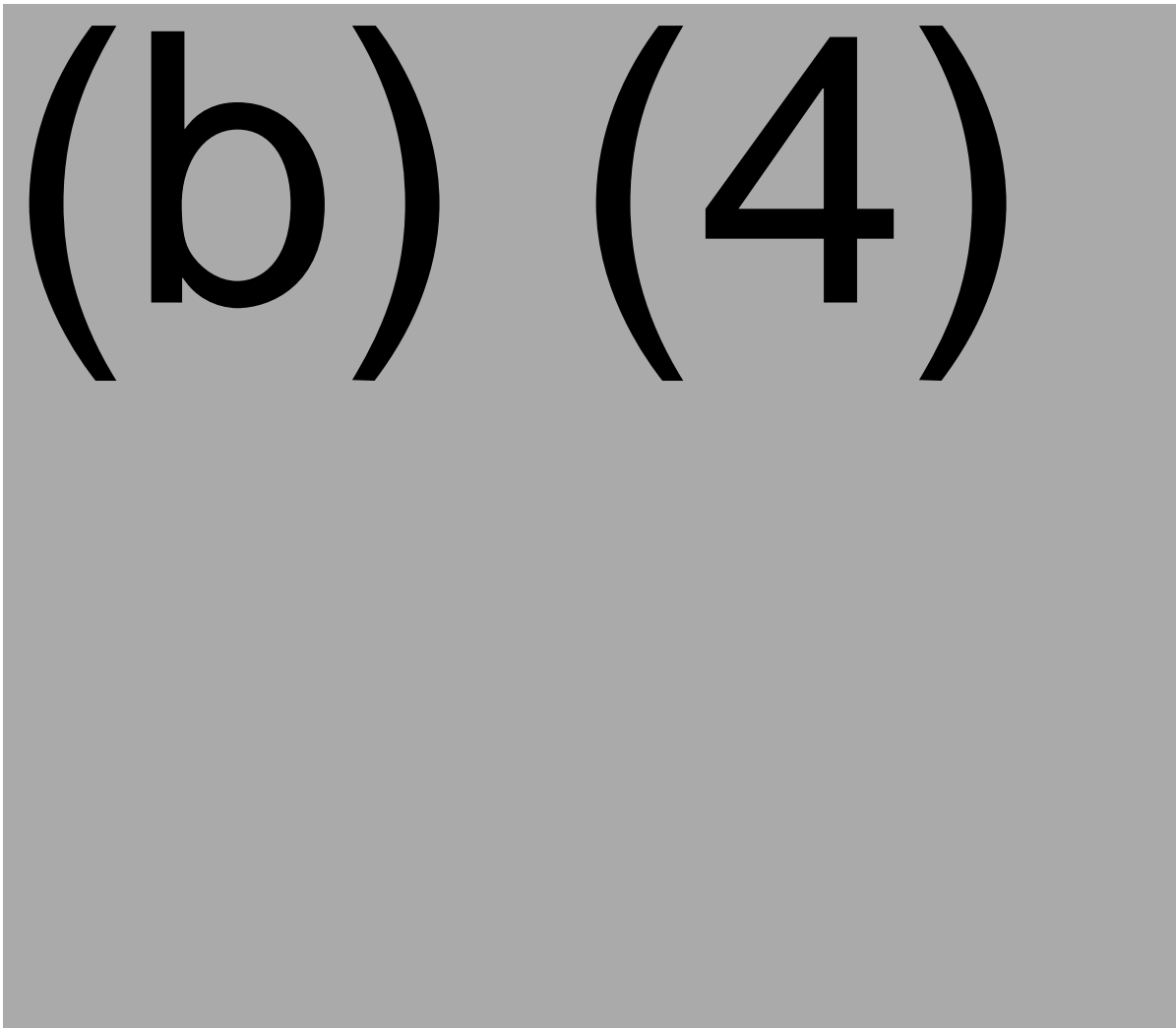


(b) (4)


As can be seen from the diagram above, air flows from clean areas to less clean areas and pressure differentials indicated in the diagram is sufficient to maintain microbial containment.

The following diagram for process flow indicates manufacturing steps:

(b) (4)



As can be seen from the diagram above, manufacturing steps are performed in the following sequence and areas: (b) (4)



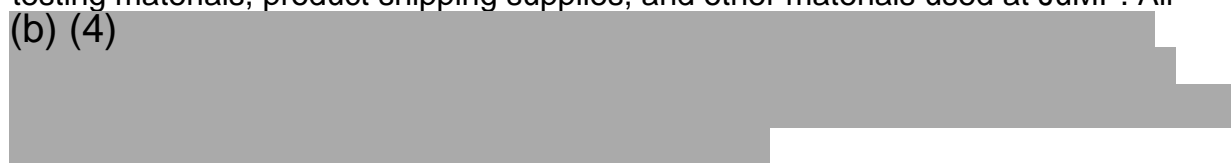
Quality Control Testing Laboratories

Quality control laboratories are segregated based on the type of testing being performed as described in the table below.


Warehouse Area

The JuMP warehouse includes access-controlled space for cGMP production and testing materials, product shipping supplies, and other materials used at JuMP. All


(b) (4)




(b) (4)



(b) (4)



(b) (4)



Utilities

Building Automation System (BAS):

The BAS is the (b) (4)

This system was also evaluated during the pre-license inspection of JuMP manufacturing facility. For additional information, refer to the EIR for this inspection.

Standby Power:

Standby (emergency) power is available for all (b) (4)

Water (COA, procedural controls, material controls as per (b) (4)):

For the cleanroom areas, a point-of-use (b) (4)

Domestic hot and cold water is supplied to sinks in the locker room for hand washing.

Additional information on the (b) (4) water was requested and provided in the **March 26th Amendment** in response to IR#4:

(b) (4) is used in the manufacture of the drug product. It is supplied by (b) (4) is used to (b) (4), which are used in the preparation of JCAR017 (b) (4) per the table below.

(b) (4)

(b) (4)

Sterile (b) (4) is not used in any other operation in the manufacturing process.

A new container of (b) (4) is used to (b) (4) for each prepared lot of (b) (4) used in the manufacture of JCAR017. The reconstitution step is typically

(b) (4)

Based on the information provided in the **June 19th Amendment** in response to the pre-inspection records request, (b) (4) is used for facility cleaning.

Drains

In the cleanroom areas, (b) (4). Sinks are installed in the Locker Room for hand washing. There are no drains in the (b) (4) cleanrooms.

Liquid Nitrogen:

Liquid Nitrogen is purchased from an external vendor and supplied from a central location. Liquid Nitrogen is used for non-product contact operations.

(b) (4)

(b) (4) is purchased from an external vendor, supplied from a central location, and distributed to the (b) (4) areas.

(b) (4)

Clean Compressed Air:

(b) (4) air is purchased, supplied from a central location, and (b) (4)

HVAC and AHU:

There are (b) (4) manufacturing cores. Each manufacturing core has its own dedicated (b) (4)

Access Control (Authorized access)

Access to the facility and support areas where subject cellular material and samples are stored, processed, and tested is limited to authorized personnel only. Personnel with work responsibilities in the controlled areas are granted access after completing the required training and documentation. The primary mechanism used to control access is a system of (b) (4)

(b) (4) issued to authorized personnel. In cases where access is controlled by (b) (4)

Environmental Monitoring Performance Qualification (EMPQ) and Routine Environmental Monitoring (EM)

Environmental Monitoring

An environmental monitoring program has been established to monitor the effectiveness of facility controls (e.g., cleaning, gowning, personnel flow, etc.). Total airborne particulate, viable airborne particulate, and surface samples are collected from ISO classified areas through the routine and concurrent (during processing/in operation) monitoring program. Both programs employ alert limits and action limits for each sample (see Table 7, Table 8, Table 9, Table 10, and Table 11 in Section 3.2.a.1 of the original BLA submission).

All EM samples and personnel monitoring samples (which include air samples and surface samples) from routine EM testing in the classified areas are processed in the EM testing lab. Samples obtained from (b) (4) are also processed in this lab.

The following tables list alert and action limits for EM of (b) (4) areas, which are acceptable.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)


(b) (4)

Routine EM program

(provided in Section 3.2.a.1 and **March 26th Amendment** in response to IR# 1.7)

The ISO classified areas are monitored for cleanliness on a routine basis as described below.

(b) (4)



(b) (4)

Concurrent program (in operation)

The ISO ^{(b) (4)} classified areas are monitored every time they are used for processing. Monitoring includes sampling for surfaces, total airborne particles, viable contaminants, and personnel monitoring.

Cleanroom Environmental Monitoring Performance Qualification (EMPQ)

Environmental Monitoring Performance Qualification (EMPQ) was performed on all classified cleanrooms at JuMP. The EMPQ is performed (b) (4) and evaluates samples of total particulates, viable air, and viable surfaces against pre-defined acceptance criteria.

Results met the acceptance criteria listed in the tables below.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

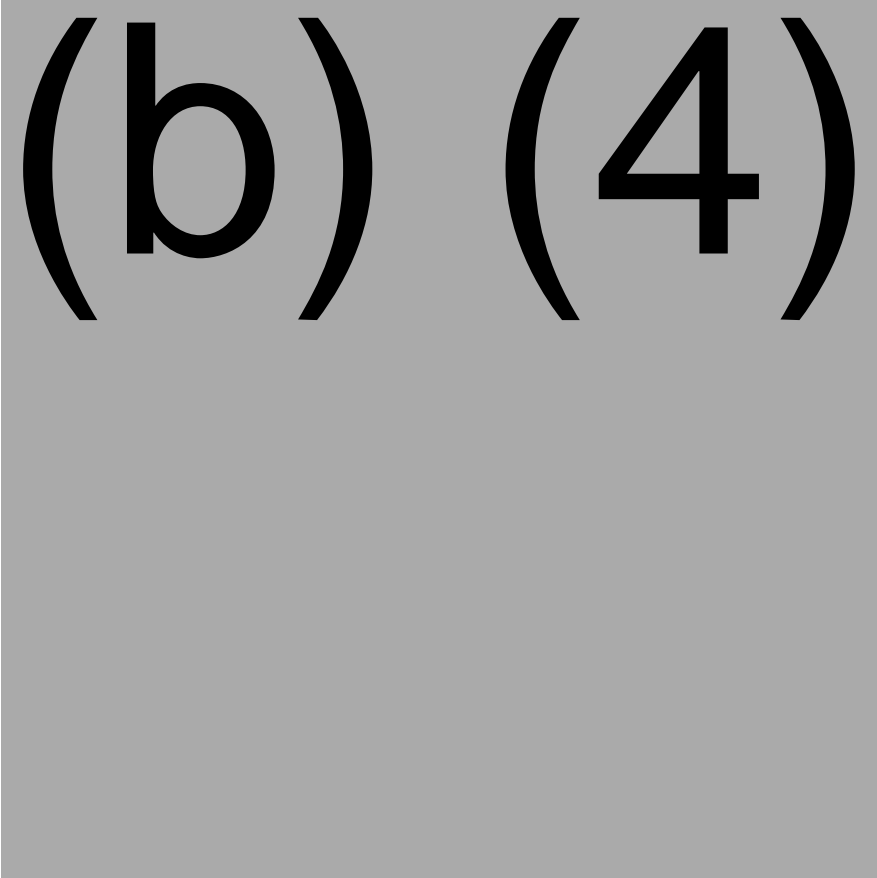
The required minimum days of EMPQ sampling was defined as (b) (4) for rooms that are cleaned (b) (4)

EMPQ results for (b) (4) areas (b) (4), support areas) at (b) (4) met the limits listed in the tables above.

EMPQ results that were not provided in the original BLA submission for the rooms (b) (4) were provided in the March 26th Amendment in response to IR# 1.4:

An EMPQ was performed for each of the cleanrooms (b) (4) prior to the introduction for GMP use. EMPQ results at static (b) (4) conditions met the limits indicated in the tables above.

(b) (4)



ISO ^{(b) (4)} areas are recertified on an (b) (4) frequency in accordance with ISO (b) (4) (noted in the **March 26th Amendment** in response to IR#1.2).

No information on personnel monitoring during EMPQ studies was provided. Response to the related IR was provided in the **March 26th Amendment** in response to IR#1.5:

Personnel monitoring was not performed as part of EMPQ. The EMPQ program is limited in scope to the cleanroom and the sampling plan is defined for the room only. Other simulation activities are used to evaluate personnel monitoring, specifically the Aseptic Process Simulation (APS) protocol and the individual Aseptic Processing Qualification (APQ) used to qualify each operator.

Surface monitoring performed during EMPQ studies, utilizing (b) (4) met the acceptance limits and representative environmental isolates recovered from the surface samples were identified to the species level. The identified organisms were listed and discussed in the summary reports. This was performed for initial facility EMPQ to establish a baseline for facility flora.

The firm indicates that the collection of personnel monitoring data, as well as ISO ^{(b) (4)} microbial and particulate data within (b) (4) APS studies provides confirmation that ISO ^{(b) (4)} controls are effective under conditions of actual use.

In summary, personnel monitoring is performed during (b) (4) and this is acceptable (discussed during the June 26th internal DMPQ meeting for the BLA).

EMPQ results for BSCs used in manufacturing was provided in the March 26th Amendment in response to IR# 1.3:

Each BSC is qualified as an individual piece of equipment and are not sampled during EMPQ. BSCs are recertified on a (b) (4) basis, which includes evaluation of total particulate measurements to ISO (b) (4). All BSCs were certified as part of initial qualification as summarized in the table below and have been re-certified to the same criteria since going into service.

Table. BSC ISO ^{(b) (4)} Results from initial certification (with date)

Note the BSCs are monitored during operations for non-viable particulates and viables (active and passive air, and surface at the end) and personnel monitoring for gloves and sterile sleeves.

Rooms with Segregated Workstations

Rooms with cells in-process from (b) (4) are processed in closed systems at workstations that are clearly defined areas or sections of rooms (or equipment), and cells from (b) (4) subject are permitted at each workstation.

Workstations where cells in **closed systems** are in-process include the following areas:

- (b) (4)
-

- (b) (4) .

Pass-Throughs

- (b) (4)
- [REDACTED]

Materials Control

Materials used for processing subject cellular material are controlled to ensure that correct materials are used and to prevent inadvertent use of incorrect materials. This control is intended to permit multiple processes that use different materials (e.g., viral vectors) to be performed in the same room or at the same station after the changeover and Line clearance detailed above.

JuMP part number

Each material is assigned a unique JuMP Part Number that is applied to all material containers. The same part number is listed in subject-specific batch records wherever that material is used in the process.

Material confirmation

MES confirms through the scanning of the material barcode, that the material being scanned is the correct material, the material is in an acceptable state and the material is not expired. Two- person verification is not required since MES performs the electronic verification.

Electronic material verification

A validated electronic inventory system and barcoded labels are employed to control the use of each material and track where the material is used. Expired and incorrect materials for the process are not authorized for use per standard operating procedures. Additional system controls are also in place. Material confirmation is necessary prior to each time a material is used in processing.

Microbial Contamination Controls

Microbial contamination controls include cleanroom design, gowning controls, cleaning/sanitization, environmental monitoring, segregated operations and changeover, single subject per room or workstation, line clearance and area changeover, materials control, pass-throughs.

Floors are cleaned and sanitized (b) (4) and walls and ceilings are cleaned and sanitized at least (b) (4). The cleaners and disinfectants used are EPA Registered Disinfectants and demonstrated to be viricidal against a (b) (4) and have demonstrated capability to inactivate typical microbial contaminants isolated from Environmental Monitoring.


For the virucidal efficacy testing study, cleaning agents were tested against (b) (4) representative of the viral vectors used in the manufacture of JCAR017. Cleaning agents and corresponding organisms were tested on representative (b) (4) were achieved, which is acceptable.

(b) (4)

(b) (4)


Information on disinfectant contact time and concentration was requested and the response was submitted in the **March 26th Amendment** (refer to the response to IR# 1.6):

(b) (4)

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Class II Biological Safety Cabinets (BSC) are equipment within the facility that maintain the ISO ^(b)₍₄₎ environment. **BSCs are cleaned** (b) (4)

(b) (4)




SOP-000183 “Cell Processing Facility Cleaning and Sanitization” (Version 14.0, Effective Date 31 May 2020) was provided in the June 19th Amendment in response to the record request item 4.3. This procedure applies to the Juno Manufacturing Plant (JuMP) Cell Processing Facility (CPF) controlled classified and controlled non-classified (CNC) environments located in Bothell, WA. The processing work surfaces and equipment in closed operating rooms (COR) and open operating rooms (OOR) are disinfected per SOP-000186.

Changeover procedures

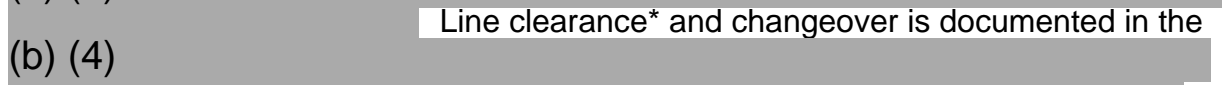
Detailed information on the changeover procedures was provided in the **March 26th Amendment** in response to IR# 1.8.

Line clearance and changeover procedures are governed by SOP-000186 (Changeover Procedure). Documented evidence of each instance of a changeover event is collected on FRM- 000077 (Changeover and Line Clearance Form).


SOP-000186 (Version 13, Effective Date 30 Mar 2020) describes the following procedures/activities: Campaigned areas and workstations are (b) (4)




Activities described in this SOP include removal of documents, labels and materials associated with the lot are (b) (4)




(b) (4) Line clearance* and changeover is documented in the



(b) (4)





(b) (4)



The latest version of SOP-000186 (Version 14.0, Effective Date 21 Aug 2020) was provided in the October 5th Amendment in response to the record request item 4.

Key design elements and operation controls

(b) (4)

Validation Program

The validation program as defined in the Validation Policy and Validation Master Plan (VMP) addresses all the qualified elements of the facility and operations. This includes facility and equipment qualification (IQ, OQ, PQ) and manufacturing process validation. The equipment and facility, including classified cleanrooms, are qualified in accordance with the VMP using a requirements-based approach which documents pre-approved testing traceable to all system requirements. The equipment validation program is a part of the asset management lifecycle which ensures all systems are qualified before release for use in GMP operations.

Equipment

Current layouts of the manufacturing equipment located in all manufacturing cores, suites/ rooms and workstations of the JuMP facility were provided in the October 5th Amendment in response to the record request item 4.2. Those layouts indicate the location of each equipment and workstation (where needed) with clear description of the equipment.

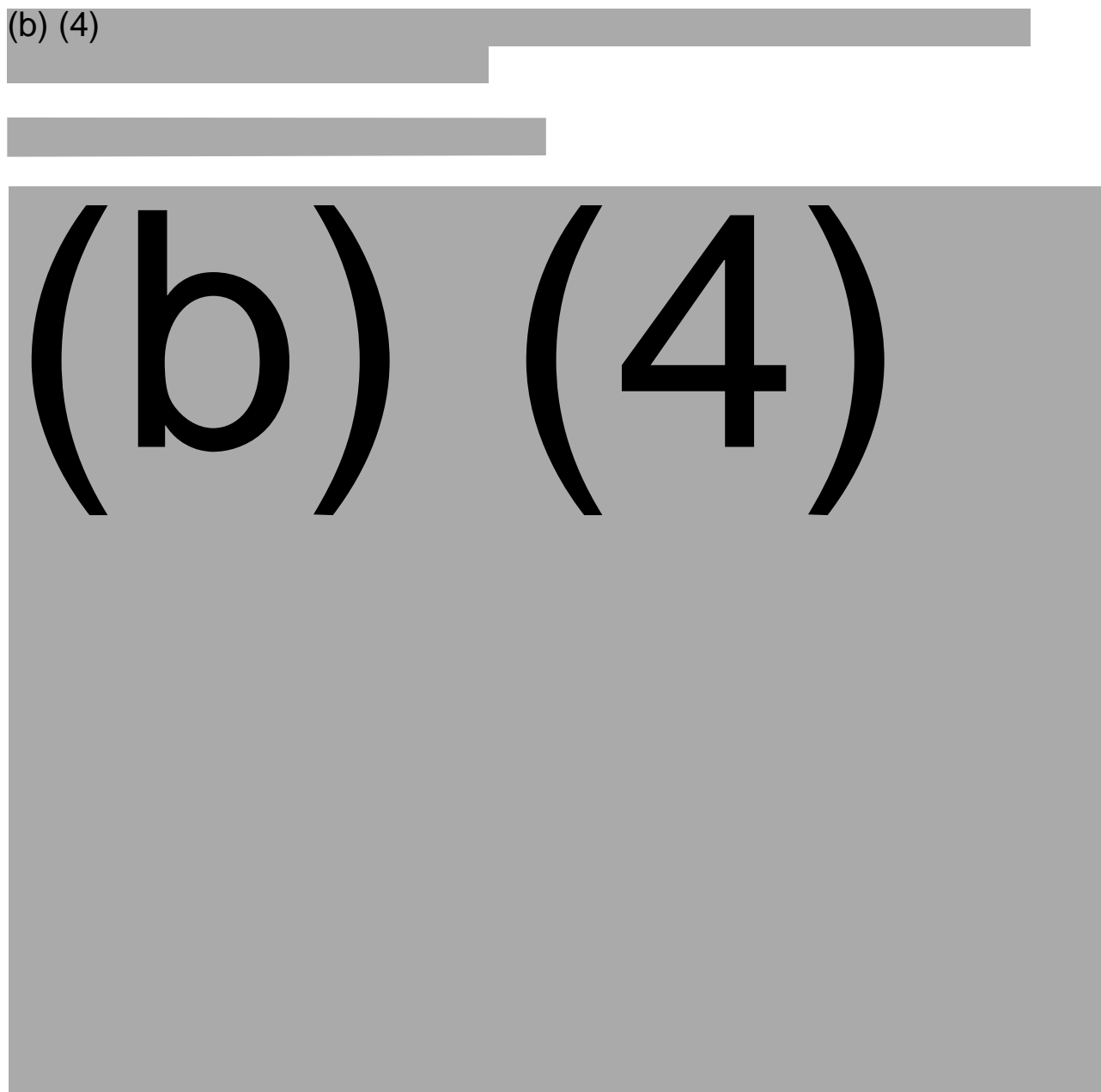
In the **October 5th Amendment**, SOP-000051 ("Asset Lifecycle" version 7.0, Effective Date 17 Jul 2020) for the equipment transfer between the rooms, suites and cores was provided in response to the record request item 4.1. Also, this response included a list of transferred/ moved equipment along with their current locations (a list for equipment transfers occurring within the previous 90 days) and described the transfer frequency of the equipment and the circumstances requiring transfer.

In the **October 5th Amendment**, a description of Juno procedures for identifying the status of equipment and workstations (e.g., tagging as cleaned/disinfected, in use, in maintenance, out of order etc.) was provided in response to the record request item 4.3. Equipment status is checked during equipment allocation to an order to ensure all equipment is in ready state. The assignment of status to workstations/equipment as cleaned/disinfected (SOP-000186 Changeover Procedure) or in use is managed by the (b) (4) Equipment status checks during (b) (4)

(b) (4) Maintenance and Out of order status for Workstation or Equipment is (b) (4) Version 8.0, 10 Jul 2020).

Note all the product-contact equipment used in the manufacture of JCAR017 DS and DP manufacture and storage are single use sterile equipment (ready to use). A list of the single use product contact materials was provided in the **March 26th Amendment** in response to IR# 2.1:

(b) (4)



There are currently (b) (4) (all equivalent, refer to Table 17 provided in the **March 26th Amendment** in response to IR# 2.2), (b) (4)

(all equivalent, refer to Table 17), (b) (4)

(all equivalent, refer to Table 17), (b) (4)

(critical QC equipment, all equivalent, refer to Table 17) released for GMP use at JuMP for manufacturing JCAR017 (provided in the March 26th Amendment in response to IR# 2.2).

IQ/OQ/PQ summary for the equipment was not provided in the original submission and therefore requested for critical manufacturing equipment and critical QC testing

equipment (b) (4) and response was provided in the **March 26th amendment** in response to IR# 2.2:

A summary of major equipment qualification (IQ/OQ/PQ) is provided in the tables below for (b) (4)

(b) (4) used for analytical purposes. As part of equipment qualification, alarm function for the equipment were qualified as well. IQ for the equipment involved verification testing of requirements associated with utility and environmental conditions, instrument calibration and software version, and review of the vendor executed protocol. OQ/PQ verified function of the equipment (such as for process/equipment specific parameters and operating ranges) for intended use/unit operation. For example, the temperature of the (b) (4) was monitored and met the acceptance criteria. No objectionable issues noted.

(b) (4)

(b) (4)


(b) (4)

Biological safety cabinets (BSCs)

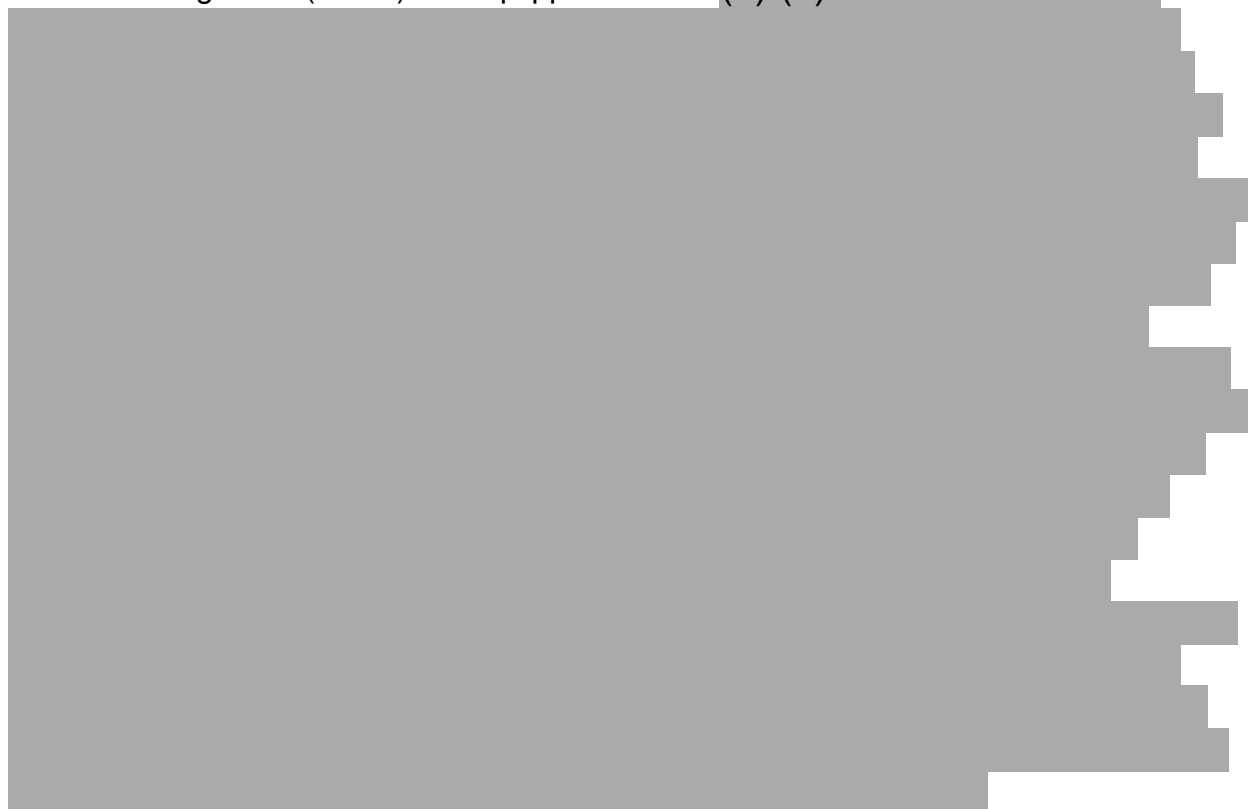
The Biosafety Cabinets (BSCs) are recertified on a (b) (4) frequency (provided in the March 26th Amendment in response to IR# 1.2). ISO (b) (4) areas are recertified on an (b) (4) frequency in accordance with ISO 1(b) (4).

The following information was provided in the March 26th Amendment in response to IR# 2:

(b) (4)




The biological safety cabinets (BSCs) utilized in manufacturing at the Juno Manufacturing Plant (JuMP) are equipped with an (b) (4)



In the October 5th Amendment in response to the record request item 4.4, re-certification documentation for the BSCs used for open manipulations

(b) (4)



were provided and reviewed no issues were noted.

Smoke study videos for BCSs were viewed during the October 7-16 inspection of the JuMP facility and no issues were found (refer to the EIR for this pre-license inspection).

Other manufacturing equipment

(b) (4) :

As per the information provided in the March 26th Amendment in response to IR#3, there is no sterile filtration performed for JCAR017 manufacturing. (b) (4)

Filling equipment for final drug product:

There is no filling equipment used for the DP filling into (b) (4) vials. CD4+ and CD8+ cell components are filled separately in the (b) (4) located ISO (b) (4) open operation rooms (OORs). The final product component is (b) (4) filled into 5ml (b) (4) vials using sterile single use syringes. 8 vials in total is filled (4 for each component). Note the filling operation was observed during the JuMP pre-license inspection, refer to the EIR.

Major Computerized Systems


Computerized systems are validated as per 21 CFR Part 11.

Computerized systems were evaluated during the pre-license inspection of JuMP manufacturing facility. Refer to the EIR for JuMP pre-license inspection.


(b) (4)

(b) (4)


(b) (4)

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(b) (4)

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(b) (4)

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Computer Systems Validation

The Computer Systems Validation (CSV) Program governing the validation of the Computer Systems listed above is performed in accordance with Regulatory body Guidance, Industry Standards such as ISPE's GAMP and industry best practices. These include:

1. Regulations pertaining to electronic systems such as:
 - **21 CFR Part 11**, Electronic Records, Electronic Signatures.
2. Regulatory body guidance such as:
 - FDA Guidance for Industry: General Principles of Software Validation, January 2002.
 - FDA Guidance for Industry: Part 11, Electronic Records; Electronic Signatures, August 2003.
 - Data Integrity and Compliance With CGMP Guidance for Industry, April 2016.
3. Industry Standards such as:
 - International Society of Pharmaceutical Engineer's (ISPE) Good Automated Manufacturing Practices (GAMP) Version5 (GAMP5): A Risk Based Approach to Compliant GxP Computerized Systems.
4. Quality Systems Controls for Computerized Systems (including Company Policies, Standards and Procedures)
 - Computerized Systems Policy, Computer Validation Master Plan and Computer System Validation Program Standard Operating Procedure(s) and Data Integrity policy outline the company's lifecycle approach to validating its computerized systems and assuring the integrity of data from its electronic systems.
 - SOPs govern the entire lifecycle spanning from procurement of a computerized system (GxP applicability assessment is performed upon procurement) to its retirement from use. Systems Requirements, Specification and design are documented, assessed for risk, prospective Validation Plans including IQ, OQ and PQ Protocols are developed and approved prior to the start of the validation activities in accordance with established SOPs. Upon completion of validation activities to demonstrate the systems suitability for 'intended use' (i.e. meeting a predetermined acceptance criteria) a validation report is prepared for review by Quality Assurance.

A formal quality assurance (QA) unit approval allows its use for GxP purposes.

- Users are trained on the use of the system prior to being granted access to perform role-based activities they are trained on.
- Once in GMP use, systems are maintained in a state of control. Change Control Quality System governs changes to the validated systems. Changes are assessed for impact on validated state, risk and adequately tested and approved by QA prior to GMP use. Changes to computerized systems are managed in a validated electronic tool.
- A periodic review SOPs is in place to review the state of control of the system on an on-going basis. SOPs govern systems retirement (decommissioning) from GMP use. Data backup and Archival policies govern the management of GMP data.
- In addition to change control and Training, the other governing quality Systems include:
 - Deviation Management
 - Corrective Action and Preventative Action (CAPA)

5. Technical Controls:

In addition to Quality Systems controls on Computerized Systems, technical controls are in place to assist in management of these systems on a routine basis. These include:

- Security controls for access to a system:

- Systems require unique user ID and password as governed by the Password policy.
- Lock out (idle time, incorrect passwords).
- Only authorized users are granted access in accordance with a User Access Management Procedures.
- Users are required to change passwords routinely.
- Audit Trails and Electronic Signatures are in place:
- System activity is monitored by Audit trails at the system and transaction levels.
- Electronic signatures are in place as applicable.
- System servers are monitored and maintained in secure locations.
- Systems are maintained in accordance with established procedures (these include routine patching, virus protection).
- Data is backed-up routinely in accordance with established procedures.

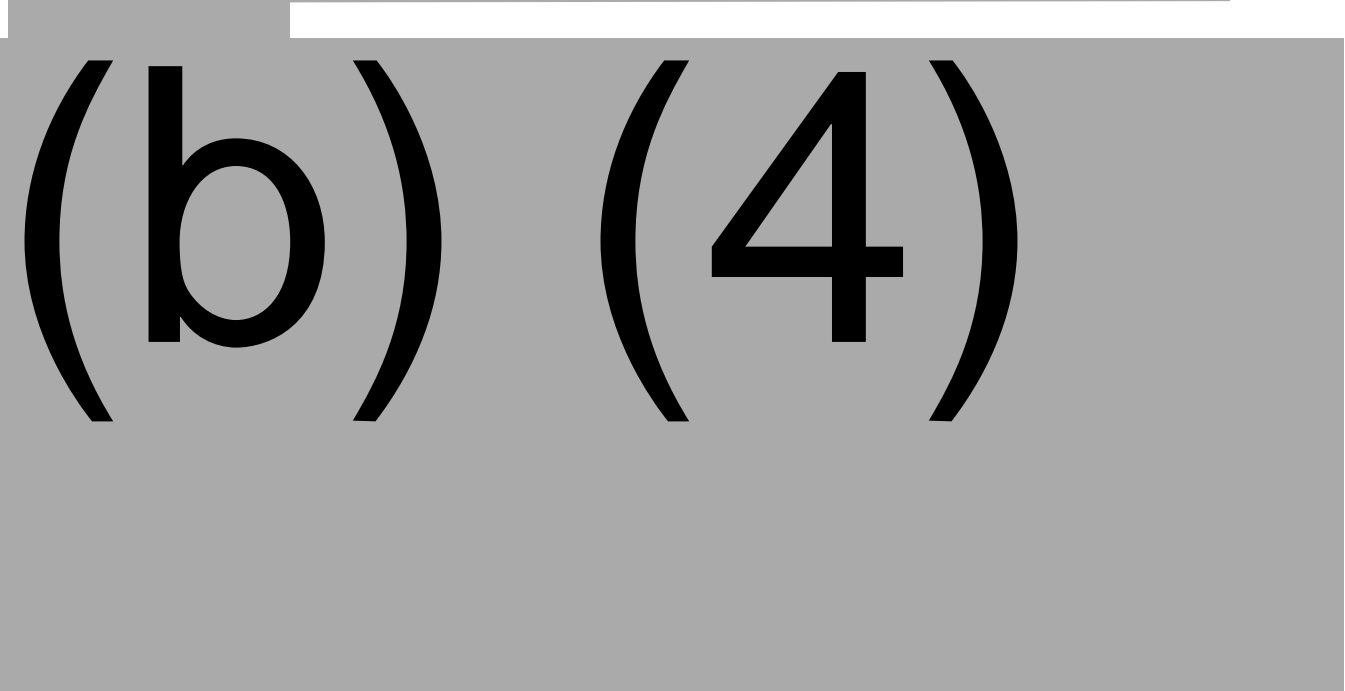
Product Identity Verification

Identity tests that distinguish each product from others that are manufactured in the facility are required. As part of the Product Identity Verification strategy, **product identity assays are required for each product** that are specific for that product and selective against all other products.

Subject Chain of Identity (COI) and Chain of Custody (COC)

Figure below illustrates the manufacturing process from patient enrollment through patient treatment, and summarizes relevant validated computer systems, data linkages, and process controls that enable COI.

(b) (4)



The electronic COI system and materials inventory system are used in combination with two-person sign-off of documentation to ensure that the subject's cells and materials transferred into the area for processing match the staged documents and raw materials (3.2.a.1).

The COI and COC controls are in place from leukapheresis receipt through production, storage, testing, release, and distribution to ensure that the identity of each subject's cellular material is tracked, subject cellular material is not accidentally exchanged with cellular material from another subject, and control is maintained over the location and access to subject cellular material. Throughout the manufacturing process, COI is checked and verified before allowing subsequent processing. As COI checks are performed, COC information is recorded allowing the tracking and tracing of all parties handling the product.

When a patient is scheduled for treatment, a unique identification number, JOIN, is assigned by the (b) (4) system to the patient's treatment. The JOIN is associated with the patient's first name, last name, and date of birth (subject identifiers). The JOIN, with associated identifiers, is communicated to the physician's site, the cell collection center, and the manufacturing site when a treatment schedule is confirmed.

Prior to the arrival of the leukapheresis product at JuMP, during the plant scheduling process, manufacturing orders (lot) are created in the (b) (4) for the production of cell therapy products. The manufacturing orders created each have order numbers containing the JOIN of the incoming leukapheresis product and will **produce output material with "Lot Numbers"** containing the JOIN of the incoming leukapheresis

product, enabling electronic COI tracking and control. The “**Lot Number**” (which contains the JOIN) represents the leukapheresis product lot number, the manufacturing batch number, and the drug product lot number. The (b) (4) system generates COI labels prior to manufacturing, and the COI labels are scanned throughout manufacturing.

Upon receipt of the leukapheresis product at the manufacturing site, the label on the leukapheresis product bag and the collection data form are verified per procedure against the source document provided at the time of the treatment schedule confirmation, to ensure all subject identifiers are accurate.

Prior to initiation of product manufacturing using the leukapheresis product, the JOIN barcode on the leukapheresis bag is electronically scanned into the (b) (4). The (b) (4) performs a COI check by comparing the scanned value of the JOIN-barcode against the order number being manufactured and only allows the order to progress if there is a match.

During manufacturing, (b) (4)

match. If the labels do not match, progress is halted until the mismatch is resolved.

Final product labels, which include the patient identifiers, are issued by quality assurance. Prior to shipment, a final electronic COI verification is done on the COI barcode on the final drug product, which is (b) (4) during the packaging process. The packaging process can only continue if there is a match between the (b) (4) value of the drug product COI barcode.

Documentation approving the drug product for infusion (release for infusion) accompanies the product during shipment to infusion sites and includes the JOIN and all patient identifiers

Before initiating infusion of drug product, physician sites are instructed to verify the subject's identity against the drug product label and the release for infusion documentation.

COI process validation has been executed for clinical processes and will be re-executed after implementation of the (b) (4) system. Verification for the validation of the computer systems were included in the inspectional activity plan for the JuMP pre-license inspection and for this verification refer to EIR.

Date/Time/Location/Person Logs

From the point that subject cellular material is received, through processing and testing, until the therapeutic cells are shipped to the treatment center, all transactions are recorded in validated computer systems. Manufacturing operations are recorded in an (b) (4) systems, and sample plans are executed and recorded in a (b) (4) system.

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

- ❑ The information provided in the original BLA submission and amendments related to facilities and equipment is acceptable and there are no outstanding review issues.
- ❑ The information provided in Section 3.2.a.1 for JuMP manufacturing site was also evaluated during the pre-license inspection of the site. Refer to the EIR and FDA Form 483 issued for this inspection.
- ❑ The information provided in Section 3.2.a.1 for (b) (4) site will be confirmed during the pre-license inspection of the site.
- ❑ (b) (4) manufacturing site was evaluated during the 2018 CBER inspection and this inspection was classified as VAI. Based on this inspection and the information provided in this BLA and its related amendments, the inspection of this site was waived for this BLA. Refer to the inspection waiver memo for this site.

3.2.A.2 Adventitious Agents Safety Evaluation

Deferred to the Product Office. Refer to the PO CMC review memo.

❑ Viral Clearance Studies

Deferred to the Product Office. Refer to the PO CMC review memo.

Overall Reviewer's Assessment of Section 3.2.A.2:

- ❑ The assessment of the information provided in section 3.2.a.2 is deferred to the Product Office.

3.2.A.3 Novel Excipients

Deferred to the Product Office. Refer to the PO CMC review memo.

3.2.R Regional Information (USA)**❑ Executed Batch Records**

Executed Batch Records for PPQ lots were provided.

Deferred to the Product Office. Refer to the PO CMC review memo.

❑ Method Validation Package

Deferred to the Product Office. Refer to the PO CMC review memo.

❑ Combination Products

Not Applicable (N/A)

Overall Reviewer's Assessment of Combination Products Section:☐ N/A☐ **Comparability Protocols**

Deferred to the Product Office. Refer to the PO CMC review memo.

Other eCTD Modules**Module 1****A. Environmental Assessment or Claim of Categorical Exclusion**

Deferred to the Product Office. Refer to the PO CMC review memo.

B. Labeling Review**Full Prescribing Information (PI):**

Deferred to the Product Office. Refer to the PO CMC review memo.

Carton and Container Label:

Deferred to the Product Office. Refer to the PO CMC review memo.