

**CBER CMC BLA Review Memorandum**

**BLA STN 125746/0**

**CARVYKTI [ciltacabtagene autoleucel]**

**David Bailey / CMC Facility Reviewer / OCBQ-DMPQ-MRBI**

1. **BLA#:** STN 125746/0

2. **APPLICANT** Janssen Biotech, Inc., US License Number: 1864

3. **PRODUCT NAME/PRODUCT TYPE**

CARVYKTI / ciltacabtagene autoleucel / LCAR-B38M Chimeric Antigen Receptor (CAR)-T cells

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

a. **Pharmacological category:** Cell

b. **Dosage form:** Cell suspension for infusion

c. **Strength/Potency:** 0.5 – 1.0 x 10<sup>6</sup> cells/kg

d. **Route of administration:** Intravenous

e. **Indication(s):** Treatment of adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody

5. **MAJOR MILESTONES**

Submitted

- Roll 1 Submission: December 18, 2020
- Roll 2 Submission: February 2, 2021
- Roll 3 Submission (final): March 31, 2021

First Committee Meeting: April 21, 2021

Filing Meeting: May 14, 2021

Internal Mid-Cycle Meeting: July 15, 2021

Mid-Cycle Applicant teleconference: July 29, 2021

Internal Late-Cycle Meeting: August 30, 2021

Late-Cycle Meeting: September 20, 2021

PDUFA Action Date: November 29, 2021

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
David Bailey CBER/OCBQ/DMPQ/Branch I	3. Quality 3.2.S Drug Substance 3.2.P Drug Product 3.2.A.1 Facilities and Equipment

7. **SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
March 31, 2021	STN 125746/0	BLA Submission

April 27, 2021	STN 125746/0.4 (response to DMPQ IR#1 April 20, 2021)	Provided details on manufacturing activities at Janssen (b) (4) facility, international regulatory inspection history, and FDA approved products manufactured at (b) (4) facility
July 6, 2021	STN 125746/0.15 (response to DMPQ IR #2 dated June 11, 2021)	(b) (4) – Records Request in Lieu of Inspection
July 30, 2021	STN 125746/0.27 (response to DMPQ IR #3 July 9, 2021)	(b) (4) - Clarification for (b) (4) process step, qualification study for (b) (4) system, clarification on (b) (4) decon, clarification on CCIT, HVAC and Utility qualification, EM clarification, waste flow, and (b) (4) qualification (b) (4) – HVAC and Utility qualification, waste segregation, Freezer, Refrigerator, (b) (4) qualification
August 31, 2021	STN 125746/0.41 (response to DMPQ IR #4 August 16, 2021)	(b) (4) – Records Request in Advance of Inspection
September 3, 2021	STN125746/0.39 (response to DMPQ IR #5 dated August 25, 2021)	(b) (4) - Clarification on CP in Section 3.2.R, (b) (4) - EMPQ data, APS reports, and disinfectant study
September 17, 2021	STN 125746/0.45 (response to DMPQ IR #6 dated September 2, 2021)	(b) (4) – Records Request additional records and deviations
September 20, 2021	STN 125746/0.46 (response to DMPQ IR #7 dated September 9, 2021)	(b) (4) – Clarification on Air Handling Units and areas serviced
October 4, 2021	STN 125746/0.50 (response to DMPQ IR#8 dated 29 September 2021)	(b) (4) – Clarification on soiling agent, (b) (4) qualification, alternative shipper, HVAC (b) (4) – transportation studies

October 8, 2021	STN 125746/0.54 (response to DMPQ IR #9 dated October 5, 2021)	(b) (4) – Acknowledgement of Agency Recommendation for CP reporting categories
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**8. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)**

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
510(k)	(b) (4)	(b) (4) freezing Bag	Yes	Information pertinent to the DP container closure system was reviewed, assessed, and documented in Section 3.2.P.7 of this memo
MF (b) (4)	(b) (4)	(b) (4) Reagent	Yes	Information pertinent to the CAR-T DP manufacturing Stage (b) (4)
MF (b) (4)	(b) (4)	(b) (4) Reagent	Yes	Information pertinent to the CAR-T DP manufacturing Stage (b) (4)

**9. REVIEWER SUMMARY AND RECOMMENDATION**

**A. EXECUTIVE SUMMARY**

Janssen Biotech, Inc. submitted a Biologics License Application (BLA) STN 125746/0 to support the licensure of CARVYKTI, a Chimeric Antigen Receptor T-cell (CAR-T) treatment of adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody. Division of Manufacturing and Product Quality (DMPQ) reviewed and evaluated the drug substance (DS) and drug product (DP) manufacturing processes and facilities proposed for the manufacture of CARVYKTI. This review memo includes summaries and assessments of the DS and DP manufacturing process, quality attributes, facility information including utilities, cross-contamination controls, qualification and maintenance of classified environments and manufacturing equipment, cleaning and sterilization processes, and types of equipment used (i.e., dedicated or shared, multi-use or single-use).

As part of the BLA review, a records request in lieu of an inspection (as per 704(a)(4)) was conducted for the Janssen Vaccines (b) (4) facility in (b) (4), which manufactures the lentiviral vector (LV), and is documented in a separate memo (approved on October 5, 2021). DMPQ reviewed Standard Operating Procedures (SOPs), study protocols, and final reports for equipment and facility qualification, and quality systems applicable to the LV manufacturing process. The facility was determined to be acceptable to support the approval of the BLA. The Janssen Vaccines (b) (4) facility will be entered into the Office of Biological Products Operations inventory and planned for a surveillance inspection post-approval.

DMPQ conducted a records request in advance of an inspection (as per 704(a)(4)) (approved on October 5, 2021) and a pre-license inspection (PLI) for the Janssen Pharmaceuticals, Inc. facility located in (b) (4), which manufactures the ciltacabtagene autoleucel product. The PLI was conducted from (b) (4) by DMPQ, Division of Cellular and Gene Therapies (DCGT), and Office of Regulatory Affairs (ORA) inspectors. The PLI was performed to ensure the product met all predetermined specifications, the production process is validated and controlled, and the facility and equipment, and their associated systems, are operated with quality oversight consistent with the current good manufacturing practice (CGMP) requirements. No Form FDA 483 was issued at the conclusion of the Janssen Pharmaceuticals, Inc. PLI and the PLI was classified as No Action Indicated (NAI).

In addition to the PLI and records review, facility inspections were waived following an evaluation of the inspection compliance histories of the DP release testing facilities for Janssen Biotech, Inc. in (b) (4) and (b) (4). Note the inspection waiver for these facilities is documented in a separate inspection waiver memo dated October 6, 2021.

Based on the information submitted to BLA 125746/0 and in conjunction with the records review, PLI, and inspectional compliance history evaluations, the product process, facilities, equipment, and quality controls appear acceptable for the licensure of CARVYKTI, and approval is recommended.

## **B. RECOMMENDATION**

### **I. APPROVAL**

I recommend approval of the BLA with the inspectional follow-up recommendations below.

CBER understands the inspectional recommendations may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

*Janssen Pharmaceuticals, Inc. in (b) (4) (FEI # (b) (4) )*

- 1. The (b) (4) were qualified as Grade (b) (4) during initial commissioning but could not be verified or monitored during (b) (4) environmental monitoring (EM) and routine EM as only viable surface sampling is performed. Please review the (b) (4) EM trending data, preventive maintenance records, and lot release data to ensure the (b) (4) are maintained in a state of control.*

## **II. SIGNATURE BLOCK**

Reviewer/Title/Affiliation	Concurrence	Signature and Date
David Bailey CBER/OCBQ/DMPQ/BI	Concur	
Lori Peters, Branch Chief CBER/OCBQ/DMPQ/BI	Concur	
John Eltermann, Division Director CBER/OCBQ/DMPQ	Concur	

## Review of CTD

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**Module 3**

**3.2.S DRUG SUBSTANCE<sup>2</sup>**

**3.2.S.2 Manufacture**

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

Janssen (b) (4) Manufacturers

Company	Address	FEI (if applicable)	Responsibilities
(b) (4)			



(b) (4)

### 3.2.S.2.2 Description of Manufacturing Process

Janssen (b) (4) Facility






(b) (4) lentiviral vector encoding a chimeric antigen receptor (CAR) targeting B-cell maturation antigen (BCMA).

#### □ **Manufacturing process steps**

(b) (4)



(b) (4)



### 3.2.P DRUG PRODUCT<sup>3</sup>

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

**Reviewer Note:** Janssen included information on the Drug Product manufactured at (b) (4) in both Section 3.2.S and 3.2.P as they consider the CAR-T manufacturing process continuous.

The Drug Product (DP) is an autologous cell suspension of transduced chimeric antigen receptor (CAR) positive viable T cells formulated in a chemically defined freezing medium ((b) (4)) containing 5% DMSO. The DP is formulated for the target dose using either a 70 mL fill volume into a single (b) (4) freezing bag or a 30 mL fill volume into a single (b) (4) freezing bag.

The DP composition consists of Ciltacabtagene autoleucel cells and (b) (4) cryoprotectant (b) (4). The composition for each DP fill is presented below.

- 70 mL DP in (b) (4) Bag
  - CAR+ viable T cells: (b) (4)
  - Total Viable Cells: (b) (4)
  - Total Viable Cells/mL: (b) (4)
  - (b) (4) : 70 mL
- 30 mL DP in (b) (4) Bag
  - CAR+ viable T cells: (b) (4)
  - Total Viable Cells: (b) (4)
  - Total Viable Cells/mL: (b) (4)
  - (b) (4) : 30 mL

### 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 Ciltacabtagene autoleucel manufacturing is a (b) (4) process as there is (b) (4) and the DP formulation and fill. The DP contains CAR+ viable T cells calculated based on the patient weight, target dose, (b) (4) and formulated in (b) (4). The active component is (b) (4) T cells that have been transduced by a lentiviral vector (LV) encoding a CAR for B-cell maturation antigen (BCMA).

I defer full review to OTAT.

#### 3.2.P.2.2 Drug Product

##### 3.2.P.2.3 Manufacturing Process Development

The commercial DP manufacturing process development refined the clinical manufacturing process from (b) (4) stages to (b) (4). A comparison of the clinical DP process and the commercial DP process is presented on Table 7. The changes are reflected only in Stage names and number of Stages. The Clinical Process Stage (b) (4) was removed from the manufacturing flow and is documented in Chain of Identity and Chain of Custody.

**Table 7: Comparison of Clinical DP Process and Commercial DP Process**

(b) (4)
---------

(b) (4)

The essential elements of the manufacturing process were retained. The DP manufacturing process was developed at the (b) (4) and refined at Janssen (b) (4) before being transferred to the Janssen (b) (4) facility for further refinement during Phase 2a. Process Validation (PV) of the commercial process were performed at Janssen (b) (4). A summary of the development history, including significant process improvements/changes, and justifications for the changes is presented on Table 8.

**Table 8: DP Development History Summary**

Process Stage and Element	(b) (4) Clinical DP Process	PV/Commercial DP Process	Justification
(b) (4)			

(b) (4)

#### 3.2.P.2.4 Container Closure System

The primary container closure system (CCS) for the DP is the (b) (4) and (b) (4) freezing bag. Both bags use the same materials of construction, ethyl vinyl acetate (EVA) film and are certified in accordance with (b) (4), Class (b) (4) and (b) (4) testing and can store blood cell product at LN<sub>2</sub> vapor temperature. The fluid path within the bag is sterile and non-pyrogenic. The bags comply with (b) (4)

Stability studies were performed to demonstrate the compatibility of the DP with the (b) (4) bags. The quality of the DP was monitored throughout the shelf life at the recommended storage condition of (b) (4). The data from the stability studies appears to demonstrate the (b) (4) bags are compatible with the DP.

Extractables and leachable studies were conducted on the (b) (4) bags based on FDA guidance and (b) (4); I defer review to OTAT.

Additional information about the CCS is reviewed in Section 3.2.P.7.

#### 3.2.P.2.5 Microbiological Attributes

Container Closure Integrity Testing (CCIT) was performed on the DP CCS to demonstrate the consistent integrity of the CCS and its ability to prevent microbial ingress. Two CCIT studies were performed, one following DP manufacturing and one after DP shipment. Commercially representative samples (b) (4) were used for

CCIT. The test samples included (b) (4) bags with 70 mL (b) (4) media and/or (b) (4) bags with 30 mL of (b) (4) media. Microbial attributes of the DP were monitored via sterility testing at release and as part of the stability studies.

CCS integrity was evaluated by (b) (4) testing, under defined (b) (4) challenge conditions. The entire DP bag (test sample) is (b) (4)

(b) (4)

The (b) (4) test threshold for the DP bags is a (b) (4). The test included positive and negative leakage controls.

The positive and negative controls were filled with (b) (4) media and sealed, using the same bags as the DP test samples. A (b) (4) is used to create the (b) (4) in at least one positive control. The acceptance criteria for the CCIT by (b) (4) test are presented on Table 9.

**Table 9: CCIT by (b) (4) Test Acceptance Criteria**

Test Article	Acceptance Criteria
Tested DP samples	(b) (4)
Negative Leakage Control	(b) (4)
Positive Leakage Control	(b) (4)

#### Post Manufacturing CCI

CCIT was performed using the (b) (4) test on commercially representative samples (b) (4) manufactured using the commercial DP process. (b) (4) bags were used for this study and are considered representative of both DP configurations as the sealing and integrity is independent of the product, fill volume, and bag size.

Three independent DP fill runs were manufactured on different days at the commercial manufacturing site and (b) (4) DP bags were filled per run. The CCIT sample batch size is (b) (4) than the typical DP batch of (b) (4) bags. The three DP batches were tested for CCIT and met the acceptance criteria (no failures detected).

#### Post Shipment CCI

The DP is shipped at temperatures  $\leq -120^{\circ}\text{C}$  and the DP freezing bags may also be subjected to physical forces during shipment. A study was performed to demonstrate CCI post-shipment using commercially representative samples (b) (4). Test

samples in the finished goods package were placed in (b) (4) dry vapor shipping system and subjected to simulated transportation. After the simulated transport study, the DP bags were visually inspected for defects and tested by CCIT.

One bag did show a visible defect and was not submitted for CCIT. CCIT was performed by (b) (4) testing and the results are presented below:

- (b) (4) bag filled with 30 mL (b) (4) : (b) (4) bags tested and met acceptance criteria, no failures.
- (b) (4) bag filled with 70 mL (b) (4) : (b) (4) bags tested and met acceptance criteria. One bag had visual defects was not submitted for CCIT but is considered a failure.

Due to the failure of the one (b) (4) bag, an additional (b) (4) bags underwent transportation simulation and CCIT. All (b) (4) of bags in this (b) (4) round of testing met CCIT criteria. The acceptance criteria for (b) (4) samples requiring (b) (4) failures out of (b) (4) samples to allow (b) (4) confidence and (b) (4) assurance. The acceptance for the combined (b) (4) test samples, allowed for (b) (4) failures out of (b) (4) samples.

### **Reviewer's Assessment:**

*The ciltacabtagene autoleucel manufacturing process is (b) (4) steps. Each DP batch is formulated based on the patient information, targeted dose, and (b) (4). Janssen provided details on excipients in the (b) (4), formulation development, overages, and physicochemical/biological properties. I defer to OTAT for full review of these items.*

*Janssen also provided descriptions of the commercial DP manufacturing process and justifications for changes made from the clinical process. The total number of manufacturing stages was (b) (4), and the process was streamlined.*

*An overview of the CCS and the (b) (4) freezing bags were described. The freezing bags comply with (b) (4) requirements and are designed to store products in LN<sub>2</sub> vapor temperatures. Extractables and leachable studies were conducted, which I defer to OTAT for review. The CCIT was performed on the CCS under test conditions that were representative of the post filling and post transportation conditions. The CCIT was conducted using (b) (4) testing and all test samples met the acceptance criteria of (b) (4).*

*The CCS and CCIT appear acceptable.*

## **3.2.P.3 Manufacture**

### **3.2.P.3.1 Manufacturer(s)**

Janssen (b) (4) Manufacturers



Company	Address	FEI (if applicable)	Responsibilities
Janssen Pharmaceuticals, Inc	(b) (4)	(b) (4)	Manufacturing, primary and secondary packaging, quality control testing
(b) (4)	(b) (4)	(b) (4)	Quality control testing – DP release tests and stability tests
Janssen Biotech, Inc	(b) (4)	(b) (4)	Quality control testing – in-process testing, DP release tests, DP stability tests

### 3.2.P.3.3 Description of Manufacturing Process

The manufacturing process for Ciltacabtagene autoleucel (cilta cell) is a (b) (4) process and there is (b) (4) and the DP final formulation and filling. The DP is manufactured in a (b) (4)-stage process.

(b) (4)

(b) (4)

(b) (4)



(b) (4)

# Stage (b) (4) – Final Formulation, Filling and Cryopreservation (Day (b) (4))

Final formulation calculation is performed based on the patient weight and target dose, using the (b) (4) viable cell count. If the patient's weight is 100.0 kg or below, the target dose of  $0.75 \times 10^6$  CAR+ viable T Cells/kg is formulated. If the patient's weight is above 100.0 kg, the target dose of  $0.75 \times 10^8$  CAR+ viable T Cells/kg is formulated.

The formulation calculation aims to formulate the full dose in a single DP bag (b) (4)

The required volume of (b) (4) cell suspension is (b) (4)

The formulated cell suspension is filled into (b) (4) (30 mL fill) or (b) (4) (70 mL fill) cryopreservation bags. The bags are single-use and received sterile. The bag selection is based on the total viable cells in the formulated dose. (b) (4) bags are used for doses (b) (4) and (b) (4) for doses above (b) (4). This enables the final cell concentration in the bag to remain at (b) (4) viable cells/mL. (b) (4). After filling, each bag is sealed by a (b) (4) sealer and visually inspected for container integrity and foreign particles.

Following inspection, the DP containers are placed in metal cassettes and cryopreserved (b) (4)

The DP is (b) (4)  
the final storage in the vapor phase of liquid nitrogen ( $\leq -120^\circ\text{C}$ ) in a (b) (4)

The following CPPs and their respective acceptance criteria and IPC are included in Stage (b) (4)

- CPPs

(b) (4)

- IPC

(b) (4)

### 3.2.P.3.4 Controls of Critical Steps and Intermediates

CPPs and IPCs for the DP manufacturing process are listed above with their respective manufacturing stage in 3.2.P.3.3.

### 3.2.P.3.5 Process Validation and/or Evaluation

#### Drug Product Manufacturing Process Validation

The number of DP PV batches was determined based on a risk assessment and control strategy and aligned with principles of the International Society for Pharmaceutical Engineering (ISPE) Good Practice Guide: Process Validation. The assessment determined that a minimum of (b) (4) consecutive batches would be required to demonstrate consistent performance of the DP manufacturing process. Janssen manufactured (b) (4) PV batches using commercially representative surplus apheresis material (from the MMY2001 pivotal study) and three lots of commercially representative (b) (4) LV.


The apheresis materials used during the PV were selected based on the following criteria:

(b) (4)

(b) (4)

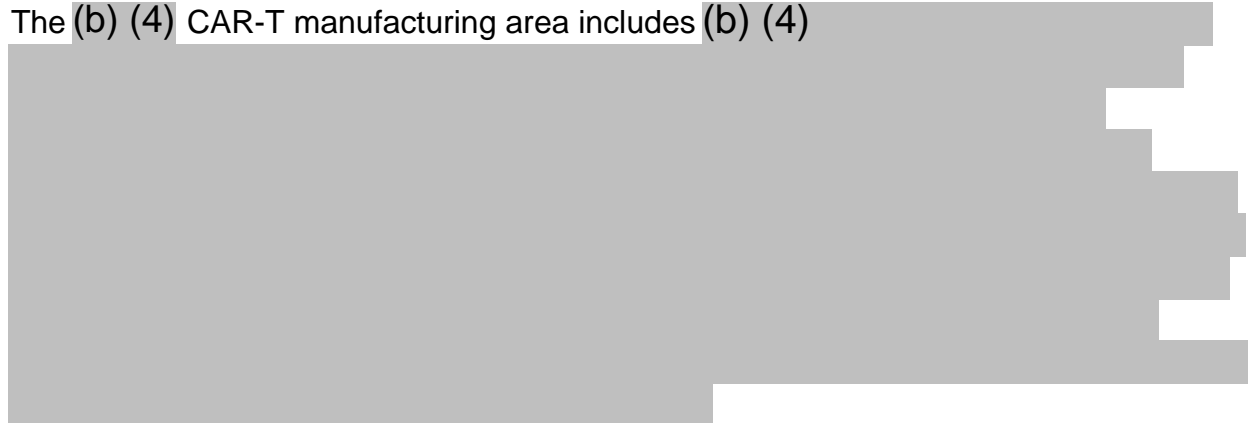


(b) (4)




Aseptic Process Simulations

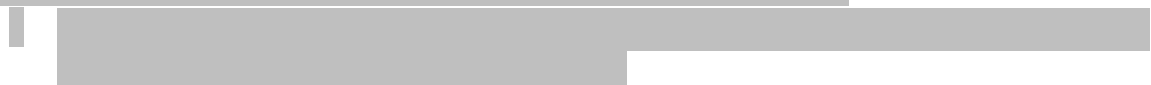


The (b) (4) CAR-T manufacturing area includes (b) (4)



The aseptic DP manufacturing process and component preparation consist of (b) (4)






The initial APS qualification of the (b) (4) facility consisted of (b) (4)





(b) (4)



**Reviewer Note:** An IR (DMPQ IR #5, sent on August 25, 2021) was sent requesting the APS protocol and reports for the (b) (4) facility. Janssen responded on September 3, 2021 and provided the APS protocol and reports. I have summarized the APS studies below. Additionally, the APS studies were reviewed during the on-site inspection and included interviews with Subject Matter Experts (SME) (documented in the Janssen (b) (4) Establishment Inspection Report (EIR) memo).

**Janssen (b) (4) APS**

Janssen uses a (b) (4) approach for the APS studies at the (b) (4) CAR-T facility. The (b) (4) APS studies simulate the following activities:

- Preparation Stage APS Studies

(b) (4)





- DP Manufacturing Process APS
  - Day 0 to Day (b) (4) Process

The APS studies (b) (4) was evaluated for growth promotion (b) (4) APS and Growth Media Accountability was concurrently conducted. Each APS (b) (4) must meet the following acceptance criteria:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The Day 0 to Day (b) (4) APS studies mimic the entire DP manufacturing process but reduce the (b) (4) steps allowing each run to be completed in (b) (4) days, instead of (b) (4). Each APS study used worst-case conditions, such as maximum personnel in the area, routine and non-routine interventions, and concurrent operations in an area. EM sampling was also collected during each APS study.

The APS studies were completed successfully, and any deviations encountered were resolved without impact. Each APS (b) (4) qualified the specific process and established the maximum allowable times each activity can be performed per day.

**Reviewer Assessment:** The APS information submitted in the BLA provided a summary of the APS studies conducted for the DP manufacturing process. Janssen provided specific APS protocols and final reports in their IR response that provided more details about the studies. The (b) (4) APS approach is acceptable and the justifications for (b) (4) times for non-critical steps are logical. The APS simulations included worst-case conditions and EM sampling. All APS studies were completed, and any deviations were resolved without impact.

The APS data appears acceptable and shows the DP manufacturing can be performed in an aseptic manner. More information, including SME feedback, about the APS studies is included in the (b) (4) EIR memo.

**Reviewer Note:** An IR (DMPQ IR #5, sent on August 25, 2021) was sent requesting the clarification if studies were conducted to evaluate the maximum (b) (4)


*manufacturing capacity for the (b) (4) facility and to request the protocol and report. Janssen responded on September 3, 2021.*

Janssen stated they have not executed a protocol driven study to determine the maximum (b) (4) manufacturing capacity for DP at the (b) (4) facility. The current capacity was established by evaluating the facility design, manufacturing experience, APS studies, and EMPQ studies. The facility is currently assessed to support up to (b) (4) patient starts per day. The maximum capacity based on the facility design would be (b) (4) patient starts per day but would require new APS studies to be performed to increase the scale.

**Reviewer Assessment:** *Janssen's response is acceptable, and the facility's capacity was discussed during the on-site inspection and documented in the inspection EIR memo. The current capacity is qualified at up to (b) (4) patient starts per day based on APS and EMPQ data.*

Process Qualification of (b) (4)

(b) (4)





(b) (4)



(b) (4)



#### Shipping Systems Qualification

Shipment of the DP uses a passive dry vapor shipping system ((b) (4) Dry Vapor Shipper System) that provides thermal protection against ambient temperatures without using a (b) (4). The system also provides physical protection against physical stresses and potential hazards during the shipping and storage. The shipping system was qualified for its intended use through the evaluation of thermal properties and physical distribution testing.

Thermal Qualification studies were performed to challenge the shipping system's ability to maintain product temperature for a specified duration. The shipping system is comprised of a container, insulating material, absorbent, and refrigerant. The system is designed to transport product without active temperature control and maintain product temperature during different seasonal temperature conditions.

Thermal qualification studies were performed using the maximum payload configuration for the shipping system. The maximum payload is defined as the largest payload in terms of mass. Janssen states the minimum payload wasn't tested as it would not pose additional risk that could not be evaluated with the maximum payload. The (b) (4) season ambient temperature profile (based on International Safe Transit Association standards) was used to evaluate the shipping system. (b) (4) ambient temperatures were not evaluated as the (b) (4).

Distribution testing was performed using tests done in accordance with (b) (4) standard. The shipping system was evaluated against anticipated shipping hazards, such as shock and vibration. Temperature measurement and recording devices were

calibrated and verified before and after testing against (b) (4) standards. The acceptance criteria were based on the required product temperature. Maximum payloads were required to maintain (b) (4) within the passive shipping system when exposed to a (b) (4) ambient profile and distribution tests.

The (b) (4) Dry Vapor Shipping System completed thermal and distribution testing. The maximum payload of (b) (4) filled DP freezing bags was maintained at temperatures of (b) (4) for the test period of (b) (4) with (b) (4) at (b) (4) ambient temperatures. The outcome of the testing confirmed the capability of the shipping system to meet the shipping requirements for the established shipping lanes.

**Reviewer Note:** Additional information about the shipper, including observation of a final product packaging, are included in the inspection EIR memo.

## Shipping Lanes

The DP (b) (4) shipping lanes, shipping modes, and conditions are outlined below:

Group	A	B	C	D
1	10%	20%	30%	40%
2	20%	30%	40%	50%
3	30%	40%	50%	60%
4	40%	50%	60%	70%

## Transportation Qualification Studies

Transportation studies were conducted to evaluate the potential impact of shipping conditions in the commercial Finished Goods (FG) package on the DP quality and CCI. The FG consists of the DP in a labeled freezing bag and the labeled aluminum cryo cassette. A real-time transportation study was conducted to evaluate the impact of the shipping logistics on the DP quality attributes.

The study covered distances of (b) (4) of (b) (4) transportation and (b) (4) of (b) (4) transport. Prior to shipping, the FG package was placed in the (b) (4) shipping system, which had an internal temperature of (b) (4) . The DP was manufactured at (b) (4) and consisted of (b) (4) concentrations in a (b) (4) bag

with a 30 mL fill and a (b) (4) bag with a 70 mL fill. The DP products were evaluated at (b) (4) Post-Shipping using the stability methods, excluding dose. The (b) (4) Post-Shipping samples was stored in a freezer at  $\leq -120^{\circ}\text{C}$  from shipping receipt until the (b) (4) timepoint.

All the shipping qualification samples, (b) (4) Post-Shipping, met the acceptance criteria for the (b) (4) methods, including (b) (4) primary container (b) (4).

**Reviewer Assessment:** *Janssen's transportation qualification studies for the DP did not state if the (b) (4) transportation distances were conducted as a single study or if they represented a worst-case distance. An IR (DMPQ IR #8) was sent requesting this information. Janssen responded in BLA Amendment 50 that the transportation study presented was (b) (4) study using the worst-case distance for transporting the DP. Their response appears acceptable.*

#### Primary Container CCIT Post Transport

CCIT was also evaluated following a simulated transportation study using commercially representative samples, (b) (4). Test samples were (b) (4) bags with 30 mL (b) (4) media fill and (b) (4) bags with 70 mL (b) (4) fill. The labeled test samples were placed in the FG package and into the (b) (4) shipping system. The shipping system was subjected to simulated transportation test sequences, including distribution tests. The test samples were then evaluated for CCI by (b) (4) testing. The samples met all acceptance criteria and is reviewed in Section 3.2.P.2.5 of this memo.

#### **Reviewer's Assessment:**

*Janssen conducted a risk assessment, aligned with (b) (4), of the DP manufacturing process for determining the number of PV runs required. The assessment determined (b) (4) consecutive, successful PV batches would be required to demonstrate consistency of the manufacturing process. The PV studies used surplus apheresis materials and (b) (4) batches used LV produced at (b) (4). To be considered successful, the batches had to meet/maintain the CPPs, IPCs, and Release Specifications.*

*(b) (4) PV batches failed based on results from the (b) (4) assay but were retested using a (b) (4) assay and met the release specifications. Janssen proposed using the (b) (4) assay as part of the commercial release assays, which I defer to OTAT for their review.*

*The PV studies were completed successfully using the (b) (4) assay, and all deviations were investigated and resolved. The data from the PV studies suggest the DP manufacturing process is consistent. The process hold study evaluated the hold times and (b) (4) for the (b) (4) process (b) (4). The study challenged the*

maximum hold times, and the process (b) (4) all met their respective IPCs and CPPs.

APS runs were conducted to evaluate the (b) (4) stages of the DP manufacturing process. Sterile (b) (4) was used in place of the media, buffer, reagents, LV, and cells. Each run included interventions and EM testing. The APS runs and the EM data from each run met the acceptance criteria. The APS will be requalified every (b) (4), minimally, and all operators must initially qualify and (b) (4) requalify during an APS. The APS data suggests the manufacturing process is controlled and can maintain aseptic conditions. The APS data appears acceptable.

Janssen qualified each (b) (4) individually for the IV/OV and used the (b) (4) strategy for the PV study. Smoke studies were also performed using the (b) (4) strategy. All of the (b) (4) completed the IV/OV studies. The PV study was completed and with one discrepancy, which was resolved. The (b) (4) underwent EMPQ during the PV study and met the acceptance criteria for particulates and viable recovery. Recovery studies were also performed. The (b) (4) qualification appears acceptable.

Janssen qualified each (b) (4) individually for the IV/OV and EMPQ, and no (b) (4) strategy was applied. The (b) (4) are installed in Grade (b) (4) manufacturing areas and maintain a Grade (b) (4) environment within the (b) (4). Static and dynamic EMPQ tests were performed over (b) (4) days and included maximum personnel in the area. Samples were collected for particulates and viable organisms. The EMPQ was completed successfully, and discrepancies were resolved. The (b) (4) appear to be able to maintain a Grade (b) (4) environment as intended. The (b) (4) qualification appears acceptable.

**Reviewer Note:** The (b) (4) were also reviewed during the on-site inspection and additional information, including SME interviews, are in the EIR memo.

The shipping system used for the DP was qualified through thermal and distribution testing using a maximum payload configuration. The tests were completed and appear to demonstrate the shipping system is capable of maintaining temperatures (b) (4) for a test period of (b) (4). The shipping lanes were described and evaluated by simulated transportation studies. CCIT was performed after the simulated transport and met all acceptance criteria. The CCIT method is reviewed in Section 3.2.P.2.5 of this memo. The shipping system appears acceptable.

### 3.2.P.4 Control of Excipients

#### 3.2.P.4.1 Specifications

The DP specifications under DMPQ purview include Sterility and Endotoxin tests. Both test methods are (b) (4) and follow (b) (4) methods. I defer review of the other specifications to OTAT.

### 3.2.P.5 Control of Drug Product

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

The release and stability specifications, test method, and criteria under DMPQ purview are the following:

- Appearance of Primary Container
  - Visual Examination: Bag is without visible defect or leaks (release and stability)
- Sterility
  - (b) (4) : No growth (release and stability)
- Endotoxin
  - (b) (4) (release test only)

The following purposes and justifications were provided for the specifications:

- Appearance of Primary Container
  - Purpose: To examine the DP primary container to ensure each DP bag is intact with no visual defects resulting in potential leakages of the product at release prior to (b) (4)
  - Justification: The appearance of the primary container was evaluated based on (b) (4) DP batches manufactured at (b) (4) and each DP was intact with no visible defects.
- Sterility
  - Purpose: To ensure product quality and sterility of the DP at release and over the shelf life. This is in compliance with applicable (b) (4) guidance.
  - Justification: The data is qualitative, and the acceptance criteria ensures the cell product is free of microbial contamination. The specification is based on (b) (4)
- Endotoxin
  - Purpose: To measure the amount of endotoxin in the DP at release to ensure quality and regulatory compliance.
  - Justification: The endotoxin limit concentration is based on a maximum human dose which ensure that a patient would not receive more than (b) (4) as required by (b) (4).

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

**Reviewer Note:** *My review will focus on the endotoxin and sterility tests performed on the DP. I defer full review of the analytical procedures to OTAT.*

#### Sterility



Janssen utilizes a (b) (4) for confirmation of sterility in the final DP, prior to (b) (4). The (b) (4) is an (b) (4)

The (b) (4) was validated in accordance with (b) (4)

The sterility test method (b) (4)

The sterility assay can be performed at (b) (4) or at Janssen Pharmaceuticals, (b) (4). Both sites validated the (b) (4) method, performed comparability studies and product-specific suitability studies. Validation studies involved testing the (b) (4) for specificity, Limit of Detection (LOD), precision/repeatability, and robustness against a panel of known microorganisms.

A study was performed to determine the appropriate test sample hold time prior to inoculation of the (b) (4). The DP samples were held at (b) (4) and pulled at predetermined time points and tested. The hold study determined the test samples can be held for up to (b) (4) at (b) (4) without adverse effects on the sterility test. However, the recommended storage condition is a maximum of (b) (4) to release the final DP to the patient in a short timeframe.

The (b) (4) was validated at Janssen (b) (4) and (b) (4), meeting all acceptance criteria. The method is considered validated for sterility testing of DP at both test sites.

#### Endotoxin

Janssen utilizes a (b) (4) technique in conformance with the (b) (4) for endotoxin testing of the final DP. The (b) (4) Assay compares the (b) (4) of the test articles against a (b) (4) and (b) (4) standard endotoxin concentrations to determine the (b) (4). The endotoxin study can be performed at either Janssen (b) (4) or Janssen (b) (4).

The endotoxin test is a (b) (4) method and does not require a full validation, but the (b) (4) provide for specific procedures to verify the method is suitable for use with the test article. The following procedures and acceptance criteria were performed to verify the method suitability:

- Recovery: (b) (4)
- Linearity: (b) (4)
- (b) (4)

The (b) (4) procedures were completed at each test site and met all acceptance criteria.

An endotoxin hold time study was performed to evaluate possible masking effects. The hold study was performed on (b) (4) batches of DP spiked with a known amount of endotoxin and testing for recoverable endotoxin over time after storage at -120°C. The hold time study confirmed a maximum hold time of (b) (4) days with no impact on the endotoxin content.

The (b) (4) was verified suitable for use with the DP at the Janssen (b) (4) and Janssen (b) (4) sites.

**Reviewer's Assessment:**

*My review focused on the sterility and endotoxin test methods; I defer to OTAT for review of the other methods.*

*The sterility test uses a commercial kit and was validated for use at the (b) (4) facility and at (b) (4). Janssen evaluated sample hold times and a maximum hold time before testing was established. The endotoxin test is a commercial kit and conforms with (b) (4) guidance. The test method was validated at (b) (4) and at Janssen (b) (4). The sample hold time was evaluated and a maximum hold time before testing was established.*

*The test methods appear acceptable.*

**3.2.P.5.4 Batch Analyses**

**Reviewer Note:** *My review will focus on the Primary Container Appearance, Sterility, and Endotoxin results for the batches. I defer full analysis to OTAT.*

Janssen provided batch analyses for the clinical, PV, and commercial stability DP batches manufactured at Janssen (b) (4). Data from a total of (b) (4) batches were provided manufactured between May 2019 and January 2021. The primary container appearance, sterility, and endotoxin acceptance criteria had to be met:

- Primary Container Appearance: Each bag is without visible defects or leaks

- Sterility: No growth
- Endotoxin: (b) (4)

Data from the (b) (4) batches met the acceptance criteria listed above for Primary Container Appearance, Sterility, and Endotoxin.

**Reviewer's Assessment:**

*The batch analyses provided showed that all (b) (4) batches met the acceptance criteria for Primary Container Appearance, Sterility, and Endotoxin. This suggests the manufacturing process is in a state of control for these attributes. The batch analysis appears acceptable.*

**3.2.P.7 Container Closure System**

The DP packaging components consist of the following:

- Freezing Bag: Primary Packaging
  - (b) (4) ethylene vinyl acetate (EVA), (b) (4) 30 mL (b) (4) mL nominal fill volume)
  - (b) (4) EVA, (b) (4) 70 mL (b) (4) mL nominal fill volume)
- Cryo Cassette: Secondary Packaging
  - (b) (4), aluminum, clear anodized, hinged with locking arm
  - (b) (4), aluminum, clear anodized, hinged with locking arm

The (b) (4) freezing bags are FDA 510(k) cleared ((b) (4)). The (b) (4) freezing bags are constructed with EVA film and certified for use in accordance with (b) (4) for storing blood cell products in LN<sub>2</sub> vapor temperatures. The (b) (4) bags do not contain any animal derived materials. The (b) (4) bags are placed in the aluminum cryo cassettes for protection during storage and shipping.

The critical dimensions for the (b) (4) freezing bags are:

- (b) (4)
  - Length excluding pocket and ports: 11.4 cm (b) (4)
  - Width: 7.6 cm (b) (4)
- (b) (4)
  - Length excluding pocket and ports: 15.2 cm (b) (4)
  - Width: 12.7 cm (b) (4)

Each lot of primary packaging materials are inspected upon receipt and must comply with the inspection acceptance criteria. The shipment must not have physical damage to the shipping containers, a verifying Certificate of Conformance, and label information for the shipment and the primary packaging materials. The freezing bag Certificate of

Conformance provides conformance of materials of construction, biocompatibility, sterilization, and seal integrity. The cryo cassette CoC provides conformance of materials of construction, dimensions, and cleanliness.

After the general shipping inspection, the following visual, physical, and functional tests are performed on the freezing bags.

- Visual inspection of freezing bag:
  - Bags are inspected for physical defects and must meet AQL. Visual inspection for product identification, physical defects (b) (4), internal/external contamination, and overall cleanliness.
- Physical inspection of freezing bag:
  - Critical dimensions must conform to the technical drawing of the freezing bag. Incoming primary packaging material testing is based on (b) (4) testing for (b) (4). Bag materials (EVA and PVC/EVA) are evaluated against a reference standard.

**Reviewer Note:** Janssen considers the Container Closure System (CCS) is a Combination Product and presented information about the Quality Management System (QMS) in place at Janssen (b) (4). The Agency does not consider CAR-T products stored in blood cell freezer bags as Combination Products. Additionally, the freezer bags used for the DP CCS are 510(k) cleared.

### 3.2.P.8 Stability

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

**Reviewer Note:** I focused my review of the stability data on sterility and bag integrity. I defer full review of the stability data to OTAT.

The recommended storage condition for the DP is  $\leq -120^{\circ}\text{C}$  in the vapor phase of liquid nitrogen (b) (4). Janssen provided stability study data from development, PV, and commercial batches of the cryopreserved DP at multiple cell concentrations. The T=0 samples, also used for release testing, (b) (4) while the other stability samples are stored in (b) (4) freezing bags. The (b) (4) bags are manufactured from the same materials as the (b) (4) bags and are considered representative for the stability studies.

(b) (4) developmental DP batches were manufactured and placed on the nine month stability program at recommended storage conditions. (b) (4) was evaluated at an accelerated temperature (b) (4) for (b) (4) then placed in  $\leq$

120°C for (b) (4). Nine months of data was provided for all the developmental batches, except (b) (4) which only had six months of data available.

(b) (4) PV batches and (b) (4) commercial batches were placed on the nine month stability program at the recommended storage condition. (b) (4) commercial batches were evaluated at the accelerated temperature (b) (4) for (b) (4) then placed in  $\leq -120^{\circ}\text{C}$  for (b) (4) months. Stability data from T=0 (release testing) was provided for the PV and commercial batches.

Stability results for the developmental batches meet all acceptance criteria through the six and nine month timepoints. The T=0 results for the PV and commercial batches met all acceptance criteria as well. The accelerated temperature study for the developmental batch (b) (4)

Stability results at T=0 for the PV and commercial batches at the recommended storage conditions and accelerated temperature met all acceptance criteria. These batches remain on the stability program.

#### Shelf Life

Janssen proposed a 3-month shelf life for the DP when stored at  $\leq -120^{\circ}\text{C}$ . The shelf line will be extended based upon available stability data from the PV and commercial stability batches, if all tests are within specification for the duration of the stability study. The proposed shelf life extension is presented on Table 12.

**Table 12: Proposed DP Shelf Life Extension Plan**

Available Real Time DP Stability Data (months)	Proposed Shelf Life (months)
3	6
6	9

Updated stability data will be submitted in the annual report and labeling information may also be updated according to stability data assessment. Janssen commits to informing the Agency of any Out of Specification (OOS) results at the recommended storage condition.

#### In-Use Stability Report

Janssen conducted an in-use stability study to evaluate the cilta-cel DP for up to (b) (4) hours post-thaw under ambient temperatures (b) (4) conditions. The study used materials manufactured with either representative in-process hold times or extended, cumulative hold times for the commercial process.

(b) (4) PV DP bags, each filled with 30 mL in a (b) (4) bag, were evaluated in the post-thaw study. The DP was monitored post-thaw (T=0), 1.5 hours post-thaw, 2.5 hours post-thaw, and (b) (4) hours post-thaw for changes in CQAs. The CQAs were required to meet their established acceptance criteria at release.

Post-thaw, T=0, each DP bag was visually inspected for defects and leaks and visible foreign particulates. No defects, leaks, or visible foreign particulates were observed. All CQAs remained within the release criteria for up to (b) (4) hours post-thaw of in-use stability.

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

Janssen proposed the following post-approval stability commitments:

- Continuing the stability study on Developmental Batch (b) (4) through 9 months at -120 (b) (4) °C
  - Confirmed OOS results will be reported, and additional stability data provided to the Agency via the Annual Report
- Continuing the stability studies for three PV batches through 9 months at -120 (b) (4) °C
  - Confirmed OOS results will be reported, and additional stability data provided to the Agency via the Annual Report
- Continuing the stability studies for (b) (4) Commercial batches through 9 months at -120 (b) (4) °C
  - Confirmed OOS results will be reported, and additional stability data provided to the Agency via the Annual Report

#### Post Approval Stability Protocol

Janssen proposed not to perform (b) (4) DP stability studies post licensure but will evaluate process changes for the potential impact on stability. These changes will be assessed in accordance with the Post Approval Stability Protocol.

The general stability protocol for stability sampling and testing for the DP during a nine month program at the recommended storage condition of  $\leq -120$  (b) (4) °C. A (b) (4) month time point is included but is optional depending on the amount of material available. The stability testing includes sterility testing at T=0, T=1 month, and end of stability, either T=9 or (b) (4) months.

Stability test methods and specifications are provided in 3.2.P.5.1 and 3.2.P.5.2. Confirmed OOS results at the recommended storage conditions will be reported to the Agency. Data from the stability studies will be submitted in the Annual Report. I defer to OTAT for full review of the post-approval stability commitment.

**Reviewer's Assessment:**

*My review of the stability data focused on the sterility of the DP and the CCS integrity; I defer to OTAT for full review of the stability data.*

*Data was provided for (b) (4) developmental DP batches, (b) (4) PV batches, and (b) (4) commercial batches. The batches were all included on the nine month stability program with (b) (4) batches being evaluated at accelerated temperatures prior to moving to the recommended storage conditions. Data from release testing (T=0) met acceptance criteria for sterility and CCS integrity for all batches. Data through six and nine months for the developmental batches at recommended conditions also met acceptance criteria.*

(b) (4) on the accelerated study (b) (4)

*Janssen proposed a three month shelf-life for the DP stored at the recommended conditions and plans to extend the shelf-life as more data becomes available. The data will be submitted in the Annual Report. Janssen also committed to continue stability testing for the current batches through nine months at the recommended storage conditions. Janssen proposed not performing (b) (4) DP stability studies but will evaluate the impact of process changes on stability (outlined in the Post-Approval Stability Protocol). Janssen justifies this proposal due to the lack of DP after nine months, due to use, but if material is available, a (b) (4) sample timepoint will be evaluated and submitted in the Annual Report.*

*The stability data appears acceptable and suggests the DP can maintain sterility at the recommended storage conditions. The post-approval commitments appear acceptable.*

**3.2.A APPENDICES**

**3.2.A.1 Facilities and Equipment**

**Janssen Vaccines (b) (4) Lentiviral Vector Manufacturing Facility**







cilta-cel manufacturing and no other products are manufactured in the CAR-T processing room. The manufacturing area is divided into separate, segregated areas for production including a (b) (4)

The final formulation and fill activities are performed in a (b) (4) manufacturing suite (b) (4).

### Manufacturing Flow

The manufacturing process and corresponding rooms are presented on Table 19.

**Table 19: DP Manufacturing Steps and Room Number**

Manufacturing Step	Room Number	Additional Information
(b) (4)		
Stage (b) (4): Final Formulation & Filling	(b) (4)	(b) (4) process steps in (b) (4)
Stage (b) (4): Cryopreservation	Kit Assembly, (b) (4) , Product Packaging (b) (4)	Cryopreservation process

The (b) (4) is a (b) (4), and maintained to exceed Grade (b) (4) conditions. The (b) (4) are located in a Grade (b) (4) rooms. The (b) (4) are Grade (b) (4) and located in the Grade (b) (4) background (b) (4).

The (b) (4) are used in (b) (4) for the open processing steps, except for the (b) (4) steps. The facility design allows for a flow of materials, products, waste, and personnel through dedicated airlocks and flows are controlled to minimize cross-contamination.

**Reviewer's Assessment:**

*Janssen provided a summary of the CAR-T manufacturing process steps, whether the step is open or closed and the room where the operation occurs. Open process steps are performed (b) (4). Airlocks are employed to reduce the risk of contamination. While the summary did not include room classification information, this information and a list of AHUs was requested by IR and is reviewed under the (b) (4) HVAC section of this memo.*

The DP manufacturing process does not have direct contact with the equipment, and Janssen states the equipment can be subsequently used with other patients after the appropriate changeover. The product contact components used in the manufacturing process consist of (b) (4)

Equipment surfaces are cleaned according to site SOPs, including being (b) (4) with (b) (4) or disinfected by trained personnel on a daily, weekly, monthly, and quarterly basis. All major equipment malfunctions or failures are investigated, and corrective actions are implemented per site SOPs.

**Contamination Control**

The (b) (4) facility was designed with facility and manufacturing process controls to ensure the DP is manufactured under GMP conditions. The facility design limits the access of microbiological contamination to products, raw materials, equipment, and production rooms. APS studies were performed to ensure no intrinsic contamination of the DP and microbial contamination control is demonstrated through in-process and release testing criteria.

The biocontamination control strategy includes procedures to prevent or minimize ingress, proliferation, and/or persistence of microorganisms in the facility, equipment, and material. Process controls include personnel and material flow, cleaning and disinfection procedures, aseptic techniques, and training to mitigate the opportunity of biocontamination.

**Reviewer's Assessment:**

*The overview of the contamination control strategy presented appears acceptable. The manufacturing rooms appear appropriately classified for the work being performed. Any open manufacturing steps are performed in a Grade (b) (4). The contamination control strategy is evaluated during the APS studies and has been demonstrated to control the ingress of microbial contamination.*

**Reviewer Note:** *Cleaning and disinfection logbooks were reviewed during the on-site inspection and are reviewed in the EIR memo.*

### Environmental Monitoring Program

The Environmental Monitoring (EM) program is in place to ensure the different GMP production areas remain in a controlled state, microbiological (b) (4) is routinely monitored by air and surface sampling. Compressed air and (b) (4) are also routinely monitored. In-process EM for the (b) (4) are established based on internal and regulatory requirements.

Air sampling is performed to assess the performance of the engineering and design controls as intended to minimize aerial contamination and meet classification requirements for total particulates per volume of air, and personnel aseptic practices and hygiene. Surface sampling is performed to assess surface cleaning and sanitization effectiveness, and personnel aseptic practices and hygiene.

The routine EM is performed under dynamic conditions with sampling locations and frequency identified by a risk assessment. Sampling frequency may increase, or decrease based on historical data, changes in practices/equipment, development of significant microbial adverse trends, and the addition of new equipment or construction in or around the areas.

In-process EM sampling is performed during the ongoing process, near the exposed product intermediate, to determine the environment quality during critical manufacturing operations for the rooms and the (b) (4). The ongoing manufacturing process represents the worst-case condition for contamination due to the open containers being in direct contact with the environment, personnel proximity, and maximum number of personnel involved.

(b) (4) process surface monitoring is performed (b) (4), as this is considered the worst-case scenario for surface sampling. Microbial surface samples are taken from within the Grade (b) (4) and from the personnel in the Grade (b) (4) suite prior to exiting the room.

Viable air and surface monitoring are performed on a routine basis by personnel who are trained and qualified in the sampling methods. Viable air monitoring is performed in Grade (b) (4) and surrounding Grade (b) (4) areas where the DP is filled. Grade (b) (4) areas are also monitored at defined sampling points. All areas are sampled with active air sampling (b) (4). Grade (b) (4) areas also utilized (b) (4) during setup and filling operations.

Surface monitoring is performed at established sample locations and frequencies using (b) (4). Surface monitoring is done at the end of production in Grade (b) (4) areas and (b) (4) in Grade (b) (4) areas. Personnel monitoring (gloves, sleeves, and chest) is conducted on all personnel who enter the Grade (b) (4) area during production. Grade (b) (4) areas are routinely monitored.

The Viable Air and Surface Action Limits for the different manufacturing areas and the types of monitoring performed are presented below:

(b) (4)	

Non-viable monitoring is performed (b) (4) at designated locations in Grade (b) (4) in Grade (b) (4) in Grade (b) (4) for Grade (b) (4) areas. The action limit for each area for non-viable particulates is presented below:

(b) (4)	

Results above the alert level are handled per site SOPs. EM results are monitored for trends per SOP. EM alert and action excursions are investigated, and corrective actions implemented per site SOPs.

**Reviewer Note:** *Janssen provided an overview of the EM program but did not provide the EMPQ reports to support their summary. An IR (DMPQ IR #5 sent on August 25, 2021) was sent requesting the EMPQ studies performed at (b) (4). Janssen responded on September 3, 2021 with the EMPQ protocols and reports for the CAR-T manufacturing areas.*

### **EMPQ Studies**

Initial and re-executed EMPQ protocols and reports were provided for the different manufacturing rooms in the CAR-T facility and included static and dynamic testing. The initial EMPQ studies for the CAR-T manufacturing area included the process rooms, airlocks, corridors, and gowning rooms. During the study, air samples were analyzed for viable and non-viable particulates and surface samples were analyzed for viable counts. The sampling was done over a (b) (4) period to replicate a typical manufacturing process.

The maximum number of personnel were in each manufacturing room during the study. The particulate counts and viable counts for the classified areas had to meet (b) (4) Grade classification and (b) (4) requirements applicable to the classified area. Diagrams were provided for locations of the air and surface sampling sites and the rationale was presented. Recovery testing for classified areas was performed and each room had to return to static conditions within (b) (4) of personnel departure. Only (b) (4) test sampling sites are used for recovery testing. Recovered viable organism counts that exceeded the area's classification were identified and all EM excursions investigated by QA.

The submitted EMPQ reports show the studies were completed and all discrepancies were investigated and resolved. EM excursions were investigated, and the recovered organisms identified and assessed for impact to the study. All discrepancies were resolved.

The re-executed EMPQ studies followed the same procedures as the initial EMPQ studies but were performed to increase the maximum number of personnel allowed in each classified area. The studies were executed under dynamic conditions and included recovery testing. The particulate levels and viable recoveries had to meet the (b) (4) Grade and (b) (4) requirements for the respective areas. These studies were completed, and all discrepancies were investigated and resolved. It is noted the EMPQ studies did not

include the Grade (b) (4) . The EMPQ for these equipment was performed as part of the (b) (4) qualification studies.

**Reviewer Assessment:** *The provided EMPQ protocols and reports detailed the static and dynamic testing of the CAR-T manufacturing areas. The studies evaluated air particulates, viable and non-viable, and (b) (4) to demonstrate the areas were able to meet their respective classification requirements. All EM excursions were investigated and recovered organisms identified. All discrepancies were resolved, and the impact was assessed. The EMPQ studies were re-executed to increase the manufacturing area capacity and these studies were also completed. The EMPQ data appears to show the facility is capable of maintaining appropriate environmental classifications. The EMPQ appears acceptable.*

#### Changeover and Cleaning Procedures

During operations in the (b) (4) , all materials entering the (b) (4) are (b) (4) to sanitize them prior to entry. The (b) (4) are maintained at a positive pressure relative to the outside environment and provide a (b) (4) flow of HEPA filtered air. The (b) (4) are cleaned with a (b) (4) prior to and after each use. All personnel and environmental monitoring during execution will be done to meet Grade (b) (4) requirements.

Changeover procedures are in place prior to the next patient sample to be processed in a (b) (4) . This includes removal of (b) (4) equipment used in the process, and (b) (4) with (b) (4) . The changeover is verified and documented prior to the next patient sample being allowed to commence.

In addition to the cleaning and changeover procedures, every production batch is tested on release for microbial contamination. The (b) (4) units are designed to contain all materials within HEPA filtration, which allows for open operations of multiple patients within a process room in separate (b) (4) .

**Reviewer Note:** *The changeover and cleaning procedures were summarized in the BLA. Line clearance is performed between batches and is verified to be complete before proceeding. The changeover procedures appear acceptable.*

Janssen states a (b) (4) are used to clean the (b) (4) before and after each use. The BLA did not include the disinfectant studies to support the use of the (b) (4) or other disinfectants used in the CAR-T manufacturing areas. The disinfectant studies were reviewed during the on-site inspection and included SME interviews. Refer to the (b) (4) EIR for review.

### Personnel Flow and Gowning

Personnel enter the facility through CNC locker rooms and proceed to the Grade (b) (4) vestibules to don sanitized plant scrubs, base sterile gloves, and safety glasses.

(b) (4) plant shoes and are sanitized and worn after crossing the demarcation line to the Grade (b) (4) area. Hands are sanitized with (b) (4) and personnel enter the Grade (b) (4) corridor. There are dedicated PALs for entry and exit of the Grade (b) (4) corridor.

From the Grade (b) (4) corridor, personnel may access the Grade (b) (4) process rooms or the Grade (b) (4). Prior to entering a Grade (b) (4) cell culture room, a (b) (4) lab coat and (b) (4) pair of disposable gloves are donned over the Grade (b) (4) attire.

The (b) (4) are accessed by their own set of unidirectional PAL-IN and PAL-OUT. Gowning for the Grade (b) (4) areas require an (b) (4) sterile one-piece suit, sterile boot covers, sterile head cover, sterile goggles, and outer sterile gloves. Hands are sanitized with (b) (4). The (b) (4) are Grade (b) (4) and require (b) (4).

Personnel exit through the (b) (4) PAL-OUT to the Grade (b) (4) corridor and proceed to the degown vestibules and into the locker rooms.

### Material and Product Flow

MALs and pass-through airlocks are used to move materials into the facility and production rooms. Materials/components are moved into the facility via CNC/Grade (b) (4) /Grade (b) (4) MAL-IN or CNC/Grade (b) (4) unidirectional passthroughs. A Grade (b) (4) MAL-IN is used to move materials/components into the Grade (b) (4) areas.

Bulk items in (b) (4) containers are (b) (4) as they are passed into the MAL or pass-through via a series of (b) (4) transfers and moving to a staging area.

Materials/components are (b) (4) sanitized as they are (b) (4). The (b) (4) are assembled into (b) (4) containers and transferred to workstations as needed. Materials used in the (b) (4) are moved through unidirectional passthroughs.

Procedures are in place for segregation of DP, raw materials, and waste. Waste is removed from the manufacturing area through the Passthrough-OUT, Grade (b) (4) MAL-OUT and a Grade (b) (4) /CNC MAL-OUT. (b) (4), and in-process products are moved throughout the facility using the same MALs and Passthroughs.

**Reviewer Note:** An IR (DMPQ IR #3) was sent to Janssen on 09 July 2021 requesting a clarification about the segregation of drug product, raw materials, and waste at the



(b) (4) facility. The Sponsor provided the requested information in Amendment 27 to the BLA.

Janssen provided the following explanation of the segregation procedures used at the (b) (4) facility:

- Drug Product
  - Each DP batch is manufactured at a dedicated workstation and use Batch ID Cards. The workstation changeover procedure is completed prior to a new DP batch entering the workstation area. All patient materials are contained in a closed container when inside (b) (4) containing multiple DP batches.
  - Chain of Custody / Chain of Identity procedures instruct how the DP batches are labeled and placed on dedicated (b) (4) .
  - Patient apheresis and DP follow specific product flows and there are dedicated rooms for in-coming and out-going patient material storage.
- Waste
  - Managed in accordance with procedural documents and includes inactivation steps, containment strategies, and appropriate labeling
- Personnel Gowning
  - Personnel flows include segregation points where additional gowning must be donned before moving to different classified space. (CNC to Grade (b) (4) through Grade (b) (4) )
  - Personnel gowning also includes gowning changes when moving from patient to patient activities.
  - A cross-contamination risk assessment and personnel safety assessment were performed and concluded the gowning procedures added to further segregation.

#### HVAC, Room Classifications and Pressurizations

The HVAC was designed to provide control and segregation of the different area classifications. Separate AHUs serve the different classified areas (Table 20) within the DP process area. A dedicated central air handling system draws (b) (4) outdoor air, filters and conditions it, and supplies the conditioned air to each room's dedicated AHU to make up for air lost to pressurization and exhaust.

(b) (4) rooms share one dedicated AHU. Each (b) (4) and CAR-T processing room has (b) (4) AHUs. The AHUs provide airflow, temperature and humidity control, and room pressurization. A dedicated central exhaust air system receives the exhaust air from all the rooms and discharges it to the outdoors.

**Table 20: Janssen (b) (4) Room Classifications**

Classification	Air Flow Standard	Airflow Direction
Grade (b) (4)	ISO Class (b) (4) at rest ISO Class (b) (4) in operation	(b) (4) flow
Grade (b) (4)	ISO Class (b) (4) at rest ISO Class (b) (4) in operation	(b) (4) flow
Grade (b) (4)	ISO Class (b) (4) at rest ISO Class (b) (4) in operation	(b) (4) flow
Grade (b) (4)	ISO Class (b) (4) at rest Undefined in operation	(b) (4) flow

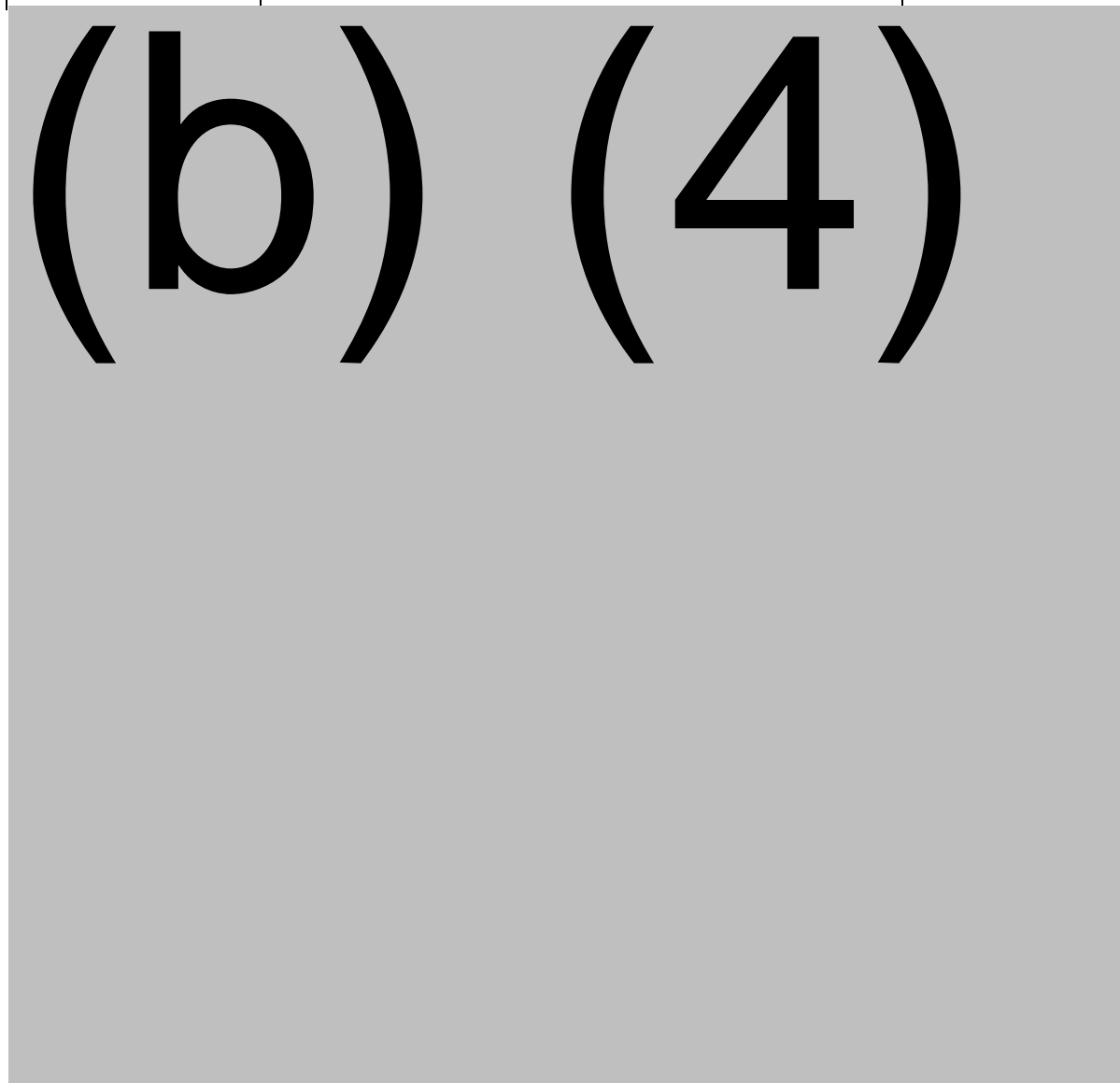
The facility has air pressure cascades flowing from the process areas, through the airlocks/gowning areas to the CNC. The pressure-differentials are monitored through sensors in the rooms, recorders, and low-point alarms that indicate when the pressure is outside the defined value.

**Reviewer Note:** The BLA did not include a list of the AHUs and areas serviced by each AHU. An IR (DMPQ IR #7 sent on September 9, 2021) was sent requesting a list of the rooms with classification and the AHU servicing each room. Janssen responded on September 20, 2021 with the requested information. See Table 21 below with the information.

**Table 21: Janssen AHU and Serviced Rooms**

(b) (4)

AHU ID and #	Area/Room Serviced	Classification Grade
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**Reviewer Assessment:** *The provided information about the AHUs and the room classifications appears acceptable for the work being performed in the different areas.*

**Reviewer Note:** *An IR (DMPQ IR #3) was sent to Janssen on 09 July 2021 requesting qualification protocols and reports for the HVAC systems at the (b) (4) facility. The Sponsor provided the requested information in Amendment 27 to the BLA.*

Janssen provided the protocols and qualification reports for the HVAC systems for the (b) (4) facility. The protocols defined the test conditions used to evaluate the HVAC

systems to ensure the facility and Air Handling Units (AHUs) operate in accordance with monitoring limits, cGMP, and classification specifications. Air flow smoke studies for static and dynamic conditions were conducted and pressure cascades were evaluated. EM acceptance criteria, based on the area's classification, for viable air, non-viable air (b) (4) and (b) (4) were provided.

The qualification reports were divided into CAR-T Facility HVAC and Media Formulation Area HVAC, with initial qualification (commissioning) and the recent expansion requalification of the HVAC systems. The HVAC qualification reports provided data supporting the IOQ studies completed on AHUs and (b) (4) supporting the different classified and controlled not classified areas within the (b) (4) facility. The discrepancies encountered during the qualification studies were considered minor and were resolved without impacting the studies.

**Reviewer's Assessment:** *The BLA and IR responses provided an overview of the HVAC system, how it was qualified, and cleanroom classifications for the manufacturing areas. The HVAC system was qualified through IOQ and EMPQ studies. The EMPQ studies were reviewed and appear to show the HVAC is capable of maintaining the respective room classifications. The CAR-T facility has (b) (4) AHUs that service the different manufacturing rooms. The HVAC system is monitored through the facility EM program. The HVAC systems appear acceptable.*

**Reviewer Note:** *An IR (DMPQ IR #3) was sent to Janssen on 09 July 2021 requesting a list of utilities along with qualification protocols and reports (such as compressed air, (b) (4) and water) used at the (b) (4) facility. The Sponsor provided the requested information in Amendment 27 to the BLA.*

Janssen states the (b) (4) manufacturing process uses (b) (4) as a product contact utility with direct impact. The system consists of (b) (4)

(b) (4)

The (b) (4) are received at Janssen's (b) (4) facility and tested for the following attributes:

(b) (4)

(b) (4)

The (b) (4) are then released and shipped to Janssen (b) (4). The (b) (4) are tested (b) (4) at the point of use for (b) (4) counts.

Janssen provided the Installation/Operational Verification (IV/OV) and Performance Verification (PV) protocols and reports for the (b) (4) distribution system at (b) (4). The studies verified that the (b) (4) distribution system and connections were properly installed and operated in accordance with the design specifications and cGMPs. The IV/OV studies were completed successfully with one discrepancy, a documentation error when recording the (b) (4), occurring during testing. The discrepancy was investigated and closed out without impacting the study results.

The PV study was performed to establish the (b) (4) distribution system and connections were capable of supplying (b) (4) in accordance with established specifications. Samples were collected at the (b) (4) generation point and at points-of-use over a (b) (4) test period. Sample sites and sampling frequency are presented in the protocol and must meet the following acceptance criteria:

(b) (4)

The PV study was completed successfully with four minor discrepancies, presented below:

- Sample points were incorrectly named in LIMS. Correct sample point names were added and approved by QA.
- (b) (4) was not available for (b) (4) sampling for (b) (4) test days. The affected sites were re-sampled with the (b) (4) and met the acceptance criteria for (b) (4).
- (b) (4) samples were observed with (b) (4), indicating (b) (4) was present. (b) (4) of the samples were re-tested without issue. (b) (4) of

the samples were not re-tested as they were the (b) (4) test sample from the location and the data was not required to complete the study.

- (b) (4) samples were not documented in the appropriate notebook or in LIMS.

The samples met the viable acceptance criteria and were correctly documented. The discrepancies were investigated and resolved without impacting the study. Janssen considers the (b) (4) distribution system suitable for GMP use.

Janssen provided a list of the other utilities in use at the (b) (4) facility, but noted that none of these utilities are product contact and qualification was not performed.

- Chilled Water, Cold/Hot Water
- Normal Power, Stand-by Power, UPS
- (b) (4) Clean Steam
- LN<sub>2</sub> (b) (4)
- LN<sub>2</sub> Storage Tank/Distribution system
- Plant Steam

**Reviewer's Assessment:**

*The (b) (4) are quality tested at Janssen (b) (4) and released for use at (b) (4). The (b) (4) distribution system is monitored through the BMS. The IV/OV and PV studies qualified the distribution system and connections for use. EM sampling was performed for the generation points and point-of-use over a (b) (4) period. All discrepancies encountered were investigated and resolved. The (b) (4) qualification information appears acceptable.*

*Jansen provided a list of additional utilities at (b) (4) and stated they were not qualified because these utilities are not product contact. This was investigated during the on-site inspection and documented in the EIR memo.*

**Reviewer Note:** *An IR (DMPQ IR #3) was sent to Janssen on 09 July 2021 requesting the Freezer ID numbers the (b) (4) Freezers used to store the filled (b) (4) bags. Additionally, the qualification protocols and reports for the freezers were requested. The Sponsor provided the requested information in Amendment 27 to the BLA.*

Janssen submitted a list of the (b) (4) Freezers along with the IV/OV/PV protocols and reports. Janssen used a grouping approach for qualification studies, as the freezers were similar, the same make and model, and a single PV study could be leveraged for all freezers. A list of the freezer IDs is below.

- (b) (4)
- (b) (4) Freezers

(b) (4)

The (b) (4) freezer IV/OV/PV protocol defines the test procedures and acceptance criteria that must be met to demonstrate the freezer has been installed, operates, and performs as intended. Empty chamber temperature mapping was performed during OV and maximum load chamber temperature distribution was performed during PV. All (b) (4) freezers completed IV/OV studies, and the PV study was completed for (b) (4). All discrepancies, which were assessed as minor, were investigated and closed out without impact. The freezers are considered acceptable for use.

The (b) (4) freezers were qualified for IV/OV individually and a grouping approach was used for the PV studies. The IV/OV protocol defines the installation and operation test procedures, specifications, and acceptance criteria. Empty chamber temperature mapping studies were conducted during the OV study over a (b) (4) test period and mapping was done using calibrated thermocouples. During the mapping study the thermocouples and freezer display shall maintain a temperature of (b) (4) and thermocouples must be within (b) (4) of the reference temperature. The locations of the thermocouples within the freezer chamber are documented in the study records. All the LN<sub>2</sub> freezers completed IV/OV tests, meeting the acceptance criteria, and all discrepancies, assessed to be minor, were investigated and resolved without impact.

The PV studies used a grouping approach, in which the (b) (4) freezers are grouped based on the make and model of the freezer and (b) (4) undergoes the PV studies and the results are applied to similar freezers. The PV studies evaluated the (b) (4) freezer for the following performance attributes and had to meet the respective acceptance criteria:

(b) (4)

The grouped PV study was completed with no discrepancies. Janssen states this demonstrates the (b) (4) freezers are suitable for use in the CAR-T facility.

**Reviewer Assessment:** The (b) (4) freezers underwent individual IV/OV studies, and a grouping approach was used for the PV study. The (b) (4) freezers and (b) (4) freezers completed all verification testing and encountered minor discrepancies, which were resolved. The IV/OV and grouped PV studies appear acceptable and the freezers appear to be acceptable for their intended use.

**Reviewer Note:** The (b) (4) freezers and distribution were reviewed during the on-site inspection and additional information, including SME interviews, are documented in the EIR memo.

**Reviewer Note:** An IR (DMPQ IR #3) was sent to Janssen on 09 July 2021 requesting the IDs for (b) (4) used for storing the (b) (4) during Stage (b) (4) of the manufacturing process. Additionally, the qualification protocols and reports for the refrigerators were requested. The Sponsor provided the requested information in Amendment 27 to the BLA.

Janssen stated only (b) (4) is used for storing the (b) (4) during Stage (b) (4) and provided the IV/OV protocol and report. The protocol defines the tests and acceptance criteria used to verify the installation and operation of the (b) (4)

(b) (4)

The (b) (4) successfully completed IV/OV testing, meeting all acceptance criteria and there were no discrepancies during the studies. Janssen states the (b) (4) was verified to be installed and operating in accordance with the design specifications and cGMPs and is suitable for GMP use.

**Reviewer Assessment:** The (b) (4) underwent IV/OV studies to verify the (b) (4) is capable of maintaining (b) (4) for (b) (4). The (b) (4) was (b) (4), and all acceptance criteria were met. The IV/OV studies for the (b) (4) appear acceptable.

**Reviewer Note:** An IR (DMPQ IR #3) was sent to Janssen on 09 July 2021 requesting the IDs for the (b) (4) systems used for the ciltacabtagene autoleucel manufacturing process. Additionally, the qualification protocols and reports for the



*refrigerators were requested. The Sponsor provided the requested information in Amendment 27 to the BLA.*

Janssen provided a list of the (b) (4) systems (listed below) used for manufacturing at (b) (4) and the IV/OV protocols and reports.

- (b) (4) System IDs
  - (b) (4)

The (b) (4) systems enable (b) (4)

(b) (4) The IV/OV studies were performed to ensure the (b) (4) systems were installed and configured according to the manufacturer and J&J requirements/specifications. The IV/OV studies must fulfill the Direct Impact Equipment requirements in the CAR-T Site Validation Master Plan for (b) (4).

The IV studies verified the (b) (4) systems were installed correctly in a controlled access room with an Uninterruptable Power Source. The OV studies verified data integrity/backup verification.

The IV/OV studies for each (b) (4) system were completed successfully and no discrepancies were noted during any of the tests. Janssen states the systems are verified to be installed and operating in accordance with design specifications and are suitable for GMP use.

The PV studies for the (b) (4) followed the grouping approach and were conducted as part of the PPQ Batches (b) (4). The Batch Records for PPQ (b) (4) was provided in the BLA submission and reviewed in Section 3.2.R of this memo.

**Reviewer's Assessment:** *The (b) (4) systems were individually evaluated during IV/OV studies. The IV/OV studies were completed, and no discrepancies were encountered. The IV/OV data appears acceptable.*

*A grouping strategy was used for the PV studies for the (b) (4) systems, and the PV was included as part of the PPQ Batches. I reviewed the PPQ batch records that were applicable for the (b) (4) systems and that review is in Section 3.2R of this memo.*

### **3.2.A.2 Adventitious Agents Safety Evaluation**

#### **Janssen (b) (4) Facility**

Non-viral adventitious agents are controlled through a program of facility and manufacturing process controls to assure the quality of the LV manufactured at (b) (4). When possible, the LV manufacturing process uses (b) (4)

(b) (4) are performed under controlled conditions. Potential sources of adventitious agents were identified as components of the (b) (4) used.

It is not possible to use viral removal steps during the LV manufacturing process, so Janssen implemented the following precautions:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

There are no animal or human derived components used in (b) (4). The (b) (4) was released based on the vendor CoA and additional release testing performed by Janssen. The (b) (4) medium contains (b) (4) which is tested for (b) (4) by the vendor.

#### Janssen (b) (4) Facility

Janssen identified potential sources of adventitious agents during the DP manufacturing process. Sources include patient-derived apheresis material, the (b) (4) used. Due to the cellular nature of the product, it is not possible to introduce viral removal steps.

The following controls for raw materials and the LV were implemented:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The following process and environmental controls were implemented in the (b) (4) facility:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The Apheresis material quality is controlled through the qualification of the collection sites. Any viruses present in the apheresis material would be patient-derived and low risk to the patient. Janssen provided a table of animal and human derived raw materials used in the DP manufacturing and formulation and CoAs for the various materials.

Release testing for Replication Competent Lentivirus, as described in 3.2.P.5.1.

### 3.2.R Regional Information (USA)

#### □ Executed Batch Records

I reviewed the executed batch records for the PPQ lots and summarized my comments below. I defer full review of the executed batch records to OTAT.

Janssen (b) (4)

Representative executed batch records were provided encompassing the (b) (4) stages of the LV manufacturing process at (b) (4). The Batch Records documented the equipment, media, reagents, and disposable materials used to produce the LV batch. The batch records were complete, and I have no objectionable findings.

Janssen (b) (4)

Representative executed batch records for PPQ (b) (4) were provided for the (b) (4) stages of drug product manufacturing process at (b) (4). The Batch Record documented the equipment (b) (4) and disposable materials used for the manufacture of PPQ (b) (4). The batch records appear complete, and I have no objectionable findings.

**Reviewer Note:** *Janssen stated in their IR response received on 30 July 2021, the (b) (4) systems PV studies were included as part of the PPQ batches. During my review of the PPQ Batch Record, I reviewed the manufacturing steps performed on the (b) (4) system and did not see any discrepancies noted. It appears the (b) (4) performed as expected and the PV was successful.*

#### **Chain of Identity / Chain of Custody**

Chain of Identity (CoI) and Chain of Custody (CoC) for the ciltacabtagene autoleucel product is maintained throughout the supply chain including the patient apheresis material, manufacturing of the DP, and shipment of the final DP to the treatment site. The control, review, tracking, and recording of patient CoI/CoC is managed through a combination of paper and electronic systems. CoC documents the physical movements of the patient cells from one step to the next. The CoI documents the identifying

personal information, apheresis collection and shipment, manufacturing, shipment, and final infusion. Both Col and CoC systems conform with 21 CFR 1271.90.

Every DP batch is specific to the patient enrolled for treatment and a unique Order ID is generated to initiate the Col process. The patient personal information and Order ID are transferred to the Janssen Col/CoC System. The Col/CoC System generates a unique Col identifier for each patient that is used to track the manufacturing process as part of the (b) (4) system. The CoC is documented in the (b) (4) system and the manufacturing batch records and all movement of patient materials must be verified by a (b) (4) operator. The final DP bag and freezer cassette are labeled and tracked by the Col/CoC system. Shipment of the final DP is tracked, and receipt is confirmed on Col/CoC forms. Sites administering the final DP are audited for local Col/CoC procedures by Janssen and are required to inform Janssen upon infusion so it can be recorded.

**Chain of Identity / Chain of Custody Manual (Paper) Validation**

Janssen provided an overview of the Chain of Identity / Chain of Custody (Col/CoC) process in Section 3.2.R of the submission and the validation study for the manual Col/CoC tracking. (b) (4) validation runs, consisting of (b) (4) stages each, were performed to validate the manual Col/CoC tracking.


(b) (4)

(b) (4)

(b) (4)


(b) (4)

(b) (4)


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**Janssen Chain of Identity / Chain of Custody Computer Validation**

Janssen provided the validation protocol and summary report for the (b) (4) computer database used to manage Chair of Custody / Chain of Identity (CoC/Col) at the (b) (4) facility. The (b) (4) computer database was validated through (b) (4) studies, (b) (4)

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(b) (4)

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(b) (4)

**Reviewer Assessment:** The (b) (4) computer system was demonstrated to manage patient CoC/Col from (b) (4) centers. The validation involved (b) (4) healthy donor apheresis materials that were collected, (b) (4), received at (b) (4), manufactured, and shipped to a simulation treatment center. This was completed and CoC/Col was maintained through the process. The (b) (4) validation appears acceptable. I defer to OTAT for full review of the CoC/Col process, as my focus was only on the computer system validation.

❑ **Method Validation Package**

Janssen provided Method Validation Package information for the (b) (4) the Drug Product. Additionally, Method Descriptions for the Sterility Assay and (b) (4) Assay were included. I reviewed the sterility and (b) (4) assays for the (b) (4) in Sections 3.2.S.4.2 and 3.2.S.4.3 and for the DP in Sections 3.2.P.5.2 and 3.2.P.5.3. Other method validations are deferred to OTAT for their review.

❑ **Comparability Protocols**

Several comparability protocols were submitted in the BLA, I reviewed the following comparability protocol related to facility modifications and equipment replacements at the (b) (4) LV manufacturing facility and the (b) (4) increase by the addition of new (b) (4) at the (b) (4) LV facility. I defer to OTAT for the remaining protocols.

The Comparability Protocol (CP) for the (b) (4) Increase proposed increasing the manufacturing (b) (4) for Stage (b) (4) of the LV manufacturing process by adding (b) (4) to Room (b) (4). The new (b) (4) will be identical to the currently used and will be dedicated to the LV product. The new (b) (4) will be cleaned and sterilized using the current processes. Data from the (b) (4) Increase CP will be submitted as a CBE-30 supplement.

**Reviewer Note:** I discussed the (b) (4) Increase CP with OTAT as it appeared that DMPQ's input was necessary for this CP as the additional (b) (4) are identical to the current ones and will use the established cleaning and sterilization procedures. I defer full review of the (b) (4) Increase CP to OTAT.

Janssen submitted a CP for proposed facility modifications/improvements at the Janssen Vaccines facility in (b) (4) to increase (b) (4) equipment. The CP includes information about the following:

- Describing the modifications associated with the (b) (4)
- Describing the replacement of (b) (4)
- Describing the validation activities and testing to be performed to demonstrate comparability with the current equipment
- Proposed content of the supporting submission

Upon completion of the CP, Janssen proposed submitting the data package in the subsequent Annual Report. Janssen notes the change in (b) (4) may be managed separately and reported accordingly.

#### Proposed Facility Modifications

(b) (4)

(b) (4)

#### Proposed Equipment Changes

(b) (4)

(b) (4)



(b) (4)

Proposed Submission

Janssen states the proposed changes are in accordance with *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* and the changes in facilities and equipment meet the requirements of a CBE-30 supplement. Janssen further states that following approval of the CP, they will provide the comparability and validation data in the subsequent Annual Report. The following modules will be updated:

(b) (4)

Janssen noted that the change in the (b) (4) may be managed separately from the facility modifications and reported accordingly.

**Reviewer's Assessment:**

*The CP did not adequately describe the proposed facility changes at the (b) (4) facility. The facility modifications diagrams showed (b) (4) installed, but the CP did not information about how the modified areas would be requalified and returned to service.*

*The (b) (4) changes were better described, and the replacement equipment will be comparable to the current equipment. The replacement equipment will undergo revalidation studies that are analogous to the (b) (4) qualification reports provided in the BLA submission.*

*The proposed reporting category for the CP data is not appropriate for the level of modifications being proposed. An IR (DMPQ IR #5, sent August 25, 2021) was sent to Janssen requesting additional details about the facility requalification plan, clarifications about the equipment qualification studies, and informing them that the reporting category for the CP should be a PAS.*

Janssen responded on September 3, 2021 with additional information about the (b) (4) facility modification and equipment replacement CP. Janssen confirmed the (b) (4) would be qualified using the same procedures, standards, and acceptance criteria as presented in BLA Section 3.2.S.2.5 ((b) (4) ) and 3.2.A.1 ((b) (4) ). Janssen additionally provided details on the HVAC requalification for the facility areas impacted by the modifications. Data from the EMPQ study for the modified (b) (4) was summarized and was shown to have met all acceptance criteria. It is noted that the HVAC qualification protocol and report for (b) (4) was submitted previously in Amendment 27 to the BLA (reviewed in Section 3.2.A.1 *Building (b) (4) HVAC* of this memo).

Janssen also provided clarifications about how EMPQ will be performed for the modified facility rooms and defined the worst-case activities that will be used to challenge the EMPQ. The impacted rooms are classified as either (b) (4) Grade (b) (4) and acceptance criteria was provided that will be used during the EMPQ. Information about establishment and monitoring of routine EM Warning Limits and Action Limits was provided.

Janssen responded to the Agency's recommendation to submit the facility implementation data as a Prior Approval Supplement, by providing a table of reporting category justifications based on the Agency's CMC Changes to an Approved Application: Certain Biological Products; Guidance for Industry; June 2021. Janssen provided the following assessments:

- Modification to the Building (b) (4) – Annual Report
- Modification to Building (b) (4) – Annual Report
- Modification to Building (b) (4) to (b) (4) for (b) (4) – Changes Being Effective in 30 Days (CBE-30)
- Replacement of (b) (4) – CBE-30
- Replacement of (b) (4) – CBE-30

Janssen states since the CP is filed in the BLA, they are requesting the Agency downgrade the assessments with CBE-30 reporting categories to Annual Reportable. Janssen claims this is a less burdensome reporting category.

**Reviewer Assessment:** The clarifications for the (b) (4) , HVAC requalification, and EMPQ studies are acceptable. However, the request to downgrade the reporting categories from CBE-30 to Annual Report are not acceptable for the changes being made at the (b) (4) facility. The Agency considers these changes to be

*moderate changes and should be reported as CBE-30s, which permits the applicant to release product 30 days after the submission is received by the Agency.*

*An IR (DMPQ IR #9, sent on October 4, 2021) was sent to Janssen requesting their acknowledgement of the Agency's comments that the proposed reporting categories justified by the guidance document should be followed and a downgrade request was not acceptable.*

*Janssen responded on October 8, 2021 and agreed to the Agency's request to submit the facility modifications to Rooms (b) (4) and (b) (4) replacement data as a CBE-30 when the supportive data is available. Janssen submitted a modified CP with the agreed upon reporting categories and additional details requested in DMPQ IR #5. The response appears acceptable.*