CBER CMC BLA Review Memorandum

BLA STN 125736/0

ABECMA
Idecabtagene vicleucel

Lily Y. Koo, Ph.D.
Consumer Safety Officer
CBER/OCBQ/DMPQ/MRB2

1. BLA#: STN 125736/0

2. APPPLICANT NAME AND LICENSE NUMBER
Celgene Corporation, a Bristol-Myers Squibb Company

3. PRODUCT NAME/PRODUCT TYPE

Non-proprietary/Proper/USAN:	Idecabtagene vicleucel
Proprietary name:	ABECMA
Company Code:	bb2121

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Pharmacological category:	Cell
Dosage form:	Cell Suspension for Infusion
Strength/Potency:	300 - 460 × 10^6 viable CAR-positive T cells
Route of Administration:	Intravenous infusion
Indication:	Treatment of adult patients with multiple myeloma who have received at least three previous therapies, including an immunomodulatory agent, a proteasome inhibitor, and/or an anti-CD38 antibody

5. MAJOR MILESTONES
Application received: 7/27/2020
Filing Action: 9/25/2020
Mid-cycle communication: 12/10/2020
Late-cycle communication: 1/19/2021:
(b) (4) facility/(b) (4) facility pre-license inspection: (b) (4)
Celgene S12 facility pre-license inspection: 2/15/2021-2/19/2021
(b) (4) facility pre-license inspection: (b) (4)
PDUFA First Action Date: 3/27/2021

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Anna Kwilas, Ph.D., OTAT/DCGT/GTB	Ide-cel process validation
Jakob Reiser, Ph.D., OTAT/DCGT/GTIB	Anti-BCMA02 CAR lentiviral vector (LVV)
Jessica Chery, Ph.D., OTAT/DCGT/GTB	Ide-cel analytical method validation, specifications, stability, reagent qualification
Bo Liang, Ph.D., OTAT/DCGT/GTB	Control of materials, adventitious agents safety, validation of analytical methods for clinical samples, categorical exclusion
Lily Koo, OCBQ/DMPQ/MRB2	Facility and Equipment, aseptic process validation

7. INTER-CENTER CONSULTS REQUESTED

Not applicable.

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
July 27, 2020	STN 125736/0	Initial BLA Submission
August 26, 2020	STN 125736/0.3	LVV Shipping Validation
October 30, 2020	STN 125736/0.12	DMPQ Information Request (IR) 1 Responses
December 11, 2020	STN 125736/0.26	DMPQ IR2 Responses
January 14, 2021	STN 125736/0.39	Applicant Name Change
January 20, 2021	STN 125736/0.40	DMPQ IR3 Responses
February 12, 2021	STN 125736/0.49	DMPQ IR4 Responses
February 26, 2021	STN 125/736/0.56	(b) (4) 483 Responses
March 15, 2021	STN 125736/0.61	Celgene 483 Responses
March 22, 2021	STN 125736/0.64	DMPQ IR5 Response and (b) (4) 483 Responses

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
(b) (4)	(b) (4)	(b) (4)	Yes	Reviewed by Lily Koo in this review memo. It was also reviewed by Zehra Tosun (CBER/OTAT/DCGT/CTB) in a consult review.
(b) (4)	(b) (4)	(b) (4)	Yes	Reviewed by Thomas Finn (CBER/OTAT/DCGT/CTB) in a consult review.
(b) (4)	(b) (4)	CryoStor medium	Yes	Reviewed by Mercy Quagraine (CBER/OTAT/DCGT/CTB).
(b) (4)	(b) (4)	Anti-CD3/Anti-CD38 antibodies	Yes	Reviewed by Elena Gubina (CBER/OTAT/DCGT/GTB) in a consult review.
(b) (4)	(b) (4)	Facility information	Yes	Reviewed by Lily Koo in this review memo.

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Information under DMPQ purview (as per CBER SOPP 8404.1) was reviewed and deemed acceptable. All identified deficiencies were addressed in firm's responses to DMPQ information requests. Records submitted in advance of an inspection pursuant to section 704(a)(4) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 374(a)(4)] were reviewed and documented in two separate records request review memos for the following facilities: (b) (4) manufacturing facility ((b) (4)) together with (b) (4) storage facility ((b) (4)) and Celgene S12 manufacturing facility (Summit, NJ). Pre-license inspection of the (b) (4) facility where anti-BCMA02 CAR LVV critical component is manufactured and the (b) (4) facility where the lentiviral vector and raw materials are stored was conducted by ORA inspectors from (b) (4) . An FDA Form 483 was issued to the (b) (4) facility with three observations and an FDA Form 483 was issued to the (b) (4) facility with one observation. Pre-license inspection of the Celgene S12 facility where idecabtagene vicleucel (ide-cel) is manufactured was conducted by CBER and ORA inspectors (ORA lead) from February 15 – February 19, 2021. An FDA Form 483 was issued to the Summit facility with three observations. Pre-license inspection of the (b) (4) facility where release and stability testing of the anti-BCMA02 CAR LVV critical component is performed was conducted by ORA inspectors from (b) (4) . An FDA Form 483 was issued with four observations. Inspection observations, discussions, and outcome were documented in the respective Establishment Inspection Report for each facility. The final classification of each of the three inspections covering four establishments is Voluntary Action Indicated (VAI). Responses to the 483 observations were reviewed and documented in three separate review memos.

Based on the totality of information reviewed, this DMPQ reviewer recommends approval with an inspectional recommendation (provided below). The inspectional recommendation will be provided to the OCBQ/DIS/PSB contact.

B. RECOMMENDATION

I. APPROVAL

Recommend approval with an inspectional recommendation. CBER understands that the recommendation may or may not be taken (based on risk and available resources), and is not requesting documentation to be submitted as evidence of completion for the following item:

> Please review the handling, shipping, and storage conditions, including durations, in association with the anti-BCMA02 chimeric antigen receptor lentiviral vector sterility samples at both the (b) (4) Manufacturing facility (FEI: (b) (4)) and the (b) (4) testing site (FEI: (b) (4)). Review method suitability/recovery tests to support the representative sterility sample handling, shipping, storage, and time-to-test conditions.

II. COMPLETE RESPONSE (CR)

Not applicable.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Lily Y. Koo, Reviewer OCBQ/DMPQ/MRB2	Concur	
Ekaterina Allen, Acting Team Lead OCBQ/DMPQ/MRB2	Concur	
Anthony Lorenzo. Acting Branch Chief OCBQ/DMPQ/MRB2	Concur	
Carolyn Renshaw, Deputy Director OCBQ/DMPQ	Concur	

Table of Contents

Module 3

3.2.S Anti-BCMA CAR LVV DRUG SUBSTANCE

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

Anti-BCMA02 chimeric antigen receptor lentiviral vector (CAR LVV) is an (b) (4) lentiviral vector (b) (4) . The anti-BCMA02 CAR LVV is manufactured in (b) (4) cells transfected with (b) (4) . The functions encoded by the (b) (4) include (b) (4) respectively. The LVV particle is (b) (4) The LVV particles are used to transduce autologous T-lymphocytes during the manufacture of ide-cel. The gene product is composed of an anti-BCMA02 single chain variable fragment (scFv) linked to the CD3ζ and CD137 (4-1BB) T cell signaling domains by a CD8α transmembrane region.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Manufacturing/Testing/Storage Site	Activities
(b) (4) FEI: (b) (4)	CAR LVV manufacture
(b) (4) FEI: (b) (4)	CAR LVV release testing (replication competent lentivirus testing, (b) (4))
(b) (4) FEI: (b) (4)	CAR LVV release testing (b) (4)
(b) (4) FEI: (b) (4)	CAR LVV release and stability testing ((b) (4)

Manufacturing/Testing/Storage Site	Activities
(b) (4) FEI: (b) (4)	CAR LVV release and stability testing (b) (4)
(b) (4) FEI: (b) (4)	CAR LVV storage
(b) (4) FEI: (b) (4)	CAR LVV storage
(b) (4) FEI: (b) (4)	CAR LVV storage
(b) (4) FEI: (b) (4)	CAR LVV storage

3.2.S.2.2 Description of Manufacturing Process

To manufacture the anti-BCMA02 CAR LVV, (b) (4)

- **Manufacturing Process Steps**

(b) (4)

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

(b) (4)

Overall Reviewer's Assessment of Section 3.2.S.2.5: *The process validation information presented in Section 3.2.S.2.5 is acceptable from a DMPQ perspective.*

3.2.S.2.6 Manufacturing Process Development

The anti-BCMA02 CAR LVV manufacturing process development history consisted of (b) (4) manufacturing processes: Processes (b) (4) . Process (b) (4) was performed at (b) (4) in

(b) (4) was included as an additional site in 2017 when Process (b) (4) was transferred to (b) (4) as Process (b) (4), which later changed to Process (b) (4). Process (b) (4) was transferred from (b) (4) to (b) (4) in (b) (4) in 2018 as Process (b) (4) for the manufacture of pivotal trial and PPQ materials. The process scale for LVV manufacturing process has not changed during process development. Comparability assessments were conducted during each process transfer, and included comparison of lot release data, characterization studies, forced degradation studies, and long-term stability studies. Of the LVV CQA and release specifications, sterility (no growth) and endotoxin (≤(b) (4)) remained unchanged throughout development. The following table summarized the process change history.

(b) (4)

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

(b) (4)

3.2.S IDE-CEL DRUG SUBSTANCE[1]

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

Ide-cel consists of autologous T cells transduced with the anti-BCMA02 CAR LVV encoding a CAR that is comprised of a BCMA-specific scFv fused to 4-1BB (CD137) costimulatory and CD3ζ activation endodomains by a hinge and transmembrane domain derived from CD8α.

Antigen-specific activation of ide-cel results in their proliferation, cytokine secretion, and cytolytic killing of BCMA-expressing cell. The product is composed of a highly pure T cell population (CD4+ and CD8+) that is free of detectable (b) (4) . The genetically modified autologous cells harvested at the end of cell culture are designated by the Applicant as the drug substance (DS) and are the active substance of the DP.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Manufacturing/Testing/Storage Site	Activities
Celgene Corporation 556 Morris Avenue, Building S12 Summit, NJ 07910, US FEI: 3004991673	Peripheral blood mononuclear cell (PBMC) preparation, ide-cel DS and DP manufacturing, packaging and labeling, release and stability testing, (b) (4) PBMC intermediate storage, ide-cel DP storage
(b) (4) FEI: (b) (4)	Excess (b) (4) PBMC intermediate storage, excess ide-cel DP storage
(b) (4) FEI: (b) (4)	Excess (b) (4) PBMC intermediate storage, excess ide-cel DP storage

3.2.S.2.2 Description of Manufacturing Process

The DS manufacturing process includes the following unit operations: (b) (4)

- **Manufacturing process steps**

(b) (4)

(b) (4)

- **Batch Numbering, Pooling and Scale Definition**
  (b) (4) patient product (b) (4) batch, which starts with (b) (4) autologous leukapheresis material and ends with the filling of (b) (4) DP bags. A unique lot number is assigned to the leukapheresis starting material, the (b) (4)

PBMC intermediate, and the final DP to provide traceability and a chain of identity (COI) throughout manufacture, packaging and distribution. The lot number consists of a patient specific 10-character alphanumeric sequence (referred to as the JOIN number), appended with a single alphabetic character (i.e., lot suffix) that sequentially designate the associated starting material, PBMC intermediate, and DP. If additional DS or DP lot(s) are manufactured from the existing PBMC intermediate of the same patient, the lot suffix will use the next available sequential alphabetic character.

- **Storage and Shipping**
  The CAR-T DS is processed into DP immediately in the same manufacturing facility.

3.2.S.2.3 Control of Materials
Control of materials during ide-cel manufacture takes into account the following four material sources: LVV starting material, leukapheresis materials, raw materials (i.e., critical reagents and media components), and inert materials (i.e., consumables).

Raw and inert materials are sourced from qualified suppliers and are managed through change controls. A process reagent is qualified by performing full testing on a minimum of (b) (4) lots using validated methods and meeting all material specifications. Once qualified, a reduced testing schedule is implemented for routine material release. Qualified materials are tested using the full release panel on an (b) (4) basis to ensure continued suitability. Incoming raw materials are quarantined on receipt pending QC testing and QA release. Each material shipment is assessed against internal material specifications which at a minimum include visual inspection, review of supplier CoA, identity testing, and other required tests if applicable.

The supplier qualification process includes the following aspects: 1) Questionnaire and/or technical visit, 2) supplier quality assessment, 3) pre-approval audit as part of the change control workflow, 4) material approval process governed by change control, 5) quality agreement, and 6) supplier approval by quality. Supplier performance is monitored through (b) (4) review, routine GMP compliance audits, and supplier related non-conformance evaluation.

Reviewer Comment: *The supplier and material qualification and monitoring processes appear acceptable.*

- **Control of Raw Materials <u>NOT</u> of Biological Origin**

(b) (4) reagents and media components that are not of biological origin, described in Table 6 of Section 3.2.S.2 [Cell] "Raw Materials", consist of (b) (4) . They are accepted based on supplier CoA, visual inspection, and in-house testing including identity testing. Respective materials acceptance specifications, suppliers, CoA, and quality testing frequency are provided. Sterility and endotoxin specifications are included for all listed reagents and components. The sterility and endotoxin acceptance criteria appear to be acceptable.

Reviewer Comment: *I defer the evaluation of raw material not of biological origin control strategy to the OTAT/DCGT reviewer.*

- **Control of Raw Materials of Biological Origin**

(b) (4) reagents and media components of biological origin include Plasma-Lyte A and (b) (4) . They are tested per their respective (b) (4) monographs in addition to (b) (4) testing. (b) (4) l reagents and media components that are of biological origin include (b) (4) and anti-CD3 and anti-CD28 antibodies. Materials of biological origin require confirmation of BSE/TSE, adventitious agents, and applicable functional/performance testing. The sourcing, adventitious agent risk control, and testing strategy are discussed. Respective materials acceptance specifications, suppliers, CoA, and quality testing frequency are provided. All listed (b) (4) reagents and components are tested in-house for (b) (4) during qualification on a minimum of (b) (4) lots and (b) (4) thereafter. (b) (4)

Reviewer Comment: *I defer the evaluation of raw material of biological origin control strategy to the OTAT/DCGT reviewer.* (b) (4) *. Likewise, the* (b) (4) *during cell activation. Given the numerous media changes and washing steps present in the ide-cel manufacturing process (including the* (b) (4) *) and that endotoxin is controlled at release, the overall risk associated with endotoxin is low.*

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

The firm considers the LVV supplied by (b) (4) as the starting material of the ide-cel manufacturing process. Refer to Section 3.2.S.2.3 [LVV] for a discussion of LVV control strategy.

- **Control of Leukapheresis**

A list of U.S. qualified leukapheresis collection centers is provided in Table 1 of Section 3.2.S.2 [Cell] “Leukapheresis”. The qualification program requires an initial qualification audit, contractual agreement with Celgene, establishment of procedures (i.e., labeling, collection, packaging, shipping, and documention), completion of Celgene-provided training. Periodic reviews are performed, including additional audits, if required, as part of ongoing monitoring. Briefly, the leukapheresis unit is collected by quailifed staff using automated blood cell separtor devices and a 510(k) cleared sterile disposable apheresis kit. Immediately following collection, the leukapheresis bag is packaged in a tamper-proof and leak-proof secondary container and shipped to the manufacturing facility using a qualified temperature-controlled shipper ((b) (4)). Upon receipt, the unit is inspected to ensure COI and product integrity.

- **Control of Inert Material(s)**

Single-use consumables used during ide-cel manufacture are summarized in Table 1 of 3.2.S.2 [Cells] "Inert Materials". All product contacting consumables are supplied sterile. Extractables and leachables studies were performed where applicable. All product contact materials are either free of animal derived components or compliant with (b) (4) in mitigating TSE/BSE risk. Representative CoA are provided.

- **Generation of the Seed Stock and Expression Construct (e.g., vector (b) (4))**

Reviewer Comment: *Refer to Section 3.2.S.2.3 [LVV] for information* (b) (4) *anti-BCMA02 CAR LVV manufacturing process.*

Reviewer Comment: *Overall, the control of materials is acceptable from a DMPQ perspective.*

3.2.S.2.4 Controls of Critical Steps and Intermediates

The ide-cel DS manufacturing process is controlled through CPPs, IPCs, and defined hold/process times. The parameters which are under DMPQ purview are summarized in the table below.

(b) (4)

3.2.S.2.5 Process Validation and/or Evaluation

The ide-cel manufacture is an end-to-end aseptic process to produce a cryopreserved cell infusion solution. The CAR-T cells harvested at the end of DS manufacture are processed into DP immediately with the additional formulation, fill/finish, and cryopreservation steps. Therefore, the validated process steps discussed in this section are inclusive of the DS and DP manufacturing process.

Process Validation

Ide-Cel Process Performance Qualification

(b) (4) PBMC isolations were prepared from (b) (4) leukapheresis materials, from which (b) (4) end-to-end PPQ lots ((b) (4) lots using a single donor material) were produced at Celgene S12 Suite (b) (4) in October 2019. The PPQ study design aimed to evaluate process variations associated with inter-donor, intra-donor, and LVV lots. DP was filled into (b) (4) (b) (4) 50 bags at a target fill volume of (b) (4) mL for each of the (b) (4) lots to present a worst-case surface area to fill volume ratio. (b) (4) lots of (b) (4) media and (b) (4) lots of LVV were used for the PPQ campaign. Validation of needle-to-

needle COI is out of scope for this PPQ campaign due to the use of healthy donor materials. However, COI was controlled from leukapheresis receipt through DP manufacture.

The table below summarizes in-process/release test results and executed process parameters that are under DMPQ purview.

Test and Acceptance Criterion	PPQ Results (Range)
Operation: PBMC Cryopreservation	
(b) (4)	
Operation: DP Release	
Appearance (Liquid, colorless cell suspension)	Conform
Sterility (No Growth)	No Growth
Endotoxin ((b) (4))	(b) (4)

(b) (4) study deviations and (b) (4) protocol deviations were reported. They primarily involved deviations from procedures, documentation errors, equipment malfunction, and protocol generation errors. DEV-2019-02773 reported an action level excursion of personnel monitoring during QC activities for Lot (b) (4) without direct impact to the PPQ validity or outcome.

> ***Reviewer Comment:*** *The appropriateness of using* (b) (4) *PBMC for the PPQ runs is deferred to the OTAT/DCGT reviewer. The complete DP filling process using all three bag sizes is validated in a different study and is reviewed below. Needle-to-needle COI is addressed in a different study and is reviewed below. The deviations are either not under DMPQ purview or have no impact on the PPQ study. The PPQ results are acceptable from a DMPQ perspective.*

The addendum report (RPT-020874) documents the post-PPQ commercial in-process control strategy. The updated parameters are related to cell concentrations and %CAR+ T cells measured at various process steps. Cell CQAs are compared to historical clinical lots. A retrospective evaluation of the release specifications based on

statistical ranges derived from the DP PPQ lots is documented in RPT-021112. A post-PPQ risk assessment is documented in RISK-011316 to define the commercial control strategy (i.e., process parameters, in-process controls, processing times, unit-operation times, hold times). Controls under DMPQ purview remained the same.

Reviewer Comment: *I defer the evaluation of final process control strategy to the OTAT/DCGT reviewers.*

PPQ Extended Characterization

Two studies were performed to characterize product related impurities and process related impurities associated with the PPQ DP materials.

Reviewer Comment: *I defer the evaluation of impurity characterization to the OTAT/DCGT reviewers.*

PPQ at (b) (4)

The (b) (4) facility is the proposed commercial manufacturing site for PBMC preparation to supply the EU market. The Applicant submitted PPQ data covering (b) (4) runs of leukapheresis receipt to PBMC (b) (4) at the (b) (4) facility and DS/DP manufacturing at the Celgene facility as supporting information. Formulated DP was filled into (b) (4) (b) (4) 250 bags at a target volume of (b) (4) (representative of clinical manufacturing). COI from leukapheresis receipt to DP release was part of this PPQ exercise.

(b) (4) PBMC lots were produced from (b) (4) nors at the (b) (4) Facility and were shipped to the Celgene facility where they were processed to DP using (b) (4) . The processing of these (b) (4) PBMC lots at the Celgene S12 facility in November 2019 is reviewed below to provide additional support for the ide-cel DS/DP process performance.

Test and Acceptance Criterion	PPQ Results (Range)
(b) (4)	
Operation DP Cryopreservation	
Cooling Rate (≤ 3 °C/min)	≤ 1 °C/min
Operation: DP Release	
Appearance (Liquid, colorless cell suspension)	Conform
Sterility (No Growth)	No Growth
Endotoxin	(b) (4)

	(b) (4)	

A visual check of all DP bags was performed for absence of damage, correct packaging, proper label, and proper seal.

(b) (4) deviations were reported. They involved procedural deviations, protocol deviations, documentation error, calibration error, inadequate training and material defect. A post-PPQ, retrospective evaluation of the commercial release specifications was performed with several acceptance criteria tightened upon evaluation.

Reviewer Comment: *I defer the evaluation of final process control strategy to the OTAT/DCGT reviewers. The supporting PPQ results are acceptable from a DMPQ perspective. The deviations are either not under DMPQ purview or have no impact on the PPQ study.*

Supplemental Filling Validation

A supplemental fill validation study was performed to validate the filling process as not all DP bag sizes were covered in the previous PPQ studies. Cryopreservation (b) (4) was (b) (4) into each of the three DP bag sizes ((b) (4) (b) (4) 50, (b) (4) 250, (b) (4) 500) with filling volume controlled by (b) (4) . The operation was performed at (b) (4) different filling stations by (b) (4) different operators using the filling matrix below. The target fill volume was selected to correspond to a Day (b) (4) CAR+% T cell count.

(b) (4)

Each operator filled (b) (4) bags (b) (4) for each bag size from a (b) (4) . Prior to each filling run, the (b) (4) was filled with 1:1 ratio of CryoStore CS10 cryopreservation medium with 10% DMSO and Plasma-Lyte DP formulation surrogate. Equipment required for the filling operation included the filling station, (b) (4) . All aseptic connections were made through welding and sealing. All fill volumes were within the target fill range for the (b) (4) 50 bags ((b) (4) mL), (b) (4) 250 bags ((b) (4) mL), and (b) (4) 500 bags (73.92-76.81 mL).

Reviewer Comment: *The final DP fill volume ranges were adjusted during the course of BLA review as the dose strength was amended. The final fill volume ranges are:* (b) (4) *50 (fill volume 13 to 27mL),* (b) (4) *250 (fill volume 34 to 66 mL), or* (b) (4) *500 (fill volume 60 to 95 mL) at a concentration of* (b) (4) *. However, as the filling process is a manual operation, the filling study demonstrates repeatable and accurate manual filling by qualified operators using qualified and/or calibrated equipment. The study is acceptable from a DMPQ perspective.*

Aseptic Process Simulation
Simulations using (b) (4) were performed for the end-to-end aseptic processes, including (b) (4) DS/DP manufacturing. The initial APS runs were performed in September 2018, with recent requalification runs performed in March 2019 and October 2019.

Reviewer Comment: *Based on room information provided in the APS protocols/reports, it appears that the simulation of the* (b) (4) *preparation and aliquoting process was performed in the Auxiliary Process Support Room* (b) (4) *rather than the Media Preparation Room* (b) (4) *during the initial APS study and the subsequent 2019 requalification* ***IR4 Comment 1*** *(below in* ***bold****) requested clarification. The response is summarized and reviewed below.*

1. **Although not explicitly stated in the BLA submission, it appears that the Auxiliary Process Support Room** (b) (4) **was used during idecabtagene vicleucel product development to manufacture** (b) (4) **before the media preparation process was transferred to Media Preparation Room** (b) (4) **for the commercial manufacturing process. It is noted that during the initial 2018 aseptic process simulation (APS) study and the two 2019 APS requalification runs, simulation of the** (b) (4) **aliquoting/QC sampling process** (b) (4) **of** (b) (4) **sterile filtration was all performed in Room** (b) (4)**, and it is unclear which Room (Room** (b) (4) **or Room** (b) (4)**) was used to execute the May 2020 APS requalification. Please address the following comments:**

   a. **Clarify if the aseptic** (b) (4) **aliquoting/sampling process** (b) (4) **of** (b) (4) **sterile filtration was validated in the commercial production suite Room** (b) (4)**. If yes, provide the APS study report if it is not already submitted. If not, justify why aseptic process validation performed in Room** (b) (4) **could be considered "equivalent" to the commercial aseptic process performed in Room** (b) (4)**. In your discussion, consider factors such as room design and classification, HVAC, equipment, layout, operator occupancy (related to room size), activities, and manipulations.**

   b. **Clarify if** (b) (4) **was prepared in Room** (b) (4) **or Room** (b) (4) **for the Process Performance Qualification lots and justify the use of Room** (b) (4) **for process validation, if applicable.**

      The firm clarified that prior to June 2019, (b) (4) preparation and aliquoting operation was performed in Room (b) (4); therefore, APS was performed in Room (b) (4). During the May 2020 APS requalification run [study report and the executed batch records were submitted under the 704(a)(4) records request], simulation of the aliquoting/QC-sampling steps (b) (4) of (b) (4) sterile filtration was performed in Room (b) (4). Celgene justified the decision for not performing the simulation in the Commercial Media Prep Room (b) (4) by confirming that all steps (b) (4) of sterile filtration are manipulations performed in a close

manifold system. In addition, Room (b) (4) represents a worst-case scenario because the room is designed to a lower classification compared to Room (b) (4) (ISO (b) (4) /Grade (b) (4) vs. ISO (b) (4) /Grade (b) (4)), while HVAC/equipment/layout/activities are considered equivalent and operator occupancy is worst-case ((b) (4)). Finally, they confirmed that the PPQ lots used (b) (4) prepared in Room (b) (4) as per the commercial process.

Reviewer Comment: *It is acceptable to simulate this operation in a different room if all the steps* (b) (4) *of sterile filtration are performed in a closed system.*

The APS study design (b) (4) all sizes and maximum number of (b) (4) and DP fill bags. All bags were (b) (4) and all filled DP containers and unused media were incubated. Each APS run was (b) (4) with all (b) (4) used concurrently inside the Process Support Suite (b) (4) with multiple personnel shifts ((b) (4) APS lots/run to simulate maximum capacity). The maximum personnel occupancy challenged in Process Support Suite (b) (4) included (b) (4) aseptic operators outside each (b) (4) , (b) (4) QA observers, and (b) (4) QC personnel performing EM activities. A shift change consisted of the complete exit of operators from Process Suite (b) (4) and the manufacturing area, followed by re-gown and re-entry or replacement by the second shift team. All aseptic manipulations/interventions related to setup and connections/disconnections (b) (4) were included in the APS study design with worst-case duration challenged using a timer in the initial run. Maximum duration of equipment contact with the growth media was determined for type of aseptic manipulation by multiplying the worst-case time for each manipulation (e.g., pipetting) by the total number of manipulations. Table 1 of Section 3.2.S.2.5 [Cells] presented a description of each manipulation/intervention, a comparison of the routine process vs. simulated process (including (b) (4) , and justifications for worst-case simulation. A majority of the interventions involved connection/disconnection performed aseptically or through (b) (4) . Other aseptic activities involved aseptic addition of reagents through pipetting. The (b) (4) preparation of (b) (4) simulated (b) (4)

Table 2 listed and justified the following Grade (b) (4) /ISO (b) (4) process steps/unit operations which were not included in the simulation: (b) (4)

(b) (4) There are no defined sterile hold times in the routine manufacturing of ide-cel. Filled DP bags (b) (4) were visually inspected and incubated for a minimum of (b) (4), followed by a minimum of (b) (4). No turbidity was observed during (b) (4) inspection. The number of filled bags and the number of incubated bags were reconciled with (b) (4) bags removed from incubation. (b) (4) used in each APS run was evaluated for growth promotion of (b) (4) organisms covering (b) (4). Growth was confirmed in all cases. The footnote under Table 7 of Section 3.2.S.2.5.1 indicated that only (b) (4) bags were filled and incubated in the 2019APV007 requalification run due to (b) (4). However, no (b) (4) bags were reported in the summary report.

Reviewer Comment: *I reviewed Table 1 and Table 2 in detail. The described manipulations are consistent with the manufacturing processes and the worst-case simulations are reasonably justified. The following questions need to be addressed: 1) Were the operations performed in Process Suite (b) (4) simulated at capacity? 2) Is* (b) (4) *Plasma-Lyte A used in PBMC preparation aseptically prepared? 3) The* (b) (4) *process should be simulated at least once to demonstrate* (b) (4) *. 4) Was material transport between different process steps and processing areas simulated? 5) Which bags (i.e.,* (b) (4) *, DP bags) were incubated and reconciled for each run? 6) The root cause of the* (b) (4) *reported in APS Run 2019APV007.* ***IR2 Comment 18*** *(below in* ***bold****) requested additional information. The response is summarized and reviewed below.*

18. Aseptic Process Simulation (APS) was performed to validate the end-to-end aseptic ide-cel manufacturing process. Please address the following comments:

a. Please clarify if APS was performed under maximum production capacity as described in the capacity ramp study. If it is not performed under maximum capacity, please describe and justify the production capacity/activity levels challenged during APS.

The firm stated that APS was performed according to the maximum capacity of Process Support Suite (b) (4) where critical/open operations are performed inside the (b) (4) BSCs. Maximum level of operational activities was performed concurrently in the BSCs with (b) (4) per BSC and a total of (b) (4) personnel. As such, the maximum capacity, as executed in the capacity study, was performed within the constraints of the APS studies.

Reviewer Comment: *The response is acceptable for the operation of open processes performed inside the BSC. However, for the initial APS study, the activity level for operations performed* (b) (4) *should be challenged at maximum capacity as well to demonstrate aseptic processing capability.* ***IR3 Comment 4*** *(below in* ***bold****) requested additional information. The response is summarized and reviewed below.*

4. **In response to Information Request #27 Comment 2a addressed to Celgene, you clarified that Aseptic Process Simulation (APS) was performed according to the maximum capacity of Process Support Suite (b) (4) where critical/open operation steps are performed inside the Biological Safety Cabinets (BSCs). However, you did not comment on the activity/capacity levels simulated in Process Suite (b) (4) where processing occurs (b) (4) functionally (b) (4) . Please describe and justify the activity level(s) for unit operations performed (b) (4) (e.g., number of (b) (4) running (b) (4) units, number of (b) (4) incubated cell culture systems per incubator unit, number of (b) (4) engaged workstations, etc.) that was challenged during APS in a side-by-side comparison to the proposed maximum capacity levels.**

   The firm stated that while they challenged maximum capacity in the critical clean area ((b) (4) lots processed in (b) (4)), the same (b) (4) APS lots were processed in the less critical Process Suite (b) (4) where processing takes placed inside functionally (b) (4) . As such, (b) (4) workstations and (b) (4) Expansion Workstations (with (b) (4) incubators at each Expansion Workstation) were in (b) (4) operation. The Table below compares the activity level challenged during APS with the firm's estimated launch capacity and facility capacity per design.

Workstations/Equipment	APS	(b) (4) (Launch Capacity)	(b) (4) (Facility Capacity)
(b) (4) workstations	(b) (4)		
Expansion workstations			
Incubators in use			

(b) (4)

   The firm stated that operations performed (b) (4) are not considered worst-case scenarios and were not challenged during APS.

   Reviewer Comment: *The response is acceptable as all aseptic connections or setup manipulations related to the (b) (4) are performed in the BSC and the impact of increased operator activities on EM inside Process Suite (b) (4) may be assessed in the Capacity Study.*

b. Please clarify if (b) (4) Plasma-Lyte A solution is aseptically prepared and if yes, is the preparation included in the APS?

The firm confirmed that the solution is prepared aseptically in the (b) (4) by removing (b) (4) via a (b) (4) and adding it to the

Plasma-Lyte A (b) (4) via a (b) (4). The preparation was included in the APS batch record.

Reviewer Comment: *The response is acceptable.*

c. It appears that the (b) (4) operation was not simulated during PBMC preparation and multiple DP operation units including the (b) (4) step. Although (b) (4) is performed on (b) (4), the (b) (4) onto the containers should be simulated during the initial APS study to confirm that the (b) (4) per their intended use. Please provide justification or additional studies and data.

The firm stated that the (b) (4) has not been simulated during APS but committed to including it with the next APS execution scheduled in December 2020. There had been no reported incidence of container breach of the (b) (4) during (b) (4) in the manufacturing history of (b) (4) clinical lots.

Reviewer Comment: *The response is acceptable.*

d. Please clarify if the transition processes (e.g., material transport and storage) between different process steps or unit operations were included in the APS per the routine process. If not, please justify.

The firm confirmed that the same transition processes as during routine manufacturing are simulated in APS. They include (b) (4). Intermediate materials are (b) (4).

Reviewer Comment: *The response is acceptable.*

e. Please list and describe all (b) (4) DP bags collected for final incubation.

The (b) (4) incubated bags are summarized and described below.

Container Type:	Sample Description
(b) (4)	
250mL Cryo Bag	(b) (4)
500mL Cryo Bag	Largest size Final Drug Product Bag
250mL Cryo Bag	Medium size Final Drug Product Bag

Container Type:	Sample Description
50mL Cryo Bag	Smallest size Final Drug Product Bag (n=(b) (4))

Reviewer Comment: *The response is acceptable.*

f. Please describe the (b) (4) bag that was rejected from incubation during APS requalification run 2019APV007.

The firm clarified that there were no (b) (4) bags rejected from incubation during the 2019 requalification. The response described another deviation related to a (b) (4).

Reviewer Comment: *The (b) (4) occurred in Requalification Run 2019APV006. It was reviewed and was deemed to have no impact. It appears that the footnote was placed in the submission in error. The response is acceptable.*

EM was performed according to EMPQ of Process Suite (b) (4). For operations inside the BSC, (b) (4) monitoring was performed. (b) (4) excursions and (b) (4) excursions were reported during (b) (4) of the initial APS study. Information was provided on the (b) (4) monitoring excursions were reported during the March 2019 APS requalification. (b) (4) and (b) (4) excursions were reported during the October 2019 APS requalification. All (b) (4) recovered from the (b) (4) 2019 studies were identified as (b) (4), suggesting material/equipment related contamination source. All viable excursions were deemed to have no impact on the APS study as each run passed without evidence of microbial contamination.

Reviewer Comment: *The APS study design and reports are acceptable. Refer to response to IR2 Comment 24e for additional discussion on EM excursions observed during APS.*

(b) (4)

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

(b) (4)

Chain of Identity (COI) Validation

COI begins with the creation of the JOIN unique identifier in (b) (4) (Patient Treatment Repository), which is a patient-specific 10-character alphanumeric sequence linked to patient-identifying information (name and date of birth). COI controls are supported by the validated Global Patient Services (GPS) computerized system, which covers end-to-end tracking from generating patient identifiers at the time of enrollment, generating JOIN at scheduling, maintaining the link between patient identifiers and JOIN, and generating apheresis labels (collection bag and shipper) containing the JOIN. During the leukapheresis collection, government approved identification is used to verify patient identification against the collection labels. A Certificate of Conformance containing the JOIN is shipped with the collection bag. Throughout the manufacturing process, product identity is verified through each step via the (b) (4) and/or (b) (4)). Prior to the arrival of the patient material at the S12 facility, manufacturing orders (lot) are created in the manufacturing systems with lot numbers containing the JOIN. The (b) (4) generates COI labels prior to manufacturing, and COI controls within the manufacturing boundary of Celgene S12 continue with JOIN affixed to all patient material labels, including primary vessels, secondary containment, and QC samples. The manufacturing system performs a COI check by comparing the scanned JOIN barcode against the order number being manufactured, and only allows the order to proceed if there is a match (refer to COI checkpoints presented in the table below). COI for QC samples is managed by (b) (4) , which interfaces with (b) (4) . This process at Celgene S12 is considered validated during the PPQ execution. A separate COI verification study inclusive of all end-to-end controls was executed to

verify COI checkpoints (shown in table below) at the leukapheresis centers (apheresis collection protocol), manufacturing sites (manufacturing paper batch records and Packaging and Shipping of Final Products batch record), and infusion centers (Patient Administration Manual).

Location	Process Step	COI Controls	COI Information
Leukapheresis Collection Center	Leukapheresis Collection	• Patient medical records • Apheresis Portal • Government-issued photo ID • Verbal verification from patient • Certificate of Conformance (or Collection Procedure Record)	Patient-identifying information verified against the certificate of conformance or collection procedure record, including: • JOIN, unique identifier assigned and used to maintain COI throughout production • Patient first and last name • Patient date of birth
Manufacturing Production Facility – Celgene S12	Leukapheresis Receipt	• Shipping waybill • Schedule Confirmation Form • Receipt and Inspection Form • Certificate of Conformance (or Collection Procedure Record) • Validated manufacturing and laboratory electronic systems	Source of leukapheresis is verified against the Schedule Confirmation Form to ensure COI is maintained during receipt at the manufacturing facility, using: • Patient first and last name • Patient date of birth • JOIN
Manufacturing Production Facility – Celgene S12	(b) (4) Intermediate Shipment/Receipt (Currently not applicable to the manufacturing of US-licensed ide-cel product)	• Shipping Waybill • Schedule Confirmation form • Intermediate CMAT receiving form • Validated manufacturing and laboratory electronic systems • Secondary containment • Storage location in (b) (4)	Source of intermediate material is verified against the Schedule Confirmation Form to ensure COI is maintained throughout shipping, using: • JOIN • Manufacturing Lot numbering
Manufacturing Production Facility – Celgene S12	Leukapheresis Wash/Isolation through Drug Product Formulation/ Cryopreservation	• Validated manufacturing and laboratory electronic systems • Batch records • SOPs • In-process labels (Primary vessels, QC samples, secondary containment) • Single lot processing areas • In-process and LN2 freezer storage locations	Primary vessels, secondary containment and QC samples are labeled throughout production to ensure COI is maintained throughout production via: • JOIN • Manufacturing lot number

Location	Process Step	COI Controls	COI Information
Manufacturing Production Facility – Celgene S12	Drug Product Pack Out	• Validated manufacturing and laboratory electronic systems • In-process labels (Primary vessels, secondary containment) • Storage location in LN2 Freezer • Product Order Confirmation Form (POCF) • Shipper expiration label	DP and location in LN2 Freezer are labeled to ensure the correct product is removed and transferred to the LN2 Shipper, and verified against patient information on the POCF, including: • JOIN • Patient first and last name • Patient date of birth • Shipping address
Treatment and Administration Site	Receipt of Drug Product at Treatment Site to Patient Administration	• Release for Infusion Certificate • Primary vessel • Secondary containment (i.e. cassette) • POCF • Medical records • Hospital patient identification band	Patient information is verified against manufacturing and DP information to ensure COI was maintained throughout production and shipping, including: • Patient first and last name • Patient date of birth • JOIN • Manufacturing lot number

During study execution, each checkpoint was verified in (b) (4) clinical runs. Transcription discrepancies were found in the Protocol Data Collection Form which documents a list of expected end-to-end COI verification steps. Since the form was not used or referenced during the execution of actual COI checks, the discrepancies were deemed to have no impact to COI or study outcomes. All COI checks were verified in all (b) (4) runs.

Reviewer Comment: *The verification study is acceptable from a DMPQ perspective. I defer the final review determination to the OTAT/DCGT reviewers.*

Leukapheresis Shipper Validation

The patient leukapheresis material is collected into a (b) (4) and shipped to Celgene S12 by (b) (4) in an (b) (4) shipper. The (b) (4), supplied by (b) (4), consists of (b) (4). The (b) (4) is placed inside the (b) (4) shipper designed to cool its content from (b) (4) within (b) (4) and to maintain (b) (4) for (b) (4) after packout.

Operational Qualification

(b) (4) shippers were tested for (b) (4) at the maximum load of (b) (4) and (b) (4) shippers were tested at the minimum load of (b) (4). (b) (4) was used as a surrogate material. The shippers subjected to ASTM D4169 distribution simulation profile ((b) (4)

(b) (4)) to simulate handling, (b) (4) transport, and (b) (4) transport, followed by visual inspection. The same shippers, with (b) (4) , were then qualified against (b) (4) . All primary packages and shippers showed no gross damages after distribution challenge. All product temperature fell below (b) (4) within (b) (4) after packout and maintained at (b) (4) at least (b) (4) after shipper closure when challenged with the (b) (4) profiles.

Performance Qualification

(b) (4) shippers containing (b) (4) different types of collection bags were distributed in real-world shipping lanes in November 2019 for PQ. (b) (4) bags were tested at the maximum load configuration and (b) (4) at the minimum load configuration. (b) (4) were tested at the maximum load configuration only. (b) (4) was used as a surrogate material. Round-trip shipments were made between Summit NJ to (b) (4) , Summit NJ to (b) (4) , and Summit NJ to (b) (4) . All primary packages and labels maintained integrity. All product temperature fell below (b) (4) within (b) (4) after packout and maintained at (b) (4) at least (b) (4) after shipper closure.

Shipping Validation

(b) (4) leukapheresis clinical lots were shipped one-way to Celgene S12 in March 2020 and were used to manufacture PBMCs upon receipt. The PBMC intermediate materials were tested for (b) (4) . There were no temperature excursions during shipment. All (b) (4) lots met the acceptance criteria.

Reviewer Comment: *The firm should state the shipping routes used during shipping validation and discuss how these routes are representative of anticipated commercial routes. The shipper qualification and shipping validation are acceptable from a DMPQ perspective otherwise.* ***IR3 Comment 6*** *(below in* ***bold****) requested additional information. The response is summarized and reviewed below.*

6. **The patient leukapheresis material is collected within a (b) (4) and shipped to the Celgene S12 facility by (b) (4) in an (b) (4) shipper. Please describe the representative or worst-case shipping route(s), modes, and duration expected for the US commercial process. In this context, please justify the shipping routes selected in the real-world shipping validation studies.**

   The firm clarified that the US commercial leukapheresis shipments will be performed via courier using (b) (4) transport. The (b) (4) is delivered to the leukapheresis collection site the morning of the scheduled collection, packed out immediately after collection, and picked up by the shipper when packout is complete. The shipping duration is expected to be (b) (4) with temperature monitoring. The longest one-way shipping distance is expected

between (b) (4) to Summit, NJ. The shipping routes validated in the shipping study included the following round trips: 1) Summit NJ to (b) (4) to Summit, NJ, 2) Summit, NJ to (b) (4) to Summit, NJ, and 3) Summit, NJ to (b) (4) to Summit, NJ.

Reviewer Comment: *The response is acceptable.*

Production Capacity

The standard process for conducting a production capacity evaluation prior to increasing weekly capacity with additional patient lots consists of the following activities: 1) Readiness assessment by a cross-functional team (manufacturing operation, QA, QC, supply chain, manufacturing sciences and technology) to assess the current state of each function's ability to meet the capacity goal and identify risks and mitigation strategies, 2) generation and approval of a capacity test protocol to detail all activities associated with the capacity test, and 3) protocol execution to test each functional area's ability to deliver against expected results. The execution of a capacity test is supplemented with healthy donor runs, but nonclinical batches are not transduced. Manufacturing/quality operations, product release, and shipment preparation are expected to be completed within defined timelines. Performance indicators (number of qualified personnel, operational equipment capacity, material supply availability, facility utility supply, IT infrastructure readiness, waste and chemical storage capacity, and quality system readiness) are evaluated to identify operational bottleneck at the proposed production capacity level.

A capacity ramp study was executed in December 2019 to challenge a capacity increase from the existing (b) (4) lots to (b) (4) lots. (b) (4) culture initiations and (b) (4) PBMC isolations performed on December 1 through December 7, 2019, including manufacturing, quality testing/reporting, and final product release. The manufacturing operations executed during the study did not exceed (b) (4) operations being performed concurrently within the (b) (4) located in the Process Support Room, which was the worst-case scenario demonstrated by the APS studies. An overview of the capacity test operational activities and results are summarized in the table below.

Operation	Status
Final Product Harvest	**Incomplete.** The execution included culture initiation (i.e., manufacturing starts) of (b) (4) clinical lots and (b) (4) lots. (b) (4) lots, including all clinical lots, completed the final product harvests. Of the (b) (4) lots, (b) (4) lots were completed through normal operation, (b) (4) lots were completed with abbreviated final product harvest operations (not requiring sample aliquoting and final bag fill), and (b) (4) lots did not complete harvest due to resource unavailability across manufacturing and QC EM as a result of an atypical (b) (4) event impacting network connectivity of the manufacturing execution system.
PBMC Isolation	**Incomplete.** (b) (4) clinical and (b) (4) PBMC isolation operations were completed. (b) (4) operations were cancelled due to late cancelation of clinical materials,

	(b) (4) isolation was cancelled due to delays in apheresis delivery and release, and (b) (4) isolation was not completed due to a snow event which impacted operator and apheresis material availability.
QC Testing and Reporting	**Complete per required timelines.** A retrospective evaluation determined that the cancelled final product and PBMC materials would not have impacted the applicable QC functions.
QA Assurance and Release	**Incomplete.** Review and release activities were completed for all clinical activities (batch record review, QC data review, release documentation). QA review was not completed for healthy donor lots due to resource constraints.
Indirect Functions (Supply, IT, Environmental Health and Safety, Facility)	**Complete.** Need for increased waste pick-up for both laundered gowning materials and bio-hazardous waste was identified.

Bottlenecks were observed in equipment/resource availability and schedule adherence. Specifically, additional training, availability of qualified manufacturing and QC personnel, (b) (4) storage capacity for raw materials/clinical materials/QC samples, out-of-service rates for (b) (4) within the Processing Suites, schedule adherence for release and receipt of apheresis materials, schedule adherence for unit operations and QC activities, QC sample management, QC equipment availability, and insufficient waste pick-up for both laundered gowning materials and bio-hazardous waste. New risks identified were added to risk monitoring activities and must be mitigated prior to future capacity increase. Deviation in schedule adherence was one of the leading observations and was due to several reasons: 1) (b) (4) lots (b) (4) required operations extended beyond the regular operation hours of (b) (4) , 2) Process Suite Station conflict due to over-allocation of resources and equipment, 3) (b) (4) system integration and WiFi connectivity issues contributing to significant delays, and 4) delayed receipt and release of PMBC materials. As a result of schedule deviations, additional overtime was required across multiple functions, and a number of PBMC isolation and final product harvest operations were not performed.

The study also compared key performance and safety indicators in December 2019 against November 2019. The review results are summarized in the table below.

Performance	**Nov2019**	**Dec2019**
Clinical Culture Initiations	(b) (4)	
Quality: Deviations per lot		
Quality: % Deviations Closed on time		
Delivery: On-time start		
Delivery: Clinical On-time % Release for infusion		
Safety	**Nov2019**	**Dec2019**
OSHA Reportable Incidents	0	0
Non-Recordable Incidents	3	0
On-time Incident Reporting	100%	N/A

Based on the evaluation, the new ide-cel capacity was set to (b) (4) lots with (b) (4) PBMC isolation. The daily combined capacity of final product harvest operation step and PBMC isolation operation step shall not exceed (b) (4).

Reviewer Comment: *Typically, capacity study mirrors that of a PPQ study executed at maximum capacity. The adequacy of production, QA/QC, logistics functions is assessed through ability to manufacture/release in-specification products and without significantly elevated level of non-conformance. As such, the design of this study is unusual as it combined product runs and simulated runs, included unfinished runs, and did not assess any impact on finished product quality and deviation reporting/closure. I defer the study evaluation to the OTAT/DCGT reviewers. From a DMPQ perspective, the Applicant should summarize EM data collected during the capacity ramp study. In addition, they should clarify how many CAR-T suites were used during the capacity study and if the (b) (4) lots would include all commercial/investigational lots manufactured on site or US commercial lots only.* ***IR2 Comment 19*** *(below in* ***bold****) requested additional information. The response is summarized and reviewed below.*

19. **Based on the Capacity Ramp Study performed in 2019, a new capacity limit of (b) (4) lots with (b) (4) PBMC isolation procedures was established. Please address the following comments:**

    a. **Please clarify and describe the implementation of 12 weekly lots with (b) (4) PBMC isolation procedures on a (b) (4) basis. Does it allow for a (b) (4) initiation or no new lots would be initiated until the manufacture of the (b) (4) lots with (b) (4) PBMC isolation procedures have been completed? In this context, please discuss the comparison of Key Performance Indicators reported in November 2019 vs. December 2019 (Table 1 of RPT-019992), which is based on a (b) (4) assessment while the capacity study was executed in one week (December 1-7, 2019) in December.**

       The firm clarified that the greater number of manufacturing lots relative to the number of PBMC isolation is to support manufacturing of non-US lots for which PBMC is shipped to S12. Initiation of the (b) (4) manufacturing lots is staggered. The firm also acknowledged that the concentration of activity from the ramp exercise in December does not extrapolate to the entire (b) (4), but each functional area still experienced an enhanced level of activity for the reminder of the (b) (4) (e.g., residual QC testing and lot disposition activities).

       Reviewer Comment: *The described implementation is acceptable. I defer the review of at-capacity performance to the OTAT/DCGT reviewers.*

    b. **Please state the maximum number of lots, and PBMC isolation that can be concurrently processed at any given time at the facility. Please clarify if this maximum number of concurrent lots was**

achieved/covered during the Capacity Ramp Study. Please justify your response.

The firm stated that the S12 manufacturing facility is designed to support (b) (4) lots per (b) (4) with (b) (4) PBMC isolation lot leading to (b) (4) manufacturing lot. Per the described schedule in a repeating (b) (4) cadence, Process Suite (b) (4) could support up to (b) (4) lots being concurrently processed. However, the capacity ramp study supports up to (b) (4) lots per (b) (4) on a repeated cadence.

Reviewer Comment: *The maximum concurrent aseptic processing was simulated during the APS studies. I defer the determination of the overall concurrent production capacity to the OTAT/DCGT reviewers.*

c. Please clarify if the (b) (4) lots with (b) (4) PBMC capacity limit would include all US and non-US commercial and investigational lots manufactured on site.

The firm clarified that the study is inclusive of US and non-US commercial and investigational lots.

Reviewer Comment: *The response is acceptable for the purpose of clarification.*

d. Please clarify how many CAR-T Processing Suites were in use during the Capacity Ramp Study. Would that same number be used during routine operations when performed at capacity? Please justify your response.

The firm clarified that the study was executed within Process Suite (b) (4) only based on routine operations that occur in that suite.

Reviewer Comment: *This is acceptable as ide-cel is currently the only product being manufactured at S12. However, it is not clear where investigational products are manufactured, how they are segregated from commercial materials and products, and if they have separate/dedicated manufacturing and QC personnel.* ***IR3 Comment 5*** *(below in* ***bold****) requested additional information. The response is summarized and reviewed below.*

5. Please clarify where investigational ide-cel products are currently being manufactured at the Celgene S12 facility and the segregation strategy you have implemented.

The firm clarified that the investigational ide-cel products are currently manufactured in Suite (b) (4) and Suite (b) (4) of the S12 facility. While these suites are dedicated to ide-cel manufacture, segregation control is not implemented between investigational vs. commercial ide-cel lots other than the segregation strategy that is already in place (e.g., COI, physical segregation, line clearance) to prevent cross-contamination and mix-up between patient lots.

Reviewer Comment: *The response is acceptable for the same reason why out-of-US (OUS) vs. US ide-cel patient lots do not require additional segregation control.*

e. Please describe and justify the EM activities performed during the Capacity Ramp Study. Also, provide a summary report of the EM data collected during capacity challenge study.

The firm confirmed that routine EM was performed during the capacity ramp study. EM activities included in-process monitoring of aseptic operations inside the (b) (4) monitoring of ISO (b) (4) /Grade (b) (4) areas, and (b) (4) monitoring of ISO (b) (4) /Grade (b) (4) areas. EM data from (b) (4) are summarized in the following table.

Clean Area	EM Test	Excursion Rate	Alert Count	Total
ISO (b) (4) /Grade (b) (4)	(b) (4)	0.00%	0	(b) (4)
ISO (b) (4) /Grade (b) (4)		0.00%	0	
ISO (b) (4) /Grade (b) (4)		0.00%	0	
ISO (b) (4) /Grade (b) (4)		0.00%	0	
ISO (b) (4) /Grade (b) (4)		(b) (4)	(b) (4)	
ISO (b) (4) /Grade (b) (4)		0.00%	0	
ISO (b) (4) /Grade (b) (4)		0.00%	0	
ISO (b) (4) /Grade (b) (4)		0.00%	0	
ISO (b) (4) /Grade (b) (4)		0.00%	0	
ISO (b) (4) /Grade (b) (4)		0.00%	0	
ISO (b) (4) /Grade (b) (4)		0.00%	0	
ISO (b) (4) /Grade (b) (4)		0.00%	0	

In addition, (b) (4) personnel monitoring excursions ((b) (4)) were reported out of (b) (4) samples. Of the (b) (4) was isolated from the (b) (4) excursion sample from the ISO (b) (4) /Grade (b) (4) area. (b) (4) was recovered from an (b) (4) sample. The response stated that improved facility controls have been implemented since the ramp study to address (b) (4) occurrences, including the use of a (b) (4) during cleaning and material handling. Operator training has been enhanced. Per SOP-003252, consecutive excursions at any sample site or clustered excursions in one room on any given day or in a given area will result in an investigation. In addition, (b) (4) occurrences are tracked as part of the EM program and are discussed at (b) (4) meetings with senior leadership. Post-EMPQ (b) (4) recovery remained below (b) (4) per (b) (4) during 2019 and 2020. No (b) (4) has been recovered in (b) (4) or personnel monitoring in 2020.

Reviewer Comment: *The EM data appears to be acceptable.*

f. During the Capacity Ramp Study, a (b) (4) atypical event impacting network connectivity of the (b) (4) was reported, which resulted in significant delay due to resource unavailability across manufacturing and QC. (b) (4) generates GMP barcode labels to maintain identity/traceability and manages/tracks product-dedicated equipment. The continuity of (b) (4) function is critical not only to production scheduling and resource allocation, but also to preventing product mix-up. Please comment on the root-cause(s) and probability of occurrence of Wi-Fi connectivity issues based on your manufacturing experience. In addition, please describe any corrective and preventive actions implemented to prevent or address the resultant disruptions and delays, including any back-up plan/procedures in place (if applicable) to ensure work can continue during Wi-Fi disruptions. Also, please describe the risk assessment and the procedures to be followed in case of manufacturing disruptions in general, and how would that impact manufacturing process flow and scheduling (multiple lots), and the disposition of the impacted lots.

The firm clarified that the root cause was later determined to be unrelated to Wi-Fi disruption but rather an issue with the domain controller that provides user account authentication and connection to various applications that support S12 operation. While the issue persisted with the domain controller, (b) (4) users could not complete the required steps. The IT and Manufacturing Operation teams identified the underlying issues and re-started the server as an immediate corrective action on the day of occurrence (July 25, 2020). The BMS IT hosting team is in the process of expanding automated system monitoring to include all domain controllers used by S12 to detect underlying issues (e.g., (b) (4) patch install) even if the domain controller server otherwise appears healthy (Change Control CHG0113151). Per internal document (b) (4)(S12)-0000092 "Disaster Recovery Business Impact Analysis for (b) (4) ", the (b) (4) system is a mission critical application and has a Recovery Time Objective of (b) (4). In case of system disruption, the site follows SOP-003261 "Business Continuity Procedure: CAR-T Manufacturing" and SOP-003319 "General Syncade (b) (4) Execution". In case of (b) (4) outage, controls normally supplied by (b) (4) will be executed using paper system to manually control and maintain COI. (b) (4) operators are required to complete all COI checks and equipment/workstation allocation checks with documentation in the batch record. SOP-003254 "Label Generation and Reconciliation" provides instructions for GMP label generation outside of (b) (4).

Reviewer Comment: *The response is acceptable.*

3.2.S.2.6 Manufacturing Process Development

The ide-cel manufacturing process development history consisted of (b) (4) manufacturing processes: Processes (b) (4) . Processes (b) (4) were developed and performed at the Celgene facility in (b) (4) which was transferred to Celgene S12 in Summit, NJ as Process (b) (4) for the manufacture of pivotal trial and PPQ materials. The table below summarizes the phased development of the ide-cel manufacturing process. The noted differences are the adoption of (b) (4) PMBC, the implementation of (b) (4) . Analytical comparability data were provided in the BLA to support process development from Process (b) (4) to Process (b) (4), and from Process (b) (4) to Process (b) (4).

(b) (4)

Information was also included in the BLA to describe process characterization of each unit operation in the ide-cel manufacturing process using (b) (4) leukapheresis material. The characterization studies and a post-PPQ risk assessment provide basis for CQAs, CPPs, and hold times selected for the PPQ/commercial process control

strategy. The CQAs and release specifications which are under DMPQ purview included sterility and endotoxin, which has not changed during process development.

Reviewer Comment: *I defer the review of analytical comparability assessment, process characterization, and post-PPQ parameter changes to the OTAT/DCGT reviewers.*

3.2.S.3 Characterization
3.2.S.3.1 Elucidation of Structure and Other Characteristics
Ide-cel characterization includes biochemical and functional characterization of the chimeric antigen receptor, vector integration, and mechanism of action. In addition, a correlative analysis was performed to assess correlation between drug product quality attributes and clinical efficacy, safety, and pharmacokinetics.

Reviewer Comment: *I defer the review of ide-cel characterization studies to the OTAT/DCGT reviewers.*

3.2.S.3.2 Impurities
Process-related impurities originated from raw materials used during the ide-cel manufacturing process. The primary mode of impurity reduction is the (b) (4) . A toxicity assessment was performed based on the established toxicity exposure limits against the total amounts of each impurity assuming no clearance. Impurities that exceeded the established limits were subjected to further characterization by direct measurement in the drug product or by measurement of clearance capacity of (b) (4) . All process-related impurities and their respective characterization strategies are described in Table 2 of Section 3.2.S.3.2 [Cell] “Process-Related Impurities”. Characterization results are provided.

Product-related impurities and their clearance are characterized through testing of PBMC and DP. Potential impurities included cells with phenotype variants associated with unintended functions (Table 1 of Section 3.2.S.3.2 [Cell] “Product-Related Impurities”), including red blood cells, platelets, nucleated non-T cells, residual multiple myeloma tumor cells, CD34+ hematopoietic stem cells, and non-viable cells.

Reviewer Comment: *I defer the review of process-related impurity characterization results to the OTAT/DCGD reviewers.*

3.2.S.4 Control of Drug Substance
3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)
The ide-cel DS is immediately processed into DP. Therefore, there are no DS specifications.

3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures
Not applicable.

3.2.S.4.4 Batch Analyses
PBMC intermediate in-process test results are provided for Process (b) (4) and Process (b) (4) ide-cel lots manufactured until October 31, 2019. The in-process test that is under DMPQ purview is sterility. Sterility results for all lots showed no growth.

> ***Reviewer Comment:*** *Results of in-process test within DMPQ purview are acceptable. I defer the review of other product quality attribute results to the OTAT/DCGT reviewers.*

3.2.S.5 Reference Standards or Materials
Not applicable.

3.2.S.6 Container Closure System
There is no container closure system for ide-cel DS as the harvested cells are immediately processed into DP without a hold step. The (b) (4) PBMC intermediate is contained in either the (b) (4) . The (b) (4) are supplied sterile ((b) (4)), and the fluid path is sterile and non-pyrogenic.

3.2.S.7 Stability
3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data
Not applicable.

3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment
Not applicable.

3.2.P DRUG PRODUCT[2]
3.2.P.1 Description and Composition of the Drug Product
Ide-cel is a genetically modified autologous T cell product formulated and cryopreserved in a 1:1 mixture of Plasma-Lyte and CryoStor CS10 cryopreservation media (final DMSO concentration: 5%). It is provided as a single-dose frozen cell suspension stored in one or more CryoStore Freezing bags ((b) (4) × 10^6 CAR-positive T cells).

> ***Reviewer Comment:*** *The final dosing of ide-cel DP is still under discussion. I defer the deliberation to the OTAT CMC and clinical reviewers.*

3.2.P.2 Pharmaceutical Development
3.2.P.2.1 Components of the Drug Product
3.2.P.2.1.1 Drug Substance
Ide-cel is a genetically modified autologous T cell immunotherapy product. Patient T cells are transduced with the anti-BCMA02 CAR LVV that recognizes BCMA expressed on cancerous B cells.

3.2.P.2.1.2 Excipients
Excipients included in the commercial formulation of ide-cel include (b) (4) Plasma-Lyte A Injection, (b) (4) (source of electrolytes) and CryoStor CS10 Freeze Media (cryoprotectant). Components of each excipient are provided in Table 2 and Table 3 of Section 3.2.P.2.1.2. A letter of authorization to (b) (4) is provided for CryoStor CS10 cryopreservation medium with 10% DMSO.

3.2.P.2.2 Drug Product
3.2.P.2.2.1 Formulation Development
Ide-cel DP is formulated in 50/50 (v/v) Plasma-Lyte A Injection (b) (4) and CryoStore CS10 cryopreservation media with a final target DMSO concentration of 5% (v/v) and a target cell concentration of 10×10^6 cells/mL. Plasma-Lyte A mimics human plasma electrolyte contents, osmolality, and pH. CryoStor CS10 contains 10% (v/v) DMSO and contains a family of large and small sugars, as well as intracellular-like salts. The selected cryopreservation formulation is based on its ability to preserve T cell viability and maintain CAR-T potency. There has been no formulation change during product and process development.

3.2.P.2.2.2 Overages
There are no overages in ide-cel DP.

3.2.P.2.2.3 Physicochemical and Biological Properties
Biochemical structure, phenotypic characterization, and functional characterization of ide-cel are described in Section 3.2.S.1.2 [Cells] and 3.2.S.3.1 [Cells] "Product Characterization".

3.2.P.2.3 Manufacturing Process Development
The DP process begins immediately after DS (b) (4) . It includes DS (b) (4) , DP filling, (b) (4) freezing, and transfer to long-term storage in vapor phase LN2 (≤ -130 °C). While the DP dose targets a cell concentration of (b) (4) total cells/mL, the ide-cel dose volumes vary widely ((b) (4)) to fulfill a dose range of (b) (4) $\times 10^6$ CAR+ T cells (target dose: 450×10^6 CAR+ T cells, (b) (4) cells/mL). To minimize dose manipulation, the commercial filling strategy uniquely determines the fill volume and number of cryobags filled for each individual patient lot to ensure constant fill volume and bag size within each lot. Three (b) (4) DP bag sizes are available: (b) (4) 50 (fill volume (b) (4) mL), (b) (4) 250 (fill volume (b) (4) mL), and (b) (4) 500 (fill volume (b) (4) mL). For each DP lot a single container size is selected to be filled with the same volume between (b) (4) DP bags. The number of bags accommodates lots with low %CAR+ T cells while limiting DP exposure to DMSO during filling. Since cell concentration and %CAR+ T cell are measured after DP cryopreservation, an in-process measurement of %CAR+ T cell ((b) (4)) is used as a surrogate to determine filling bag size and fill volume. Cell concentration and %CAR+ T measured at release after cryopreservation ((b) (4)) are then used to determine the number of bags necessary to be shipped to the administration site to achieve the desired dose. An adjustment factor is included in filling volume calculation to correct for the offset

between the release results and the surrogate in-process measurements. The remaining unused bags will remain stored. For the commercial process, the following equation was used to calculate the target fill volume per bag (where N is the number of bags):

(b) (4)

Reviewer Comment: *In addition, the proposed dose strength was tightened from* (b) (4) *× 10^6 to 300 - 460 × 10^6 viable CAR-positive T cells* (b) (4) *bags) during the course of BLA review, and the fill volume ranges were correspondingly updated to* (b) (4) *50 (fill volume 13 to 27 mL),* (b) (4) *250 (fill volume 34 to 66 mL), or* (b) (4) *500 (fill volume 60 to 95 mL) at a concentration of* (b) (4) *cells per mL.*

DP release testing sampling procedures are also discussed. QC samples other than sterility and mycoplasma are pulled during the DP (b) (4) to ensure cells in all filled bags to have similar and minimal DMSO exposure. These samples are (b) (4) . The sterility samples are filled into bags along with DP bags (b) (4) . These samples are tested fresh to avoid potential impact on recovery by the cryopreservation step. The mycoplasma samples are pulled from the (b) (4) .

The development history of DP fill strategy included the following (b) (4) modifications: (b) (4)

The ide-cel DP labels for each of the three DP bags ((b) (4) 50, (b) (4) 250, and (b) (4) 500) are supplied to the manufacturing site as pre-printed label stocks. Label stocks are managed by the (b) (4) system through the life-cycle of receipt, inspection, release, and controlled storage. Finished DP label is generated prior to DP harvest inside the access-controlled Label Control Room where batch-dependent variable data elements (i.e., patient identification information, lot number, expiration date, volume per bag) are printed onto the pre-printed label stocks, followed by verification. The (b) (4) system supplies all variable data elements, the printing operation steps are captured in the batch record. Both the Label Control Room and the label printing operation are managed by QA, who then brings the finished DP labels to Manufacturing. COI is verified before the labels are applied to the DP bags and the corresponding aluminum cassettes prior to cryopreservation. All unused lot-specific DP labels or unfilled labeled cryopreservation DP bags are reconciled and destroyed. Example images of labeled DP primary and secondary containers are provided in the submission. Lot-specific variable DP label data elements are described in Table 5 of Section 3.2.P.2.3.

In this section, the Applicant also provided justification to support the removal of RCL from DP release testing.

Reviewer Comment: *I defer the evaluation of DP fill strategy and the removal of RCL release test to the OTAT/DCGT reviewers. The DP label management and control appears to be acceptable based on the information provided.*

3.2.P.2.4 Container Closure System

The primary container closure system of ide-cel DP are the (b) (4) 50, (b) (4) 250, and (b) (4) 500 cryopreservation bags supplied sterile (by (b) (4)) by (b) (4) . The bags are constructed with (b) (4) and are designed with (b) (4) loading tube made of (b) (4) co-extrusion and two crimped ports made of (b) (4). Refer to Section 3.2.P.7 for additional details on the DP container closure system. Product compatibility with the (b) (4) bags are demonstrated through a (b) (4) extractable study, a simulated leachable study, and an end-of-shelf leachable study. Refer to Section 3.2.P.7 for container closure integrity testing and validation.

Reviewer Comment: *I defer the evaluation of container closure system compatibility with the ide-cel DP to the OTAT/DCGT reviewers.*

3.2.P.2.5 Microbiological Attributes

Aseptic process simulation, release (mycoplasma, endotoxin, sterility) and stability (sterility) testing, and container closure integrity validation were performed as a part of the overall contamination control strategy for the ide-cel manufacturing process. They are reviewed in the respective sections of this memo.

3.2.P.2.6 Compatibility

Infusion set compatibility and in-use DP stability studies are discussed in this Section.

Reviewer Comment: *I defer the evaluation of in-use DP compatibility and stability to the OTAT/DCGT reviewers.*

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The ide-cel DP manufacturers are the same as those provided under 3.2.S.2.1.

3.2.P.3.2 Batch Formula

A single dose of ide-cel batch has the following formulation: (b) (4) $\times 10^6$ CAR+ T cells in 1:1 (v/v) Plasma-Lyte A, pH 7.4 and CryoStor CS10 cryopreservation media, filled in (b) (4) DP cryopreservation bags.

3.2.P.3.3 Description of Manufacturing Process

Ide-cel DS is immediately formulated and filled to generate DP.

Briefly, bulk DS in (b) (4) to achieve the target cell concentration of (b) (4) and a target (b) (4) hold time limit of

(b) (4) is in place to minimize exposure to (b) (4). The formulated bulk is filled into (b) (4) bags per lot, depending in the in-process %CAR+ T cell count measured on (b) (4) of the cell expansion operation. The (b) (4) are provided by (b) (4) with (b) (4) available to accommodate the fill volumes indicated in the table below. For each lot, each DP bag is gravity filled with the same fill volume.

(b) (4)

Filled DP bags are cryopreserved (b) (4) , and transported to the (b) (4) for storage in the vapor phase N2 (≤ -130 °C) until shipping. Each DP bag is individually packaged in a metal protective cassette during cryo-storage. The cryopreserved DP is shipped to the infusion site in a temperature controlled LN2 shipper. Prior to shipping, cassettes containing the DP bags are loaded into a protective rack which is then inserted into the LN2 shipper, which in turn is closed using zip ties.

No reprocessing is allowed in the ide-cel manufacturing process.

> ***Reviewer Comment:*** *The filling process was included in the APS studies and is acceptable from a DMPQ perspective. I defer the review of the filling strategy to the OTAT/DCGT reviewers.*

3.2.P.3.4 Controls of Critical Steps and Intermediates

No critical process parameters were identified for the ide-cel DP manufacturing process. In-process control (%CAR+ T cells) and process time limit ((b) (4) CS10 exposure) are not under DMPQ purview.

3.2.P.3.5 Process Validation and/or Evaluation

The formulation, filling, visual inspection, and cryopreservation process steps were validated together with the DS manufacturing steps during PPQ (refer to Section 3.2.S.2.5). The cryopreserved DP is shipped to the infusion site in a temperature controlled LN2 shipper to maintain an internal temperature at (b) (4) °C for a minimum of (b) (4) from the time when liquid nitrogen is initially charged. The (b) (4) is an off-the-shelf, dry vapor dewar (figure below) with 1-8 cassettes load range. The shipper consists of a double-walled storage cylinder, walls filled with absorbent materials which absorbs the LN2 when the dewar is charged, a foam vapor plug that closes the dewar. The dewar is housed inside an outer protective plastic shell with foam inserts.

SOP-002194 v.10.0 (effective June 4, 2020) describes the preparation and shipment of investigational product for Bristol Meyers Squib (BMS). It appears that the dry shippers

are made available by (b) (4) , a third-party provider, the morning of the expected shipment. The supplied shipper is charged and equipped with a valid data logger with a calibration certificate. The DP bags/cassettes are removed from the cryo storage tank and placed into a charged (b) (4) before being transported to the shipping area and placed in a slotted metal rack, which is then placed inside the shipper.

Reviewer Comment: *It appears that this shipper is used to ship ide-cel DP manufactured at Celgene S12 to US, EU, and Japan, as well as* (b) (4) *from* (b) (4) *to Celgene S12. For commercial ide-cel, DP shipment is expected to be within US only between Celgene S12 and US infusion sites.*

(b) (4)

Reviewer Comment: *The (b) (4) Profile was described in Section 3.2.S.2.5 for the LVV shipper OQ. The sole use of (b) (4) profile is acceptable in this case as it presents the worst-case for thermal challenge. Overall, the OQ execution presented reasonable thermal challenges as it included additional shipping time from (b) (4) and opening the shipper to allowing wiring prior to executing the (b) (4) profile. Based on the results, the shipper hold time does not appear to depend on the load size and there is ample cryo-capacity for time well-extended from the (b) (4) baseline requirement. The deviations do not impact study validity or outcome.*

A PQ study was performed in November 2019 to qualify shipper design, shipping process, time and temperature requirements, and post-shipping primary package integrity. The scope of PQ included the ide-cel DP bags (b) (4) The review here focuses on the (b) (4) DP bags. Shippers containing DP bags filled with (b) (4) were distributed in real-world representative transportation lanes to demonstrate mechanical and thermal protection during PQ. (b) (4) shippers were tested for each bag size, with (b) (4) cassettes loaded in each shipment. Each DP bag was filled to the maximum fill volumes ((b) (4)). A temperature probe was placed inside each shipper to monitor internal temperature. The following shipping routes were challenged as round trips with multiple rounds of air/truck transit and handling steps:

- Summit, NJ ←→ (b) (4) ((b) (4) 50 and (b) (4) 250 bags)
- Summit, NJ ←→ (b) (4) ((b) (4) 50 and (b) (4) 500 bags)
- Summit NJ ←→ (b) (4) ((b) (4) 250 and (b) (4) 500 bags)

PQ acceptance criteria included test probes maintaining temperatures of (b) (4) °C for a minimum of (b) (4) from time of shipper charge, visual inspection of the primary packaging for the absence of gross damages, labels remain adhered/legible, barcodes scanability after shipping, and DP bags CCIT after shipping. Post-shipping bags were shipped to (b) (4), where CCIT was performed. One of the shippers containing the (b) (4) 500 bags was invalidated due to a damaged temperature probe. The run was repeated and passed. All temperature probes associated with (b) (4) successful runs showed interior/product temperature ranging (b) (4) °C during the required (b) (4). All shippers were able to hold temperatures (b) (4) from (b) (4). The shortest duration ((b) (4)) occurred with the (b) (4) 500 bags was attributed to the expiration of the datalogger battery. At the time of battery expiration, the internal temperature was (b) (4). All post-shipping DP bags passed CCIT using the (b) (4) method, which is validated to (b) (4) detection limit. All acceptance criteria were met in all runs. Four deviations were reported. One deviation was a protocol generation error with no study impact. Deviation PROT-016971-DEV2 was related to a broken (b) (4) 500 bag detected after (b) (4) freezing during Run (b) (4). As the damage was found before packout and shipping, there was no impact. The root-cause of the broken bag is still under investigation. Deviation PROT-016971-DEV3 was related to a

damaged thermocouple used in Run (b) (4), which was invalidated, and the run was repeated as Run (b) (4). Deviation PROT-016971-DEV4 was related to temperature data loss of (b) (4) due to unexpected battery expiration in Run (b) (4). Since the data logger began to resume function after the battery was replaced and the shipper temperature remained acceptable for over (b) (4), the deviation was deemed to have no impact. CAPA is being implemented to track vendor's implementation of new firmware.

> ***Reviewer Comment:*** *The overall results are acceptable. The temperature and duration data did not show dependence on bag size or shipping route. They demonstrated ample cryo-capacity for the shipper's intended use.*

A supplemental DP shipping validation study was performed in May 2020 using (b) (4) final ide-cel DP to assess potential impact the shipping process may have on critical product quality attributes. This review focuses on ide-cel DP only as (b) (4) shipping is not relevant to US licensed ide-cel. Shipping duration, temperature, shipper performance, package protection, label performance, and CCIT were not within the scope of this supplemental PQ study. The DP was shipped round-trip from the S12 facility to (b) (4) DP lots were packed out in (b) (4) shippers with (b) (4) DP bag/cassette per shipper. Quality attributes tested included appearance, %CAR+ T, viability, T cell purity, cell concentration, (b) (4), and potency. There were no temperature excursions and all (b) (4) lots met post-shipping product attribute requirements. Four deviations were reported. Deviation PROT-017335-DEV1 was related to a broken DP bag found upon receipt after shipping. Retain samples from the same lot were shipped to repeat the run. Investigation of the broken bag is ongoing. Deviation PROT-017335-DEV2 was related to incorrectly performed potency testing. The run was repeated with retained samples. Deviation PROT-017335-DEV3 was related to shippers having undergone (b) (4) due to the lack of appropriate customs paperwork at the (b) (4) was not a routine shipping route between US and Europe, which usually transit through (b) (4) with all proper paperwork set up. However, there was no impact because all QC results were passing. Deviation PROT-017335-DEV4 was related to a shattered DP bag found at pack-out due to a fallen frame inside the shipper. The report stated that there had been zero reported incidents of broken DP bags in clinical lots.

> ***Reviewer Comment:*** *I defer the review of product quality data to the OTAT/DCGT reviewers. The submission stated that minimum and maximum load shipping configurations were challenged during OQ, nominal shipping load was challenged during PQ; therefore, shipping load configurations were not under the scope of this shipping validation study. This conclusion is insufficiently justified since OQ did not include distribution challenges to ensure mechanical protection and post-shipping DP bag integrity and the initial PQ study only tested mechanical impact to the nominal load. Given the several bag breakages reported in the PQ studies, the Applicant should discuss why the challenges presented in OQ represented worst-case thermal and mechanical distribution conditions compared to real-world shipping or provide additional data to support the maximum load. The Applicant should also clarify if datalogger is routinely included inside the shipper during the commercial*

shipping process, if in-route recharge is at all allowed, and if the shippers are transported by approved courier in temperature-controlled vehicles. ***IR2 Comment 21*** *(below in* ***bold****) requested additional information. The response is summarized and reviewed below.*

21. The cryopreserved DP is shipped to the infusion site in a temperature-controlled (b) (4) to maintain an internal temperature at (b) (4) for a minimum of (b) (4) from the time when liquid nitrogen is initially charged. Protocols and reports were included in the BLA for shipper qualification and DP shipping validation. Please address the following comments:

a. You provided SOP-002194 which describes the preparation and shipment of investigational products. However, it is not clear if the same SOP is also used for commercial products. Please clarify the following: 1) if datalogger is routinely included inside the shipper during the commercial shipping process, 2) if in-route recharge is allowed and if yes, describe the conditions and procedures, and 3) if the DP shippers are transported by an approved courier in temperature-controlled vehicles.

The firm committed to revise SOP-002194 prior to commercial launch to provide instructions for both clinical and commercial shipping preparation. Their response also confirmed the routine usage of a datalogger during shipping. In addition, recharging of the shipper is not allowed. Upon receipt, DP can remain in the shipper up to shipper expiration ((b) (4) from charge) or transfer to onsite LN2 storage. DP shipment is managed by approved courier and transported in courier vehicles which do not need to be temperature controlled. There had been no temperature excursions to date.

Reviewer Comment: *The response is acceptable.*

b. You stated that since the minimum-load and maximum-load shipping configurations were challenged during OQ and the nominal shipping load was challenged during PQ, only the minimum-load shipping configuration needed to be included in the real-world shipping validation study. This conclusion is insufficiently justified because the OQ study did not include distribution challenges to ensure mechanical protection and (b) (4) DP bag integrity, and the initial PQ study only tested mechanical impact to the nominal load. Since several incidents of bag breakage were reported in the PQ studies, please discuss why the challenges presented in OQ represented worst-case thermal and mechanical distribution conditions compared to real-world shipping experience. Alternatively, provide additional data to support the maximum load.

The firm clarified that the maximum load ((b) (4) bags per lot per shipper) was based on the clinical fill strategy. The proposed commercial fill

strategy would require a maximum of (b) (4) bags per lot per shipper using the (b) (4) 500 bag ((b) (4) mL target fill volume/bag). The firm stated that shipping OQ was designed to challenge thermal loads with (b) (4) load configurations for worst-case loading, while shipping PQ was designed to challenge the "nominal" load with real-world thermal and mechanical stresses over worst-case shipping distance and time. This "nominal" load represented the anticipated maximum load ((b) (4)) for commercial shipping based on historical data of (b) (4) clinical lots. In terms of mass, (b) (4) (b) (4) 500 bags with (b) (4) as described in PQ represented a greater challenge than the commercial maximum load of (b) (4) (b) (4) 500 bags with (b) (4) . There has been only one report of a broken bag for more than (b) (4) clinical lots shipped within the US, which was observed during PQ and was discovered prior to shipment. The probable root cause was the use of (b) (4) as the DP surrogate.

Reviewer Comment: *While a maximum of (b) (4) bags could be filled, Celgene only ships the number of bags needed to meet the required dose with the remaining bags retained at S12. The maximum commercial shipping load of (b) (4) DP bags was verified by the OTAT/DCGT reviewer/chair, Dr. Anna Kwilas. She confirmed that based on the commercial specification for % CAR+ T cells, the firm is not expected to ship more than (b) (4) bags. The response is acceptable.*

c. Two broken DP bags were detected after (b) (4) freezing during PQ Run (b) (4) . Another shattered DP bag was found at pack-out during the DP shipping validation study. In addition, shattered bags were found upon thawing in DP bags prepared for the CCIT study. Please discuss the root-cause(s) for frozen DP bag breakage prior to shipping and the implementation of any corrective and preventive actions.

The firm clarified that the broken bags discovered during CCIT validation and shipping PQ study were filled with (b) (4) . The bag that broke during shipping validation was due to mishandling as the investigation determined that the bag was accidentally dropped during retrieval from the LN2 storage. No broken DP bags have been reported for over (b) (4) clinical lots manufactured. All DP bags are subject to 100% inspection prior to pack-out. However, as a result of these reported incidences, CAPAs were implemented to eliminate the usage of (b) (4) as a surrogate material and redesign LN2 frames for easier handling during bag retrieval.

Reviewer Comment: *The response is acceptable. During the investigation of DP bag breakage which occurred during CCIT validation, it was discovered that the (b) (4) make it a sub-optimal surrogate for DP formulated with cryopreservation excipients.*

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

Plasma-Lyte A Injection (b) (4) is a (b) (4) FDA-approved excipient. CryoStor CS10 Freeze Media containing 10% DMSO is (b) (4), proprietary product supplied by (b) (4). A representative CoA was provided. Specifications include (b) (4)

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

Reviewer Comment: *I defer the review of analytical procedures and methods validation to the OTAT/DCGT and DBSQC reviewers.*

3.2.P.4.4 Justification of Specifications

The submission provided the respective (b) (4) specifications to justify each excipient's intended use either as a source of electrolytes or as a cryoprotectant for the ide-cel DP

Reviewer Comment: *I defer the evaluation of justification to the OTAT/DCGT reviewers.*

3.2.P.4.5 Excipients of Human or Animal Origin

CryoStor CS10 cryoprotectant solution contains (b) (4) that is derived from (b) (4).

3.2.P.4.6 Novel Excipient

There are no novel excipients.

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 ide-cel DP is released on a panel of identity, purity, potency, strength, and safety tests. The release tests under DMPQ purview include appearance (liquid, colorless cell suspension), sterility (no growth), and endotoxin ((b) (4)) testing. The appearance specification is consistent with clinical experience for ide-cel DP material used during the pivotal study. The sterility specification ensures DP sterility at release for an intravenously administered product. Endotoxin release specification is set to meet the maximum exposure limit of (b) (4) based on a maximum DP volume of (b) (4) mL.

Reviewer Comment: *The described specifications appear to be acceptable from a DMPQ perspective. I defer the final evaluation to the OTAT and DBSQC reviewers.*

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

The color attribute of the appearance test is based on comparison of DP to color standards per (b) (4). The liquid cell suspension attribute is based on comparison of DP to a negative control ((b) (4)). The test is performed (b) (4). Sterility and endotoxin tests are performed using (b) (4) test methods. Sterility is tested using the (b) (4) system. Endotoxin is evaluated using a (b) (4) procedure.

Reviewer Comment: *I defer the evaluation of analytical method and method validation to the OTAT and DBSQC reviewers.*

3.2.P.5.4 Batch Analyses

The batch release data from all ide-cel DP lots manufactured and released by October 31, 2019 and select lots manufactured at Celgene S12 after October 31, 2019 using LVV from (b) (4) are provided. Of the (b) (4) lots that were manufactured, (b) (4) lots were not released because the patient was discontinued from the study, (b) (4) lots were released but not infused as the subjects were no longer eligible to receive treatment, (b) (4) patients received a single-dose comprised of (b) (4) separate released lots, (b) (4) patients received retreatment from the same DP lot as their primary dose, (b) (4) patients being re-dosed with a separate DP lot (manufactured from the same (b) (4) PBMC lot). (b) (4) lots were out of specification for viability ((b) (4) lots), potency ((b) (4)), or (b) (4), and were all released under FDA approved exception. The medium time from leukapheresis to product delivery was (b) (4). There had been no sterility or endotoxin excursions.

Reviewer Comment: *I defer the evaluation of batch release data to the OTAT/DCGT reviewers. The sterility and endotoxin release data are acceptable.*

3.2.P.5.5 Characterization of Impurities

Refer to Section 3.2.S.3.2 [Cell].

3.2.P.6 Reference Standards or Materials

There are no reference standards for the ide-cel DP.

3.2.P.7 Container Closure System

The primary container closure system for ide-cel DP consists of (b) (4) cryopreservation bags supplied by (b) (4) in 3 sizes: (b) (4) 50, (b) (4) 250, and (b) (4) 500. These bags are 510(k) cleared for the US market ((b) (4)) and are supplied (b) (4). Each bag is connected to a loading tube (stub tube) and two crimped ports. The loading tube is part of the tubing set used for DP filling and is sealed (with the tubing set removed) using a tubing sealer post-fill. The crimped ports are hermetically sealed to the bag and are used for DP withdrawal during administration. The bag and the crimped ports are made of (b) (4) and the loading tube is made of (b) (4) co-extrusion.

Reviewer Comment: *The (b) (4) cryopreservation bags were 510(k) cleared by CBER in October 2003 under Regulation 864.9100 and Product Code KSR. They are indicated to cryogenically freeze blood components. The original review memo or 510(k) Summary cannot be located in the CBER database. However, in the 510(k) Summary for (b) (4), which used the (b) (4) bag as the predicate device, the (b) (4) bags are stated to preserve (b) (4) ", provided (b) (4), and has a shelf-life of (b) (4). Based on this information, it appears that the cryobags are being used per its indication.*

The DP cryopreservation bags are accepted based on supplier's Certification of Conformance, which includes attestation to compliance with (b) (4), and integrity by (b) (4) test. Additional testing performed on site includes identity by (b) (4).

The secondary packaging for each DP bag is an aluminum cassette, which houses the labeled DP bag throughout storage and shipping to provide protection from movement. Up to (b) (4) cassettes are placed into a rack, which is then inserted into the LN2 shipper for shipping.

CCIT of the primary DP cryopreservation bags, as well as the (b) (4) supplied by (b) (4), was performed using the (b) (4) method by (b) (4). In this deterministic method, (b) (4) This method was validated by testing bag samples with known defect sizes ((b) (4)). (b) (4) During CCIT, (b) (4) lots with (b) (4) bags/lot for each DP bag size were tested, with additional bags for instrument setup. All bags were filled with (b) (4) to the maximum freeze capacity. Bags were frozen and cryostored before being thawed, inspected, and shipped to the testing facility. Before test execution, method suitability was established with empty chambers and chambers with a (b) (4) control bags, which provided (b) (4) acceptance criteria as shown in the table below. Subsequently, (b) (4) were recorded for each test bag. All bags passed CCIT.

Bag Type		Acceptance Criteria Rate ((b) (4))
(b) (4)	50	(b) (4)
(b) (4)	250	
(b) (4)	500	
(b) (4)		

Eleven deviations were reported for procedures performed prior to CCIT, which included shattered bags found upon thawing with the plastic hang tag as a contributing factor, erroneous temperature reading of the (b) (4) freezer due to sensor contact with

metal, broken outer seal with inner seal intact, bag overfill, missed inspection, protocol and records generation error, etc. All deviations were either corrected, resolved, or deemed to have no impact. Deviation #1 involving the (b) (4) shattered bags is still under investigation. No deviations reported during CCIT.

Reviewer Comment: *The (b) (4) method is suitable for testing DP bag integrity using (b) (4), which would not result in artifacts due to defect clogging. This is acceptable since CCIT is not performed at release or on stability on bags containing cells and media. The outcome of the investigation associated with Deviation #1 needs to be understood since DP bag breakage with an identifiable root-cause needs to be evaluated and mitigated to prevent similar incidents in the future.* ***IR2 Comment 20*** *(below in* ***bold****) requested additional information on DP bag breakage and preventive measures. The response is summarized and reviewed below.*

20. CCIT of the (b) (4) PBMC (b) (4) and the (b) (4) primary ide-cel drug product (DP) cryopreservation bags was performed using the mass leak extraction method. Deviation #1 was related to (b) (4) shattered DP bags found prior to CCIT. You stated that the deviation is still under investigation. Please provide updated information from your investigation and describe the measures in place to prevent cryopreservation bag breakage during routine storage and handling.

The firm emphasized that there had been no reported incidence of broken DP bags for over (b) (4) clinical lots manufactured at S12. Regarding the shattered, (b) (4)-filled DP bags reported during CCIT validation, the deviation was closed out with CAPA-2019-01205. Contributing factors evaluated during the investigation included use of (b) (4). The most probable root cause was determined to be mishandling while being stored at cryo conditions which placed non-routine stress on the DP packaging during bag transfer steps. The investigation also found high amount of (b) (4) within the (b) (4)-filled bags, which was not observed in bags filled with DP formulated with Plasma Lyte A/CS10. Preventive actions included (b) (4)

Reviewer Comment: *The response is acceptable. Bag breakage was also reported during DP shipping validation. Refer to discussions under Section 3.2.P.3.5.*

3.2.P.8 Stability

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

The proposed DP shelf-life is 12 months when stored in vapor phase LN2 at ≤ -130 °C, which is supported by long-term stability data from (b) (4) primary DP lots manufactured using (b) (4) cells and the commercial manufacturing Process (b) (4) (including (b) (4) PPQ DP lots each derived from (b) (4) PBMC lots vs. (b) (4) PBMC lots, and (b) (4) process-transfer lots from Celgene (b) (4) facility to Summit S12 facility) and (b) (4) supportive

DP lots manufactured using (b) (4) cells and Process (b) (4) at the Celgene (b) (4) facility. A (b) (4) strategy was adopted to evaluate potential correlation between DP stability and surface area to fill volume ratio using the (b) (4) cryopreservation bags. Specifically, (b) (4) 50 bag with minimum fill volume ((b) (4) mL) and (b) (4) 250 bag with maximum fill volume ((b) (4) mL) were included in long-term stability evaluation to represent the highest and lowest surface area to fill volume ratios. In addition, the supportive lots were included in a comparative long-term stability study aim to identify potential differences between storage in cryopreservation bag vs. (b) (4). The long-term stability studies for the primary lots include time points 0, 3, 6, 9, 12, and (b) (4) months with appearance assessed at each time point and sterility assessed at 0, 12, and (b) (4) months. The long-term stability studies for the supportive lots include time points 0, 1, 3, 6, 12, and (b) (4) months with appearance assessed at each time point and sterility assessed at 0, 3, 12, and (b) (4) months. Up to (b) (4) months of stability data are available from the (b) (4) primary process transfer lots and the (b) (4) supportive lots (studies completed). All appearance and sterility tests met the respective acceptance criterion at all time points evaluated.

A cyclic temperature stress ((b) (4)) study was performed on (b) (4) DP lots derived from (b) (4) PBMCs and processed using Process (b) (4) at the (b) (4) facility to identify stability indicating product attributes. The DP materials were stored in (b) (4). The results showed post-stress adverse impact on cell viability, %CAR+ T cells, and (b) (4).

> ***Reviewer Comment:*** *DP stability data are acceptable from a DMPQ perspective. I defer the final evaluation to the OTAT reviewers.*

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

There is no post-approval stability commitment. The shelf-life of ide-cel DP will be (b) (4) initial expiration date as additional real-time stability data become available.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

The following facilities are involved in the manufacturing and testing of ide-cel DP.

Facility Table for BLA 125736/0

Manufacturing/ Testing Activities and Facilities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
CAR Lentiviral Vector (LVV) manufacture **Facility:** (b) (4) **FEI:** (b) (4)	Inspection	Yes	Yes	No FDA inspectional history
CAR LVV release testing (Replication Competent Lentivirus testing, (b) (4) **)** **Facility:** (b) (4) **FEI:** (b) (4)	Not Required	No	Yes	ORA Inspection, VAI (b) (4)
CAR LVV release testing ((b) (4) **Facility:** (b) (4) **FEI:** (b) (4)	Not Required	No	Yes	ORA Inspection, VAI (b) (4)

Manufacturing/ Testing Activities and Facilities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
CAR LVV release and stability testing ((b) (4) **Facility:** (b) (4) **FEI:** (b) (4)	Inspection (per special request by OTAT)	Yes	Yes	No FDA inspectional history,
CAR LVV release and stability testing ((b) (4) **)** **Facility:** (b) (4) **FEI:** (b) (4)	Not Required	No	Yes	ORA Inspection, NAI (b) (4)
Peripheral blood mononuclear cell (PBMC) preparation, Drug Substance (DS) and Drug Product (DP) manufacturing, packaging and labeling, release and stability testing, (b) (4) **PBMC intermediate storage, DP storage** **Facility:** Celgene Corporation 556 Morris Avenue, Building S12 Summit, NJ 07910, US **FEI: 3004991673**	Inspection	Yes	Yes	ORA Inspection, NAI April 21-29, 2014 (Note: Previous inspections covered CDER products including (b) (4) ; Building S12 is a new production space dedicated to CAR-T cell manufacturing)

Manufacturing/ Testing Activities and Facilities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
CAR LVV storage, raw material acceptance and storage **Facility:** (b) (4) **FEI:** (b) (4)	Inspection	Yes	Yes	No FDA inspectional history
CAR LVV storage **Facility:** (b) (4) **FEI:** (b) (4)	Not Required	No	Yes	No FDA inspectional history
CAR LVV storage, excess (b) (4) **PBMC intermediate storage, excess DP storage** **Facility:** (b) (4) **FEI:** (b) (4)	Not Required	No	Yes	ORA Inspection, NAI (b) (4)
CAR LVV storage, excess (b) (4) **PBMC intermediate storage, excess DP storage** **Facility:** (b) (4) **FEI:** (b) (4)	Not Required	No	Yes	ORA Inspection, NAI (b) (4)

Reviewer Comment: IR1 Comment *(below in **bold**) requested the Applicant to update Form FDA 356h to include the FEI numbers for three storage facilities. The response is summarized and reviewed below.*

In the establishment information provided in Module 1 of your Biologics License Application, you indicated that (b) (4) **GMP storage facilities** ((b) (4) **) are not currently registered with the FDA and do not have a Federal Establishment Indicator (FEI) numbers. However, our database indicates that these facilities have been assigned FEI numbers. Please submit an updated Form FDA 356h to include all applicable storage facilities and their respective FEI numbers.**

The firm clarified that the FEI numbers for these (b) (4) storage facilities were not found in the FDA database but were obtained from the facilities themselves. Form FDA 356h was updated. In addition, Section 3.2.P.3.1 was updated to indicate that only "excess" PBMC and "excess" DP retains are stored in the (b) (4) storage facilities.

Reviewer Comment: *The response is acceptable.*

Reviewer Comment: IR5 Comment 1 *(below in **bold**) requested clarification on the DUNS number in association with the Celgene Summit facility. The response is summarized and reviewed below.*

1. **In the Form FDA 356h of your Biologics License Application, you provided the Establishment DUNS Number for the Celgene Corporation Summit, NJ facility as 080392427. However, our database indicates there are two DUNS numbers in association with this facility, 117766889 and 080392427. Please clarify and submit an updated Form FDA 356h with the current DUNS number, if necessary.**

   The firm clarified that the DUNS number provided in the current FDA Form 356h is correct and applicable for BLA 125736. DUNS number 117766889 is a separate registration generated due to the acquisition of Celgene Corporation by Bristol Myers Squibb.

   Reviewer Comment: *The response is acceptable.*

(b) (4)

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

(b) (4)

3.2.A.1 Facilities and Equipment [Celgene S12, Summit, NJ]

Overview

Ide-cel CAR-T cell DS and DP are manufactured in Building S12 of Celgene's multi-product facility located in Summer, NJ. Building S12 houses (b) (4) product-dedicated Process Suites ((b) (4)) surrounded by (b) (4) . The (b) (4) Process Suites are flanged on the left by the Leukapheresis Receipt and Release area Media Preparation area, PBMC (b) (4) area, DP freezer/cryopreservation area, and DP shipment area. Flanging on the right of the main processing suites are the Material Receiving area, the Material Staging and Kitting area, the Auxiliary Process Support area, the QC Sample Management area, and the waste/trash area. QC laboratories, administration offices, and conference rooms are located on the (b) (4) floor.

Ide-cel is currently the only CAR-T product being manufactured on site. Both Process Suite (b) (4) (Room (b) (4)) and Process Suite (b) (4) (Room (b) (4)) are dedicated to the manufacture of ide-cel. However, the current BLA only supports the licensed use of Process Suite (b) (4) . The manufacturing process of another CAR-T product (lisocabtagene maraleucel) is being (b) (4) . Process Suite (b) (4) is currently not in use. Each ISO (b) (4) Process Suite is equipped with entry PAL/MAL and an exit AL, and contains workstations dedicated to the initiation, transduction, expansion, and harvest unit operation steps. The workstations are identified by function and equipment as follows:

Incubator Station (x(b) (4)): Each station is equipped with a (b) (4) unit operations is performed here.

(b) (4) Station (x(b) (4)): Each station is equipped with a (b) (4) . Unit operations performed at a (b) (4) station include PBMC Isolation, PBMC (b) (4) , Cell Culture Initiation, DP Harvest, and DP cryopreservation. While any (b) (4) station can be used for any process step, Isolation and Culture Initiation typically occur in (b) (4) Stations (b) (4). DP harvest typically occurs in (b) (4) Station (b) (4).

Shared Station (x(b) (4)): Each station is equipped with a (b) (4) . Materials and samples are transported from the (b) (4) or Incubator station to a Shared Station for tasks such as (b) (4) .

(b) (4) clusters of (b) (4) Stations flank a middle cluster of Incubator Stations, with the Shared Stations interface the (b) (4) and Incubator Stations.

Only one patient lot is processed at a workstation at a time with station clearance performed before and after batch-specific processing activities. Multiple patient lots may be simultaneously incubated within an incubator but using batch-dedicated shelves. All activities taking place at the work stations involve (b) (4) connected/disconnected using (b) (4) . (b) (4) assigned operators may work at a work station at a time. The (b) (4) and Incubator Stations are subject to line clearance procedures per SOP-010124 “Workstation Line Clearance Procedure for S12” v1.0 (Effective February 3, 2020), which describes the line clearance process flow (primary check, secondary check, QA check and release). Post-use cleaning is performed per SOP-003056 “Cleaning and Sanitization for S12”.

Reviewer Comment: *The pre-use activities described in the batch records (Section 3.2.R) include clearance of designated workstation, logbook verification of appropriate decontamination per SOP-003056, and opening in* (b) (4) *the order number corresponding to the Batch Record to scan in the allocated equipment. However, Table 1 in SOP-010124 appears to suggest that station clearance procedure does not apply to the Shared Work Stations.* ***IR2 Comment 23*** *(below in* ***bold****) requested justification. The response is summarized and reviewed below.*

23. Table 1 in SOP-010124 indicated that Shared Stations in the Processing Suite does not require station clearance. In the absence of station clearance, please clarify and describe the procedures in place to prevent product cross-contamination and mix-up at these Shared Stations, which station shared equipment and is used to process one patient lot at a time.

The firm clarified that appropriate station clearance is executed for all shared stations in the processing suite, which is reflected in the Master Batch Records (MBR) steps, SOP requirements, and cleaning logbooks for the Shared Stations.

SOP-003056 provides cleaning/sanitization/decontamination frequency and instructions for stations and equipment. The MBR also includes instructions to ensure the clearance of the (b) (4) r, label printer, and (b) (4) (equipment of the Shared Stations) from the previous lot, in addition to pre-use and post-use cleaning. All steps require signatures from the performer and a verifier.

Reviewer Comment: *The response is acceptable.*

Each Process Suite also houses a Grade (b) (4) /ISO (b) (4) dynamic Process Support Room with bidirectional Grade (b) (4) /ISO (b) (4) MAL/PAL. This inner suite is used for the aseptic preparation of reagents to be used immediately. As such, the Process Support Room is equipped with Grade (b) (4) /ISO (b) (4). Only one patient lot may be processed inside a (b) (4) at a time. Aseptic manipulations performed inside the (b) (4) include (b) (4) EM is performed during aseptic manipulation. Line clearance is performed post-use and inspected pre-use. (b) (4) decontamination using (b) (4) is required pre-use and post-use. SOP-003061 "Aseptic Techniques for Working in the (b) (4)" v4.0 is provided in the submission to describe aseptic practices when operating in the ISO (b) (4) space, including the sanitization requirement for introducing materials into the (b) (4).

The Media Preparation Room (Room (b) (4)) is classified as Grade (b) (4) /ISO (b) (4) dynamic. It is equipped with entry PAL/MAL and an exit AL. All other areas (primary gowning area, corridors, freezer rooms, material dispensary/kit staging area, QC sample receiving area) associated with ide-cel manufacturing are classified as CNC. QC Lab area on the (b) (4) floor is not classified.

Reviewer Comment: *Non-RTF Issue #11a issued to the Applicant on May 11,2020 for the March 31, 2020 BLA submission (STN 125724) was related to the appropriateness of ISO (b) (4) classification for the Process Support Room where open manipulations occur inside the (b) (4) for a cellular product that cannot be sterile filtered or terminally sterilized. In response, Celgene upgraded the classification to Grade (b) (4) /ISO (b) (4) dynamic. The CNC classification of the shared support area is acceptable.*

The summary narratives provided in Section 3.2.A.1 [Cell] do not associate room numbers with its function or name. As such, the use of Rooms (b) (4) , as related to ide-cel manufacturing, is unclear. Room (b) (4) is the suite where (b) (4) preparation was simulated during aseptic process validation. It is also unclear which materials/equipment is/are being transported through the passthroughs for each relevant cleanroom. ***IR2 Comment 22*** *(below in* ***bold****) requested additional information. The response is summarized and reviewed below.*

22. Please clarify and describe the use of Rooms (b) (4) (Media Preparation), (b) (4) (Auxiliary Process Support), (b) (4) (Small Scale Reagent Prep), and (b) (4) (Media Prep-AMPS) as related to the ide-cel manufacturing process. Please also describe the materials and/or equipment which are transported

through the passthroughs in each cleanroom associated with ide-cel manufacture.

The firm clarified that Room (b) (4) is used to prepare (b) (4) used in the ide-cel manufacturing process. Room (b) (4) is used by S12 Training Organization to conduct aseptic qualifications of manufacturing and QC personnel. Room (b) (4) is used to prepare reagents used in the liso-cel manufacturing process. And Room (b) (4) is used to prepare media components for use in the liso-cel manufacturing process.

There are (b) (4) passthroughs between Room (b) (4) and Room (b) (4) (PBMC (b) (4) Room). They are used for retained samples that are submitted to QC Sample Management. The passthrough is cleaned with (b) (4) daily and pre-use. The (b) (4) passthroughs between Room (b) (4) and Room (b) (4) (Apheresis Receipt) are not in use during the ide-cel manufacturing process.

Reviewer Comment: IR4 Comment 2 *(below in* ***bold****) requested clarification for the use of Room* (b) (4) *to conduct aseptic operator qualification. The response is summarized and reviewed below.*

2. **In response to Information Request #27 Comment 6 addressed to Celgene Corporation dated November 17, 2020, you described Room** (b) (4) **as a support suite used by S12 Training Organization to perform aseptic Qualifications of Manufacturing and Quality Control personnel. We also noted in the May 2020 executed APS batch records that several operations which are routinely performed in different suites were simulated using the same workstation (e.g., Workstation** (b) (4) **was used for** (b) (4) **preparation,** (b) (4) **preparation, CS10-DP preparation,** (b) (4) **, DP harvest steps). It is the Agency's expectation that aseptic process validation and aseptic operator qualification are performed in suites where the commercial manufacturing processes occur to ensure the simulation is as close as possible to the actual process. In this context please address the following:**

    a. **Describe the types of aseptic qualifications being performed in Room** (b) (4) **and clarify if APS runs are routinely performed in the training Room** (b) (4)**.**

    b. **Confirm that the aseptic process for idecabtagene vicleucel manufacture was and will be simulated in the suites designated for the commercial process. If not, describe and justify the operation steps which were simulated elsewhere.**

    The firm confirmed that Room (b) (4) is used to perform aseptic operator qualification for the ide-cel manufacturing process. The equipment, workstation layout, and gowning procedures closely match the routine process, but with worst-case room classification (ISO (b) (4) /Grade (b) (4) with ISO (b) (4) /Grade (b) (4) vs. the commercial ISO

(b) (4) /Grade (b) (4) with ISO (b) (4) /Grade (b) (4). The firm also confirmed that that the aseptic process for ide-cel manufacture was and will continue to be simulated/validated in suites designated for the commercial process (Room (b) (4)), with the exception of (b) (4) preparation which is routinely performed in Room (b) (4) but simulated in Room (b) (4).

Reviewer Comment: *It appears that the aseptic processes are validated in the commercial rooms and Room (b) (4) is used strictly for operator qualification. This is acceptable based on the information provided in the response.*

The identity and flow of patient material between the work stations is controlled by the use of GMP barcode labels generated by the electronic (b) (4) to maintain identity and traceability. Barcodes on patient material bags and work stations are scanned to allocate space and equipment to one patient batch in (b) (4) to prevent product mix-up. The labels are verified by the operators, QA, and production lead per approved procedures. Likewise, QC samples are labelled to maintain COI.

Reviewer Comment: *The described activities can be found in the batch records provided in Section 3.2.R. It appears that the electronic barcode system is used extensively at S12. In addition to printing and scanning barcodes on Apheresis/intermediate/product/QC sample/workstation/equipment (including (b) (4)), (b) (4) appears to be also used to record the quantities of reagents used during processing and the number of intermediate/product bags generated.*

Process Flows

Personnel flow starts with entry to the (b) (4) Rooms (Rooms (b) (4) or Rooms (b) (4)) where street clothes are changed into plant uniforms and shoes. Secondary gowning takes place inside the (b) (4) entry (b) (4) prior to entering the ISO (b) (4). Entry into the ISO (b) (4) (b) (4) the ISO (b) (4). Sterile frock, face mask, sterile sleeves, and sterile gloves are donned for conducting aseptic manipulations in the ISO (b) (4) space. Staff degown in the ISO (b) (4) to exit the (b) (4). Finally, staff exit the (b) (4) via the exit (b) (4) in a unidirectional flow. Staff can also access other supporting suites from the CNC corridors. Media Prep Room (Room (b) (4)), Small Scale Reagent Prep Room (Room (b) (4)), Media Prep-AMPS Room (Room (b) (4)) are equipped with unidirectional ALs. Auxiliary Process Support Room (Room (b) (4)) is accessed from the Dispensary area.

Leukapheresis material is (b) (4) after inspection and release by QA from the Leukapheresis Receiving and Receipt Room (Room (b) (4)). Isolated PBMCs are taken to the PBMC (b) (4) Room (Room (b) (4)) for (b) (4). (b) (4) PBMCs are (b) (4)

(b) (4) . All material containers are sanitized in the ISO (b) (4) prior to entering the (b) (4) . Finished patient product (b) (4) the ISO (b) (4) and is frozen/cryopreserved in the Product Freezer Room (Room (b) (4)).

Raw materials and supplies are received at the (b) (4) (Room (b) (4)) per approved procedures. Each item is individually labeled with a tracking number and placed (b) (4) . Individual items are (b) (4) within the Material Transfer AL (Room (b) (4)) (b) (4) area (Room (b) (4)) (b) (4) to the Process Suites through the ISO (b) (4) associated with the suites. Prior to entry, the (b) (4) All items within each kit are tracked by the (b) (4) system.

> ***Reviewer Comment:*** *Non-RTF Issue #11b issued to the Applicant on May 11, 2020 for the March 31, 2020 BLA submission (STN 125724) was related to the appropriateness of the CNC classification for the Dispensary/Kit Staging area. In responses provided on May 22, 2020, Celgene clarified that these areas are cleaned and sanitized per SOP and the kit assembly process is conducted by trained and gowned personnel. The kitting process groups materials used for each lot for a specific manufacturing operation into one container or "kit". There are no instances where direct or indirect product-contact material surfaces are exposed to the CNC environment, and there are no instances of equipment being opened and/or assembled there. The* (b) (4) *the CNC area. The CNC classification was deemed acceptable based on the information provided at that time. However, the numerous viable excursions in critical manufacturing space reported during APS and EMPQ studies raised concern if the CNC classification for GMP areas including the common corridors and material staging/kitting space is appropriate (see discussion below in the IR) and if the material sanitization procedures are adequate. Refer to the review of aseptic process validation and EMPQ.*

Each Process Suite and each Process Support Suite is equipped with a pass-through for transfer for QC sample delivery to the QC Sample Management area (Room (b) (4)). Frozen samples may also be transported to Room (b) (4) from the Freezer Rooms in (b) (4) . Labeled samples are then transported to the QC Lab on the (b) (4) floor via (b) (4) .

All general and biohazard waste generated inside a Process Suite is collected locally in sealed bags/containers and is picked up from the CNC Corridor via the Waste-Out AL (WAL). Waste is transferred to the Waste and Trash Room (Room (b) (4)) in a waste cart through the Waste Transfer AL (Room (b) (4)) and Material Staging area (Room (b) (4)). Waste from the Media Preparation Room is similarly transported out of the suite via the associated exit AL. The risk of cross-contaminating the Room (b) (4) during

waste transport is mitigated through the use of double bags, buckets, overpack containers, sharps containers, and carts. The materials and the operating personnel in Room (b) (4) do not come into direct contact with waste. WP-001495 "NJ-EHS-Waste Handling Procedures for S12" v3.0 (effective February 10, 2020) was provided to describe waste management and disposal in Building S12.

> ***Reviewer Comment:*** *WP-001495 explains the immediate transfer of waste from the Process Support Suite via the associated MAL on cart to the Process Suite WAL. Biohazardous solid waste are double-bagged and placed in designated waste container/overpack in ALs where waste is picked up from the CNC corridors. Biohazardous liquid waste is collected in sealed bags and transported in secondary buckets/bins. Waste transport does not appear to be temporally segregated from process flows, which is acceptable given the use of closed primary and secondary containers.*

Utilities
Site utilities include the HVAC system, liquid nitrogen (LN2) (b) (4) storage and distribution systems.

HVAC
Air with controlled temperature and humidity is provided to the CAR-T manufacturing areas through (b) (4) AHUs ((b) (4) recirculation). HVAC zoning diagram showed dedicated AHU for each Process Suite and associated Process Support Suite and ALs, as well as for areas used for general support. Low wall exhaust returns and AHU exhaust fans control the required differential pressure between areas. Each Process Suite is equipped with dedicated circulating AHU with (b) (4), and (b) (4) terminal HEPA filtration. Common exhaust fan manifolds are utilized among suites but do not recirculate any air and are (b) (4) exhausted. The AHUs are connected to (b) (4) to allow control, monitoring, and alarm. AHU servicing non-classified areas are considered as having no impact and are therefore not commissioned. Air cascades out from areas of higher cleanliness to adjacent areas of less cleanliness. Inner entry AL features a pressure bubble with the outer AL cascade out. Exit ALs and WALs cascade out to the CNC corridor or the CNC Material Dispensary areas. Pressure differentials are monitored and alarmed by the (b) (4) when they fall below (b) (4).

> ***Reviewer Comment:*** *The use of dedicated AHU for the cell processing suites and media preparation suite is acceptable. The overall design of pressure differentials is acceptable.*

2018 Commissioning Summary Reports were included in the BLA submission for AHU-(b) (4) (Rooms (b) (4) and associated ALs), AHU-(b) (4) (Room (b) (4)), AHU-(b) (4) (CNC corridor, apheresis receiving, (b) (4) product freezer rooms, cryo shipment logistics, men/women locker rooms), AHU-(b) (4) (QC sample receiving, dispensary, kit staging, material stating, doc staging, waste/trash, lobby), and AHU-(b) (4) (Room (b) (4)).

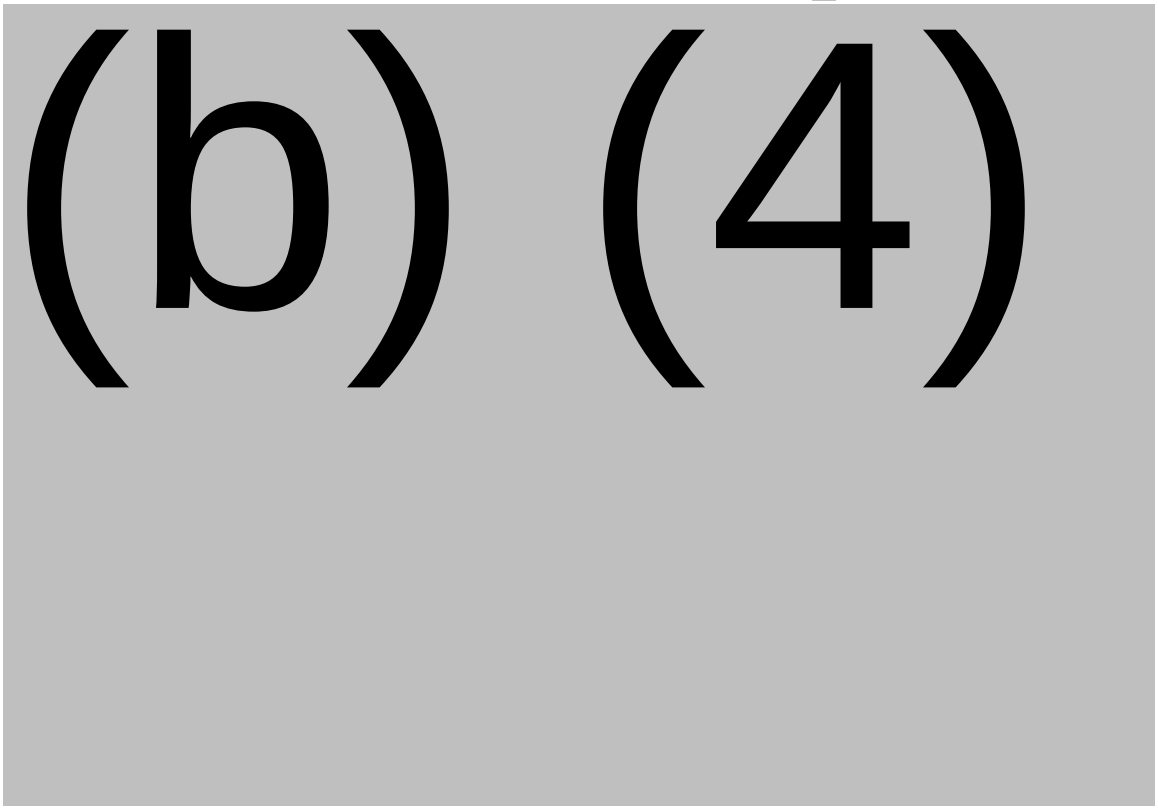
Reviewer Comment: *The summary reports are very high-level without a description of the test plan or deliverables. They each included a brief description of deviations and a conclusion that the equipment is deemed suitable for GMP use within the defined temperature* (b) (4) *range. Based on the deviation descriptions, it appears that tests such as* (b) (4) *were performed. The information provided is sufficient for the purpose of BLA review.*

EMPQ for all GMP areas was performed under (b) (4) conditions for a period of (b) (4) days each. The Applicant provided EMPQ report for Process Suite (b) (4) Room (b) (4) (AHU-(b) (4)), Media (b) (4) Room (b) (4) (known as the "Auxiliary Process Support Room" in the current layout; AHU-(b) (4)) , Bulk Media Room (b) (4) (AHU-(b) (4)), and associated (b) (4), ALs and pass-throughs.

Reviewer Comment: *The reports cover production areas classified as ISO* (b) (4) *or higher. The* (b) (4) *duration of EMPQ should be justified.*

Room (b) (4) *and Room* (b) (4) *EMPQ*

The study protocols and reports for the initial EMPQ of Process Suite (b) (4) (Room (b) (4)), Process Support (b) (4) (Room (b) (4)), and Auxiliary Process Support (Room (b) (4)) and all associated ALs, (b) (4), and passthroughs were provided and reviewed. Rooms (b) (4) are used to manufacture ide-cel and are supplied by AHU(b) (4). Room (b) (4) was previously used to manufacture (b) (4) and is supplied by AHU-(b) (4). The areas qualified are described in the table below. During routine in-use monitoring, Grade (b) (4) gowning and airlock areas (as qualified) would meet Grade (b) (4) viable levels.



(b) (4)

Reviewer Comment: *The room classifications listed in the table represent air classification at rest and appear appropriate. The firm described the air classification of the passthroughs and their use/maintenance in their response to IR2 Comment 24b.*

The following viable air, non-viable air, and viable surface action limits were applied during EMPQ under (b) (4) conditions.

(b) (4)

Reviewer Comment: *The action limits are compliant with the* (b) (4) *system. Per RTF Issue # 11a, Celgene agreed to implement an ISO* (b) (4) *environment surrounding the ISO* (b) (4) *in Process Support Room 1203 to replace the original classification of ISO* (b) (4) *for the Process Support Room where open manipulations occur inside the* (b) (4)*. The EMPQ showed that the cleanrooms with* (b) (4) *were initially qualified to be ISO* (b) (4) *compliant under dynamic conditions; therefore, the nominal upgrade could be easily implemented.*

The minimum number of air sampling sites was determined per (b) (4) guidelines, which takes into consideration the room size. Surface sampling locations for each room was established based on room size, equipment orientation, activities, personnel/material flow, and microbial risk. (b) (4) sampling of Room (b) (4) included (b) (4) Acceptance criteria of the passthroughs were held to the higher-grade cleanroom in which they are located. (b) (4) Attachment 8 of the protocol explained the risk assessment performed to select risk-based EM sample locations based on personnel occupancy, activity duration, and proximity to potential contamination sources. The result was an overall risk ranking for each sample location. The highest risk locations are those associated with the(b) (4).

Reviewer Comment: *The sampling location diagrams are provided in the study protocol. The sample numbers and locations appear acceptable based on room size, equipment and anticipated operations.*

The qualification study was preceded with a baseline environmental monitoring to assess the level and type of bioburden present in the cleanrooms/areas prior to (b) (4) cleaning/sanitization with (b) (4) . No microorganisms were recovered from the Grade (b) (4) areas and the most commonly observed genera were (b) (4) . Low levels of (b) (4) were also recovered from Grade (b) (4) areas. After (b) (4) cleaning/sanitization sessions and final QC verification of equipment and room readiness, (b) (4) monitoring was conducted over a (b) (4) period with equipment (b) (4) . (b) (4) cleaning and sanitization of all cleanrooms and associated ALs were performed. The EMPQ duration is based on the typical, anticipated process period. (b) (4) action level excursions ((b) (4)) were observed in Room (b) (4) (Media Prep), Room (b) (4) (Process Support), (b) (4) PAL, and (b) (4) in Room (b) (4). (b) (4)

excursions ((b) (4)) were observed in Room (b) (4) (Media Prep), Room (b) (4) (Process Support), and (b) (4) Gowning/PALs/MALs. (b) (4) excursion ((b) (4)) were observed in (b) (4) PAL ((b) (4)).

(b) (4) monitoring occurred over a (b) (4) period with maximum personnel occupancy and simulation of manufacturing activities. Specifically, the (b) (4) monitoring studies were completed (b) (4) with the initial 2018 APS study for Process Suite (b) (4). The operational activities included (b) (4) excursions ((b) (4)) were observed in Room (b) (4) (Process Suite (b) (4)), (b) (4) gowning AL, (b) (4) inside Room (b) (4) and (b) (4) inside Room (b) (4). (b) (4) excursions (b) (4)) were observed in Room (b) (4) (Process Support), Room 1021 (Media Prep), and (b) (4) Gowning/PALs/MALs, with high-percentage excursion rates limited to the ALs. All Grade (b) (4) areas reported (b) (4) excursions, with highest incidence rates observed in the ALs ((b) (4)). (b) (4) excursions ((b) (4)) were observed in Room (b) (4) (Process Support) and Room (b) (4) (Media Prep).

There were no temperature or humidity alarms observed during (b) (4) testing. Differential (b) (4) alarms observed during EMPQ generally correlated with sampling activities. The (b) (4) excursions mostly occurred at locations near the door or adjacent to the (b) (4) (linked to (b) (4) during aseptic operations). The (b) (4) excursions observed during (b) (4) monitoring were attributed to QC analysts not implementing a delay for (b) (4) collection as required for (b) (4) samplers (i.e., sampling started while the QC personnel was existing the areas). The (b) (4) excursions were mostly observed at locations near the doors, adjacent to the (b) (4) where there are heightened activities, or where gowning or material handling activities occurred. In addition, personnel were not required to wear facility-dedicated footwear at the time of (b) (4) EMPQ, which would contribute to the bioburden load observed during the study. The number of organisms recovered from (b) (4) testing are tabulated below for comparison:

(b) (4)

Reviewer Comment: *Based on the organism identification pie charts provided for each test performed in each Grade environment, there appears to be a significant reduction of* (b) (4) *species (e.g.,* (b) (4) *) and a number of other* (b) (4) *after the* (b) (4) *-cleaning (*(b) (4) *). Compared to the baseline recoveries, the most commonly observed genera during* (b) (4) *challenges remained to be* (b) (4) *. However, the number of microorganisms recovered and identified in the Grade* (b) (4) *,*

*Grade (b) (4), and Grade (b) (4) areas appeared to have increased significantly between (b) (4) testing despite the (b) (4) facility cleaning. And the data showed that there was still a considerable presence of non-human (e.g., (b) (4)) (b) (4) present in Grade (b) (4) under (b) (4) conditions. This is consistent with microorganisms recovered and identified from personnel monitoring performed during APS. The firm claims that they were derived from material/package handling. This may be an indication of inadequate decontamination of materials before introducing them into the GMP space and aseptic space. However, it is unclear if any corrective/preventive actions have been implemented. In addition, the increased number of organisms recovered during (b) (4) testing compared to the (b) (4) testing is puzzling. It also appears that the facility cleaning/sanitization program has limited effectiveness on (b) (4). Finally, no results from pass-throughs were provided. An **IR2 Comment 24a-e** (below in **bold**) requested additional information. The response is summarized and reviewed below.*

24. Environmental qualification (EMPQ) was performed for Process Suite (b) (4) Room (b) (4), Auxiliary Process Support Room (b) (4) Media Room (b) (4), and their associated airlocks, (b) (4), and passthroughs. Please address the following comments:

a. Please justify the duration of (b) (4) EMPQ studies.

The firm stated that the (b) (4) testing was selected to provide a (b) (4) assessment of environmental control of the post-cleaning environment. The (b) (4) EMPQ represented the period of time during which the majority of ide-cel manufacturing processes are performed in the Grade (b) (4) /ISO (b) (4) areas and all critical aseptic manipulations are performed in the Grade (b) (4) /ISO (b) (4).

Reviewer Comment: *The PBMC cell isolation step is performed primarily inside the (b) (4) prior to (b) (4). The PBMC cell transduction, expansion, and harvest process spans about (b) (4) with a majority of the time spent in the (b) (4) during the expansion phase or inside the (b) (4) during (b) (4) steps. As such, the (b) (4) environmental exposure to the cleanroom or (b) (4) appears to be acceptable.*

b. Please describe the applicable passthroughs (e.g., air classification, (b) (4), HEPA, etc.) and their intended use. In addition, the EMPQ reports do not include EM results from the passthroughs. Please provide this information for all applicable passthroughs tested under (b) (4) conditions.

The firm clarified that the passthroughs are HEPA filtered (b) (4) passthroughs. They are used for the movement of patient material and product samples between Room (b) (4) and Room (b) (4) (classified as Grade (b) (4) /ISO (b) (4)) and between Room (b) (4) and the CNC corridor (classified as Grade (b) (4) /ISO (b) (4)). The EMPQ data for the passthrough met all acceptance criteria for (b) (4) sampling.

Reviewer Comment: *The results are acceptable.*

c. While the acceptance criteria for (b) (4) and (b) (4) for Grade (b) (4), Grade (b) (4), Grade (b) (4), and Grade (b) (4) spaces comply with (b) (4), they are less stringent than those recommended by the Agency for the corresponding ISO spaces in the FDA 2004 Guidance "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice". Please justify.

The firm compared the EU and FDA (b) (4) limits per Grade/ISO classification and determined that they are the same.

Reviewer Comment: *Celgene's comparison aligned EU Grade (b) (4) specification and FDA ISO (b) (4) specifications and concluded equivalence. However, Grade (b) (4) is more aligned with ISO (b) (4) specifications. This is acceptable as long as the air classification surrounding the (b) (4) where aseptic processing takes place is consistent with ISO (b) (4) requirements, which appears to be the case based on the RTF response and the updated floor diagrams.*

d. Regarding EMPQ Report (RPT-013280) for Process Suite (b) (4) Room (b) (4) and Auxiliary Process Support Room (b) (4), please address the following concerns:

i. You noted that excursions related to (b) (4) monitoring were observed in all Grade (b) (4) areas at a pronounced rate. Many of the excursions occurred inside the airlocks, near the doors, or in areas immediately adjacent to the (b) (4). However, you did not investigate or address the gross failures observed in (b) (4) in the areas where ide-cell processing or supportive activities take place, including areas where aseptic operations occur inside the (b) (4). Please discuss the course of actions you have taken to prevent (b) (4) excursions, especially in the critical production areas where aseptic processes take place. Please justify your response.

The firm described the following improvements made to enhance contamination control:

- Improvements were made to the gowning procedures, including improved instructions on shoe cover application, hand washing and hand sanitization with (b) (4), and increased use of face masks throughout the classified areas. The use of facility-dedicated footwear was additionally implemented.
- Improvements were made to material handling and wipe-down during kitting and transfer, including added use of (b) (4) wipes after the existing use of (b) (4) when introducing materials into the kitting area.

The use of (b) (4) was implemented in the first quarter of 2020.

- Improvements were made to aseptic technique, including clarifying instructions on material handling/de-wrapping and opening containers inside the (b) (4). The existing practice of (b) (4) application was replaced by a (b) (4) of materials with (b) (4) prior to transfer into the (b) (4).
- The aseptic training program was expanded to include more detailed coaching and the development of an interactive training presentation.
- Areas immediately adjacent to the (b) (4) are monitored to ISO (b) (4)/Grade (b) (4) requirements in the third quarter 2020 in response to FDA feedback.

The firm also stated that all locations where excursions (meet or exceed alert levels) occurred were included in the routine EM program. The 2019 annual EM summary report (RPT-021207), first/second/third Quarter 2020 S12 EM trend reports (RPT-021518, RPT-022085, RPT-022733) were provided in the response to demonstrate improved microbial control. Process Suite (b) (4) EM excursion rates from January through October 2020 are summarized in the table below. The firm also stated that a follow-up EMPQ of Process Suite (b) (4) was completed in November 2020 with final report available for FDA review on inspection.

(b) (4)

Reviewer Comment: *Based on the recent EM data, there appeared to be improvement in (b) (4) control since EMPQ.*

ii. Several (b) (4) excursions were observed inside the (b) (4) under (b) (4) conditions, including (b) (4) instances where (b) (4) was recovered under (b) (4) conditions. Please discuss the potential root cause(s) and corrective/preventive actions taken to mitigate the risk of (b) (4) contamination inside the (b) (4) aseptic environment.

The firm acknowledged the concerns and attributed the (b) (4) excursions in the (b) (4) to lack of clarity in aseptic technique, material handling, (b) (4), and staging procedures. The

corrective actions implemented since the initial EMPQ included the following:

(b) (4)

(b) (4)

(b) (4)

Reviewer Comment: *The continued recovery of* (b) (4) *from aseptic operators is still a concern. Refer to response to IR2 Comment 24e for additional information.*

iii. D areas at (b) (4) **, and under** (b) (4) **conditions at about comparable rate of occurrence. Please discuss the course of actions you have taken to investigate and mitigate the presence of** (b) (4) **in your GMP areas, which did not appear to have been reduced after the** (b) (4) **facility cleaning between baseline and static studies.**

The firm acknowledged the concerns and described measures implemented since the initial EMPQ to manage (b) (4) control. In addition to those described in response to IR2 Comment 24d,ii, every (b) (4) recovery is responded with a (b) (4) cleaning of the affected area and a deviation investigation. The firm emphasized that the (b) (4) strategy has kept (b) (4) from contaminating the (b) (4), as shown by 2020 EM data. The sponsor emphasized that the incidence rate ((b) (4) in 2019 and (b) (4) in 2020) has been kept low despite increased activities since the initial EMPQ.

Reviewer Comment: *(b) (4) recovery occurred (b) (4) in 2020. However, there appears to be a (b) (4) control strategy in place, which is acceptable.*

iv. The number of (b) (4) recovered and identified in the Grade (b) (4), Grade (b) (4), and Grade (b) (4) areas increased significantly between (b) (4) sampling and (b) (4) sampling, which were separated by the execution of a (b) (4) facility cleaning. Please discuss your assessment on the effectiveness of your facility cleaning program.

The firm clarified that the total organisms recovered under the (b) (4) conditions represented those from (b) (4) samplings while those from the (b) (4) study represented (b) (4) sampling. When averaged, the number of organisms recovered under the (b) (4) conditions is lower.

- ISO (b) (4)/Grade (b) (4) areas: (b) (4)
- ISO (b) (4)/Grade (b) (4) areas: (b) (4)
- ISO (b) (4)/Grade (b) (4) areas: (b) (4)
- ISO (b) (4)/Grade (b) (4) areas: (b) (4).

Reviewer Comment: *The reduction is less than (b) (4) in most cases. However, the more recent EM data collected after the implementation of improved practices and procedures appear to be acceptable.*

e. Many of the (b) (4) recovered and in the Grade (b) (4), Grade (b) (4), and Grade (b) (4) areas are not of (b) (4) origin, but are related to (b) (4) This also correlates with the numerous (b) (4) and (b) (4) excursions reported in the Grade (b) (4) environment during aseptic process validation (including Grade (b) (4) environment and garments). The frequent recovery of (b) (4) with (b) (4) origin suggests material/equipment related contamination sources and raises concern for adequacy of the existing procedures used to introduce sanitized materials into the GMP space and process stream. Please discuss your assessment on the adequacy of the existing procedures and

controls, including if the current CNC classification of the GMP corridors and material staging/kitting space is appropriate.

The firm acknowledged the concerns. Materials have been identified as a potential source of (b) (4) origin organisms and (b) (4). As a corrective action, (b) (4) of materials with (b) (4) was introduced in the first quarter of 2020.

Regarding the (b) (4) organisms recovered during APS, the firm explained that ensuing investigation attributed the material related excursions to the (b) (4), which were initially shipped to Celgene in (b) (4) (b) (4) cleaning agents were not applied due to their incompatibility with the (b) (4) Studies conducted during the investigation demonstrated a high rate of (b) (4) species recovery from the (b) (4) directly after removal from the (b) (4). The majority of organisms recovered during the APS-related personnel and environment monitoring were (b) (4) recovered from operators who had handled (b) (4). The initial corrective actions, including enhanced (b) (4) of the (b) (4) with (b) (4) and sourcing (b) (4), resulted in limited improvement in reducing (b) (4) species in the subsequent APS studies. A new (b) (4) using (b) (4) followed by (b) (4) showed significant reduction in (b) (4) recovery (reduced from (b) (4) in a later study, which also showed the absence of growth inhibitory effect of (b) (4) on (b) (4). Additionally, (b) (4) is now transferred from the original (b) (4) into (b) (4) identical to those used in the ide-cel manufacturing process prior to use. Collectively, these actions reduced the incidence of (b) (4) recovery on personnel monitoring in the most recent September 2020 APS, which reported (b) (4) excursion out of (b) (4) samples. The recovered organism was (b) (4). No organisms were recovered from the EM samples taken within the (b) (4) (total (b) (4) samples). The next APS for Process Suite is to be scheduled for late December 2020. Refer to response to IR2 Comment 24d,ii for (b) (4) recovery rates in routine EM performed for (b) (4) ide-cel manufacturing from September 2019 to September 2020.

The firm also noted their opinion that the CNC classification for GMP corridors and kitting areas is adequate in that all materials/reagents are kitted and placed in closed containers during transport and all critical manipulations with potential product exposure are performed inside the (b) (4). The pressure differentials and cascading airflow from critical area to less critical area are deemed to be effective controls.

> ***Reviewer Comment:*** *The response provided evidence that the firm has been actively investigating the root causes for the high rates of* (b) (4) *excursions observed during EMPQ and APS. The findings and corrective actions appear to be acceptable.*

Nine deviations were reported during study execution. They included protocol generation errors with no study impact, invalidated samples due to (b) (4) malfunction, reports/forms required to be verified prior to the baseline testing were not fully approved/closed at the time of testing but were successfully executed subsequently, adjustment made to the number of personnel present during (b) (4) monitoring to more accurately reflect the routine processes, one missed (b) (4) iculate sampling, and insufficient personnel presence ((b) (4)) during EMPQ in Room (b) (4) (the new routine operation limit for this gowning area was lowered to (b) (4) people as a result).

> ***Reviewer Comment:*** *The overall low levels of* (b) (4) *excursion supported the adequate air handling system performance. The overall low levels of* (b) (4) *excursion generally supported the effectiveness of the cleaning/sanitization program, although manual cleaning thoroughness is needed especially for the* (b) (4) *surfaces. No* (b) (4) *excursions were observed inside the* (b) (4)*, which indicates adequate environmental isolation of the aseptic working environment.*

Room (b) (4) *EMPQ*

The study protocol and report for the initial EMPQ of Media Preparation Room (b) (4) and all associated ALs and (b) (4) passthroughs are provided. Room (b) (4) is a dual-use suite designed for (b) (4) production and the isolation process (not for ide-cel). Clean air to Room (b) (4) and associated areas is supplied by AHU-(b) (4). The qualified areas are described in the table below. (b) (4) passthroughs associated with Room (b) (4) were included in the EMPQ.

(b) (4)

> ***Reviewer Comment:*** *The room classifications listed in the table above represent air classification at rest and appear appropriate.*

The following (b) (4) action limits were applied during EMPQ under (b) (4) conditions.

(b) (4)

(b) (4)

(b) (4) action levels are provided in the following table.

(b) (4)

The previously described EMPQ study design and risk assessment approach to sampling sites determination were also applied to this study. A (b) (4) environmental monitoring was performed (b) (4) to (b) (4) cleaning/sanitization with (b) (4) . The most commonly observed genera were (b) (4) . Low levels of (b) (4) were also recovered from the Grade (b) (4) areas. After (b) (4) cleaning/sanitization sessions and final QA verification of equipment and room readiness, (b) (4) monitoring was conducted over a (b) (4) period with (b) (4) cleaning and sanitization. No excursions were reported. Identification of (b) (4) was not performed on the (b) (4) samples due to analyst error; however, the absence of (b) (4) was confirmed. (b) (4) monitoring occurred over a (b) (4) period. No excursions were reported. Locations with higher (b) (4) counts were high-traffic areas and areas near the doors or equipment/supplies. Floor at high-traffic areas represented the surface with higher (b) (4) . There were no (b) (4) alarms observed during (b) (4) testing. (b) (4) alarms reported during EMPQ generally correlated with sampling activities. The number of organisms recovered from (b) (4) testing are tabulated and compared below.

(b) (4)

> ***Reviewer Comment:*** *The EMPQ for Room (b) (4) was conducted about (b) (4) after the EMPQ for Process Suite (b) (4) and shortly before PPQ. The data in this report demonstrated reduction in the number of (b) (4) under (b) (4) conditions following the cleaning/sanitization program. However, a significant number of non-human derived bacteria were still identified under (b) (4) conditions. Refer to the review of firm's response to IR2 Comment 24 above.*

Five deviations were reported during study execution. They included protocol generation errors with no study impact, electronic sampling label generation error (resolved by using manual labels), and reports/forms required to be verified prior to the baseline testing were not fully approved/closed at the time of testing but were successfully executed subsequently,

Reviewer Comment: *The EMPQ results for cleanroom (b) (4) is acceptable.*

Room (b) (4) EM Requalification

Process Suite (b) (4) (Room (b) (4)) was requalified in 2019 to allow an increase in personnel occupancy from (b) (4). Study protocol (RPT-017981 v1.0, approved February 16, 2019) and report (RPT-018413 v1.0, approved April 30, 2019) were provided. (b) (4) monitoring were performed under (b) (4) conditions after (b) (4) cleaning of all cleanrooms and associated airlocks for a minimum of (b) (4). The protocol stated that Room (b) (4) have been in operation for about (b) (4). No EM non-conformances had been reported since release. During the requalification, Room (b) (4) was qualified as ISO (b) (4) /Grade (b) (4) with the following action limits:

(b) (4)

Reviewer Comment: *The lowered air classification used during requalification (ISO (b) (4) /Grade (b) (4)) is consistent with the current cleanroom classification for Room (b) (4). As only closed-system operations are performed in Room (b) (4), this is acceptable.*

All results were within the action limits. No (b) (4) were recovered. No high-risk areas were identified. No (b) (4) alarms were observed during EMPQ. (b) (4) alarms generally correlated to the times of sampling or heighten activities. No deviations were observed during study protocol execution. Data from the 2019 requalification ((b) (4) people) were compared to the 2018 EMPQ ((b) (4) people). No consistent trends or statistically meaningful differences could be made across the types of EM results.

Reviewer Comment: *The requalification results met acceptance criteria. However, this may not be reflective of an improvement in the environmental control since the most problematic AL areas associated with Room (b) (4) were not included in the requalification (which are expected to experience more traffic and use due to the increased number of entry/exits made by an increased number of personnel). In addition, the classification of Room (b) (4) has been downgraded from Grade (b) (4) /ISO (b) (4) to Grade (b) (4) /ISO (b) (4) during requalification, which may also contribute to the more favorable EMPQ outcomes.* ***IR2 Comment 24f*** *(below in* ***bold****) requested additional information. The response is summarized and reviewed below.*

f. The 2019 environmental requalification of Process Suite (b) (4) Room (b) (4) was performed to allow an increase in personnel occupancy from (b) (4). However, the requalification did not include the adjacent

airlocks. Please justify your decision not to include the adjacent airlocks since they are expected to experience a corresponding increase in traffic flows and frequency of use. This is especially a concern since the initial EMPQ identified the airlocks as one of the most problematic areas with the highest rates of (b) (4) excursions.

The firm responded that even though the traffic through the ALs increased, the maximum personnel permitted at any given time in the AL remained the same. EM data collected after the Personnel Occupancy EMPQ study until the present reported no excursions ((b) (4)) in the PALs and MALs immediately adjacent to the Room (b) (4).

Reviewer Comment: *The response is acceptable.*

(b) (4)

Reviewer Comment: IR2 Comment 27 *(below in **bold**) requested additional information on the PQ activities and routine monitoring activities. The response is summarized and reviewed below.*

27. High-level narratives were provided describing the (b) (4) storage and distribution system, and the qualification activities associated with this utility system. Please address the following comments:

a. Please describe the PQ activities in more detail, including the duration of the qualification studies, all the sampling ports relevant to the ide-cel manufacturing process, and a summary of results obtained from these sampling locations. If a (b) (4) is used during sample collection, please describe and justify how the qualification sampling compares to the routine process sampling.

The firm described that PQ was performed over (b) (4) from (b) (4) test points for (b) (4)

A (b) (4) is not used during sample collection but (b) (4) . The sampling sites included the (b) (4) . All results met the acceptance criteria.

The (b) (4) levels are very low and viable results were all (b) (4).

Reviewer Comment: *The response is acceptable.*

b. Please provide a brief description of the routine in-line monitoring program that is in place for the (b) (4) system, including the sampling locations (room number included) and alert/action limits.

The firm stated that no routine in-line monitoring is performed for the (b) (4) system because the (b) (4) does not have direct product contact in the ide-cel manufacturing process. Purity is verified by COA provided by supplier upon delivery

Reviewer Comment: *Given that the (b) (4) is (b) (4) prior to distribution and by the (b) (4), sterility assurance should be adequate. Verification of (b) (4) by COA is acceptable.*

Liquid Nitrogen

Vapor phase LN2 is supplied by an external vendor. It supplies LN2 to the (b) (4) freezers, (b) (4) LN2 distribution system. The system is intended to supply LN2 at (b) (4) from the (b) (4). It is classified as a GMP indirect utility and was commissioned. Commissioning activities included general equipment verification, piping and instrumentation diagram verification, system component verification, instrument calibration verification, system pressure verification, and system flow verification. Qualification activities included testing for pressure and flow. Qualification protocols and reports were not provided.

Reviewer Comment: *The information provided is acceptable. The LN2 system poses low risk to sterility assurance due to its inherently low temperature.*

Equipment

A combination of (b) (4) are used for the ide-cel manufacture. A list of major equipment is presented in the table below.

(b) (4)

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

(b) (4)

Equipment Qualification

IOPQ summary report for each major manufacturing equipment were provided in the BLA. They are briefly described below.

Reviewer Comment: *Most of the information provided in the summary reports supported equipment IQ and OQ. Adequate performance qualification for the equipment was demonstrated during the PPQ activities when they were used as intended during ide-cel manufacture. This is acceptable.*

(b) (4)

(b) (4)

Reviewer Comment: *OTAT reviewer, Zehra Tosun, has been assigned to review the* (b) (4) *and her review scope included biocompatibility, sterilization of the product-contact parts/components, and design change history.*

(b) (4)

Reviewer Comment: *Additional information is requested about the* (b) (4) *associated with* (b) (4) *as this issue was mentioned in the* (b) (4) *as well.* ***IR2 Comment 25*** *(below in* ***bold****) requested additional information. The response is summarized and reviewed below.*

25. Table 6 of Section 3.2.A indicated that (b) (4) **units are also present in the Media Preparation Room** (b) (4)**. Please clarify and describe the** (b) (4) **operations performed in Room** (b) (4)**. In addition, please discuss the risk of**

(b) (4) the (b) (4) upon system detection of (b) (4) and the measures to mitigate such risk if applicable.

The firm clarified that the (b) (4) units in Room (b) (4) are not used for ide-cel production. Room (b) (4) was originally intended for PBMC preparation but is now dedicated to (b) (4) preparation only. Table 6 of Section 3.2.A.1 will be updated. Regarding the risk of (b) (4), the firm explained that (b) (4) uses (b) (4) Specific instructions on alert response are available in the equipment SOP. The operators are trained to inspect the (b) (4) kit prior to responding to the alert. If a wrong selection is made, (b) (4) has the capability to detect the (b) (4) and present another alert.

Reviewer Comment: *The response is acceptable. Alerts are in place to pause procedure, request intervention, and prevent catastrophic failures.*

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4) *Freezer*

There are (b) (4) units of (b) (4) freezer used during (b) (4) DP cryopreservation operations in Room (b) (4) Freezer Room) and Room (b) (4) (Product Freezer Room). Each freezer unit can accommodate up to (b) (4) user-defined profiles, in addition to (b) (4) pre-set freezing profiles. The operating temperature range is (b) (4) . Freezer qualification was performed in accordance with protocol PROT-013154 v1.0 (approved on March 5, 2018). IQ consisted of verification of system components, instrument calibration, documentation, utilities and environmental conditions, and spare/change parts. OQ consisted of verification of SOP availability, testing of sequence of operation per manufacturer's specification, testing of alarm and interlock, and temperature mapping of the (b) (4) . PQ consisted of loaded (b) (4) . During temperature mapping studies, (b) (4) temperature (b) (4) were placed in (b) (4) . Additional temperature

(b) (4) were placed (b) (4) . The acceptance criteria were: (b) (4)

Qualification summary reports (RPT-013709 v1.0 and RPT-013690 v1.0, approved in 2018) for two representative units of (b) (4) freezer were provided in the BLA. The (b) (4) was within the limits during all (b) (4) . All acceptance criteria were met without deviations. RPT-013279 (v1.0, approved November 2018) was a high-level report certifying the release of all (b) (4) upon successful qualification of each individual unit.

Reviewer Comment: *The information provided is acceptable and sufficient to support equipment qualification.*

Liquid Nitrogen Freezer – Vapor Phase Storage

There are (b) (4) units of (b) (4) LN2 freezer in Room (b) (4) Freezer Room) and Room (b) (4) (Product Freezer Room) to store (b) (4) DP at cryogenic temperature ((b) (4)). The system is (b) (4) IQ consisted of verification of equipment and installation, instrumentation and calibration, documentation, utility and environmental calibration, and spare/change parts. OQ consisted of SOP verification, control panel testing, alarm (including automatic refill) testing, security testing, and (b) (4) mapping. PQ consisted of (b) (4) mapping. In the mapping studies, the unit must demonstrate capability to maintain (b) (4) for an undisturbed (b) (4) period in (b) (4) conditions. High-level validation summary reports (RPT-013264 v1.0, RPT-013216 v1.0, and RPT-013705 v1.0, approved 2018) were provided to certify the release of all LN2 freezer units based on the acceptable outcome of the qualification deliverables.

Reviewer Comment: *The automatic LN2 refilling feature provides additional assurance of cryogenic temperature maintenance. The information provided is acceptable.*

(b) (4)

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

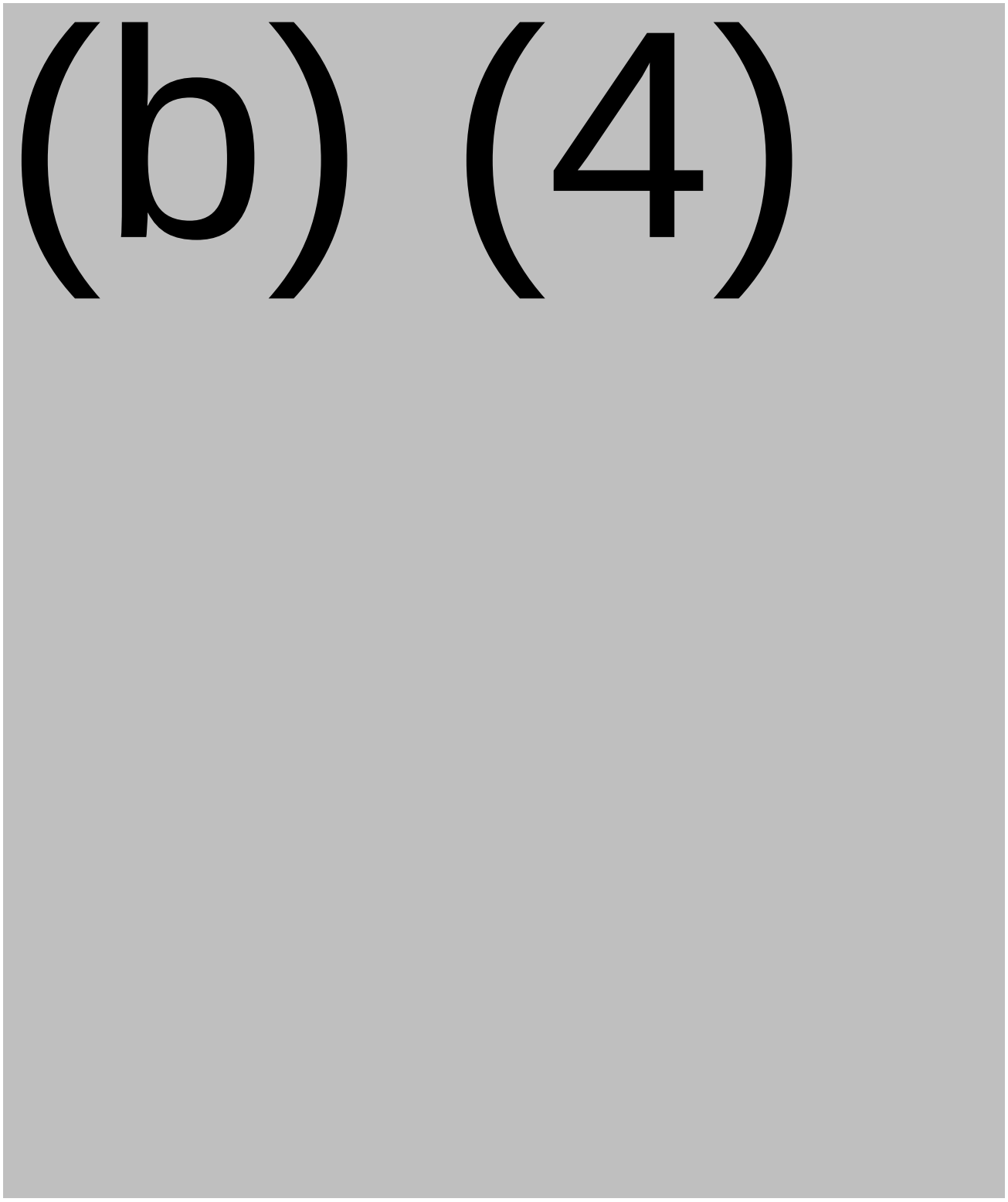
(b) (4)

Equipment Cleaning

There is no reusable product contact equipment in the ide-cel manufacturing process; therefore, no product contact equipment cleaning is required. The following table summarizes the cleaning of all reusable, non-product contact equipment. Equipment surfaces are cleaned either by (b) (4)

.

(b) (4)



Reviewer Comment: *The equipment cleaning schedule appears acceptable.*

Cleaning and Sanitization

Cleaning/sanitization/disinfection of facility cleanroom surface is performed at pre-determined intervals depending on area criticality. It is performed prior to and after production activities, after shutdowns, and following major maintenance or construction activities. The disinfectants used at the S12 facility include the following:

(b) (4)

All manufacturing areas are cleaned and sanitized using established procedures and pre-specified frequencies which are specific to the room classification. It is briefly summarized below:

Grade (b) (4) Environment

Frequency	Surface	Cleaning Agent	Direct Application	Indirect Application
(b) (4)				

Grade (b) (4) Environment

Frequency	Surface	Cleaning Agent	Direct Application	Indirect Application
(b) (4)				

(b) (4)

CNC Environment

Frequency	Surface	Cleaning Agent	Direct Application	Indirect Application
(b) (4)				

According to the efficacy claims made by the supplier, (b) (4) is effective against (b) (4) is effective against (b) (4)

Disinfectant Effectiveness Study

Celgene performed a disinfectant effectiveness study (RPT-021127) in which all disinfectants tested were in the (b) (4) format with (b) (4) stability tested at (b) (4). The challenge microorganisms were common S12 facility environmental isolates recovered from the EM program, including (b) (4) (b) (4) testing was performed prior to performing disinfectant efficacy. (b) (4) The recovered viable organisms were enumerated. Microbial recovery was compared to recovery from respective (b) (4) without disinfectant application. The study matrix is described in the table below.

Disinfectant	Contact Times	S12 Environmental Isolates
(b) (4)		

The acceptance criteria are as follows:

(b) (4)

All acceptance criteria were met under all test conditions. No significant differences were observed based on contact time ((b) (4)) or disinfectant shelf life ((b) (4)). The reported log-reduction values are summarized in the table below. No deviations were reported.

(b) (4)

As a result, routine disinfectant contact time (b) (4)) and a shelf-life of up to (b) (4) are deemed acceptable. No testing was done on viral efficacy. Virucidal activity for (b) (4) is based on vendor claims.

Reviewer Comment: *The most common genera identified in the 2018 and 2019 EMPQ reports were* (b) (4) *. In addition,* (b) (4) *were recovered during EMPQ as representative* (b) (4) *. The selected challenge microorganisms did not include* (b) (4) *and did not include* (b) (4) *. No information was provided regarding the* (b) (4) *in which the microorganisms were* (b) (4) *. In addition, Celgene should justify their* (b) (4) *selection and why the* (b) (4) *surfaces are deemed representative and inclusive (e.g.,* (b) (4) *). Justification should be based on sanitization/disinfectant resistance as a function of material surface properties and temperature (e.g.,* (b) (4) *). All disinfectants/sanitizer are commercially supplied and does not appear to require on-site dilution or preparation. As such, no dilution/concentration study is required. Finally, Celgene should justify why viral challenge is not deemed necessary as viral materials are used on site during manufacturing.* ***IR2 Comment 26*** *(below in* ***bold****) requested additional justification. The response is summarized and reviewed below.*

28. A disinfectant effectiveness study was performed to qualify the sanitizers and disinfectants used at the S12 facility. Please address the following comments:

a. Please justify the selection of (b) (4) **challenged in the study (**(b) (4) **) and explain how their surface properties represent all the critical surfaces present in the S12 facility, including sterile gloves,** (b) (4) **, and packaging materials. The justification should take into consideration the viable excursions (surfaces from which microorganisms are discovered and potential sources) reported in the EMPQ and APS studies.**

The firm responded that the selected surfaces represent the prevalent surfaces in S12 with the (b) (4) being the most critical physical surface representing the material of (b) (4) . They noted that patient materials do not enter the (b) (4) .

In the response, the firm stated that since all product contact surface are (b) (4) , disinfectant effectiveness is not applicable to those surfaces. The (b) (4) is sanitized (b) (4) use. However, it was not included in the study because the (b) (4) . As such, the risk of microbial contamination is low. Sterile gloves are frequently sanitized with sterile (b) (4) materials. Its material of construction was not included in the study due to the irregular surface. The porous nature of packaging materials is also the reason why they are excluded from the study. Since the anti-microbial properties of (b) (4) are demonstrated via (b) (4) properties, the firm expects results on other surfaces tested in the study would apply to the glove and porous

construction materials as well. In cases where the packaging materials are not porous, (b) (4) is the disinfectant of choice to reduce the bioburden load of potential (b) (4) .

The response also included the summary report (RPT-022830 v1.0, approved December 2, 2020) from the most recent APS requalification performed in Process Suite (b) (4) (Room (b) (4)) and Process Support Suite (b) (4) (Room (b) (4)) in September 2020. One APS run was executed on the processing of (b) (4) lots. The results were passing. One (b) (4) excursion was observed from the operator glove ((b) (4)). No CAPA was required besides a "reinforcement discussion" as this was the first excursion identified for the affected operator.

Reviewer Comment: *The response is acceptable in light of the improved EM data since EMPQ.*

b. Insufficient information was provided to support disinfectant qualification. Please provide information and/or data to demonstrate disinfectant effectiveness based on use temperature (i.e., (b) (4)) and inoculate composition (e.g., (b) (4)).

The firm confirmed that all disinfectants used at S12 are applied at (b) (4) . The inoculum consisted of representative isolates at a (b) (4) . The (b) (4) were (b) (4) . Since S12 uses a (b) (4) a soil was not simulated on the coupon.

Reviewer Comment: *Since the study design includes a test on microbial recovery from (b) (4) , the response is acceptable.*

c. The current disinfectant effectiveness study did not include model viruses in the panel of challenge microorganism but based virucidal activity on vendor claims. The S12 facility manufactures multiple CAR-T cell products transduced by different viral vectors. In addition, there may be additional adventitious virus concerns associated with the patient/donor materials. Please justify your decision not to include model viruses in the facility's disinfectant effectiveness study. Please also provide additional information (e.g., historical experience) to demonstrate that the risk of viral contamination and cross-contamination at the Celgene S12 facility is low.

The firm stated that the S12 employs segregation to control viral product for different products. In addition, TRN-010386 proceduralizes response to vector or patient/donor material spills, which requires the use of (b) (4) or other EPA approved viral inactivation disinfectants for cleanup of spills. The manipulation of viral vector occurs inside a (b) (4) using a

(b) (4) step to minimize viral vector exposure in the facility. In addition, (b) (4) has been shown by the manufacturer to be effective against (b) (4), which is a type of (b) (4). Finally, the response included RPT-000291, which documented the evaluation of (b) (4) on (b) (4) model viruses with contact times of (b) (4). (b) (4) demonstrated (b) (4) clearance on all surfaces tested with (b) (4), respectively. (b) (4) demonstrated (b) (4) clearance on (b) (4) model viruses.

Reviewer Comment: *Based on the results from RPT-000291,* (b) (4) *demonstrated effectiveness against* (b) (4) *model viruses, including* (b) (4). *Although the study did not include a* (b) (4) *model virus, the totality of the information provided to describe the control in place to contain viral materials is acceptable.*

Computerized Systems

The major computerized systems and respective validation activities are briefly described below. These GMP regulated systems are 21 CFR Part 11 compliant. "Computer System Validation Program" (SOP-000045 v6.0, effective February 21, 2020) was included in the BLA to describe the validation lifecycle of on-premise or cloud/hosted computerized systems in compliance with Juno Therapeutics quality requirements. Post-validation changes are managed through the change control process. The SOP described in detail the phase-specific activities and requirements with User Requirement Specification, Functional Requirements Specifications, Design/Configuration Specifications, and Functional Risk Assessment as the key components of system build and validation. The BLA also provided "Celgene Computer Validation Master Plan" (IT-MP-0003 v3.0, effective August 14, 2019), which outlined a similar framework for computer system validation, implementation, and maintenance.

- (b) (4) is an integrated, off-the-shelf (COTS), platform application that provides (b) (4) capabilities to Celgene laboratories and manufacturing facilities. The system is classified as Class (b) (4) – closed system and is 21 CFR Part 11 compliant. At Celgene S12, it is used to automate laboratory processes, manages sample inventory, documents data entry/review/reporting, and maintains COI and COC in sample flow. The validation of (b) (4) performed according to IT-MP-0003 and covered under "Master Validation Plan for (b) (4)" ((b) (4)-0000001 v3, effective February 20, 2019). Per the master plan, IQ was performed by Celgene IT on all system hardware components (e.g., servers). OQ included system and functional testing at Celgene based on User Requirement and Functional Requirement Specifications. PQ included user acceptance testing conducted jointly by Celgene and the vendor. Additionally, the vendor conducted data integrity testing and was responsible for traceability requirement. Periodic review is performed on an (b) (4) basis. Validation

Summary Report for (b) (4) Release 7.0_4.0.0 was provided in the BLA ((b) (4) 0000061 v1, effective April 17, 2020) to demonstrate the current validated state of the system with the required OPQ script execution, data verification and regression testing. All requirements were met, and all defects were closed.

- (b) (4) is a COTS system used to manage global supply chain, process manufacturing, finance, and legal operations. As a GMP system, it manages inventory control, raw material disposition status, material expiry, and lot disposition status. It also facilitates transmission of COI information to the (b) (4). The system was implemented and validated by Celgene in 2009 in accordance with "Information Technology Computer Validation" (IT-SOP-2043). Additional capabilities have since been added to the Celgene S12 facility to include the following GxP modules: Inventory, Warehouse Management, Process Manufacturing, Order Management, Quality, Enterprise Asset Management, and Mobile Supply Chain Planning. The last periodic review was completed in Q4 2019. A validation summary report (EBS-0002158 v2, effective November 2019) was provided in the BLA to summarize the extensive IOPQ testing performed to validate changes made in the (b) (4) system (including its interface with (b) (4)) to support the Cell Therapy Digital Platform Commercial Backbone in preparation of (b) (4) implementation/integration at the Celgene Summit and (b) (4) sites in NJ.

- (b) (4) is an integrated, COTS system based on the (b) (4) platform to manage the production activities (i.e., manufacturing order, equipment, materials) and to allow for the execution of the electronic batch records (EBR). (b) (4) also interfaces with (b) (4) systems to allow information flow. It serves as the system of record for material use, batch review, equipment tracking, and labeling. It also maintains COI control during the manufacturing process via barcode scanning of labels to ensure correct patient material is being processed. Together with (b) (4), the two systems maintain control of material usage and expiry dating, batch management, and lot genealogy for drug products manufactured at Celgene S12. (b) (4) was originally validated (Release 1.0) in March 2019 with subsequent releases (up to Release 5.0) to introduce new functionality and EBR revisions. A high-level validation summary report for S12 (b) (4)-EBR ((b) (4)(S12)-0000104 v2, effective April 9, 2020) was provided in the BLA to demonstrate validation work performed for the (b) (4) 5.0 release.

- Global Patient Services (GPS) is a collection of cloud-based applications which are accessible through a web browser. It is used to enroll patients, schedule treatments, and manage delivery logistics. It also initiates the JOIN number and shares data with (b) (4). GPS Release 1 (R1) was originally validated in April 2018, followed by R2, R3, and R4 going live in October 2018, May 2019, and December 2019, respectively. Validation was performed in accordance with SOP-000045. A high-level validation summary report (HQ.IT.033-SR-04.01, approved on December 8, 2019), prepared by (b) (4) to support the commercial CTDP backbone release, was provided in the BLA to demonstrate the completion of IOPQ activities.

Procedures to Prevent Contamination and Cross-Contamination
Each CAR-T product is manufactured in a product-dedicated Process Suite (serviced by a dedicated AHU) using product-dedicated equipment by product-dedicated process operators. All QC tests are performed with product segregation. Within a Process Suite, only one patient lot is processed in a workstation or (b) (4) at a time with changeover and cleaning activities performed between uses. Specific shelves in an incubator are dedicated to a single patient lot. Trained operators are assigned to a specific patient lot number each processing day. All (b) (4) are labeled with electronic barcode encoding patient lot information to maintain COI. Location of in-process materials and final product is documented in the batch record and tracked in (b) (4). Material inventory is managed by the validated (b) (4) system ((b) (4)). Product-dedicated equipment is managed and tracked by the validated (b) (4) system. (b) (4) storage are divided for viral vs. non-viral use. Gowns are color-coded by product and badge access is limited to product-specific areas. Primary, secondary, and tertiary gowning procedures are in place based on potential product contact. All product-contact surfaces consist of sterile and single-use consumables. Facility and non-product contact equipment surfaces are cleaned and disinfected at specified frequency, concentration, and contact time with verified efficacy. Disinfectant effectiveness is further verified by routine EM. Personnel and material flows are unidirectional through the Process Suite. Waste materials are placed in sealed containers within secondary containers before moving through the corridor. The building and equipment are on back-up power supply. In case of a disruption, aseptic operators are to complete the process step, close all open components, and leave the materials inside the (b) (4), unless otherwise instructed, to ensure COI. Post-disruption actions are to be triaged with QA approval.

Reviewer Comment: *The procedures appear acceptable. S12 also manufactures ide-cel DP for non-USA patients. It is unclear if any segregation procedures are in place between US vs. non-US patient materials and products.* ***IR2 Comment 17*** *(below in* ***bold****) requested additional information. The response is summarized and reviewed below.*

17. **Please clarify if the ide-cel manufacture of PBMCs from non-USA patients are also processed in Process Suite (b) (4) (Room (b) (4)) and Process Support Suite (b) (4) (Room (b) (4)). Please discuss your risk assessment on the need of product segregation between intermediates and products for US vs. non-US patient products, and any related mitigation and control strategies you have implemented based on the risk assessment. Please justify your response.**

    The firm stated that non-US patient materials are received as (b) (4) PMBCs or leukapheresis, and they are processed in Room (b) (4). Controls in place include physical segregation of individual patient lots, line clearance procedures between lots, COI controls, and (b) (4) management of lot-specific operation/equipment allocation through electronic scanning transaction.

Reviewer Response: *Based on the response, there does not appear to be additional controls in place to segregate US and non-US patient materials. During the December 21, 2020 review committee meeting, the OTAT/DCGT reviewers confirmed that additional segregation control is not necessary as the US and non-US ide-cel are manufactured using the same process and stored in the same container closure system. The inherent risk associated with autologous starting materials is the same for any ide-cel product. The response is acceptable.*

Procedures for Introducing a New Product into S12 Facility

New product introduction is managed under the Global Change Control procedures. A New Product and Process Introduction (NPPI) risk assessment is conducted per STD-000049 "Risk Management" procedures and in accordance with approved protocols. Procedures (e.g., Leukapheresis receipt, cryo-storage, gowning, process flows, badge access) may be updated as required by the risk mitigation strategy. All CAR-T products manufactured in S12 are assigned a unique JOIN number. Product/process specific labels are attached to every in-process and DP containers to maintain COI.

Reviewer Comment: *Procedures are in place to introduce new CAR-T products into the S12 facility. The procedures that are already in place to prevent contamination, cross-contamination, and mix-ups (described in the previous section) appear to be adequate for multi-product production. The introduction of liso-cel will be reviewed in a future supplement. This is acceptable.*

At-Capacity Concurrent Manufacturing Scheme and Management

The current capacity in Process Suite (b) (4) is (b) (4), which requires for (b) (4). The future target capacity is (b) (4) which requires (b) (4). Patient lots are temporally segregated through Work Station and (b) (4) scheduling in advance of daily operation. Aseptic operators are similarly assigned to (b) (4) of the (b) (4). Line clearance and cleaning activities are performed between lots.

Reviewer Comment: *Refer to the Capacity Ramp Study discussed under Section 3.2.S.2.5 Process Validation and/or Evaluation.*

Environmental Monitoring

The Applicant provided SOP-003252 "Environmental Monitoring for Production Areas" v6.0 (effective May 15, 2020) and LIST-010179 "Environmental Monitoring for Process Suite (b) (4) and Process Support with Associated Airlocks" v1.0 (effective June 25, 2019) to describe the routine EM program that is currently in place at the Celgene S12 facility. The ISO (b) (4) are monitored (b) (4). (b) (4) samples are taken at (b) (4). (b) (4) is sampled continuously with (b) (4). Personnel monitoring is performed upon exiting the (b) (4) and at pre-defined steps during aseptic processing. (b) (4) sampling is performed (b) (4) operation and (b) (4) to decontamination. Routine EM for all classified areas is performed at the following frequency:

- **ISO (b) (4) /Grade (b) (4) :** (b) (4)
- **ISO (b) (4) /Grade (b) (4) :** (b) (4)
- **ISO (b) (4) /Grade (b) (4) :** (b) (4)
- **ISO (b) (4) /Grade (b) (4) :** (b) (4)

(b) (4) is sampled at a volume of (b) (4) using (b) (4) with (b) (4) . Aseptic operator monitoring is performed at pre-defined steps using (b) (4) on gloves and sleeves. (b) (4) are identified if they are recovered in the ISO (b) (4) areas or if the alert/action levels are met/exceeded in the ISO (b) (4) and ISO (b) (4) areas. (b) (4) is measured using (b) (4) that samples (b) (4) . (b) (4) samples in the (b) (4) are collected continuously with consecutive samples during operation. (b) (4) alert and action limits are presented below.

(b) (4)

(b) (4) alert and action levels are provided in the following table.

(b) (4)

Reviewer Comment: *The action limits are compliant with the* (b) (4) *"Grade" system. Per RTF Issue # 11a, Celgene agreed to implement an ISO* (b) (4) *dynamic environment surrounding the ISO* (b) (4) *to replace the original classification of ISO* (b) (4)*. The limits are acceptable.*

The Applicant also provided LIST-010179 "Environmental Monitoring Sites for Process Suite (b) (4) and Process Support with Associated Airlocks" v1.0 (Effective June 25, 2019), which illustrates the equipment, wall, floor, and door sampling locations in Process Suite (b) (4). Equipment surface viable sampling includes (b) (4) of all (b) (4) samples are taken at various locations in the ALs, passthroughs, and suites. Compared to the Process Suite where only closed system processing takes place, the number of sampling sites are significantly higher inside the Process Support Suite where aseptic manipulations occur in ISO (b) (4) with an ISO (b) (4) surrounding environment. EM coverage is also higher in the ALs.

Reviewer Comment: *The EM sampling locations appear to be adequate in number and coverage. They represent a subset from the extended sampling performed during initial 2018 EMPQ, including all locations that had* (b) (4) *excursions during the 2018 EMPQ. The sampling locations inside the Process Suite* (b) (4) *(Room* (b) (4)*) resembled those from the 2019 requalification.*

3.2.A.2 Adventitious Agents Safety Evaluation

The risk of adventitious agent contamination is controlled through adventitious agent testing performed on the LVV starting materials, raw material certification and testing, manufacturing environmental monitoring and control, facility and equipment sanitization/decontamination, and procedures in place to minimize the risk of contamination and cross-contamination.

Reviewer Comment: *I defer the evaluation of LVV starting material and raw materials in terms of adventitious agents' safety evaluation to the OTAT/DCGT reviewers. Refer to Sections 3.2.A [*(b) (4) *] and 3.2.A [Celgene] for facility and equipment review and discussions.*

- **Viral Clearance Studies**

No viral clearance studies related to the manufacturing process were provided.

Reviewer Comment: *I defer the evaluation of viral clearance studies to the OTAT/DCGT reviewers.*

3.2.A.3 Novel Excipients

There are no novel excipients used in the ide-cel DP.

3.2.R Regional Information (USA)

- **Executed Batch Records**

The executed batch record for the following anti-BCMA02 CAR LVV manufacturing operations were provided for PPQ Lot (b) (4) .

Unit Operation	Batch Record Number
(b) (4)	(b) (4)
Final Filling	
Stability (b) (4)	

In addition, a compilation of Ide-cel manufacturing batch records for PPQ Lot (b) (4) were provided. The BLA also included unexecuted batch records to reflect the updated, post-PPQ controls described in Sections 3.2.S.2.2 [LVV], 3.2.S.2.4 [LVV], 3.2.S.2.2 [Cell], 3.2.P.3.3 [Cell]. The following unit operations and associated batch record number were included:

(b) (4)

Drug Product Cryopreservation	(b) (4)
(b) (4) Preparation	(b) (4)

Reviewer Comment: *I reviewed the process parameters and in-process controls which are under DMPQ purview, as well as the processing steps in each unit operation, EM documentation, line clearance requirements, and equipment release and use activities. The batch records at both facilities appear to be paper-based. Comments about the Master Batch Records are provided throughout the review memo under the relevant sections. Overall, the representative batch records are acceptable from a DMPQ perspective.*

- **Method Validation Package**

Release method SOPs and method qualification/validation reports are provided.

Reviewer Comment: *I defer method validation review to the OTAT/DCGT and DBSQC reviewers.*

- **Combination Products**

The ide-cel DP is not considered a combination product.

- **Comparability Protocols**

No comparability protocols are included in the application.

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

Reviewer Comment: *I defer the review of environmental assessment or Categorical Exclusion to the OTAT/DCGT reviewer.*

B. Labeling Review
Full Prescribing Information (PI):

Reviewer Comment: *I defer labeling review to the APLB reviewer.*

Modules 4 and 5
Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

Reviewer Comment: *I defer the review of analytical procedures and their validation for assessment of clinical and animal study endpoints to the OTAT reviewer.*