BLA STN 125736

ABECMA
Idecabtagene vicleucel

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1. BLA#: STN 125736

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
UNII Code:	8PX1X7UG4D
NDC Codes:	59572-515-01, 59572-515-02, 59572-515-03

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Pharmacological category:	BCMA-directed genetically modified autologous T cell immunotherapy
Dosage form:	Cell Suspension for Infusion
Strength/Potency:	300 - 460 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 with an immunomodulatory agent, a proteasome inhibitor, and/or an anti-CD38 antibody

5. MAJOR MILESTONES

BB-IND 16664 initial submission:	September 30, 2015
BB-IND 16664 Orphan Drug Designation:	May 11, 2016
BB-IND 16664 Breakthrough Therapy Designation:	November 14, 2017
BB-IND 16664 Pre-BLA Meeting:	December 12, 2019
BLA 125736 received:	July 27, 2020
BLA 125736 filed:	September 21, 2020
BLA 125736 Mid-cycle meeting:	November 19, 2020
BLA 125736 Late-cycle meeting:	January 29, 2021
BLA 125736 PDUFA action date:	March 26, 2021

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Anna Kwilas, Ph.D.; CBER/OTAT/DCGT/GTB	Ide-cel manufacturing process and process validation
Jakob Reiser, Ph.D.; CBER/OTAT/DCGT/GTIB	Anti-BCMA CAR lentiviral vector (LVV)
Jessica Chery, Ph.D.; CBER/OTAT/DCGT/GTB	Ide-cel analytical method validation, specifications, stability
Bo Liang, Ph.D.; CBER/OTAT/DCGT/GTB	Control of materials, adventitious agents safety, validation of analytical methods for clinical samples, categorical exclusion
Elena Gubina, Ph.D.; CBER/OTAT/DCGT/GTB	Consult review for (b) (4)
Thomas Finn, PhD.; CBER/OTAT/DCGT/CTB	Consult review for (b) (4) media

Zehra Tosun, Ph.D.; CBER/OTAT/DCGT/CTB	Consult review for (b) (4)

7. INTER-CENTER CONSULTS REQUESTED

Not applicable

8. SUBMISSION(S) REVIEWED

Date Received	Submission/amendment	Comments/ Status
July 27, 2020	125736/0	Initial submission
August 25, 2020	125736/2	LVV supplemental shipping validation
October 23, 2020	125736/11	(b) (4) & Celgene S12 704 Responses
October 30, 2020	125736/12	Response to IR #11 (CMC)
November 13, 2020	125736/17	Response to IR #11 ((b) (4))
November 13, 2020	125736/22	Response to IR #11 (LVV MCB)
December 10, 2020	125736/25	Response to IR #28 (CMC)
December 11, 2020	125736/26	Response to IR #27 (DMPQ)
December 16, 2020	125736/28	Response to IR #28 (Ide-cel analytical methods, stability)
December 30, 2020	125736/34	LVV stability data & updates on %CAR expression OOS and (b) (4) investigations
January 12, 2021	125736/36	Response to IR #38
January 15, 2021	125736/37	Response to IR #38 ((b) (4))
January 26, 2021	125736/42	Module 3 updates based on responses to CMC IRs
February 2, 2021	125736/45	Response to IR #43
February 2, 2021	125736/46	Response to IR #45 ((b) (4) records)
February 3, 2021	125736/47	Slides for Late-cycle Meeting
February 8, 2021	125736/48	Updated PI
February 12, 2021	125736/50	Response to IR #50
February 12, 2021	125736/51	Updated PI
February 26, 2021	125736/54	S12 (b) (4) capacity study interim report
February 26, 2021	125736/55	(b) (4) 483 responses
March 15, 2021	125736/61	Celgene S12 483 responses
March 17, 2021	125736/62	Agreement to DBSQC PMC
March 17, 2021	125736/63	Response to IR#62 (DBSQC)
March 22, 2021	125736/64	(b) (4) 483 responses Response to IR#63
March 22, 2021	125736/66	Response to (b) (4) 483 IR Response to (b) (4) 483 IR

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) Cell Processing System	Yes	CMC: Zehra Tosun (CBER/OTAT/DCGT/CTB) All information may be cross referenced; Consult Review acceptable
(b) (4)	(b) (4)	(b) (4) medium (without (b) (4))	Yes	CMC: Thomas Finn (CBER/OTAT/DCGT/CTB); X-(b) (4) Medium with (b) (4) ; Previously reviewed for BLA 125646, BLA 125714, acceptable.
(b) (4)	(b) (4)	CryoStor medium (CS10)	Yes	CMC: Mercy Quagraine (CBER/OTAT/DCGT/CTB) Review not needed
(b) (4)	(b) (4)	Anti-CD3/Anti-CD38 antibodies	Yes	CMC: Elena Gubina (CBER/OTAT/DCGT/GTB) All information may be cross referenced; Consult Review acceptable
(b) (4)	(b) (4)	Manufacturing facility	Yes	Refer to DMPQ memo for details (facility information also included in BLA)
(b) (4)	(b) (4)	SOPs for the (b) (4) assay used in investigational study	Yes	The assay qualification report is provided in Section 5.3.1.4. The assay is adequately qualified.

10. REVIEWER SUMMARY AND RECOMMENDATION

I. EXECUTIVE SUMMARY

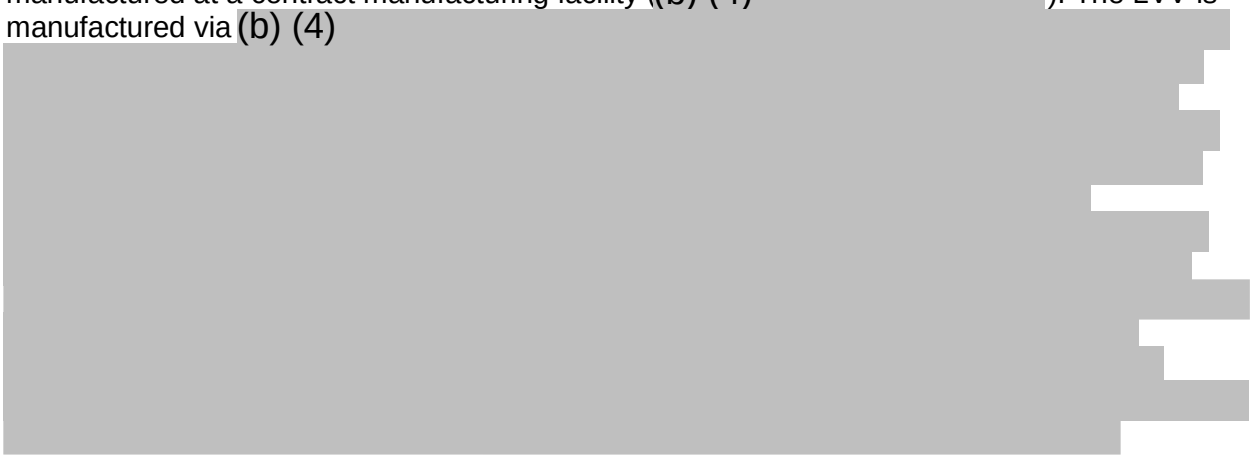
The CMC review team concludes that the manufacturing process, test methods and control measures for idecabtagene vicleucel (ide-cel; Abecma) is capable of yielding autologous products with consistent quality attributes.

Ide-cel is a genetically modified T cell immunotherapy product consisting of autologous T cells transduced with a lentiviral vector (LVV) expressing a chimeric antigen receptor (CAR) targeting the B-cell maturation antigen (BCMA). BCMA is expressed on mature B cells and plays a role in B cell survival, particularly in the setting of multiple myeloma. The CAR is comprised of a murine extracellular single-chain variable fragment (scFv) specific for BCMA, a human CD8α hinge and transmembrane domain and the 4-1BB and CD3ζ chain T cell intracellular signaling domains. Binding of ide-cel to BCMA-expressing target cells leads to signaling through the CD3ζ and 4-1BB domains, and subsequent CAR+ T cell activation. Antigen-specific activation of ide-cel

results in CAR+ T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells. Ide-cel is indicated for the treatment of adult patients with multiple myeloma who have received at least three previous therapies with an immunomodulatory agent, a proteasome inhibitor, and/or an anti-CD38 antibody.

Ide-cel is formulated at (b) (4) mL and is cryopreserved at ≤-130°C in an infusible solution composed of 50% Plasma-Lyte A and 50% CryoStor CS10. An ide-cel lot is filled into 1-(b) (4) cryopreservation bags depending on the % CAR+ T cells present in the lot. Each ide-cel lot can be filled into one of the following (b) (4) cryopreservation bag sizes: (b) (4) 50 (fill volume (b) (4) mL), (b) (4) 250 (fill volume (b) (4) mL), or (b) (4) 500 (fill volume (b) (4) mL). The bags size and fill volume are also dependent on the % CAR+ T cells present in the lot, but each lot is only filled into one bag size and each bag will contain the same fill volume. The clinically approvable commercial dose range will be 300 to 460 x 10^6 CAR+ T cells, provided as a single dose for infusion in one or more bags. The patient will receive the entire quantity of product shipped to the administration site. Ide-cel is shipped frozen in a vapor phase liquid nitrogen shipper. The number of bags necessary to meet dose, contained within individual cassettes, are secured in a metal rack within the shipper. Following receipt at the administration site, ide-cel is stored in vapor phase liquid nitrogen (≤-130°C) until the scheduled treatment time, when it is thawed and infused within 2 hours.

The anti-BCMA02 CAR LVV is a nonreplicating, self-inactivated lentivirus, based on (b) (4) . The LVV is manufactured at a contract manufacturing facility ((b) (4)). The LVV is manufactured via (b) (4)



Ide-cel drug product (DP) is manufactured using leukapheresis material collected from patients at qualified apheresis centers. The leukapheresis material is shipped to the Celgene S12 manufacturing facility (Summit, NJ) where it is inspected, and the manufacturing process is initiated. First, the leukapheresis material is washed and peripheral blood mononuclear cells (PBMCs) are isolated via (b) (4) . The PBMCs are then (b) (4) . Stability data has been provided supporting storage of the PBMCs for (b) (4) . To initiate ide-cel DP manufacture, the PBMCs are (b) (4) cultured in the presence of anti-CD3 and anti-CD28 antibodies to stimulate T cell proliferation. The cells are then transduced with the anti-BCMA02 CAR LVV and expanded in culture until sufficient cells are available to meet dose requirements (total expansion culture time is (b) (4)). The harvested DS is formulated directly to the DP with no intermediates or extended hold steps. The cells are washed and formulated in 50% Plasma-Lyte A and 50% CryoStor CS10 to (b) (4) . The appropriate volume of cells is then filled into the appropriate number and size (b) (4) cryopreservation bags based on the % CAR+ T cells

present in the lot on Day (b) (4). Filled bags are examined for appearance, placed in individual metal cassettes, then cryopreserved using a controlled rate freezer and stored at ≤-130°C in vapor phase liquid nitrogen until lot release testing is complete. The lot release testing results are used to determine the number of bags needed to treat the patient with a dose within the approved dose range. The number of bags required for administration are packaged into a vapor phase liquid nitrogen shipper and shipped to the administration site once patient administration has been scheduled. Note, during review of the BLA, the target fill volume of each bag was adjusted to account for the modification in approvable dose range. Ide-cel stability at ≤-130°C in vapor phase liquid nitrogen was determined to be 12 months. Ide-cel is stable for 2 hours after thaw at the administration site.

The ide-cel control strategy begins with material qualification. Raw materials and reagents are accepted based on specified quality attributes. Raw materials derived from animals and humans are appropriately controlled to ensure the absence of microbial contaminants and adventitious agents. Samples for lot release testing are collected at the appropriate stages in manufacture. Mycoplasma test samples are taken from the (b) (4). All other lot release testing is performed on samples taken from the final formulated DP during (b) (4). Sterility is assessed on samples (b) (4) and all other tests are performed (b) (4) of DP in QC vials. Note, during inspection of the S12 facility, it was determined that final DP sampling was taking place (b) (4) to DP bag filling and from a separate line from that used to fill the DP bags. Celgene was informed that this was not the recommended timing/method of QC sampling and was asked to modify their process. Celgene is currently evaluating an improved QC sampling process. (b) (4) Lot release test methods are suitably validated, or verified and product specifications are adequate to ensure product quality and consistency with DP used in the clinical study. Due to the autologous nature of the product Chain of Identity/Chain of Custody (COI/COC) is established at the collection site and maintained through the manufacturing process and administration by conducting label checks at specified times throughout the process.

J. RECOMMENDATION: APPROVAL

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of the new drug product idecabtagene vicleucel (ide-cel; Abecma). The CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, is capable of yielding a product with consistent quality characteristics. This information, along with post-marketing commitments (PMC) from Celgene Corporation, satisfies the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products. Based on the information provided in the BLA submission and the information gather during inspection of the (b) (4), Celgene S12 and (b) (4) QC facilities, the CMC review team recommends regular approval of this BLA.

CBER Lot release:
Ide-cel has been deemed exempt from CBER lot release testing or protocol review.

Post-Marketing Commitments
Celgene commits to conduct a comparability study between the Mycoplasma (b) (4) and (b) (4) method as per (b) (4) to provide assurance that the alternate method is equal to or greater than the assurances provided by the (b) (4) method for ide-cel. A final

study report will be provided as a Postmarketing Commitment Final Study Report by August 31, 2021.

- **COMPLETE RESPONSE (CR)**
  Not applicable

- **SIGNATURE BLOCK**

Reviewer/Title/Affiliation	**Signature and Date**
Anna Kwilas Review Committee Chair Lead Biologist OTAT/DCGT/GTB	
Jakob Reiser Research Biologist OTAT/DCGT/GTIB	
Jessica Chery Staff Fellow OTAT/DCGT/GTB	
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Raj Puri Director, Division of Cellular and Gene Therapies CBER/OTAT/DCGT	

Review of CTD

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Module 3

3.2.S Anti-BCMA CAR LVV DRUG SUBSTANCE

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

The anti-BCMA02 CAR lentiviral vector (LVV) is manufactured using a (b) (4)

(b) (4)

(b) (4)

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Anti-BCMA02 CAR LVV used to manufacture ide-cel for commercial use will be manufactured, tested, and stored at the sites listed in Table 1.

Table 1. Anti-BCMA02 CAR LVV Manufacturer, Testing and Storage Sites

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Manufacturing Step(s) or Type of Testing [Establishment Function]
(b) (4)	(b) (4)	(b) (4)	Anti-BCMA02 CAR LVV manufacture
(b) (4)	(b) (4)	(b) (4)	Anti-BCMA02 CAR LVV storage
(b) (4)	(b) (4)	(b) (4)	Anti-BCMA02 CAR LVV release test(s): RCL Anti-BCMA02 CAR LVV release test(s): (b) (4)
(b) (4)	(b) (4)	(b) (4)	Anti-BCMA02 CAR LVV release test(s): (b) (4)
(b) (4)	(b) (4)	(b) (4)	Anti-BCMA02 CAR LVV release and stability test(s): • (b) (4)
(b) (4)	(b) (4)	(b) (4)	Anti-BCMA02 CAR LVV release and stability test(s): • (b) (4) • (b) (4)
(b) (4)	(b) (4)	N/A [b]	Anti-BCMA02 CAR LVV storage
(b) (4)	(b) (4)	N/A [b]	Anti-BCMA02 CAR LVV storage

(b) (4)	(b) (4)	N/A[a]	Anti-BCMA02 CAR LVV storage

[a] (b) (4)

[b] Storage facilities which do not perform any manufacturing function are exempt for facility registration. These facilities do not conduct any manufacturing, including repacking or relabeling, and is not a controlled storage facility for GMP stability testing.

[c] (b) (4)

Reviewer Comments:
The involvement of the Storage Facilities at (b) (4) *is not clear. In response to IR#50, sent 2/5/2021, Celgene indicated in Amendment 50 that* (b) (4) *, is used to store anti-BCMA02 CAR LVV final vialed QA retains. The* (b) (4) *, Inc. facilities are long-term GMP storage facilities of final filled and released anti-BCMA02 CAR LVV vials for inventory.*

3.2.S.2.2 Description of Manufacturing Process

Anti-BCMA02 CAR LVV is produced by (b) (4)

- **Manufacturing process steps**

(b) (4)

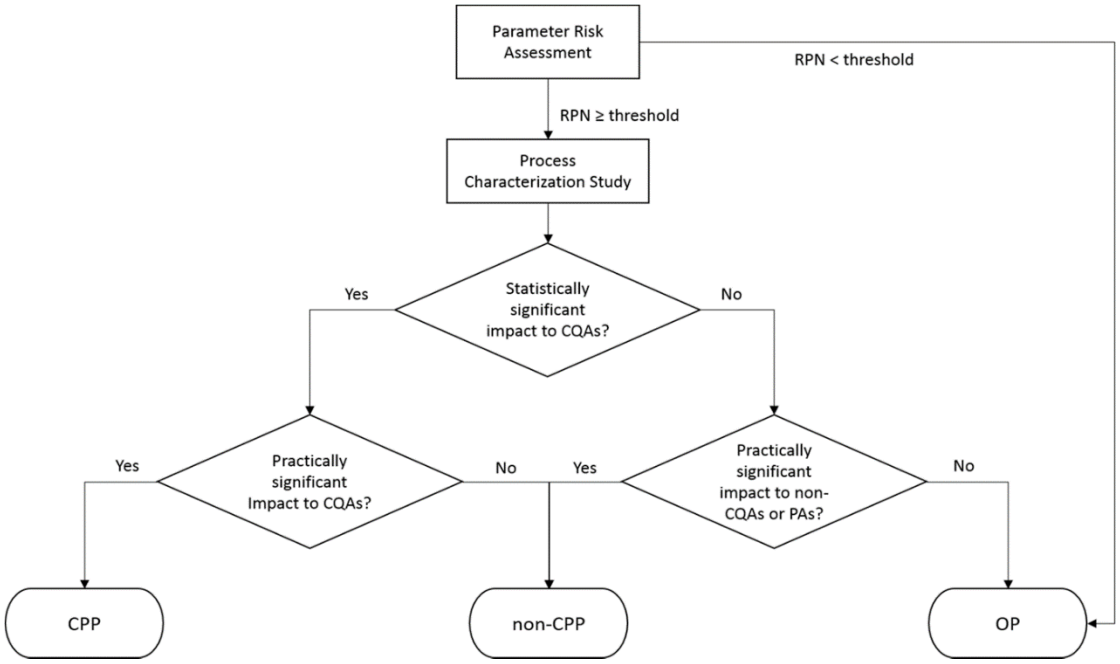
25 pages have been determined to be not releasable: (b)(4)

3.2.S.2.6.2 Process Parameter Risk Assessment and Process Characterization

Process Development and Characterization

To study and optimize process parameters for each unit operation, small-scale experiments were conducted. Parameters selected for further characterization were chosen based on a risk assessment. Parameter classification was assessed following the decision tree shown in Figure 5**.** Statistical significance was established where the correlation between the parameter and an attribute had a p-value ≤ 0.05.

Figure 5. Parameter Classification Decision Tree Based on Process Characterization Data



The majority of parameters were studied using scale-down models. In addition, studies were performed using the full-scale manufacturing process at (b) (4) in some instances either due to the quantity of LVV needed or due to scale-dependence of the parameters evaluated.

Reviewer Comments:
Data supporting comparability of the small-scale and full-scale manufacturing runs, including data on (b) (4) *unit operations* were requested in IR #38, sent on 12/28/2020.*Celgene's response, provided in Amendment #36 received 1/6/2021 is as follows:* "T*he majority of parameters were studied using these scale-down models. In some instances, studies were performed using the full-scale manufacturing process at* (b) (4) *(3.2.S.2.5 [LVV]) either due to the quantity of LVV needed or due to scale-dependence of the parameters evaluated*".

The scale-down model qualification report is provided in 3.2.R – Manufacturing Process Development – LVV – Scale-Down Models Qualification and Process Consistency Improvements Evaluation RPT-0849. The scale down model report assesses performance against full-scale clinical manufacturing lots representative of Process (b) (4)*. The scale-down model branch representative of the commercial process (Process* (b) (4)*), including additional scale-down model center point runs executed as part of process characterization studies, was*

compared against full-scale (b) (4) *data generated using Process* (b) (4)*, and the comparison is provided in 3.2.S.2.6 [LVV], subsection 6.2.2.1.*

Celgene's response is acceptable.

(b) (4)

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

(b) (4)

(b) (4)

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and Other Characteristics

3.2.S.3.1.1 Introduction

Characterization testing

Characterization testing of the structure and biological activity of LVV included determination of (b) (4) . The techniques used to characterize these attributes are summarized in Table 20.

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

(b) (4)

(b) (4)

3.2.S IDE-CEL DRUG SUBSTANCE

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

Recommended International Nonproprietary Name (INN):	idecabtagene vicleucel
United States Adopted Name (USAN):	idecabtagene vicleucel
Company or laboratory code:	bb2121; ide-cel

Ide-cel is a is a genetically modified T cell immunotherapy product consisting of autologous T cells transduced with an anti-BCMA02 CAR lentiviral vector (LVV). The anti-BCMA02 CAR LVV expresses a chimeric antigen receptor (CAR) targeting the B-cell maturation antigen (BCMA). The CAR is comprised of a murine extracellular single-chain variable fragment (scFv) specific for BCMA ((b) (4)) followed by a human CD8α hinge and transmembrane domain fused to the T cell intracellular signaling domains of CD137 (4-1BB) and CD3ζ chain, in tandem (Figure 8).

(b) (4)

Binding of ABECMA to BCMA-expressing target cells leads to signaling through theCD3ζ and 4-1BB domains, and subsequent CAR+ T cell activation. Antigen-specific activation of ABECMA results in CAR+ T cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The ide-cel DS manufacturing process consists of (b) (4) steps: (b) (4) . The site involved in (b) (4) , testing of the (b) (4) is listed Table 46.

Table 46. Ide-cel Manufacturer, Testing and Storage Sites

Site	Address	Function
Celgene Corporation (Celgene S12 facility)	Building S12 556 Morris Avenue Summit, NJ 07901	(b) (4) in-process testing DS manufacturing DS in-process testing

3.2.S.2.2 Description of Manufacturing Process

Briefly, autologous peripheral blood mononuclear cells (PBMCs) are obtained via a standard leukapheresis procedure. T cells are activated with anti-CD3 and anti-CD28 antibodies and transduced ex vivo with the anti-BCMA02 CAR LVV. After transduction, the T cells are expanded, harvested, and formulated as a cell suspension for intravenous administration. The cells harvested at the end of cell culture are designated as the DS.

- **Manufacturing process steps**

An overview of the ide-cel DS manufacturing process is presented in Figure 9. The ide-cel drug substance manufacturing process consists of (b) (4) major phases:

Figure 9. Ide-cel Drug Substance Manufacturing Process

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

(b) (4)

(b) (4)

Reviewer Comments:
In response to IR#11, sent 10/19/2020, Celgene indicated in Amendment 12 that (b) (4)

Of note, for the US market, manufacturing of (b) (4) is executed at the Celgene S12 facility and forward processed for DP manufacturing within the same site. However, for the EU market, manufacturing of (b) (4) is executed at the (b) (4) in (b) (4) Celgene S12 facility for DP manufacturing.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

A unique lot number is assigned to each DP lot and associated starting material (leukapheresis) and intermediate ((b) (4) PBMCs). The lot numbering structure consists of a patient specific 10-character alphanumeric sequence (referred throughout the filing as a JOIN number), appended with a single alphabetic character (Lot Suffix) which sequentially designates associated starting material, intermediate and DP. The leukapheresis product is assigned a lot number comprised of the JOIN with an "A" appended. Subsequent intermediates and products manufactured from the leukapheresis product are numbered with the same JOIN and an increasing sequential lot suffix. The suffix assigned to any additional DP manufactured after an initial DS or DP lot using existing cryopreserved PBMCs from the same patient will use the next available sequential suffix. If the patient requires a new leukapheresis collection, a new JOIN is assigned. An example of the lot numbering scheme is shown in Table 50.

Table 50. Example Lot Number Assignments

Material	JOIN	Lot Suffix	Lot Number
Leukapheresis	(b) (4)		
(b) (4) PBMC (Intermediate)			
Drug Product			
Additional Drug Product from the same PBMC Intermediate			

Reviewer Comments:
In response to IR#11, sent 10/19/2020, Celgene clarified in Amendment 12 that suffixes (b) (4) are reserved for pre-manufacturing components that are not utilized in the ide-cel manufacturing process. Manufacturing components (i.e., PBMC intermediate, DP) are assigned a suffix (b) (4), sequentially.

Chain of Identity (COI) is described in **Section 3.2.S.2.5 Process Validation and/or Evaluation**.

- **Storage and Shipping**

(b) (4)

3.2.S.2.3 Control of Materials
3.2.S.2.3 Control of Materials – Raw Materials

Raw materials used in the manufacturer of the ide-cel are sourced from Celgene qualified suppliers. The qualification of incoming raw material is managed by established procedures that utilize specifications including full and reduced testing requirements. Raw materials are qualified by performing the full testing on a minimum of (b) (4) lots using validated methods. Once qualified, a

reduced testing may be conducted for subsequent lot release. To demonstrate the continued suitability for use in manufacturing, qualified materials are subjected to the full testing (b) (4) .

Raw materials are categorized based on risk assessments according to the (b) (4) classification for ancillary material used in cell manufacturing. (b) (4) risk tiers ((b) (4)) are categorized from low to high risk levels according to (b) (4) .

Incoming raw materials are quarantined and released by QA for use in manufacturing following QC testing. The raw material is assessed (by visual inspection, COA review, and performing tests) according to internal material specifications prior to acceptance for use in product manufacturing. The rationale for the intended use in manufacturing and justification of the full and reduced testing strategy are described in the Justification of Specification (JOS) documents for all raw materials.

Reviewer comments:
JOS documents for all raw materials were requested in IR#28, sent on 11/19/2020, and were submitted in Amendment 25. JOS documents for all raw materials have been reviewed and the raw material specifications are acceptable.

(b) (4) **Reagents and Media Components**
Plasma-Lyte A and (b) (4) are clinical-grade materials and are both approved by FDA for intravenous infusion.

Plasma-Lyte A Injection pH 7.4 (Plasma-Lyte A) is used for the manufacturing of ide-cel and is present in the cell infusion product. It is a salt solution supplied by (b) (4) that contains sodium, potassium, magnesium, and chloride ions and contains no antimicrobial agents. Plasma-Lyte A is an FDA and Health Canada approved human prescription drug that meets the USP monograph requirements for Multiple Electrolytes Injection, Type 1. The internal release testing includes visual examination of the appearance and identity test per (b) (4) requirement.

(b) (4)

(b) (4) **Reagents and Media Components**

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

(b) (4) reagents and media components of biological used in the manufacture of ide-cel are listed in the Table 51. These materials are accepted upon visual inspection, COA review, and in-house testing with validated tests. Representative quality documents (COA, COO, BSE/TSE certificate) are provided.

Table 51: (b) (4) Reagents and Media Components of Biological Origin Used in Ide-cel Manufacturing

Raw Material	Abbreviation / Common Name	(b) (4)	Unit Operation
(b) (4)			

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

(b) (4)

- **Control of Raw Materials NOT of Biological Origin**

(b) (4) reagents and media components of non-biological origin are listed in Table 52. Upon receipt, the incoming materials are tested with validated test methods as indicated.

Table 52. (b) (4) **Reagents and Media Components of Non-Biological Origin Used in Ide-cel Manufacturing**

Raw Material	Abbreviation / Common Name	(b) (4)	Unit Operation	In-house Testing
(b) (4)				

3.2.S.2.3 Control of Materials – Inert Materials

A list of media preparation and product contacting consumables used in the manufacturing of ide-cel are provided in Table 53. All materials listed are sterile and free of animal-derived components. Product contacting consumables were subjected to a risk analysis, and where appropriate, extractable and leachable testing was conducted as described in **Section 3.2.S.2.5 Process Validation and/or Evaluation**. All inert materials listed are deemed suitable for use in the ide-cel manufacturing process.

Table 53. List of Inert Materials Used in Ide-cel Manufacturing

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

In response to IR#28, sent 11/19/2020, specifications for all inert materials were submitted to the BLA in Amendment 25. Quality testing for all incoming inert materials include visual examination and verification of COAs.

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

3.2.S.2.3 Control of Materials – LVV
Control of material information for the anti-BCMA02 CAR LVV is described in **Section 3.2.S.2.3 Control of Materials.**

3.2.S.2.3 Control of Materials – Leukapheresis
Ide-cel autologous PBMC starting material is collected according to written procedures outlining the equipment, equipment settings, materials, run targets, subject identity verification, labeling, and packaging required for the leukapheresis unit. The leukapheresis unit is collected using one of the following FDA cleared automated blood cell separator devices and associated sterile disposable apheresis kits:

- (b) (4)

Prior to initiating the collection, patient identity is verified and the leukapheresis collection bag is labeled with patient identifiers. During the collection, (b) (4) is added to prevent coagulation. The whole blood target volumes are as follows:

- (b) (4)

A minimum of (b) (4) is collected in the sealed collection bag. Immediately following collection, the leukapheresis bag is packaged as outlined below, and shipped to the manufacturing facility. The bag is sealed and the labeled bag is placed in a tamper-proof and leak-proof secondary containment bag with absorbent material. The packaged leukapheresis unit is then placed in a qualified temperature-controlled shipper preconditioned to (b) (4). The established shipping procedure has been validated. Please see DMPQ review for additional details on the shipper validation. The leukapheresis unit can be held at (b) (4) for up to (b) (4) as supported by leukapheresis age studies in proceeds characterization study in **Section 3.2.S.2.6 Manufacturing Process Development**.

The shipper containing the leukapheresis unit is transported by courier to the Celgene manufacturing facility. Upon receipt at the manufacturing facility, the leukapheresis unit is inspected to ensure chain of identity (COI) and product integrity. Upon acceptance, the leukapheresis unit is transferred to the manufacturing suite for PBMC Isolation. The PBMC starting material is collected at qualified centers by qualified staff with adequate education, training, and experience as required by state and local requirement for this activity. Leukapheresis collection facilities are qualified by Celgene through the initial qualification audit to evaluate compliance with Celgene's requirements and applicable sections of 21 CFR Part 1271. Each collection center must complete the following site readiness activities prior to performing leukapheresis collections for Celgene:

- Sign a contract that specifies the services to be rendered and commitments for compliance with quality, regulatory, and legal requirements
- Establish a procedure to meet Celgene's requirements for labeling, collecting, sealing, packaging, shipping, and documenting leukapheresis collections

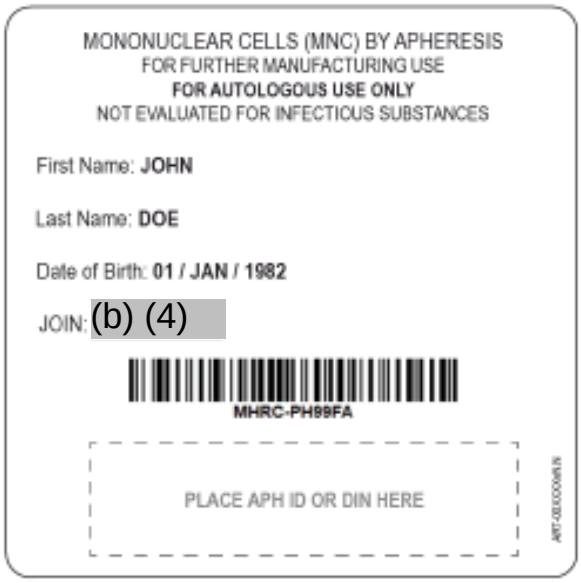
- Complete Celgene-provided training on Celgene-specific procedures for verification of subject identity, labeling, equipment settings, run targets, sealing the collection bag, packaging, and shipping the leukapheresis unit

A list of the collection facilities that were qualified to perform leukapheresis collections for the pivotal trial BB2121-MM-001 in the U.S was provided. Celgene stated that commercial collection facilities will be approved in accordance with the currently established criteria.

Reviewer Comments:
In IR#28. sent 11/19/2020, Celgene was asked to provide a description of the qualification audit, the requirements for the collection, labeling, packaging, shipping, and documentation of the leukapheresis material and the training provided and indicate how often each facility undergoes requalification. In Amendment 25, Celgene indicated that the audits are conducted to demonstrate the site's ability to comply with relevant sections of 21 CFR Part 1271, the Celgene collection protocol requirements, and the Quality Agreement. Each year, sites are assessed on past collection performance and all sites undergo a requalification audit at least once every three years. An outline of the training was provided. Initial training will be delivered by a Celgene qualified trainer and may be provided on-site or via web/teleconference. After the initial training has been provided, Collection Centers are responsible for on-going staff training on the Celgene collection process.

The leukapheresis bag label (Figure 10) will either be printed by Celgene and shipped to the Collection Center prior to the collection date or printed at the Collection Center using Celgene's web-based Apheresis Portal, part of the Global Patient Services (GPS) system, on label stock provided by Celgene. Prior to initiating the collection and in the presence of the patient, the site verifies the spelling of the patient's first and last name as well as date of birth. After collection, the bag is sealed per leukapheresis collection instructions, placed in a tamper-proof and leak-proof secondary containment bag with adequate absorbent material. The packaged leukapheresis unit is then placed in a qualified temperature-controlled shipper preconditioned to (b) (4) *. Collection Centers document patient specific collection information in Celgene's web-based Apheresis Portal or on the MNC Collection Procedure Record Form. See* ***Section 3.2.S.2.5 Process Validation and/or Evaluation*** *for additional details on COI.*

Figure 10. Example Leukapheresis Bag Label



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

- *Celgene provided adequate information for materials and reagents used in the manufacturing of ide-cel.*
- *The justification of specification (JOS) for materials and reagents used in the ide-cel manufacturing were not submitted. A request for JOS was sent in IR 28. Celgene submitted the JOS as requested in the Amendment 25. More detailed descriptions of the incoming material qualification tests and the acceptance criteria are available in the JOS.*
- *It is noted that the* (b) (4) *is not* (b) (4) *. The control for blood-borne pathogens in the* (b) (4) *is accomplished by screening and testing at the individual donation level and the* (b) (4) *plasma level.*
- *Control of the PBMC starting material is adequate.*

3.2.S.2.4 Controls of Critical Steps and Intermediates

DS manufacturing process

The CPPs, nCPPs, IPCs and hold times for the ide-cel DS manufacturing process are listed in Table 54, Table 55, Table 56, Table 57, and Table 58, respectively. Excursions of CPPs, IPCs, hold times and processing times will be investigated as part of a deviation. Any failure in IPCs with defined acceptance criteria would result in batch/solution lot rejection. Any failure in IPCs with defined action limits will be assessed for impact to product quality and investigated within the quality system prior to batch disposition. The criticality, acceptable range and/or action limits presented were based on the risk analysis and experimental work performed as part of the process characterization studies described in **Section 3.2.S.2.6 Manufacturing Process Development**. The parameters were examined using 1 or more lot manufactured from normal healthy donor starting material, and the data to support these ranges (e.g., study reports) were provided.

Reviewer Comment: The tables below have been updated based on the interactions with Celgene during the BLA review. Details on the IRs sent, and the changes made in response are described in ***Section 3.2.S.2.6 Manufacturing Process Development****.*

(b) (4)

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

(b) (4)

Overall Reviewer's Assessment of Section 3.2.S.2.4:
The proposed process controls are supported by data and are adequate to ensure consistent DS quality.

3.2.S.2.5 Process Validation and/or Evaluation
Process Validation and/or Evaluation Overview
Ide-cel process validation was composed of 2 process validation studies and a Extractable and Leachable Risk Assessment.

Process validation
Two ide-cel PPQ campaigns were performed. The first PPQ campaign covered the process from leukapheresis receipt through ide-cel DP manufacture. For this campaign, (b) (4) PPQ lots were executed end-to-end at the Celgene S12 facility. The second PPQ campaign consisted of 3 runs using (b) (4) PBMCs manufactured at the (b) (4) facility as starting material. The data from the second campaign was provided as additional supporting data for ide-cel manufacturing consistency and the commercial filling strategy.

For the initial PPQ campaign, (b) (4) consecutive DP lots were manufactured from (b) (4) different (b) (4) PBMC lots (Figure 11). (b) (4) of the PPQ DP lots were executed utilizing PBMCs from (b) (4) . The other (b) (4) PPQ DP lots were executed utilizing PBMCs from (b) (4) different (b) (4) . (b) (4) 50 bags were filled at a target fill volume ((b) (4)) for each of the (b) (4) PPQ lots. Filling a max number of bags within the allowed DMSO exposure time represented a worst-case scenario in terms of processing time durations. (b) (4) lots of (b) (4) Media and (b) (4) Anti-BCMA02 CAR LVV lots were used for the PPQ campaign. The LVV lots were manufactured at (b) (4) and were tested with validated commercial analytical methods.

Reviewer Comment: Following execution of the PPQ campaign, a deviation related to one of the LVV lots (BMS Lot # (b) (4) , corresponding to (b) (4) Lot # (b) (4)) was discovered. An insufficient amount of (b) (4) cells was provided for RCL testing. (b) (4) testing was negative. This should not affect the ide-cel PPQ.

(b) (4)

The PPQ runs met acceptance criteria for CQAs and CPPs as defined in the PPQ protocol (Table 60, Table 61, respectively).

Table 60. Critical Quality Attribute Results for PPQ Runs

		Individual (b) (4)			**Same** (b) (4)			
Attribute	**Acceptance Criteria**	(b) (4)						
Appearance	Liquid, colorless cell suspension	Liquid, colorless cell suspension	Liquid, colorless cell suspension	Liquid, colorless cell suspension	Liquid, colorless cell suspension	Liquid, colorless cell suspension	Liquid, colorless cell suspension	Liquid, colorless cell suspension
CAR T cell Percentage	(b) (4)							
Viability								
T cell Purity								
Cell Concentration								
Endotoxin								
Sterility								
Mycoplasma								
(b) (4)								

CAR T cell Activation (Potency)	(b) (4)
Dose	(b) (4) × 10^6 CAR+ T cells (b) (4)

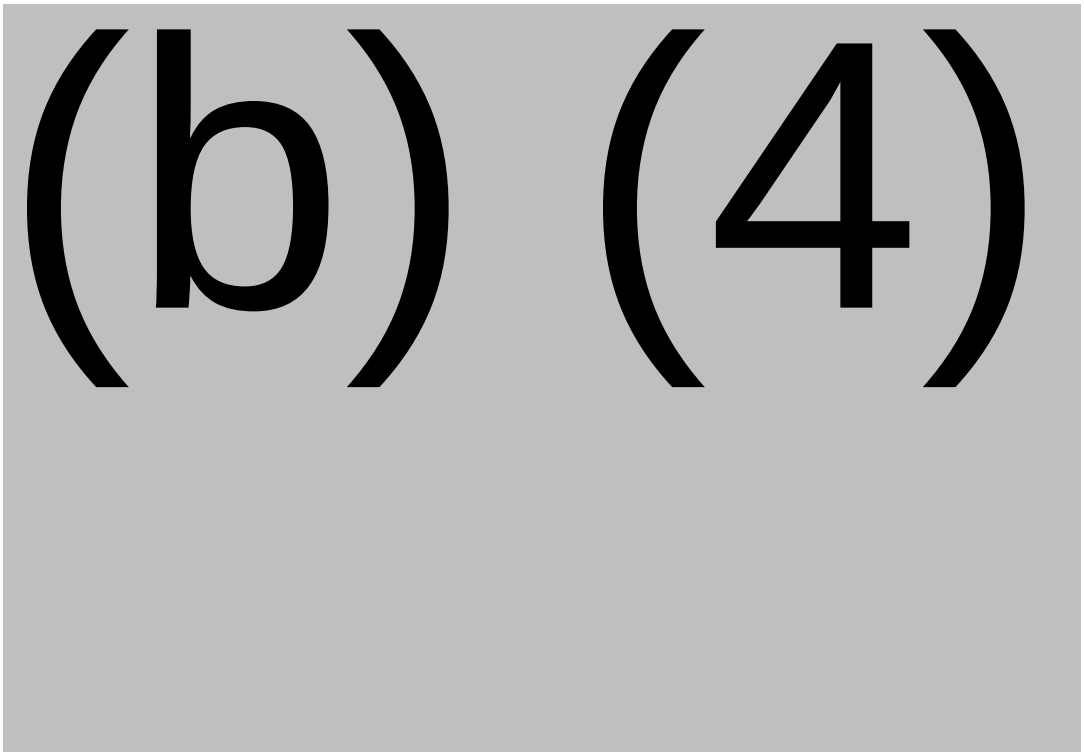
Reviewer Comments:
CQAs were within the Study BB2121-MM-001 clinical experience, inclusive of both S12 and (b) (4) *sites, as well as the Celgene S12 historical pre-PPQ clinical experience. All lots also met proposed and agreed upon commercial lot release criteria.*

Table 61. Critical Process Parameter Results for PPQ Runs

			Individual (b) (4)	Same (b) (4)
Unit Operation	**CPPs**	**PAR**	(b) (4)	
(b) (4)				

The results from monitoring of IPCs. processing times, non-CPPS, and PCPs were also provided. All IPC results met predefined acceptance criteria and action limits: (b) (4) test; PBMC total cells (b) (4)), viability (b) (4) and sterility; final PBMC cell concentration ((b) (4));(b) (4) PBMC cell concentration (b) (4)); post-final adjustment cell concentration ((b) (4) ; only performed for (b) (4)). All nCPP results were within the PARs (Table 55). All PCP results were within the control limits. With one noted exception, all hold and processing times also met the predefined acceptance criteria (Table 58, Table 59). The deviation in (b) (4)

and Activation Duration is described in more detail below. The growth profile of the PPQ lots is summarized in Figure 12.



A list of all deviations encountered during the PPQ runs, the root cause analyses, CAPAs, and effects on PPQ was provided.

- Atypical (b) (4) observed in assay control (all lots except (b) (4)): didn't affect CAR frequency
- Personnel Monitoring Action Level Excursion during Harvest QC Activities ((b) (4)): did not affect final product sterility testing
- (b) (4) assay run file unreadable: (b) (4) retested
- Incorrect cell concentration utilized for (b) (4) calculation: (b) (4) retested
- Day (b) (4) QC (b) (4) Atypical Result ((b) (4)): atypical result was due to an instrument error
- (b) (4) in S12QC Laboratories missed (b) (4) qualification (all lots): qualification was passed following PPQ performance
- (b) (4) and Activation Duration exceeded (b) (4). ((b) (4)): an extended total initiation time was evaluated. The study performed under this CAPA determined that there was no impact to DP CQAs at a (b) (4) time point and up to (b) (4) .
    - *Reviewer Comments: In IR#28, sent 11/19/2020, additional information on this deviation was requested. In Amendment 25, Celgene provided additional data from 1 PBMC lot supporting an acceptable culture initiation time up to* (b) (4)*. However, due to the statistically significant effect on CD137 Activation and cumulative PDL, Celgene was asked to tighten this range to* (b) (4) *in IR#38, sent 12/28/2020. Celgene agreed to tighten the range in Amendment 36.*

The PPQ batches were also subjected to impurity testing to demonstrate clearance of process-related impurities (Table 62) and a profile of product-related impurities consistent with the ide-cel clinical experience.

Reviewer Comments:
Residual (b) (4) *was not evaluated because an assay capable of accurate detection in the DP matrix could not be identified. Residual anti-CD3 and Anti-CD28 antibodies were not evaluated because the amount added to the process was considered below the exposure limit. Please see further discussion of these issues in* ***Section 3.2.S.2.6 Manufacturing Process Development.***

Table 62. Summary of Process-Related Impurities Evaluated During PPQ Campaign 1

Process Related Impurities	Acceptance Criteria (Measured in DP)	Amount measured in DP	Log Reduction of Impurity by Mass
(b) (4)			

(b) (4) were also tested in the (b) (4)

Product related impurities (e.g., (b) (4)) were evaluated and found to be very low and well within the (b) (4) . (b) (4) residual tumor cells and % hematopoietic stem/progenitor cells were both below the lower limit of quantification ((b) (4) , respectively).
Extended characterization of the PPQ lots was also performed and was shown to be consistent with the ide-cel clinical experience (Table 63).

Table 63. Summary of Extended Characterization Performed During PPQ Campaign 1

Characterization Attribute	Clinical Experience (Min/Max)	DP Lot: (b) (4)	DP Lot: (b) (4)	DP Lot: (b) (4)	DP Lot: (b) (4)	DP Lot: (b) (4)	DP Lot: (b) (4)	DP Lot: (b) (4)
(b) (4)								

(b) (4)

For the second PPQ campaign, 3 PPQ runs were executed at Celgene S12 (Suite (b) (4)) using (b) (4) PBMC lots generated at (b) (4) from (b) (4) leukapheresis units. A total of (b) (4) Media lots and (b) (4) Anti-BCMA02 CAR LVV lots were used for the PPQ campaign. This PPQ focused on validating the filling strategy for the (b) (4) 250 bags. The filling strategy was designed to fill (b) (4) 250 bags at target fill volume of (b) (4). This is the maximum fill volume for this bag size based on the proposed commercial filling strategy.

For this PPQ campaign, all PBMC lots met both the proposed Celgene and (b) (4) release specifications. The PPQ lots met all predefined PPQ CQA acceptance criteria and the proposed commercial release specifications. In addition, CPPs, IPCs, nCPPs, PCPs and processing times were within their respective limits and/or ranges as defined in the PPQ protocol. A consistent cell growth profile was also observed. The PPQ runs were also negative for RCL (no other extended characterization data was provided).

A list of all deviations encountered during execution of the PPQ runs was provided. Of note, a (b) (4) leak was observed (lot #(b) (4)) and only (b) (4) bags were filled and fewer retain vials were filled for lot #(b) (4) due to a lower final formulated DP volume.

Reviewer Comments:

CQAs from PPQ Campaign #2 were within the Study BB2121-MM-001 clinical experience, inclusive of both S12 and (b) (4) sites, in addition to the Celgene S12 historical pre-PPQ clinical experience. Overall, the data provided supports a consistent, robust manufacturing process.

Following execution of the PPQ batches, the Failure Mode Effect Analysis (FMEA) risk assessment of the ide-cel DP manufacturing process was updated and the proposed process control strategy for the commercial process was established.

(b) (4) Homogeneity and Hold Time Validation

(b) (4)

(b) (4)

Process Validation and/or Evaluation -Extractable and Leachable Risk Assessment
A risk assessment was performed for product-contacting materials used in the ide-cel manufacturing process based on proximity to the DP, relation to the wash steps, interacting solvent, duration of contact, contact surface area, and temperature of the solution. Extractable testing was conducted on materials considered to be at the highest risk of contributing impurities to the DP, via (b) (4) extraction studies and in-use simulation studies. In-use testing was not conducted for materials for which extractables were not identified in the (b) (4) extraction studies (Table 64).

The (b) (4) extraction studies evaluated the extractables by (b) (4) the product-contacting materials (b) (4) and subjecting them to extreme conditions: (b) (4) . The PBMC (b) (4) was not (b) (4) . Extractables data for the (b) (4) for Media ((b) (4)), Filter Assembly (b) (4), (b) (4) with (b) (4) Tubing, and the LVV Final Container, were obtained from the vendor. Volatile organics were evaluated by (b) (4) . Semi-volatile organics were evaluated by (b) (4) . Elemental impurities were evaluated by (b) (4) . Non-volatile organic analysis methods varied.

The Threshold of Toxicological Concern (TTC) of (b) (4) for a treatment duration of (b) (4) from the (b) (4) guidance was used to define thresholds for organic compounds. The limit of (b) (4) of Permitted Daily Exposure (PDE) from (b) (4) was used to define thresholds for elemental impurities.

Table 64. High-Risk Raw Material Groups Selected for Extractable/Leachable Evaluation

Raw Material Group	Specific Material
Media Preparation Consumables	
(b) (4)	(b) (4)
Filter Assembly (b) (4)	Filter Assembly (b) (4)
(b) (4) Storage (b) (4)	(b) (4)
Product Contact Consumables	
PBMC (b) (4)	(b) (4)
LVV Final Container	LVV Final Container
Cell Culture Initiation (b) (4)	(b) (4)
Cell Expansion (b) (4) (Various Volumes)	Cell Expansion (b) (4) (Various Volumes) ((b) (4))
(b) (4)	(b) (4)
Transfer Pack (various volumes)	Transfer Pack (Various Volumes) ((b) (4))

Harness (multiple lead amounts)	Harness (multiple lead amounts) ((b) (4))
Transfer Set	24" Plasma Transfer Set with Two Spikes ((b) (4))
Harness (multiple lead amounts)	Harness (multiple lead amounts) ((b) (4))
(b) (4) (various volumes) (PBMC (b) (4)	(b) (4) (various volumes) ((b) (4))

a Filter assembly results include both filter and filter housing.

b The PBMC (b) (4) listed here is the same material as the DP final container listed in section **3.2.P.2.4**. Solely its use as a PBMC (b) (4) and an intermediate (b) (4) upstream of final DP container will be shown within this section, and solely its use as a DP container will be shown in the alternate section. However, all impurity contributions by the (b) (4) throughout the process were considered within this study.

Multiple extractables above the set limits (non-specific TTC) were identified in the extractables study for the following materials: (b) (4), Transfer Pack (Various Volumes) ((b) (4)), Harness (multiple lead amounts) ((b) (4)), 24" Plasma Transfer Set with Two Spikes (b) (4) (various volumes) (PBMC (b) (4)). Extractables above TTC included semi-volatile, non-volatile, and unidentified compounds plus elemental impurities. The amount of extractables extracted per dose for the filter did not surpass the recommended non-specific TTC (b) (4), although the amount extracted per material did surpass the threshold for organic compounds.

Reviewer Comments:

In response to IR#28, sent 11/19/2020, Celgene provided the PDE for an elemental impurity ((b) (4)) identified in the (b) (4) extraction studies and additional information about elemental impurities identified in Amendment 25. Elemental impurities identified in the extractable and leachable studies did not exceed the PDE or TTC (mg/dose) limit, and had (b) (4) fold margin of safety (MOS = PDE/Estimate Maximum Exposure). For elemental impurities without a PDE in (b) (4), and FDA guidances or human dietary guidelines, a toxicologist established those PDEs. The (b) (4) PDE was established by extrapolation to humans from preclinical rat studies. The (b) (4) PDE was established from human studies. PDE for other impurities ((b) (4)) was based on TTC of (b) (4) (adjusted for less than lifetime exposure). Celgene also clarified that compounds listed as "unknown" in the extractables studies did not match any compound in the reference library used in the extractable study. These compounds were characterized by their (b) (4) using (b) (4). However, none of the unidentified compounds above the evaluation thresholds in the (b) (4) extraction studies were detected above evaluation thresholds in the in-use simulation studies. Celgene stated that the ide-cel manufacturing process does not incorporate specific chemically mediated transformations that form (b) (4) compounds. Therefore, the unknown compounds are unlikely to be from the cohort of concern, and there is a low risk for the presence of compounds from the cohort of concern in the ide-cel DP. This is acceptable.

Leachables stimulation testing was performed on materials that generated extractables above safety thresholds: (b) (4) (various volumes), Transfer Pack (various volumes), 24" Plasma Transfer Set with Two Spikes, Harness (multiple lead amounts), and the (b) (4) Disposable Kit. Leachables simulation testing used mildly exaggerated temperature and duration conditions based on materials' worst-case process exposure determined from the extractables study ((b) (4)). The total quantity of each raw material used was integrated into calculating the maximum amount of leachable in the ide-cel DP. For materials with multiple sizes, only one size was

tested and those results adjusted based on surface area and volume to calculate the maximum amount leached per dose.

Two of the materials tested resulted in leachables above the TTC (b) (4) or (b) (4) PDE limit: the transfer pack ((b) (4)) and (b) (4) disposable kit ((b) (4)). One compound ((b) (4)) exceeded the non-specific TTC of (b) (4). For the impurities that exceeded (b) (4) TTC or the (b) (4) PDE limit, a compound-specific TTC or PDE was established by a toxicologist.

Celgene concluded that, while the levels of these leachables were above the threshold levels in one dose of DP, based on a calculation of the margin of safety [difference between the maximum amount in one dose of DP and the levels from the toxicologist established PDE or TTC], the maximum exposure from a one-time intravenous dose of the DP is several folds lower than the specification limit set by TTC or PDE. Additionally, subjects are likely to have significantly higher exposure to these leachables through daily exposure, than would be exposed to in one dose of the DP.

Reviewer Comments:
In response to IR#28, sent 11/19/2020, Celgene provided the methodology and considerations used by the toxicologist (Amendment # 25) to establish the compound specific exposure limits (PDEs) for leachables above TTC: (b) (4) *. The PDEs were established on a per-compound basis using the procedure in* (b) (4) *and calculated using no-observed-adverse-effect-level (NOAELs) data from preclinical (rat and rabbit) studies. The PDE for the elemental impurity,* (b) (4)*, was established per* (b) (4) *guidance (*(b) (4) *). This is acceptable.*

Extractable/Leachables testing of the ide-cel final, (b) (4) , is reviewed in **Section 3.2.P.2.4 Container Closure System** of this memo.

Chain of Identity (COI) Validation

A comprehensive chain of identity (COI) control strategy, that makes use of electronic systems, risk assessment, and procedural controls (SOPs), has been established to ensure in-process material, ide-cel DP, and QC sample COI is maintained across all operations from leukapheresis collection to administration. At every step, from leukapheresis collection to administration of the final DP, COI is checked and verified prior to execution of subsequent processing. COI controls are supported by the Global Patient Services (GPS) computerized system. GPS captures the patient identifiers at the time of enrollment (patient name, date of birth, subject number), generates the JOIN at scheduling, maintains the link between patient identifiers and the JOIN, and generates the apheresis labels (collection bag, shipper labels) containing the JOIN. Prior to the arrival of the leukapheresis material at the S12 facility, manufacturing orders are created that contain the batch numbers for the leukapheresis material, the (b) (4) PBMC intermediate and the final DP (all containing the JOIN). Labels are generated for all in-process, final product and QC samples that are scanned throughout the manufacturing process. A summary of the COI strategy is provided in Table 65.

Table 65. Chain of Identity Checkpoints

Process Step	COI Controls	COI Information
Leukapheresis Collection	• Patient medical records • Apheresis Portal • Government-issued photo ID • Verbal verification from patient	Patient-identifying information verified against the certificate of conformance or collection procedure record, including:

	• Certificate of Conformance *(or Collection Procedure Record)*	• JOIN, unique identifier assigned and used to maintain COI throughout production • Patient first and last name • Patient date of birth Identity verified on the collection bag labels, Schedule Confirmation Form, shipping labels during every step of collection/packaging.
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
(b) (4) Intermediate Shipment/Receipt	• 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 number
Leukapheresis Wash / Isolation through DP 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 LN_2 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
DP Pack Out	• Validated manufacturing and laboratory electronic systems • In-process labels (Primary vessels, secondary containment) • Storage location in LN_2 Freezer • Product Order Confirmation Form (POCF) • Shipper expiration label • Shipping waybill	DP and location in LN_2 Freezer are labeled to ensure the correct product is removed and transferred to the LN_2 Shipper, and verified against patient information on the POCF, including: • JOIN • Patient first and last name • Patient date of birth • Shipping address
Receipt of DP at Treatment Site to Patient Administration	• Release for Infusion Certificate • Primary vessel • Secondary containment (i.e. cassette) • Product Order Confirmation Form (POCF) • Medical records	Patient information is verified upon receipt, transfer to on-site storage, product thawing, and immediately prior to infusion against manufacturing and DP information by 2 site staff to ensure COI was maintained throughout production and shipping, including:

	• Hospital patient identification band • Verbal verification from patient	• Patient first and last name • Patient date of birth • Subject number • JOIN • Manufacturing lot number

To validate the COI, a protocol inclusive of all end-to-end controls was executed to demonstrate the effectiveness of the overall COI strategy. The protocol captured all COI checks intended to be executed at the leukapheresis centers, manufacturing sites, and infusion centers, for 3 clinical runs.

Production Capacity

The production capacity at the S12 facility during ide-cel clinical investigation was (b) (4) culture initiations per (b) (4). In order in increase capacity, a Readiness Assessment, Capacity Test and Capacity Evaluation are performed. These procedures evaluate all direct and indirect activities and functions required to successfully complete manufacturing, quality operations, product release, and shipment preparation of patient material in a suitable timeframe. The capacity test consists of clinical ide-cel batches and non-clinical capacity test batches that are mock transduced. The non-clinical capacity test batches will undergo all routine lot release testing but will have "Report Results" as the acceptance criteria for transduction dependent parameters.

The results of the most recent capacity test (December 2019) were provided in the initial BLA submission (RPT-019992). This capacity test evaluated the ability of the S12 facility to perform (b) (4) culture initiations ((b) (4) clinical lots and (b) (4) non-clinical lots) and (b) (4) PBMC isolations per (b) (4). (b) (4) clinical lots were completed. However, only (b) (4) non-clinical lots were completed. Additionally, of these (b) (4) lots, (b) (4) were harvested using abbreviated operations that did not include (b) (4). This was identified as being due to unavailability of material, personnel and equipment resources. Quality control testing and results generation were completed for all available final product and PBMC lots according to protocol requirements. However, QA document review was not completed for any of the non-clinical lots. Only (b) (4) PBMC isolations were completed due to impacted starting material delivery. Based on these results, the ide-cel capacity at S12 was set at (b) (4) culture initiation and (b) (4) PBMC isolations per (b) (4). It was also identified that the most significant capacity constraints were related to the number of daily unit operations for final product harvest and PBMC isolation. The daily combined capacity of these unit operations was set at (b) (4).

Risks identified that require mitigation prior to further increasing capacity included: lack of schedule adherence leading to personnel and equipment constraints, need for additional apheresis receipt and release training, additional personnel needed, additional equipment needs to be put into use, additional refrigerator/freezer storage needed, document (batch record, label) availability needs to be improved, and additional gowning/hazardous waste pickups need to be scheduled.

Celgene also stated that increases in production capacity at the Celgene S12 facility will be established on an on-going basis through the execution of capacity test protocols.

Reviewer comments:
Based on the results of this capacity test, the performance of (b) (4) culture initiation and (b) (4) PBMC isolations per (b) (4) is not supported. In IR#38, sent 12/28/2020, Celgene was informed of this and other general issues with their capacity study. In Amendment 36, Celgene provided the following responses and the results of a new capacity test (July 2020). Celgene confirmed that all testing and data analysis will be performed on (b) (4) product lots, QC test criteria

for transduced capacity test batches will meet final commercial specifications and that full QA batch review will be required for all future capacity studies. The new capacity test evaluated the feasibility of (b) (4) culture initiations ((b) (4) clinical and (b) (4) non-clinical) and (b) (4) PBMC isolations ((b) (4) clinical and (b) (4) non-clinical) per week. Again, supply chain operations did not meet all resources expectations and manufacturing operations did not meet all resource, equipment, and delivery expectations. Thus, operations were not completed within scheduled times and overtime was required. Operation hours will need to be extended, new personnel will need to be hired and trained and additional equipment will need to be put into service. More importantly, delivery criteria for QA disposition and QA operations were not met in that (b) (4) non-clinical lots did not satisfy RFI requirements of release no more than (b) (4) days post-harvest due to inability to closure of deviations. Again, this resulted in fewer than (b) (4) lots that could be considered completed in this study. However, Celgene concluded that this study supported an increase to (b) (4) culture initiations per (b) (4), which they implemented in November 2020. Celgene went on to say that since the establishment of the (b) (4) culture initiations and (b) (4) PBMC isolations per (b) (4) (January 2020) and through the implementation of (b) (4) culture initiations and (b) (4) PBMC isolations per (b) (4) (November 2020) there have not been any patient lot terminations or deviations attributed to over utilization of established capacity limits.

We did not agree that the data provided supported the proposed capacity, and this issue was further discussed during the on-site on inspection of the Celgene S12 facility. In response to our discussions during the on-site inspection, an interim assessment of PROT-018316: ide-cel 25 (b) (4) Capacity Test (1/26/2021 to 1/30/2021) was provided in Amendment 54 to support the S12 capacity of (b) (4) Culture Initiations and (b) (4) PBMC Isolation per (b) (4). This interim assessment was prepared after the successful completion of the first (b) (4) manufacturing lots executed (b) (4) clinical, (b) (4) non-clinical) and (b) (4) PBMC Isolations. The (b) (4) lots underwent full release testing, met release requirements, completed batch record review and Quality Assurance disposition activities within the required (b) (4) days post-harvest (b) (4)). (b) (4) deviations were initiated for these lots. This deviation rate is consistent with historical ide-cel rates. All deviations completed the QA assessment phase, including Interim Disposition Assessment, where applicable, and all deviations remain on track for closure in accordance with procedural requirements. The successful completion of these lots demonstrates effectiveness of the actions taken since the ramp test previously executed under PROT-017777: increased staffing in Manufacturing Operations and Quality Assurance from (b) (4) operation; increased staffing in Quality Control laboratories enabling on-time testing and results generation; and implementation of a specialized, dedicated deviation investigation team, and enhanced investigation training and tools, enabling on-time deviation investigation processing. Therefore, this interim report supports the S12 capacity of (b) (4) Culture Initiations and (b) (4) PBMC Isolations per (b) (4).

Celgene also acknowledged that all future capacity increase study results, including the complete results from the (b) (4) Culture Initiations per (b) (4) study will be submitted to FDA for review in the form of CBE-30s.

Continued Process Verification (CPV)

The ide-cel CPV plan includes evaluation of CQAs, CPPs, IPCs, and processing times on a (b) (4) basis, after at least (b) (4) lots have been manufactured in the time frame using the commercial manufacturing process. The evaluation includes comparing the results to control limits established using all available data from the (b) (4) ide-cel clinical batches (pre- and post-PPQ) and (b) (4) PPQ batches manufactured at the S12 facility using the commercial manufacturing process (Process (b) (4)) from 11/30/2018 to 1/31/2020. Shewhart control charts and exponentially weighted moving average (EWMA) charts will be used to identify trends in quantitative parameters with defined control limits. Run charts will be used for monitoring

process parameters and attributes without defined control limits. Any potential shift or drifting trend or points exceeding control limits identified during the data review will be evaluated to identify any potential impact to process performance and product quality.

Overall Reviewer's Assessment of Section 3.2.S.2.5:
The data and information provided supports successful validation of the ide-cel manufacturing process.

3.2.S.2.6 Manufacturing Process Development
(b) (4) manufacturing process versions have been used to date for ide-cel clinical studies. Processes(b) (4) were primarily used to manufacture lots for Study CRB-401 cohort 1. Process (b) (4) was used to manufacture all lots for Study BB2121-MM-001 and the other cohorts for Study CRB-401. Process (b) (4) is the current manufacturing process and represents the commercial process. A high-level overview of the processes is presented in Table 66.

(b) (4)

(b) (4)

Process (b) (4) -Process (b) (4) Comparability

Given the similarity of Process (b) (4), they were combined in the comparability assessment with Process (b) (4). This comparability study involved (b) (4) runs. It was observed that the DP lots from Process (b) (4) exhibited an increase in (b) (4)

(b) (4)

(b) (4)

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

(b) (4)

Process Characterization
Parameters within each unit operation were identified and the potential for each parameter to impact product quality was evaluated in a risk assessment based on manufacturing experience, process knowledge, and literature. Failure modes within each parameter were evaluated for severity [using High (9), Medium (3), and Low (1) quantifiers] and uncertainty [using High (3), Medium (2), and Low (1) quantifiers]. Risk Prioritization Number (RPN) scores were generated by adding the severity and uncertainty scores. Characterization was performed for parameters with severity scores of High or Medium or with RPN scores above 5.

The risk assessment evaluated (b) (4) parameters, (b) (4) were further evaluated in the process characterization studies using (b) (4) material. (b) (4) material was deemed appropriate based on a retrospective analysis comparing PBMC and DP attributes from (b) (4) clinical manufacturing runs to (b) (4) runs performed in developmental labs, at-scale. Parameters were evaluated either at-scale or using a qualified scale-down model ((b) (4)). The scale-down model ((b) (4) scale) was demonstrated to be representative of the manufacturing process using (b) (4) runs.

Reviewer comments:
In all instances the (b) (4) *results fell within the clinical experience, however, in most cases the* (b) (4) *results had a tighter range and were more consistent. Scale down did not affect the culture conditions and the scale down model was not used to study the* (b) (4) *parameters. This is acceptable.*

Criticality Assessment of Product Quality Attributes
Ide-cel quality attributes are listed in Table 67. Celgene utilized an RPN scoring model (evaluating severity and uncertainty) to determine the criticality of product quality attributes based on known or potential impact on product safety and efficacy based on CMC development history, product and process characterization studies, correlative analysis of product attributes to clinical outcomes, general understanding of T cell biology and the degree of uncertainty regarding the effect of the attribute on product quality. Attributes assigned an RPN (b) (4) or scoring a high degree of uncertainly were classified as CQAs. Table 67 also summarizes the final list of ide-cel CQAs and the quality attributes evaluated during the process characterization studies. Of (b) (4) parameters evaluated, (b) (4) were identified as CQAs and (b) (4) were evaluated during the process characterization studies. Cell growth was evaluated using (b) (4) throughout the (b) (4) culture period. To evaluate the impact of a process parameter on dose the combined effects on CAR+ T cell Percentage and cell growth were considered.

The ide-cel control strategy for the CQAs is also outlined in Table 67. CQAs that do not have a release specification are controlled indirectly if correlated with another CQA that does have a release specification, or based on a combination of characterization, manufacturing experience, and validation where sustained control has been demonstrated.

Table 67. Summary of ide-cel Quality Attributes and Control Strategy

Category	Attributes Evaluated	Score (Severity, Uncertainty)	CQA	Evaluated in PC studies	Control Strategy

Appearance	Color	(b) (4)	**Yes**	No	Release & stability testing
	Opacity			No	
Safety	Sterility		**Yes**	No	Release & stability testing
	Mycoplasma		**Yes**	No	Release testing
	Endotoxin		**Yes**	No	Release testing
	(b) (4)		**Yes**	**Yes**	Release testing
	Replication Competent Lentivirus (RCL)		**Yes**	No	PPQ
Purity	T cell Percentage		**Yes**	**Yes**	Release testing
	CAR+ T cell Percentage		**Yes**	**Yes**	In-process, release & stability testing
	Cell Concentration		No		In-process & release testing
	Viability		**Yes**	**Yes**	Release & stability testing
	Cell Health		**Yes**	No	PPQ
	CD4:CD8 Ratio		No		PPQ
	CAR+ T cell memory composition		No		PPQ
Potency/ Antigen Specific Function	(b) (4)		**Yes**	**Yes**	Release & stability testing
			Yes	No	Process characterization
			Yes	No	PPQ
Strength	Dose		**Yes**	**Yes**	Release testing
Product-Related Impurities	(b) (4)		No		Release testing
			Yes	No	PPQ
			No		PPQ
			Yes	No	In-process & release testing
			Yes	No	PPQ
Excipients	CryoStore 10		No		Raw material testing
	Plasma-Lyte A		No		Raw material testing
DP Process-related Impurities	(b) (4)		No		Process Knowledge
			Yes	**Yes**	Process Knowledge
			No		PPQ
			No		PPQ
			No		Process characterization
			No		PPQ
			No		PPQ
			No		Process knowledge
Vector-related Impurities			**Yes**	**Yes**	Process characterization
			No		Process characterization

	(b) (4)	**Yes**	**Yes**	Process characterization
		Yes	**Yes**	Process knowledge
		Yes	**Yes**	PPQ
		Yes	**Yes**	Process characterization
		Yes	**Yes**	Process knowledge

For the process characterization studies, the acceptability and criticality of parameter ranges were determined based on the effect on the attributes indicated in Table 67. The statistical significance of the effect and its representation of a "meaningful" effect were used to dictate parameter range acceptability and criticality. The meaningful effect thresholds were calculated from the standard deviation of the clinical manufacturing experience from the pivotal trial, multiplied by a factor of (b) (4). Linear regression models were used where appropriate to determine the effect size of the evaluated parameter. Parameters were deemed statistically significant if the p value < 0.1. If the p-value was greater than or equal to 0.1, then the parameter was categorized as a nCPP. For each parameter with a p value < 0.1, the effect size was compared to the meaningful effect thresholds. Parameters were labeled as CPPs if they were found to have both a statistically significant effect from the regression model and a meaningful effect across the anticipated processing range. A summary of the process characterization studies, as well as all the study reports were provided. The acceptable ranges listed in Table 54, Table 55, Table 56, Table 57, Table 58 and Table 59 were tested and found to be acceptable. (b) (4) CPPs, (b) (4) IPCs and (b) (4) processing times were identified. The RPN for each parameter was updated as additional understanding was gained or as controls were added/modified to the manufacturing process. After completion of the PPQ batches, a post-PPQ risk assessment was completed to support the proposed commercial process control strategy.

Reviewer Comments:
In IR#28, sent 11/19/2020, Celgene was asked to justify the effect threshold, was told that we recommend that all parameters that exhibit a statistically significant effect regardless of whether it was within the effect threshold should be considered CPPs and was asked to tighten the acceptable ranges for (b) (4) *and justify the used of an acellular study to support bag fill volume. In Amendment 25, Celgene provided the following responses. Celgene stated that the effect threshold of* (b) (4) *standard deviations was chosen because it encompasses the majority of events within a normal distribution (*(b) (4)*). Celgene agreed to include Operation* (b) (4) *and Unit Operation* (b) (4) *as CPPs. Celgene tightened the acceptable ranges as requested. Celgene also stated that the* (b) (4) *study involving DP filled in cryopreservation vials was used to support bag fill volume.*

In IR#38, sent 12/28/2020, Celgene was asked to tighten the acceptable range for (b) (4) *and justify the use of a study in vials to support bag fill volume or* (b) (4) *. In Amendment 36, Celgene tightened the* (b) (4) *range and stated that the* (b) (4) *study design accommodated for differences between vials and bags (material composition and surface area/volume ratio) through empirical measurement of* (b) (4) *.* (b) (4) *in* (b) (4) *studies were demonstrated to be higher than those measured in* (b) (4) *studies with no observed impact on DP CQAs. The* (b) (4) *of the* (b) (4) *were also similar.*

Overall Reviewer's Assessment of Section 3.2.S.2.6:
The data provided were sufficient to support the acceptable ranges proposed.

3.2.S.3 Characterization
3.2.S.3.1 Elucidation of Structure and Other Characteristics
To further elucidate the composition and activity of the ide-cel DP, studies were performed to characterize the structure and function of the ide-cel CAR in addition to phenotypic and functional characteristics of the T cells in the DP. Phenotypic and functional characteristics were also assessed for correlations with clinical response, clinical safety, and pharmacokinetics.

The following biochemical and functional studies were performed on the anti-BCMA CAR:

The following studies of LVV mediated transduction and integration in ide-cel DP were performed:

(b) (4)

The following mechanism of action studies were performed on representative ide-cel DP lots generated in development laboratories using the full-scale commercial manufacturing process from (b) (4) PBMCs:

(b) (4)

The following extended characterization was performed on ide-cel DP lots from Study BB2121-MM-001 to reinforce understanding of the composition and mechanism of action for ide-cel DP:

(b) (4)

- *Reviewer Comments: In IR#43, sent 12/28/2020, Celgene was asked to correlate the specific (b) (4) data with (b) (4) . In Amendment 45, Celgene indicated that no statistically significant correlation between (b) (4) and the specific (b) (4) was observed using data from (b) (4) ide-cel clinical lots. However, data from these lots also indicated that there was no correlation between IFN γ secretion and cytolytic activity either.*

(b) (4)

(b) (4)

Clinical Correlative Analyses

Univariate statistical assessments were performed to determine whether statistically significant correlations exist between ide-cel quality attributes (lot release and extended characterization) and clinical outcomes (response, safety, and pharmacokinetics) observed in BB2121-MM-001 across the dose range of (b) (4) × 10^6 CAR+ T cells. All the DP lots used in these analyses were manufactured using Process (b) (4) . Data classifications for the clinical endpoints informed the type of statistical analyses performed to assess the significance and strength of correlations between DP quality attributes and clinical endpoints. Several DP attributes were found to have statistically significant or potentially significant relationships with efficacy, safety, and PK endpoints. However, none of these correlations are able to independently predict outcomes for patients (i.e., acute safety events or lack of response). Additional information on the clinical assays used to obtain the data for these correlative analyses can be found in the review of **Modules 4 and 5**. A summary of the findings are as follows:

- Higher absolute number of infused CAR+ T cells (strength/dose), increased CAR+ T cell percentage and (b) (4) demonstrated a potential relationship with increase in PFS.
- The total number of ide-cel CAR T cells infused, CAR T cell activation and IFNγ secretion were higher in subjects who experienced any grade of CRS compared with those that did not experience CRS. Less differentiated T cell phenotypes (CD3+CAR+CCR7+CD45RA-) were inversely correlated with the occurrence of any

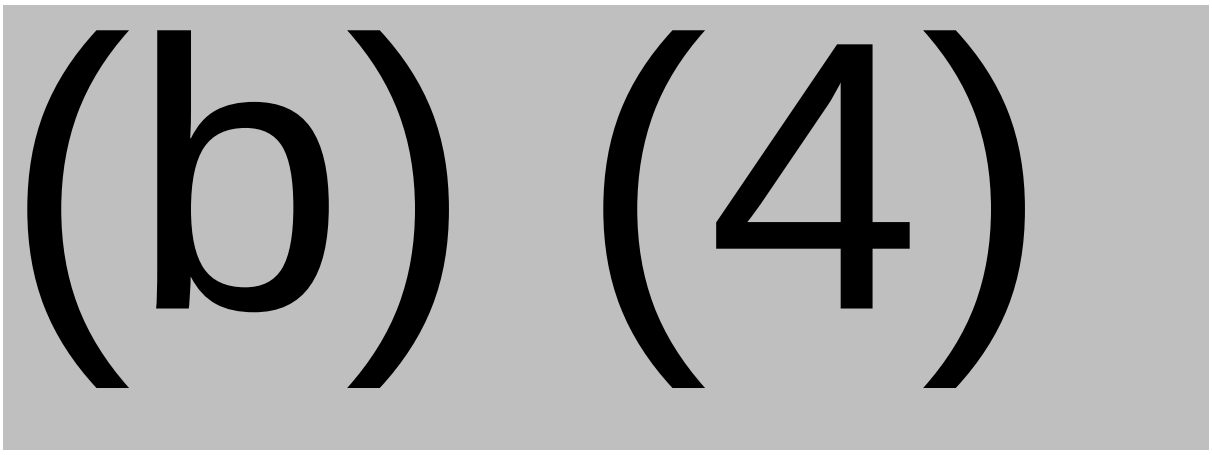
CRS. No ide-cel product characterization attributes were related to CRS requiring tocilizumab or Grade ≥ 3 CRS vs. Grade 0-1 CRS.

- Increased CAR T cell activation as well as decreased composition of memory T cells were observed to be potentially related to the occurrence of neurotoxicity of any grade.
- The total frequency of CD3+CAR+CCR7-CD45RA+ cells correlated with longer time to recovery after experiencing Grade 3+ thrombocytopenia.
- A more differentiated T cell state (CD3+CAR+CCR7-CD45RA+) correlated with increased total CAR T cell expansion and peak CAR T cell expansion in vivo.

3.2.S.3.2 Impurities

Product Related Impurities

The median frequency of CD3+ T cells in (b) (4) ide-cel lots administered in Study BB2121-MM-001 was (b) (4) of viable CD45+ leukocytes as compared to (b) (4) for (b) (4) PBMC lots Figure 14.



(b) (4) patient-matched PBMCs and DP lots were also characterized for leukocyte cell composition ((b) (4) from Study CRB-401 and (b) (4) from Study BB2121-MM-001) and further confirmed the ability of the ide-cel DP manufacturing process to produce a highly pure T cell product in spite of the heterogenous nature of the starting material.

A risk-based approach was used to define the criticality of the product-related cellular impurities primarily based on theoretical transduction of non-T cells.

- Based on an assessment performed using (b) (4) unique PBMC isolations from (b) (4) leukapheresis material, the PBMC isolation process has demonstrated the capability to clear residual (b) (4) with (b) (4) mean reduction for (b) (4) and (b) (4) mean reduction for (b) (4) .
- Non-viable cells are controlled through the DP viability release specification.
- (b) (4) ide-cel clinical DP lots ((b) (4) from Study CRB-401 and (b) (4) from Study BB2121-MM-001) were characterized for product-related cellular impurities.
  - (b) (4)

(b) (4)

Additional analyses of product related impurities can be found in **Section 3.2.S.2.5 Process Validation and/or Evaluation**. Taken together, the data provided demonstrate ide-cel is a highly pure, T cell product with a low likelihood of containing high-risk product related impurities, such as (b) (4) .

Process Related Impurities

For all process-related impurities, a safety assessment based on a toxicology review was conducted. An exposure limit (EL) was derived for each impurity from published nonclinical and clinical data (Table 68). Citations for all published reports from which data were obtained were provided. Exposure limits have taken into consideration the ide-cel single dose regimen and utilized an assumed adult body weight of 60 kg when applicable. LVV and (b) (4) were not included since their exposure limits cannot be established.

Table 68. Summary of Exposure Limits of ide-cel Process-Related Impurities

Impurities	Study Species	Limit from the Original Publication	Adjustment Factors (Value Used)	Exposure Limit per ide-cel Dose
(b) (4)				

(b) (4)

First, a safety margin was calculated for each impurity (Exposure Limit/Impurity level in a single dose) assuming no clearance. If the safety margin was above (b) (4), no further characterization studies were performed because the total amount of the impurity added during product manufacture is already below the exposure limit without any clearance. If the safety margin assuming no clearance is below (b) (4), data was collected to understand impurity levels after clearance by either dividing the maximum amount of impurity that could be introduced to the process by the minimum empirically measured clearance factor of the impurity or the suitable surrogate or by directly measuring the amount of the impurity in the DP.

Reviewer Comment: In IR#28, sent 11/19, 2020, additional details on the limits identified from the original publications and any adjustment factors applied was requested. Celgene provided the requested information in Amendment 25 and indicated that where a limit was not available in the published literature, a hazard and risk assessment was carried out for each impurity and documented in internal monographs.

Each of the (b) (4) is designed to (b) (4) . Therefore, the combined effect of the (b) (4) is theoretically a (b) (4) . The ide-cel DP process-related impurities, the steps at which they are introduced, the impurity characterization strategies and results are summarized in Table 69.

Table 69. Summary of ide-cel Process-Related Impurities Studies

Category (Unit Operation)	Process-related Impurity	Characterization Strategy	Results
LVV and Associated Impurities (Transduction)	(b) (4)	• At-scale characterization study • Testing of clinical lot samples	(b) (4)
		• At-scale characterization study • Testing of PPQ lot samples • Testing of clinical lot samples	
		• (b) (4) study	

	(b) (4)	• (b) (4) characterization	(b) (4)
		• At-scale characterization study using (b) (4)	
		• Calculation based on (b) (4)	
		• At-scale characterization study using (b) (4)	
		• Calculation based on (b) (4)	
Raw Materials (Activation, Transduction, Expansion)		• At-scale characterization study using (b) (4)	
		• At-scale characterization study	
		• At-scale characterization study • Testing of PPQ lot samples	
		• Testing of PPQ lot samples • Testing of clinical lot	

	(b) (4)	samples	(b) (4)
		• Testing of PPQ lot samples • Testing of clinical lot samples	
		• At-scale characterization study using [b]	
		• Calculation based on (b) (4)	
		• Calculation based on (b) (4)	
		• Calculation based on (b) (4)	

Reviewer Comments:
In IR#28, sent 11/19/2020, Celgene was asked to provide additional data supporting clearance of the anti-CD3 and anti-CD28 antibodies. In Amendment 25, Celgene stated that a spiking study was performed where a detectable amount of anti-CD3 antibody and anti-CD28 antibody (i.e. (b) (4) *in total) was* (b) (4) *. The* (b) (4) *material contained below the LLOQ (*(b) (4) *) of mouse IgG for a log clearance of* (b) (4)*. Based on the amounts of each antibody used in the ide-cel manufacturing process, the safety margins for anti-CD3 antibody and anti- CD28 antibody were calculated to be* (b) (4) *, respectively.*

Overall Reviewer's Assessment of Section 3.2.S.3.1 and 3.2.S.3.2:
The data provided were sufficient to support the appropriate characterization of the ide-cel product.

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)
There is no release testing performed on ide-cel DS. The DS is immediately processed into DP. See **Section**
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)for information on the DP specifications.

3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures
There is no testing performed on the ide-cel DS because there are no hold steps in between DS and DP manufacturing. This section evaluates the analytical procedure used to determine the identity, purity, and viability and cell concentration of the PBMCs.
See **Section 3.2.P.5.2 Analytical Procedures and 3.2.P.5.3 Validation of Analytical Procedures** for information on the DP analytical procedures. In process testing of PBMCs includes PBMC (b) (4) . PBMC (b) (4) is tested for cell concentration and total PBMC cells using the (b) (4) . PBMC (b) (4) includes testing for (b) (4) . Viability and %CD3 T cells are assessed using (b) (4) , and sterility is tested using (b) (4) .

Analytical Procedure - PBMC identity, purity, viability (IPV)
(b) (4)

(b) (4)

(b) (4)

(b) (4)

Validation Study Summary

Validation study for the (b) (4) assay is supplied in the submission. For the validation specificity, precision, linearity, accuracy, range/limit of quantitation LOQ, and stability were assessed. The validation studies were done at the Celgene summit facility.

Reviewer Comments: Validation data supports assay control.

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

3.2.S.5 Reference Standards or Materials
The ide-cel DS has no reference standards.

3.2.S.6 Container Closure System
There is no container closure for ide-cel DS because the DS is not stored. Information on the container closure for the (b) (4) PBMC intermediate is reviewed in this section.

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

(b) (4)

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product
Ide-cel DP is a genetically modified autologous T cell immunotherapy directed to BCMA, formulated as a single dose cell suspension for intravenous administration at a target cell concentration of (b) (4) in a solution containing 50/50 (v/v) Plasma-Lyte A and CryoStor CS10. A batch of ide-cel is filled into (b) (4) cryobags (either (b) (4) 50s, (b) (4) 250s, or (b) (4) 500s). For any given ide-cel batch, the same nominal fill volume is targeted in all bags filled. Celgene proposed a commercial dose range of (b) (4) x 10^6 CAR+ T cells, provided as a single dose for infusion in one or more bags. However, the clinical review team is approving a dose range of 300 to 460 x 10^6 CAR+ T cells. Following filling, ide-cel is cryopreserved and stored in the vapor phase of liquid nitrogen (≤ -130°C).

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 T cell immunotherapy consisting of autologous T cells transduced with the anti-BCMA02 CAR LVV encoding a CAR that recognizes BCMA.

3.2.P.2.1.2 Excipients
A list of the ide-cel excipients, their concentration and function is provided in Table 73. The components of Plasma-Lyte A and CryoStor CS10 were also provided.

Table 73. Excipients in the Commercial Formulation of ide-cel

Excipient	Quality Standard	Function	Concentration
Plasma-Lyte A Injection, pH 7.4 (Multiple Electrolytes Injection, Type 1)	(b) (4)	Source of electrolytes	50% (v/v)
CryoStor CS10 Freeze Media	(b) (4)	Cryoprotectant	50% (v/v)

3.2.P.2.2 Drug Product
3.2.P.2.2.1 Formulation Development
The formulation of 50/50 (v/v) Plasma-Lyte A and CryoStor CS10 was developed to (b) (4) Plasma-Lyte A mimics human plasma in its content of electrolytes, osmolality, and pH. CryoStor CS10 acts as a cryoprotectant during long term storage. There has been no formulation change during ide-cel manufacturing development history.

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
Physicochemical and biological properties are described in **Sections 3.2.P.1 Description and Composition of the Drug Product** and **3.2.S.3.1 Elucidation of Structure and Other Characteristics**. There are no differences between the properties of the DS and the DP.

3.2.P.2.3 Manufacturing Process Development
Process development and comparability studies performed during the product lifecycle are described in **Section 3.2.S.2.6 Manufacturing Process Development**. The studies described apply to the DP as well as DS. Information unique to the DP is described here.

Ide-cel Filling Strategy
The ide-cel DP manufacturing process begins after (b) (4) The DP is then filled into bags (b) (4) (for release testing), and subsequently cryopreserved in a (b) (4) vapor phase of liquid nitrogen (≤ -130°C).

During the ide-cel manufacturing process, DP is filled into the final container closure prior to testing the cell concentration and CAR+ T cell percentage, which is performed after cryopreservation. To eliminate dose manipulation at the administration site, the cells are divided across multiple bags ((b) (4) minimum) to provide flexibility in adjusting the dose volume via the number of bags shipped to the site for administration after the final cell concentration and CAR+ T cell percentage values are obtained. An in-process measurement of CAR+ T cell percentage (Day (b) (4)) and the target cell concentration ((b) (4)) are used to determine the cryopreservation bag size and fill volume (Table 74). Given the wide range of ide-cel dose volumes required ((b) (4)), three cryopreservation bag sizes are used to package the DP (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). Though for any given ide-cel batch, the DP is only filled into one bag size with a consistent fill volume.

The fill strategy is designed to target as close to a dose of 450 × 10^6 CAR+ T cells as possible using the equation:

Target Fill Volume per bag = (b) (4)

(b) (4) . Across the clinical manufacturing experience within the pivotal BB2121-MM-001 study, the resulting total volume to meet dose was on average (b) (4)-fold higher than the volume based on the in-process value. Therefore, an adjustment factor of (b) (4) is used to offset between the in-process values and the release test results obtained from the post-thaw DP for CAR+ T cell percentage and cell concentration. If there is a sufficient number of cells, up to (b) (4) cryopreservation bags are filled.

The cell concentration and CAR+ T cell percentage values obtained after cryopreservation represent the actual number of CAR+ cells in each bag and are used to identify the number of bags needed to obtain the target dose that will be shipped and administered. Only the number of bags necessary for dosing are sent to the administration site and all bags sent are to be administered to the patient.

Table 74. Target Number of Bags

In-process CAR+ T cell Percentage	Number of bags (N)	Bag Size	Target Fill Volume
(b) (4)	(b) (4)	(b) (4) 50	(b) (4)
		(b) (4) 50	
		(b) (4) 250	
		(b) (4) 500	
		(b) (4) 250	
		(b) (4) 500	
		(b) (4) 500	
		(b) (4) 500	
		(b) (4) 500	
		(b) (4) 500	

The approach to filling ide-cel DP has remained the same across process versions, utilizing an in-process measurement of CAR+ T cell percentage, the target cell concentration, and a constant adjustment factor to determine the target DP fill volume per cryopreservation bag. (b) (4) modifications have been made to the fill strategy as the method has been refined throughout clinical development including (b) (4)

Fill volume Normal Operating Range (NORs) were defined for the different bag sizes based on a review of the process capability within the historical manufacturing batches. The acceptable range for the fill volume in each bag size were defined based on the minimum and maximum recommended volumes from the vendor (Table 75).

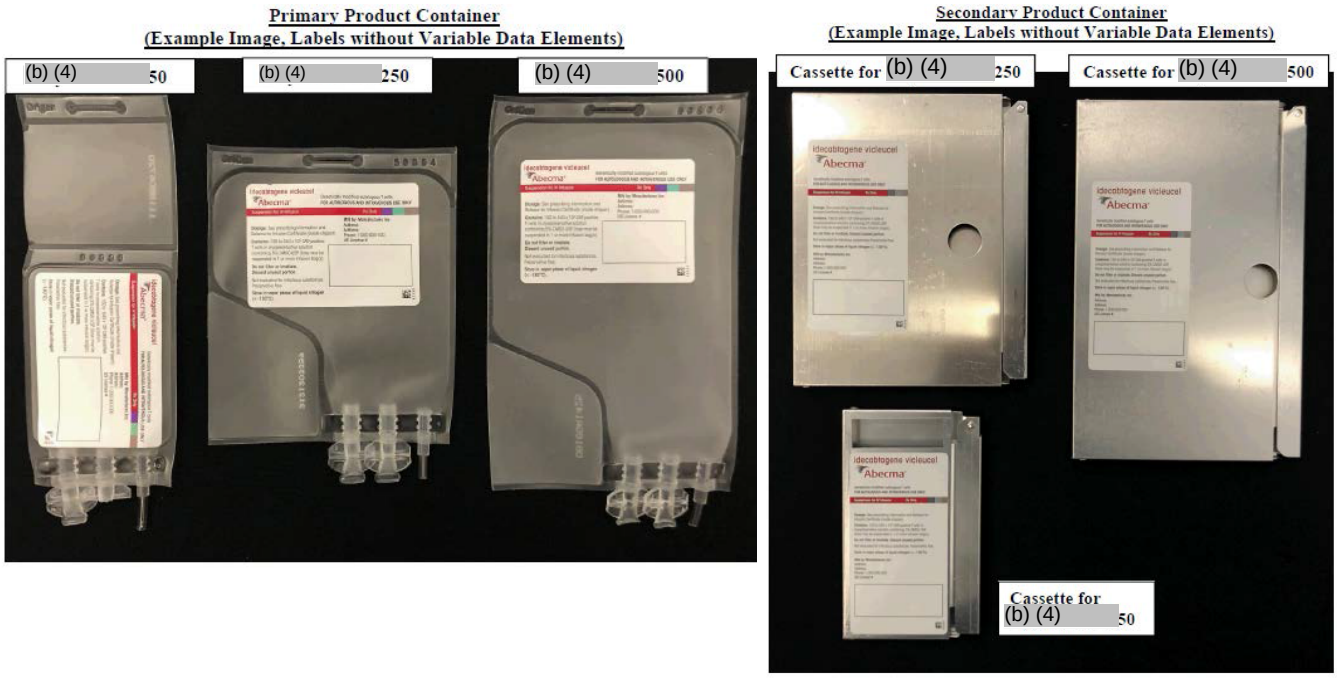
Table 75. Bag Fill Volume Control Strategy

Parameter	Target	Surface area/ volume ratio	Normal Operating Range	Acceptable Range
Bag Fill Volume (mL)	(b) (4) 50 ((b) (4) mL)	(b) (4)	(b) (4) ml from target fill volume	(b) (4) 50 (10 – 30 mL)
	(b) (4) 250 ((b) (4) rnL)	(b) (4)	(b) (4) ml from target fill volume	(b) (4) 250 ((b) (4) mL)
	(b) (4) 500 ((b) (4) mL)	(b) (4)	(b) (4) ml from target fill volume	(b) (4) 500 ((b) (4) mL)

Reviewer Comments:
In the original submission, Celgene proposed a dose range of (b) (4) *x 10^6 CAR+ T cells and proposed a filling strategy to target 450 × 10^6 CAR+ T cells. After clinical informed Celgene that they would only be approving a dose range of 300 to 460 x 10^6 CAR+ T cells, Celgene further optimized their filling scheme by expanding their target fill volumes in order to obtain doses closer to the 450 × 10^6 CAR+ T cell target. The expanded fill volumes (listed in Table 75) are still within the validated ranges. Therefore, this change is acceptable. This optimized filling strategy was discussed during the Celgene S12 inspection and is further described in the EIR. In response to IR#63, sent 3/11/2021, Celgene updated the target fill volumes throughout the BLA in Amendment 64.*

Ide-cel Labeling
The ide-cel DP labels for each of the three final container sizes are supplied as preprinted label stocks with defined text and graphics. Upon delivery to the S12 facility, the pre-printed label stocks are received and managed through the site's Enterprise Resource Planning (ERP) system. Prior to DP harvest, the ide-cel finished DP label is generated through a printing operation in the Label Control Room. The printing operation converts the pre-printed label stocks to a finished DP label by printing variable data elements onto the label, including patient identifying information (name, date of birth, JOIN, DIN/Aph ID), lot number and expiration date. The target volume per bag and NDC (human readable and barcode) are identified based on the bag size. The finished labels are then verified for correctness by QA. All steps in the printing operation are driven by the Manufacturing Execution System (MES) and captured as part of the batch record. The finished DP labels are then transferred by QA to Manufacturing, checked for COI verification, and applied to the cryopreservation bags and the corresponding secondary cassettes in a pre-harvest preparation procedure. Upon completion of the container labeling process, all unused lot-specific labels are reconciled and destroyed. An illustration of the labeled containers is provided in Figure 15. An example of the DP label is shown in **Section B. Labeling Review.**

Figure 15. Example Images of Labeled Ide-cel Containers



Justification to remove RCL testing from Drug Product

A risk assessment was performed based on the currently proposed control strategy for RCL. The design properties of the plasmids, LVV, production processes, and the LVV control strategy, including testing (b) (4) final LVV product for RCL were considered. Risk elements assessed include severity of impact in terms of RCL generation, detectability of RCL at any point within the LVV or DP production process as well as the likelihood of occurrence for any given event leading to RCL generation. The overall level of risk for generation of RCL during the manufacture of the anti-BCMA02 CAR LVV and ide-cel DP was determined to be extremely low. Therefore, Celgene would like to drop RCL testing of the commercial ide-cel DP.

The LVV production system is composed of (b) (4)

(b) (4)

The anti-BCMA02 CAR LLV does not code for any viral proteins and only contains regulatory elements ((b) (4)) that are required for (b) (4) No RCL has ever been detected during

the manufacture of ide-cel DP across the entirety of ide-cel manufacturing experience using a qualified (b) (4) method. To date, there has been no evidence of RCL generation following treatment with ide-cel up to 24 months from initial infusion.

Reviewer Comments:
There are significant (b) (4) sequence overlaps between the (b) (4) . These overlaps may result in (rare) partial recombinants. However, these partial recombinants would not be replication-competent. Recombination of envelope sequences to form RCL is impaired by a lack of sequence homology between the (b) (4) . No RCL has ever been observed in ide-cel DP. Therefore, based on the cumulative data, it is acceptable to drop DP RCL testing.

3.2.P.2.4 Container Closure System
The ide-cel container closure is the (b) (4) 50, (b) (4) 250, or (b) (4) 500 cryopreservation bags ((b) (4)) with (b) (4) tube and (b) (4) ports. These bags are made of virgin, (b) (4) , supplied (b) (4) , FDA 510(k) cleared ((b) (4)) and CE-marked.

E/L data on the bags alone are summarized and reviewed in **Section 3.2.S.2.5 Process Validation and/or Evaluation**. However, this section summarizes the studies performed on the bags with labels. E/L testing on the bag material was done in two stages: 1) (b) (4) extraction studies and 2) leachable simulation studies. The (b) (4) extraction studies were done to identify all compounds that could be extracted from the bag. The leachable simulation studies were performed to determine if any compounds could leach from the bag under standard conditions of use. The (b) (4) extraction studies focused on identifying volatile organic compounds, semi-volatile organic compounds, non-volatile organic compounds, and elemental impurities. Celgene set the Analytical Evaluation Threshold (AET) as (b) (4) based on a justification of (b) (4) for volatile organic, semi-volatile, non-volatile organic compounds. The threshold for elemental impurities was set based on the (b) (4) guidelines of (b) (4) of the PDE.

Bags without Labels
E/l studies for cryobag without labels are described in section 3.2.S.2.5

Bags with Labels
E/L testing was repeated on the (b) (4) 250 bag with the primary DP label attached to assess extractables and leachables due to the label. (b) (4) extraction studies were conducted using (b) (4) **.** No volatile organic, semi-volatile organic, non-volatile organic, or elemental impurities were identified. Similarly, a leachables simulation study with the labeled bag was conducted using (b) (4) . No any leached compounds were identified. Leachable studies were not performed on end shelf-life material (12 months ≤ -130ºC). The justification was that the lack of organic and elemental compounds at levels above AET from the leachables studies, and the DP storage temperature (≤ -130ºC) is significantly lower than the highest temperatures ((b) (4)) tested in the simulation studies.

Reviewer Comments: No leachables of concern were identified.

Ide-cel Shipping
The required number of ide-cel bags to meet dose, in their respective secondary cryopreservation cassettes are shipped to the administration site in a liquid nitrogen shipper (LN2 shipper). The release for infusion (RFI) certificate, prescribing information (PI), and medication guide are included in the shipper in a plastic sleeve. The RFI includes information on the number of bags shipped to meet the dose, volume per bag, cell concentration, dose, patient identifiers (name, date of birth (DOB), apheresis ID/DIN, and the unique identification code (JOIN). The LN2 shipper is validated to ship (b) (4) cryopreservation bags at (b) (4) up to (b) (4) .

Reviewer Comments:
The RFI certificate was requested in IR#38, sent 12/28/2020, and was provided in Amendment 36. The RFI clearly indicates the number of bags shipped, the number of bags needed to meet the dose, the volume per bag, the total dose volume and the total CAR T cell dose. The information provided in the RFI is adequate.

Celgene states that the product can be kept up to the maximum allowable LN2 shipper storage duration (up to (b) (4)) or stored in the vapor phase of liquid nitrogen at ≤-130ºC following receipt at the administration site. Stability studies for this temperature are reviewed in **Section 3.2.P.8 Stability**. Shipper validation studies were provided in the submission and are reviewed in **Section 3.2.P.3.5 Process Validation and/or Evaluation**.

Ide-cel preparation and administration instructions that are included in the package insert.
The DP is to be thawed in a pre-heated 37ºC instrument, such as a water bath. The cryopreservation bag is removed from the cassette and put into another plastic bag for thawing. Ide-cel is to be administered within 1 hour from start of thaw. If a clinical site's institutional policy requires the use of filters, a high surface area blood filter with a nominal pore size of 200 micron (170 to 260 micron) is recommended to ensure product quality, product recovery and infusion flow are not impacted. Smaller pore sizes, such as 0.2-micron infusion filters (sterilizing filters) and 40-micron blood filters (micro-aggregate filters) are not to be used. Data supporting compatibility of ide-cel with (b) (4) types of Y-type infusion sets ((b) (4)) is summarized and reviewed in Section 3.2.P.2.6 Compatibility.

3.2.P.2.5 Microbiological Attributes
The studies outlined in Table 76 were performed to verify the aseptic processing and filling of the ide-cel DP into the (b) (4) cryopreservation bags ((b) (4) 50, (b) (4) 250, (b) (4) 500) and filling of the PBMCs into the (b) (4) .

Table 76. Summary of Studies Related to Microbiological Attributes of Ide-cel

Study Name	Study Description
Release Testing (Mycoplasma, Endotoxin and Sterility)	Routine monitoring of microbiological attributes is conducted via Mycoplasma, Sterility and Endotoxin
Stability Testing (Sterility)	Stability monitoring of microbiological attributes is conducted via Sterility testing of DP on (b) (4) basis at defined timepoints
Container Closure Integrity (CCI) Validation	(b) (4) study is the method selected for container closure integrity. The validation focused on sensitivity, detectability of defects and confirmatory testing with predefined acceptance criteria.
Container Closure Integrity (CCI) testing after shipping	Shipping qualification was performed using the (b) (4) (b) (4) 50, (b) (4) 250, (b) (4) 500, and (b) (4) cryopreservation

	bags. After shipping studies were complete, the various bag sizes were tested for CCI.

Reviewer Comments:
Mycoplasma is performed by (b) (4). *Sterility is performed using* (b) (4) *and Endotoxin is tested using* (b) (4) *method according to* (b) (4).
Analytical methods for mycoplasma, endotoxin, and sterility testing are further described in **Section 3.2.P.5.2 Analytical Procedures and 3.2.P.5.3 Validation of Analytical Procedures**.

Container Closure integrity (CCI) of the (b) (4) 50, (b) (4) 250, and (b) (4) 500 and (b) (4) bags was tested via (b) (4) All bags met the prespecified acceptance criteria.

Reviewer Comments:
The container closure integrity validation summary report (REC 127122) was provided in Section 3.2.R of the submission. Additional information can be found in the DMPQ review.

3.2.P.2.6 Compatibility
A Y-type administration set with the option for an in-line filter is used for administration of ide-cel DP. If a clinical site's institutional policy requires the use of filters, a high surface area blood filter with a nominal pore size of 200 micron (170 to 260 micron) is recommended to ensure product quality, product recovery and infusion flow are not impacted. Compatibility of the infusion set with the ide-cel DP was evaluated using (b) (4) infusion sets and (b) (4) integrated blood filter:
(b) (4)

(b) (4) DP lots, (b) (4), manufactured from patient PBMCs via Process (b) (4) and Process (b) (4) respectively, were used to test each infusion set. Each lot was thawed, (b) (4) into (b) (4) 250 bags which were used to test the infusion sets at (b) (4) hours post-thaw after being held at room temperature. To test the infusion sets, the contents of each (b) (4) 250 bag was divided into (b) (4) 50 bags to test each infusion set. The remaining contents of the (b) (4) 250 bag was used as a control. After the DP had passed through the infusion sets, critical quality attributes such as cell viability percentage, CAR T cell percentage, and CD137 activation were assessed. Cell recovery was calculated by (b) (4). All product quality attributes tested were consistent following flow through of each infusion set evaluated.

Reviewer Comments:
No loss or deviations in critical quality attributes of the ide-cel DP was observed up to 2 hours post-thaw at room temperature when using the (b) (4) *Y-type infusion sets evaluated. The data supports compatibility of the infusion sets tested with the DP.*

The pore sizes of the filters that can be used were given as a range of (b) (4) in the original BLA submission, but only compatibility data for the (b) (4) blood filter was provided. If filters with pore sizes smaller than (b) (4) are to used, then compatibility data needs to be provided for these filters to ensure that the product is compatible with these type of infusion filters. In response to IR#63, sent 3/11/2021, Celgene agreed to update the lower bound of the blood filter acceptable pore size to (b) (4) in Amendment 64. This is acceptable. Note, the prescribing information states that a leukodepleting filter should not be used during ide-cel administration.

In-use stability studies

In-use stability of ide-cel DP was tested using 3 lots manufactured by Process (b) (4) using PBCMs from (b) (4). Each lot was stored in (b) (4) 50 (b) (4) mL) (b) (4) 250 (b) (4) mL), and (b) (4) 500 (b) (4) mL) bags. The lots were thawed and tested after 0, 2, and (b) (4) hours at room temperature. Conditions and preparation procedures performed represented those proposed for commercial use. Lots are assessed for cell appearance, viability, T cell percentage, CAR+ T cell percentage, and CD137 activation.

Reviewer Comments:
The in-use stability data support stability of the ide-cel DP up to 2 hours post-thaw when stored at room temperature (2 hours is the proposed storage limit). All acceptance criteria were met. A small consistent loss in CAR+ T cell percentage and CD137 activation was observed. However, the magnitudes of the decreases were within the variability of the analytical assays.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

A list of organizations involved in the manufacture, storage and testing of ide-cel DP is provided in Table 77.

Table 77. Site of Manufacture and Testing of ide-cel Drug Product

Site	Address	Function
Celgene S12 facility	Building S12 556 Morris Avenue Summit, NJ 07901 United States	ide-cel manufacturing; (b) (4) PBMC storage; ide-cel release and stability testing; packaging and labeling; ide-cel DP storage
(b) (4)	(b) (4)	(b) (4) PBMC storage; ide-cel DP storage
(b) (4)	(b) (4)	(b) (4) PBMC storage; ide-cel DP storage

3.2.P.3.2 Batch Formula

A batch is defined as the (b) (4) bags of ide-cel DP obtained from patient PBMCs in a single production run formulated in Plasma-Lyte A and CryoStor CS10 (Table 78). A single dose of ide-cel contains a cell suspension of 300 to 460 × 10^6 CAR+ T cells provided in 1 or more cryopreservation bags.

Table 78. Ide-cel Batch Formula

Excipient	Quality Standard	Function	Concentration
Ide-cel	N/A	DP	300 to 460 × 10^6

			CAR+ T cells
Plasma-Lyte A Injection, pH 7.4 (Multiple Electrolytes Injection, Type 1)	(b) (4)	Source of electrolytes	50% (v/v)
CryoStor CS10 Freeze Media	(b) (4)	Cryoprotectant	50% (v/v)

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

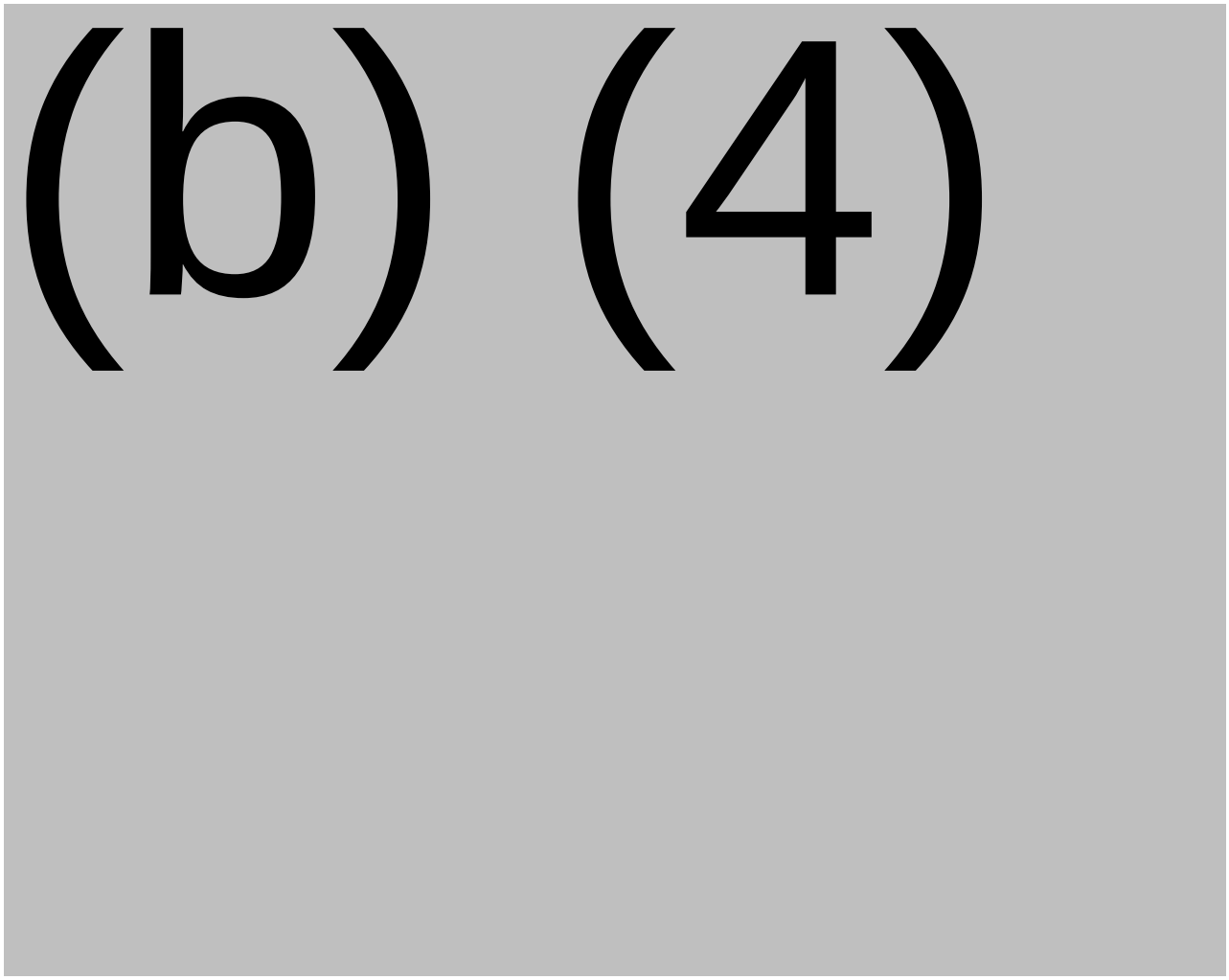
Please see **Section 3.2.S.2.2 Batch Numbering, Pooling and Scale Definition** for details.

- **Storage and Shipping**

Ide-cel DP is stored in (b) (4) 50, (b) (4) 250, and (b) (4) 500 cryopreservation bags in cryo-cassettes in LN2 freezers. The required number of ide-cel bags needed to meet dose, in their respective secondary cryopreservation cassettes are shipped to the administration site in an LN2 shipper.

3.2.P.3.3 Description of Manufacturing Process

Ide-cel DS is immediately processed into DP. The ide-cel DP manufacturing process flow diagram and process controls are presented in Figure 16.



Unit Operation (b) (4): Drug Product - Formulation

The cell suspension from the DS harvest step is diluted with CryoStor CS10 at a (b) (4) ratio (v/v) to achieve the target cell concentration of (b) (4) in 50% CS10%. The acceptable cell range is (b) (4) and CS10% is (b) (4).

Unit Operation (b) (4): Drug Product – Filling
The in-process CAR+ T cell percentage measured from the Unit Operation (b) (4) is used to determine the target DP fill volume per cryopreservation bag. The fill strategy is designed to target as close to 450 × 10^6 CAR+ T cells to provide a dose within the range of 300 to 460 × 10^6 CAR+ T cells in one (b) (4) cryopreservation bags. For any given ide-cel lot, the cells are filled into one of three infusion bag sizes; (b) (4) 50 ((b) (4) mL), (b) (4) 250 ((b) (4) mL), or (b) (4) 500 ((b) (4) mL). Each infusion bag is filled with the same fill volume per lot. The values from the cell concentration and CAR+ T cell percentage measured after cryopreservation represent the actual number of CAR+ cells in each bag and are used to identify the number of bags needed to achieve dose that will be shipped and administered. Following filling, each final DP bag is individually packaged in a metal cassette. One in process control for filling operations is % CAR+ T cells with an action limit of (b) (4) which is measured on Day (b) (4) of Unit Operation (b) (4) – Cell Expansion.

Mycoplasma samples are pulled from (b) (4). All other QC release and retain samples are pulled from a (b) (4) QC sample bag filled from the (b) (4) through a single line of tubing immediately (b) (4) to DP bag filling. All QC samples and retains are filled in vials and cryopreserved concurrently with the DP bags with the exception of the sterility samples. Sterility samples are tested fresh.

Unit Operation (b) (4): Drug Product – Cryopreservation
The final DP bags and QC vials are cryopreserved in a (b) (4) (at (b) (4)) and stored in the vapor phase of liquid nitrogen (≤ -130°C). The nCPP and storage time for the cryopreservation unit operation is ≤12 months (Refer to **Section 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data** for details).

To prevent potential impact to cell viability from prolonged exposure to DMSO during processing, the (b) (4)-freeze hold time of the ide-cel DP (i.e. (b) (4)) is limited to (b) (4).

All batch manufacturing and testing records are reviewed and approved by QA. Any deviations observed are investigated and assessed for impact to product quality, safety, efficacy and compliance of the batch with GMP standards prior to product disposition. Any new information that is received after the product is released for commercial supply will be reviewed and investigated. Please see Celgene S12 EIR for a description of the ide-cel recall procedures.

The cryopreserved DP is shipped from the manufacturing facility to the infusion site in a temperature-controlled LN2 dry vapor shipper. The LN2 Shipper maintains product temperatures of (b) (4) for a minimum of (b) (4) from when liquid nitrogen is initially charged. When the DP is ready for shipping, the necessary bag-filled cassettes for dosage are loaded from cryo-storage into a rack which protects the cassettes from movement during shipping. The loaded rack is then inserted into the LN2 shipper for transit.

Overall Reviewer's Assessment of Section 3.2.P.3.3:
The information provided on the ide-cel DP manufacturing process is adequate and acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates
No CPPs were identified for the ide-cel DP manufacturing process based on the process characterization and validation studies performed (see **Section 3.2.S.2.6 Manufacturing Process Development** for additional details). A summary of the in-process controls for the manufacture of ide-cel DP are provided in Table 56 and Table 57. There are no process intermediates/solutions with extended hold times during the manufacture of ide-cel DP.

Excursions of CPPs, IPCs, and processing times will be investigated as part of a deviation. The final batch disposition and/or forward processing decisions for the excursions in the CPPs, IPCs, hold times, storage times and processing times is subject to the outcome of the deviation investigation. Any failure in IPCs with defined acceptance criteria would result in batch/solution lot rejection. Any failure in IPCs with defined action limits will be assessed for impact to product quality and investigated within the quality system prior to batch disposition.

Ide-cel is manufactured using aseptic techniques and closed system manipulations, whenever possible. Critical aseptic manipulations are performed within and ISO (b) (4)/Grade (b) (4). Aseptic process simulations are completed (b) (4).

Overall Reviewer's Assessment of Section 3.2.P.3.4:
The characterization/validation data support the selection and justifications for the DP manufacturing process controls.

3.2.P.3.5 Process Validation and/or Evaluation
The (b) (4) complete ide-cel PPQ campaigns are described **in Section 3.2.S.2.5 Process Validation and/or Evaluation**. During the first PPQ Campaign, the DP was filled into (b) (4) 50 bags at a target fill volume of (b) (4) for all (b) (4) PPQ lots to represent a worst-case high-end surface area to fill volume scenario (Figure 11). Filling by (b) (4) to meet a low target fill volume also represents worst case from a processing perspective. During the (b) (4) PPQ campaign, DP was filled into (b) (4) 250 bags at a target fill volume of (b) (4) in order to fill larger volumes into a fewer number of cryopreservation bags. These lots more closely represent configurations encountered during routine clinical manufacturing.

A supplemental filling validation study was performed to demonstrate that DP can be consistently and accurately filled to a specified volume into all 3 DP bag sizes ((b) (4) 50, (b) (4) 250 and (b) (4) 500), during ide-cel DP commercial manufacturing. The cryopreservation buffer (1:1 ratio of CryoStor CS10 and Plasma-Lyte) was used as a surrogate for DP in this study. The cryopreservation buffer was filled into (b) (4) bags each of the (b) (4) 50 ((b) (4) mL), (b) (4) 250 ((b) (4) mL), and (b) (4) 500 ((b) (4) mL) bags according to the commercial fill strategy. Filling of each bag size was performed at (b) (4) different fill stations by (b) (4) different operators.

The results from the study demonstrated that DP could be consistently and accurately filled to a specified volume into all 3 cryopreservation bags during ide-cel DP manufacturing (Table 79). The acceptance criteria based on the tolerance limits for each bag type were defined based on the process capability analysis for filling into the three different bag types during the clinical, PPQ and post-PPQ runs.

Table 79. Bag Fill Volume – Tolerance Range

Bag Type	Target Fill Volume (mL)	Acceptance Criteria (mL)	Validation Results (mL, mean ± SD)
(b) (4) 50	(b) (4)		
(b) (4) 250			
(b) (4) 500			

Drug Product Homogeneity Validation
The homogeneity of filled ide-cel DP bags was demonstrated through a validation study where cryopreserved DP bags from the (b) (4) of DP filling from 3 DP lots manufactured from (b) (4) material and filled into (b) (4) 250 bags were tested for cell concentration. Acceptance criteria for DP bag fill homogeneity were as follows:

(b) (4)

The 3 DP lots were filled into (b) (4) bags, respectively. The CVs were (b) (4), respectively. The maximum deviations from the grand mean were (b) (4), respectively. Thus, the cell concentration results of each bag tested, along with the release testing samples for each lot, met the prespecified acceptance criteria.

Drug Product Shipper Validation

The ide-cel shipper is designed to maintain internal temperatures of (b) (4) for a minimum duration of (b) (4). The shipper was selected by evaluating vendor qualification data against the product requirements and shipping conditions. The selected shipper uses charging with liquid nitrogen to maintain cryogenic product temperatures. The DP shipping validation study involved shipping of 3 DP lots ((b) (4) bags) from the S12 facility to (b) (4) and back using the planned commercial packout procedures. Product quality was then evaluated by assessing impact on critical quality attributes. There were no temperature excursions encountered during the 3 shipments, the DP lots met all commercial acceptance criteria post-shipment and no significant impacts to ide-cel critical quality attributes were observed. Please see DMPQ review for additional details on the shipper validation.

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

The information provided supports validation of the ide-cel mixing, filling and shipping procedures.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

This section evaluates the specifications for (b) (4) excipients to determine the quality and quality control of the excipients in the DP. The only (b) (4) excipient cited is Plasma Lyte A Injection pH 7.4 (Multiple Electrolytes Injection, Type 1). The FDA code (0338-0221-04) for the Plasma Lyte is provided; specification is listed as compliant with (b) (4). In addition, COA is supplied for PlasmaLyte from (b) (4). The (b) (4) excipient used in the DP is CryoStor CS10 Freeze Media that contains 10% dimethyl sulfoxide (DMSO). The CryoStor CS10 is obtained from (b) (4). A COA was provided for the CryoStor CS10. Release specifications for CryoStor CS10 are defined and include controls for (b) (4)

Celgene states that both the supplier ((b) (4)) and Celgene use the same specifications to release the CryoSTor CS10.

Reviewer Comments:

A letter of authorization to cross-reference the master file (MF) BB-MF (b) (4) from (b) (4) was provided and reviewed elsewhere in this review memo.

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

The analytical procedures for the (b) (4) excipient Plasma-Lyte A Injection pH 7.4 are stated as compliant with (b) (4). Analytical procedures for Plasma-Lyte A lot release are stated as

verified (3.2.P.4.3), and method validation is considered unnecessary. Summary descriptions are provided for the (b) (4) analytical procedures for CryoStor lot release (3.2.P.4.2). Appearance is visually inspected by Celgene and evaluated using what's termed "pre-specified Acceptance Quality Limit (AQL)." Both supplier and Celgene perform identity testing using (b) (4) from a control CryoStor CS10 is used as a benchmark for the testing by Celgene. Lots are (b) (4) for assessing DMSO content.

Reviewer Comments:
Plasma-Lyte A Injection is compliant with (b) (4)*. CyroStor CS10 is referenced to the Master File (MF)* (b) (4) *which is in good standing to support manufacturing. Validation summaries for the* (b) (4) *assays used for CryoStor CS10 lot release,* (b) (4) *Assay and determination of DMSO content by* (b) (4)*, are provided and are acceptable.*

3.2.P.4.5 Excipients of Human or Animal Origin
Not applicable.

3.2.P.4.6 Novel Excipient
Not applicable.

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)
This section evaluates the lot release specifications for the DP to assess the justifications for the critical quality attributes (CQAs) (appearance, identity, purity, strength, potency, and safety) of the ide-cel DP. Celgene performed statistical analysis for each CQA for DP lots manufactured with Process (b) (4) for the pivotal trial MM-001 to determine the proposed lot release acceptance criteria for Process (b) (4), the proposed commercial process. A comparability study was performed to support comparability of Process (b) (4) and Process (b) (4). Three criteria were used to choose which DP lots manufactured in the MM-001 trial to include in the statistical analysis:

1) lots that passed specifications,
2) lots that were infused,
3) lots for which infused subjects were assessed for safety and efficacy, and infusion was not associated with any therapy related adverse events.

Reviewer Comments:
In response IR#38, sent 12/28/2020, Celgene provided additional information on the lots that were excluded from the statistical analysis used to set the acceptance criteria in Amendment 36. DP lots made from a single patient PBMCs and infused separately, as part of a retreatment, were excluded, because subject outcomes could not be correlated with a single DP lot. Other lots were excluded for the following reasons: subject was enrolled but not treated, lots were combined, dose was not met (BB2121-MM001-(b) (6)*), lot was manufactured for a second infusion, infusion was associated with a serious adverse event, or the subject was from the Japanese cohort for the MM-001-Japan trial. This is acceptable.*

Celgene provided additional information on manufacturing failures in Amendment 37. Of 169 clinical lots manufactured at Celgene (b) (4) *and Celgene S12 for the pivotal trial MM-001, only* (b) (4) *lots failed because they did not meet release specifications or manufacturing error.* (b) (4) *lots were remanufactured and successfully released.* (b) (4) *lots were released through exception. There was only* (b) (4) *instance where a lot failed, and a* (b) (4) *lot was manufactured from a second apheresis and also failed. Overall, the data supports manufacturing capability. This is acceptable.*

Celgene performed a statistical assessment of the critical quality attributes data from the ide-cel lots used in the BB2121-MM001 clinical trial using a one-sided tolerance interval (TI) approach with 95% confidence and 95% or 99.73% coverage. Using the 95% confidence with 95% coverage (95/95) approach, Celgene found that there were more outlier lots which previously were not identified as outliers in the quantile range outliers method. Celgene stated that these lots were also associated with similar patient outcomes compared to other lots. Therefore, Celgene chose to use the 95% confidence with 99.73% coverage (95/99.73) approach to establish the proposed acceptance criteria.

Reviewer Comments:
FDA did not agree with the use of the 95% confidence with 99.73% coverage approach, and proposed Celgene use 95% confidence with 97% coverage to set the commercial acceptance criteria in IR#38, sent 12/28/2020. Celgene agreed to 95/97 tolerance intervals and updated the commercial acceptance criteria in Amendment 36. In response to IR#63, sent 3/11/2021, Celgene provided an updated specification table incuding the approved dose range in Amendment 64. Celgene also updated the approved dose range throughout Module 3 in this amendment (e.g., Sections P.1, P.3.2, P.5.6). Table 80 includes the updated and final commercial lot release acceptance criteria.

Table 80. Quality Control Specifications for ide-cel

Test	Method	Acceptance Criteria	
		Release	Stability
General			
Appearance	Evaluation of visual appearance	Liquid, colorless cell suspension	
Identity			
CAR-positive T cell Percentage[a]	(b) (4)	Anti-BCMA02 CAR-positive T cells detected: LOQ (b) (4)	N/A
Purity			
T cell Percentage	(b) (4)	(b) (4)	N/A
Cell Viability Percentage	(b) (4)	(b) (4)	
CAR-positive T cell Percentage	(b) (4)	(b) (4)	
Potency			
(b) (4)	(b) (4)	(b) (4)	
Strength			
Dose	N/A (Calculation) [b]	300 × 10^6 to 460 × 10^6 CAR+T cells	N/A
Safety			
(b) (4)	(b) (4)	(b) (4)	N/A
Mycoplasma	(b) (4)	None detected	N/A
Sterility	(b) (4) sterility assay ((b) (4)	No growth	

Endotoxin	(b) (4)	(b) (4)	N/A

a Denoted as CAR+ T cell Percentage
b Dose is derived from cell concentration ,CAR+ T cell percentage, the volume/number of product bags shipped for infusion
BCMA = B cell maturation antigen; CAR = Chimeric antigen receptor; N/A = Not applicable
N/A = Not applicable; (b) (4)

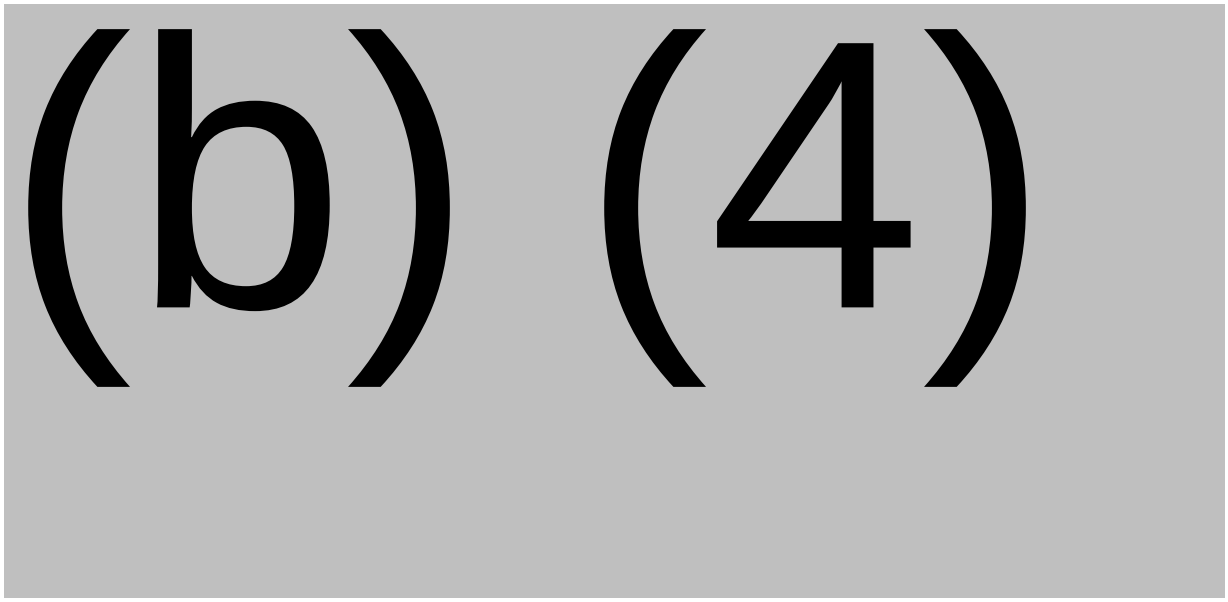
Appearance
The proposed appearance specification is assessed by (b) (4) . Color is determined with the (b) (4)

Reviewer Comments: This is acceptable.

Identity: CAR+ T cell Percentage
The proposed Identity specification is assessed with (b) (4)

Reviewer Comments:
In IR 38, we requested that the acceptance criterion be updated to LOQ of the assay in the lot release charts in the submission. In response to IR#38, sent 12/28/2020, Celgene agreed to revise the acceptance criterion from "CD3 positive CAR positive T cells detected" to "Anti-BCMA02 CAR-positive T cells detected" in Amendment 36. This is acceptable.

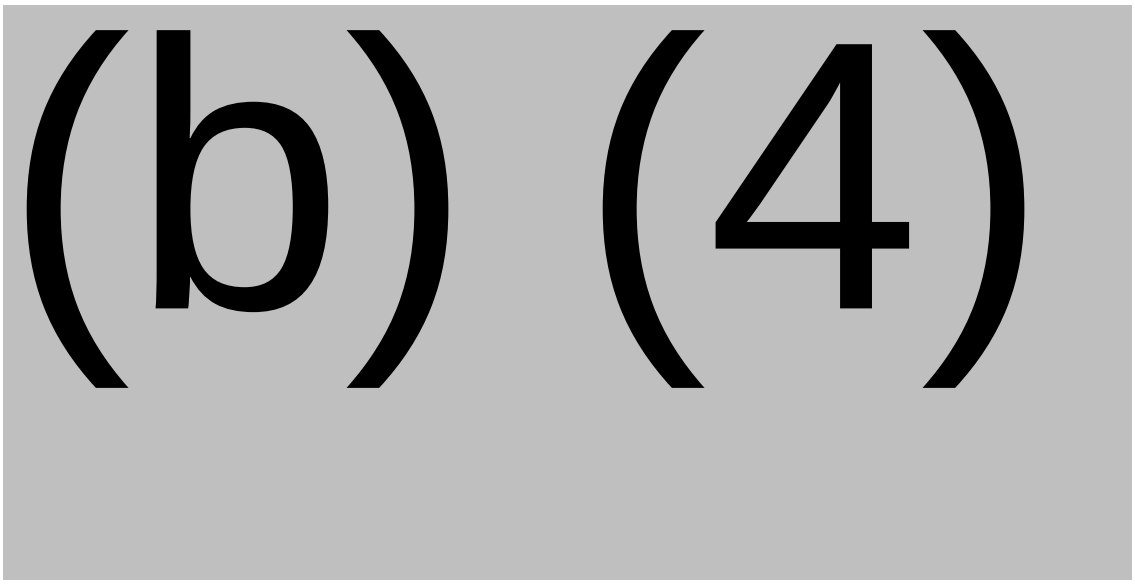
Purity: CAR+ T cell Percentage
The proposed Purity specification is assessed also by the (b) (4)



Reviewer Comments:
In response to IR#38, sent 12/28/2020, Celgene agreed to reassess the data for CAR+ T cell percentage with a 95% confidence and 97% coverage (95/97) two-sided tolerance interval. This request was made because the acceptance criterion ((b) (4)* CAR+ T cells) based on 95/99 tolerance interval results in a wide range that is not supported by the clinical experience of Celgene. Celgene declined to set an upper bound for two reasons. 1) CAR T cell percentage is a measure of content of the DP and not used for product potency. 2) Because* (b) (4) *and CAR T cell percentage are correlated, Celgene states that the proposed upper limit for* (b) (4) *will serve as a "de facto upper limit for CAR T cell percentage." Celgene agreed to revise the lower limit for CAR T cell percentage from* (b) (4) *CAR+ T cells to* (b) (4) *anti-BCMA02 CAR+ T cells which is based on 95/97 tolerance interval in Amendment 36. This is acceptable.*

Purity: T cell Percentage

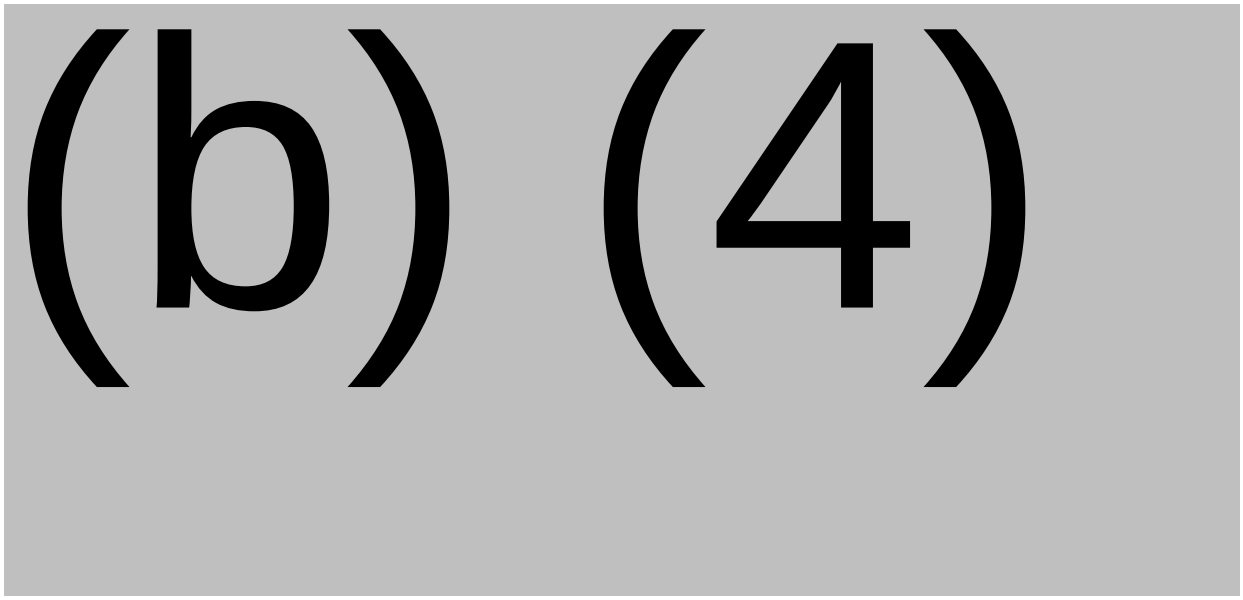
T cell percentage is assessed by (b) (4) . The acceptance criteria for T cell percentage was established similarly to CAR+T cell percentage specifications described above. A TI with 95% confidence and 99.73% coverage was used to set the proposed lower limit ≥ 95% (b) (4) T cells. Celgene's rationale for using a 95/99.73 TI as opposed to 95/95 TI is that a 95/95 TI led to exclusion of DP lots associated with safe and efficacious outcomes, such as lot with 96.0% (b) (4) cells. A summary of the T cell Percentage values for (b) (4) ide-cel DP lots included in Study BB2121-MM-001 was provided (mean: 99.1, min 96.0, max 100%; Figure 18). Statistical analyses were also provided: Lower limit 95/95 TI: 98.1%; 95/99.73% TI: 96.7%. The acceptance criterion for the clinical trial was (b) (4).



Reviewer Comments:
In response to IR#38, sent 12/28/2020), Celgene agreed to reassess the data for T cell percentage with a 95% confidence and 97% coverage (95/97) two-sided TI. This was requested because the data supports ability to set higher acceptance criterion. The 95/97 TI yielded a TI limit of 97.9%. Celgene revised the acceptance criteria from (b) (4) *to* [redacted] *in Amendment 36. This is acceptable.*

Cell Viability

Cell viability is assessed using (b) (4) [redacted] The proposed acceptance criterion (b) (4) [redacted]" was established as the midpoint between the TI analysis with 95% confidence and 99.73% coverage (95/99.73) and 95/95 TI analysis. The 95/95 TI excluded DP lots associated with safe and efficacious outcomes, such as lots with (b) (4) viable cells. Celgene considers the 95/99.73 TI analysis to better represent their clinical experience with cell viability percentages that are safe and efficacious. A summary of the of Cell Viability for (b) (4) ide-cel DP lots included in Study BB2121-MM-001 was provided ((b) (4) [redacted]; Figure 19). Statistical analyses were provided: Lower limit 95/95 TI: 83.1%; 95/99.73% TI: 74.8%. The acceptance criterion for the clinical trial was (b) (4) for the commercial product Celgene proposed (b) (4).



Reviewer Comments:
In response to IR#38, sent 12/28/2020, Celgene agreed to reassess the data for viable cells percentage with a 95% confidence and 97% coverage (95/97) two-sided TI. This request was made because the data indicate ability to set a tighter acceptance criterion. Celgene revised their acceptance criterion to (b) (4) *viable cells in Amendment 36 based on the 95/97 tolerance interval which yielded a limit of* (b) (4)*. This is acceptable.*

Potency: (b) (4)
Potency is assessed by (b) (4) . The proposed acceptance criterion for potency (b) (4) " was established using a TI with 95% confidence and 95% coverage. TI analysis with 95% confidence and 99.73% coverage was also performed. The 95/99.73 TI analysis was rejected for setting the acceptance criterion because it encompassed (b) (4) lots of DP "associated with a subject that did not respond to ide-cel therapy" according to Celgene. A summary of (b) (4) values for (b) (4) ide-cel DP lots included in Study BB2121-MM-001 was provided (mean: (b) (4) ; Figure 20). Statistical analyses were also provided: Lower limit 95/95 TI: 11.0%; 95/99.73% TI: 4%. The acceptance criterion for the clinical trial was (b) (4) for commercial DP Celgene proposed (b) (4).

(b) (4)

Reviewer Comments:
In response to IR#38, 12/28/2020, Celgene agreed to reassess the data for (b) (4) *percentage with a 95% confidence and 97% coverage (95/97) two-sided TI. This request was made because the distribution of* (b) (4) *in the MM-001 trial supports a higher lower limit than the proposed lower limit* (b) (4) *. The percentage of* (b) (4) *is on average* (b) (4) *in the MM-001 trial. Also, an upper limit is needed given the lack of clinical experience with* (b) (4) *beyond the distribution observed in the data. Celgene agreed to revise the lower limit acceptance criterion for* (b) (4) *to* (b) (4) *" and to add an upper limit of* (b) (4) *" based on 95/97 two-sided TI in Amendment 36. This is acceptable.*

Dose

Ide-cel dose is determined by multiplying the viable cell concentration by the CAR T cell percentage. The proposed acceptance criterion for dose ((b) (4) $\times 10^6$ CAR+ T cells to (b) (4) $\times 10^6$ CAR+ T cells) was determined based on safety and efficacy data from the clinical trials.

Reviewer Comments:
The pprovable dose was revised by clinical to be 300 - 460$\times 10^6$ CAR+ T cells. Though the calculation remains the same.

(b) (4)

(b) (4)

(b) (4)

Mycoplasma
Mycoplasma is assessed by (b) (4) from Mycoplasma species. The assay has a detection limit of (b) (4) per sample. The proposed acceptance criteria "None Detected" is based on (b) (4)

Reviewer Comments:
This assay is reviewed by DBSQC. DBSQC determined that insufficient data had been provided to support the comparability of the (b) (4) test to the (b) (4) method so a PMC to provide additional comparability data was issued. Celgene has agreed to this PMC to address DBSQC's concerns. Please see DBSQC review for additional details.

Sterility
The proposed sterility specification is performed with the (b) (4) system to detect the (b) (4) . The proposed acceptance criteria "No Growth" is based on the (b) (4)

Reviewer Comments: This assay is reviewed by DBSQC. DBSQC found the assay to be acceptable. Please see DBSQC review for additional details.

Endotoxin
The proposed Endotoxin acceptance criteria is based on the limits in the (b) (4) so that (b) (4) is not exceeded. With an average patient weight of ≥60 kg, a single dose limit is (b) (4). With a maximum dose volume of 250mL, the proposed endotoxin limit is (b) (4) .

Reviewer Comments: This assay is reviewed by DBSQC. DBSQC found the assay to be acceptable. Please see DBSQC review for additional details.

Replication Competent Lentivirus (RCL)
Justification for the exclusion of RCL testing is provided and reviewed in **Section 3.2.S.2.5 Process Validation and/or Evaluation**.

Cell Concentration
Cell concentration is performed as part of dose determination and is therefore monitored during that specification. Cell concentration is conducted in-process during (b) (4) . The range of cell concentration for (b) (4) lots administered in the pivotal trial MM-001 was provided ((b) (4)).

Reviewer Comments:
In response to IR#38, sent 12/28/2020, Celgene agreed to include (b) (4) DP lots manufactured with the proposed commercial process, Process (b) (4), at the proposed commercial facility (Celgene S12) in the data used to establish the acceptance criteria using 95/97 TI (Amendment 36). This request was made because the acceptance criteria initially proposed only used lots manufactured with a comparable process, Process (b) (4) at Celgene (b) (4) which is not the proposed commercial facility. Celgene stated that these lots were previously excluded because they were manufactured for subjects in the ongoing MM-001-Japan trial which was considered a separate study for safety and efficacy.

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:
Following Interaction with the applicant, agreement on the commercial ide-cel release specifications has been reached.

3.2.P.5.2 Analytical Procedures and 3.2.P.5.3 Validation of Analytical Procedures
3.2.P.5.2 Analytical Procedures
This section describes the analytical procedures for ide-cel DP lot release to determine if the methods are suitable for their intended purpose. Step by step procedures/SOPs for each method used for lot release is provided. For example, formulas for calculations needed to prepare solutions, determine appropriate cell concentrations and number of DP vials, voltage settings, instrument set-up for sample acquisition are included in the analytical procedures for identity, purity, and viability.

Appearance Analytical Procedure
(b) (4) used for the appearance test is performed on the thawed DP and as part of stability assessment. The analytical procedure includes the (b) (4) DP samples are thawed in a (b) (4) . The method allows for flexibility in the size of (b) (4) and time for thawing depending on the number of samples to be thawed. All samples are viewed (b) (4) . Color and form of the samples are documented on FORM-003692. Settings for the (b) (4) are referenced to SOP-003203.

Reviewer Comments:
In response to IR#28, sent 11/19/2020, Celgene provided several missing SOPs that are referenced in the procedure, such as the SOP for calibration of the (b) (4) *used to assess appearance of the samples was supplied in Amendment 25. The method uses* (b) (4) *Celgene instruments* (b) (4) *). This is acceptable.*

Identity (CAR+), Viability, and Purity (%T cell) Analytical Procedure ((b) (4) **)**
The (b) (4) method is used for identity, purity, and viability testing of in-process, lot release, and stability of the DP. The method is intended to be used at the NJ CAR T manufacturing sites. For DP assessment, (b) (4) . The system suitability criteria were added in Table 81 for additional detail.

Table 81. System Suitability and General Assay Acceptance Criteria

Sample Type	Sample Name	Acceptance Criteria
System Suitability	(b) (4)	(b) (4)
	Compensation Controls	
	(b) (4) Controls	
	Assay Controls	
Samples	Test Samples	
Number of Events	Minimum Number of (b) (4) or Limit of Quantification of (b) (4)	
If the criteria above do not conform to the acceptance criteria, notify supervisor and follow SOP-003073, SOP-001145 and SOP-001146		

In instances, where (b) (4) .

Reviewer Comments:
In response to IR#28, sent 11/19/2020, Celgene justified the use of (b) (4) *. Celgene clarified that* (b) (4) *are used when* (b) (4) *differ due to normal donor to donor variability.* (b) (4) *are considered valid as long as* (b) (4) *can be clearly distinguished. In cases where distinction of* (b) (4) *is not*

(b) (4)

Celgene states that (b) (4) *Graphs were also supplied in Celgene response to support detection of* (b) (4) *. This is acceptable.*

System suitability testing has been appropriately included in the (b) (4) *assay. There are multiple internal controls with acceptance criteria that must be met before the DP samples are evaluated. According to the* (b) (4) *guidelines, system suitability parameters are established to ensure that the validity of the analytical procedure is maintained whenever used. The assay controls used to determine system suitability have acceptance criteria that support the robustness of the system (intra-assay precision* (b) (4) *CV for T cell percentage, CAR+T cell percentage, and cell viability) for the assay's intended purpose. The main purpose of the* (b) (4) *method is to detect T cells, CAR+T cells, and viable cells. This is acceptable.*

The (b) (4) data is analyzed using the mean, standard deviation and % coefficient of variation (%CV) of (b) (4), T Cell Percentage and CAR T Cell Percentage. Rounding is not performed until the final results. Percent expression is reported to the tenth place, and %CV reported as a whole number. A validated (b) (4) spreadsheet is referenced for performing calculations, as well as antibody calculations for (b) (4) used to detect T cells and CAR T cells.

Reviewer Comments:
In IR#28, sent 11/19/2020, additional information was requested for review of the (b) (4) *assay. In Amendment 25, Celgene provided several missing SOPs that are referenced in the procedure (but were omitted), the method/procedure for generating validated* (b) (4) *spreadsheet used for data analysis, how the expiration dates for* (b) (4) *working solutions are determined, how working* (b) (4) *is prepared, and bridging studies for previously and newly prepared working* (b) (4) *. Bridging data for in-use working* (b) (4) *labeled* (b) (4) *lot* (b) (4) *supports precise (*(b) (4) *CV intra-assay,* (b) (4) *difference between current and new lot) bridging assay. Celgene also clarified that one model of* (b) (4) *) is used to generate final results for lot release testing of DP lots and in-process testing* (b) (4) *in the* (b) (4) *assay. Characterization studies such as* (b) (4)
assay done for DP are performed on the (b) (4) *, as well as* (b) (4) *assay for* (b) (4) *DP. This is acceptable.*

Potency Assay: (b) (4) **Analytical Procedure**
The potency assay for the ide-cel DP uses (b) (4) to measure (b) (4) by measuring the (b) (4) . (b) (4) is defined by Celgene as (b) (4)

CAR+ T Cell Percentage is the percent CAR+ of unstimulated replicates. (b) (4) is the percent activated (b) (4) . Compensation Controls are used to correct for (b) (4)
are used as negative controls to distinguish (b) (4)
. (b) (4) controls are (b) (4)

(b) (4) . The assay system suitability acceptance criteria are provided in Table 82. The method is intended for use at New Jersey CAR T operations sites.

Table 82. System Suitability and General Assay Acceptance Criteria

Sample Type	Sample Name	Acceptance Criteria
System Suitability	(b) (4)	(b) (4)
	(b) (4)	
	Compensation Controls	
	(b) (4) Controls	
	Assay Control	
Samples	Test Samples	
(b) (4)	(b) (4)	
If the criteria above are not met, notify a supervisor and follow SOP-003073, SOP-001145 and SOP-001146.		

Figures are provided in the procedure, to help the operator (b) (4) . Data is analyzed with the (b) (4) software using mean, standard deviation, coefficient of variance (CV) expressed as a percentage, (b) (4) . The percent expression is determined from (b) (4) Raw data formulas were provided in the BLA, were reviewed and *determined to be acceptable*.

Reviewer Comments:
In response to IR#28, sent 11/19/2020, Celgene provided several missing SOPs in Amendment 25 that are referenced in the procedure but were omitted. Celgene provided a rationale for non-

BMCA specific (b) (4) *. They stated that residual cellular activation is expected due to the use of anti-CD3 and anti-CD28 antibodies to stimulate T cell expansion in the ide-cel DP manufacturing process. The background expression is subtracted during data analysis. They also provided list of critical reagents, source, grade, storage conditions, stability, and validated shelf life for reagents used in the validation studies. Overall, reagent storage and stability/shelf life is based on the manufacturers guidelines, except for working solutions for which stability is determined by Celgene studies. In addition, SOPs were provided for multiple in-process procedures, such as creating working solutions of reagents (including* (b) (4) *, etc), determining acceptance criteria for the routine calibration of the* (b) (4) *, invalidating data, qualifying assay control.*
This is acceptable.

The acceptance criteria for system suitability for the potency assay adequately meets FDA recommendations for a controlled assay: intra-assay precisions (CV) (b) (4) *. Of note, the acceptance criteria for intra-assay precision for* (b) (4) *is higher than intra-assay precisions (CV)* (b) (4) *for CAR+ T cell Percentage. In response to IR#28, sent 11/19/2020, in Amendment 25, Celgene attributed the higher intra-assay precision for* (b) (4) *to the inherent variability in a stimulated assay compared to expression of the ide-cel CAR T protein. In addition, there were higher %CVs in the intra-assay precision experiments for* (b) (4) *relative to CAR+ T cell Percentage. This rationale is acceptable.*

Cell Concentration Analytical Procedure

The cell concentration analytical procedure is used for the DP lot release and stability testing. An average of (b) (4) runs within a sample are used to calculate the cell concentration. First, instrument controls are run with instrument specific control beads and must meet defined acceptance criteria that include (b) (4) difference between measured value and concentration assay value in COA for (b) (4) replicates of (b) (4) . Instructions are provided in the case the (b) (4) do not meet the acceptance criteria. The settings to be used for T Cell counting in the (b) (4) analyzer instrument are provided in the T cell counting script (T cell counting SOP). After the system suitability runs, blank controls consisting of (b) (4) are also run and must pass the acceptance criterion before proceeding. After the blank control meets the acceptance criteria for system suitability, (b) (4) assay controls are run and must meet acceptance criteria before the DP samples are tested. The SOP states that (b) (4) .
Thaw times for frozen DP samples are provided ((b) (4)). (b) (4) sample (b) (4) are tested for DP lot release. Blank controls are run in between analysis of different lots, and the machine is cleaned or flushed (b) (4) of runs. The acceptance criteria that the assay and samples must meet for results to be considered valid are provided in the submission. Results are to be reported to three significant figures, and are calculated as the mean cell concentration multiplied by the dilution factor used to dilute samples. Cell concentration is considered valid for a range of (b) (4) .

Reviewer Comments:
Overall the assay specifications provided support a controlled assay for determining cell concentration. The acceptance criteria (AC) for inter-assay precision (%CV (b) (4) *for the assay control meets FDA recommendation for a controlled assay. In addition,* (b) (4) *sample* (b) (4) *are run facilitating statistical robustness to the calculation of cell concentration. The Cell concentration assay has several controls (*(b) (4) *, blank, sample runs) with AC built into the SOP to ensure the assay performs as intended. These*

controls and the AC for these controls are intended to ensure the validity of the cell concentration method. The internal controls need to pass the established specifications before DP samples are analyzed. Therefore, system suitability is established for the assay. This is acceptable.

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.5.2

Overall, the methods for analytical procedures (along with the referenced SOPs) for appearance, identity, purity, viability, potency ((b) (4)), cell concentration, and (b) (4) provide detailed step by step procedures for each of the assays used for lot release. Directions are provided for samples and standards preparation (mixing, dilutions, hold times, etc). The list of reagents, equipment/apparatus used, and operating parameters is provided for each assay, with drawings or figures supplied for additional clarity. Acronyms are defined. Standards to maintain validity of the system suitability and operating ranges are provided. System suitability acceptance criteria is established. Representative calculation formulas for data analysis (standards, controls, samples) are also included. The format to report results is specified by the number of significant figures needed. This is acceptable.

3.2.P.5.3 Validation of Analytical Procedures

This section of the review evaluates the validation of analytical procedures used for DP lot release to determine whether the methods are appropriately validated for their intended use. The tests used for lot release include appearance, identity, purity and viability (T cell percentage, Cell Viability Percentage, CAR+T cell percentage), Potency by (b) (4) , Strength (Cell concentration), Safety ((b) (4) , Mycoplasma, Sterility, and Endotoxin). Validation of the analytical procedures for mycoplasma, sterility, and endotoxin are the purview of the DBSQC reviewer. Validation is assessed by evaluating parameters: specificity, linearity, limits of detection (LOD), limits of quantification (LOQ), range, accuracy, and precision of the assays.

Appearance: Validation of Analytical Procedure

The appearance test is described above and in (b) (4) *bb2121 Appearance Test* for bb2121(idecabtagene vicleucel aka ide-cel) to determine suitability for (b) (4) DP lot release. PROT-014652 (VAL-008755) *Appearance for bb2121 Drug Product by Visual Evaluation* was used to validate (b) (4) . Appearance is performed according to (b) (4) . Acceptance criteria for system suitability is provided in the submission. The

summary of the validation study results for the appearance assay is provided below. The (b) (4) derived DP lots (b) (4) were used for the validation studies for the appearance test and (b) (4).

Reviewer Comments:
In response to IR#28, sent 11/19/2020, in Amendment 25, Celgene provided a justification for the use of a (b) (4) *in the intermediate precision studies is that differences in cell concentration are most likely to influence changes in appearance of cell suspension because the formulation buffer concentration does not change. Appearance variability is attributed to sample heterogeneity, which is mimicked by varying concentration of cells. This is acceptable.*

A list of all reagents used to assess the color or appearance of samples, and determine the acceptance criteria for the assay were provided. Not shown for space constraints. They were appropriate.

Reviewer Comments:
(b) (4) *are used to set acceptance criteria for the DP appearance. The* (b) (4) *are used as a benchmark, and* (b) (4) *to ensure DP sample contains* (b) (4) *DP sample as an* (b) (4) *for the intermediate precision studies. Stability data and SOP for stability studies for the* (b) (4) *was provided by Celgene in Amendment 25 in response to IR#28, sent 11/19/2020. This is acceptable.*

The validation study was done over (b) (4) runs, (b) (4) analysts ((b) (4)), (b) (4) instruments ((b) (4)), (b) (4) cryopreservation solution lots ((b) (4)), (b) (4) DP test samples ((b) (4)) (b) (4) of which (b) (4) was (b) (4). The assay was appropriately controlled and system suitability was provided. 4 deviations were reported and corrective actions were taken.

Reviewer Comments:
Overall the validation studies support that the appearance method is fit for purpose. Additional information and clarifications were resolved over IR.

Identity, Purity, Viability (IPV): Validation of Analytical Procedure

The *Identity, Purity and Viability for bb2121 In-process and DP by* (b) (4) *validation protocol* PROT-016016 was used for the validation studies for the (b) (4) *Identity, Purity, and Viability Method for bb2121(ide-cel) In-process and DP by* (b) (4). The samples used in the validation study include (b) (4) DP lots with viable cells, (b) (4) DP lot with non-viable cells and (b) (4) lot.

Reviewer Comments:
In response to IR#28, sent 11/19/2020, Celgene clarified that all lots (validation samples) are from a (b) (4) *except for* (b) (4) *sample* (b) (4) *which was used in the specificity test , in Amendment 25. The different validation samples (*(b) (4)*) were generated by using different multiplicity of infection (MOI) to create a range of CAR+ T cell percentages.* (b) (4) *lot was made into non-viable DP sample by* (b) (4) *. Viability linearity study was done with the* (b) (4) *sample. In Amendment 42 Celgene performed Sadler's Precision modeling to evaluate differences between results obtained from clinical DP lots and the validated assay ranges. Specifically, the analysis focused on trends at higher end of ranges for linearity, accuracy,*

precision. Overall the Sadler's modeling insights support low %CVs or high precision at the upper ends of the validated ranges. This is acceptable.

Informal consult with Heba Degheidy has concluded that (b) (4) *control* (b) (4) *is acceptable for this type of assay. In response to IR#28, sent 11/19/2020, Celgene provided missing SOPs, such as the SOP-002683 used for calibration of the* (b) (4) *system and RPT-018124 used to set the qualified range for assay controls in Amendment 25. Celgene also provided a justification for setting the compensation controls* (b) (4) *not to exceed* (b) (4) *from the* (b) (4) *in Amendment 25. This* (b) (4) *acceptance criteria (*(b) (4) *was based on literature and because it provides* (b) (4) *This is acceptable.*

Deviations

8 deviations are reported for the validation studies, and corrective measures were applied.

A summary of the validation parameters tested is provided in Table 83.

(b) (4)

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

(b) (4)

Reviewer Comments:
Overall, the validation results support the use of the assay for its intended purpose. The identity, purity, and viability analytical procedure is a (b) (4) *assay; and the validation process has evaluated the characteristics (specificity, linearity, accuracy, precision, range, quantitation limit) recommended in the FDA guidance "Analytical Procedures and Methods Validation for Drugs and Biologics July 2015" and* (b) (4) *. The acceptance criteria meet FDA recommendations for a controlled assay: intra-assay precision %CV* (b) (4) *, intermediate precision %CV* (b) (4) *, linearity* (b) (4) *. The reported results pass the acceptance criteria. Additionally, the identity, purity, and viability analytical procedures can detect differences in the percentage of* (b) (4) *, CAR+, and are viable in the DP during storage, therefore this assay can be considered a stability indicating test.*

Samples failed the stability specifications (b) (4) *. Therefore, Celgene concluded that samples must be processed* (b) (4) *. However, the term "* (b) (4) *" did not specify a time frame for operators. In response to IR#28, sent 11/19/2020, in Amendment 25, Celgene agreed to revise the language in the method validation package to "* (b) (4) *", and to emphasize* (b) (4) *during training of analysts. This is acceptable.*

The validation was conducted with cryopreserved DP. Celgene concluded that the acceptance criteria from the validation studies is applicable to in-process and final DP. In Amendment 25, Celgene provided pre-validation data comparing repeatability and Intermediate precision of cell viability, T cell, CAR+T cell percentages for (b) (4) *, materials.Validation studies were done with material* (b) (4) *. Overall the data supports low variability between the samples (* (b) (4) *intra-assay precision,* (b) (4) *intermediate precision for cell viability;* (b) (4) *inter-assay precision,*

(b) (4) *intermediate precision for T cell;* (b) (4) *inter-assay precision,* (b) (4) *intermediate precision for CAR+T cell). Based on consistency between pre-validation and validation studies, Celgene has concluded the validated results apply to in-process and final DP. This is acceptable.*

Potency: Validation of Analytical Procedure

Potency is evaluated by (b) (4) in the DP. This assay is performed with (b) (4) . The assay is performed (b) (4) . As a result, the (b) (4)

(b) (4)

Celgene statement; "The anti-BCMA02 CAR protein contains the (b) (4) of the CD137 (4-1BB) receptor (amino acid (b) (4) , Figure 22) as part of its intracellular domain. The monoclonal anti- CD137 antibody ((b) (4)) used in the CAR T Cell Activation method was generated using (b) (4)

Method

(b) (4) *CAR T Cell Activation Method for bb2121 (ide-cel) DP by* (b) (4) is used for lot release and stability testing of the bb2121 DP. PROT-016358, *CAR T cell activation for bb2121 (ide-cel) DP by* (b) (4) *Validation Protocol* was used for the validation studies for (b) (4) . The CAR T Cell Activation assay ((b) (4)) is performed by (b) (4)

Reviewer Comments:
In response to IR#28, sent 11/19/2020, in Amendment 25, Celgene clarified that all DP validation test samples originated from (b) (4) *donor lots of PBMCS (*(b) (4) *) and the PBMC sample (*(b) (4) *) used in the specificity studies came from another donor.*

DP lots are transduced at different (b) (4) *to yield samples with different CAR+T cell percentages. This is acceptable.*

In response to IR#28, sent 11/19/2020, Celgene provided missing SOPs such as SOP-002427, version 2.0 referenced for the acceptance criteria for the (b) (4) *for system suitability; and SOP-002683, version 3.0 referenced for the acceptance criteria for the* (b) (4) *for system suitability in Amendment 25. In addition, Celgene provided justification for setting the acceptance criteria for the* (b) (4) *control as the* (b) (4) *must not exceed* (b) (4) *from the* (b) (4) *for system suitability. This* (b) (4) *acceptance criteria (*(b) (4) *) was based on literature and because it provides "a threshold* (b) (4) *relative to the* (b) (4) *occurs for all* (b) (4) *controls." This is acceptable.*

Celgene also provided a rationale for the acceptance criteria for intra-assay precision (CV) (b) (4) *of* (b) (4) *being higher than that (*(b) (4) *) for CAR+ T cell Percentage. This difference is attributed to higher variability in the* (b) (4) *assay (*(b) (4) *) compared to transgene (CAR) expression, and results from the validation studies. This is acceptable.*

Deviations

7 deviations are reported, and corrective measures taken.

(b) (4)

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

Reviewer Comments:
During the review questions arose concerning assay controls and acceptance criteria for the validaitons studies. These were all resolved. The validation data support that the assay is fit for its intended purpose. This is acceptable.

Cell Concentration: Validation of Analytical Procedure

The concentration analytical procedures, (b) (4) (*Cell Concentration Determination in bb2121 Drug Product*) and (b) (4) (*Cell Concentration Determination of PBMC used for bb2121 Drug Product Manufacture*), are used to assess the target concentration for (b) (4) DP ((b) (4)) and (b) (4) PBMCs ((b) (4)) lot release. (b) (4) is used for PBMC release after thawing and before transduction and stability testing. (b) (4) is for lot release before infusion and stability testing of the DP. The PROT-016068, *Cell Concentration for bb2121 Drug Product and PBMC by* (b) (4) *Method* validation protocol was used for the validation studies for (b) (4). To conduct the validation studies, samples were (b) (4)

Reviewer Comments:
In response to IR#28, sent 11/19/2020, Celgene clarified that all the DP validation samples were generated from (b) (4)*, and PBMC samples were manufactured from* (b) (4) *in Amendment 25. This is acceptable.*

In Amendment 25, Celgene also provided justification and additional data to support the use of (b) (4) *run to establish system suitability in. Instrument Accuracy studies with* (b) (4) *were done prior to validation.* (b) (4) *were done in* (b) (4) *replicates, and averaged for calculations. All* (b) (4) *runs done on the* (b) (4) *instrument had mean measurements* ((b) (4)*) that passed acceptance criteria intra-assay* (b) (4) *CV and* (b) (4) *Bias of nominal value or COA value from vendor. This is acceptable.*

Deviations

Five deviations are reported for the validation studies, and corrective measures taken.

(b) (4)

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

(b) (4)

Reviewer Comments:
The validation studies support that the cell concentration assay is fit for the intended prupose. The acceptance criteria for this assay meet the FDA recommendations to demonstrate control: intra-assay precision CV (b) (4)*, accuracy* (b) (4) *intermediate precision (CV)* (b) (4)*, R^2≥* (b) (4)*. The assay is able to detect changes in concentrations of cells over a* (b) (4) *time period, therefore this assay can be considered a stability-indicating test. No spiking challenges with samples of known concentrations were done. However, matrix and sample interference were tested with the* (b) (4) *the DP. In the absence of identified leachables or extractables that could perturb the concentration of cells, these challenges support specificity of this assay since the* (b) (4) *are the other known mediums present with the possibility of perturbing detection of concentration of cells. Missing SOPs were provided in Amendment 25, in response to IR#28, sent 11/19/2020. This is acceptable.*

In response to IR#28, sent 11/19/2020, Celgene provided data to support the range of concentration from (b) (4) *for the PBMC in Amendment 25. Justification for the use of* (b) (4) *DP, and* (b) (4) *PBMC to establish stability was provided by Celgene in Amendment 25 in response to IR#28, sent 11/19/2020. Celgene has used stability data from in-use DP stability studies to support stability of samples in this assay and the lack of donor to donor variability. Additional post-thaw DP stability data up to* (b) (4) *hours was provided in the response to support stable cell concentration across donors. Celgene also justified the time points tested as being in line with ICH Q1A(R1) guidelines for stability studies and for achievement of maximum flexibility for QC operators. This is acceptable.*

In Amendment 25, Celgene also explained how the cell concentration assay was evaluated for robustness. Robustness studies were done by testing (b) (4) *DP and* (b) (4) *PMBC validation samples (concentrations:* (b) (4) *) with* (b) (4) *lots of* (b) (4) *per concentration were tested in* (b) (4) *replicate. Robustness was considered met if the mean of the* (b) (4)

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

(b) (4)

3.2.P.5.4 Batch Analyses

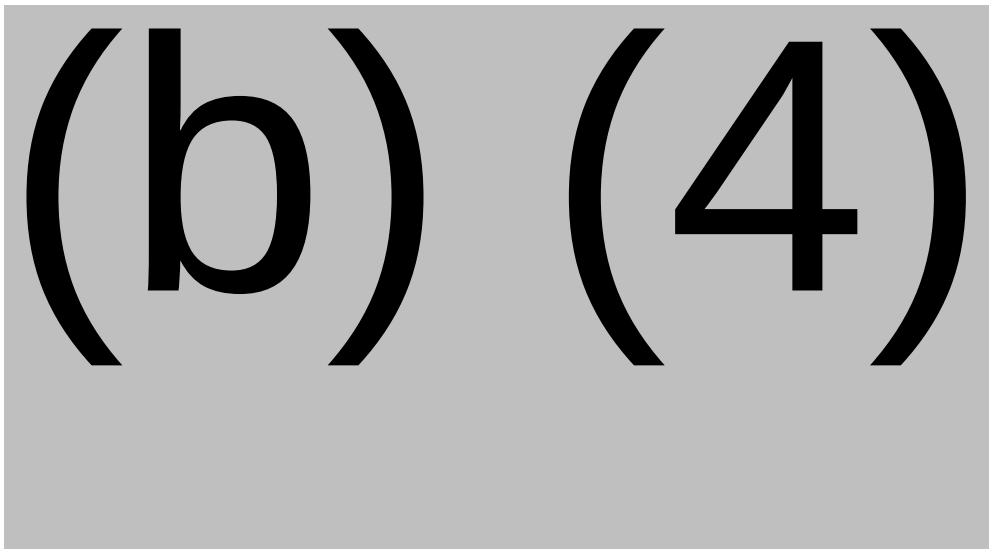
This section evaluates the DP batch analysis to determine acceptable parameters for commercial DP lot release. (b) (4) lots out of (b) (4) lots manufactured at the (b) (4) facility for BB2121-MM-001(MM-001) clinical trial were used to set the acceptance criteria for commercial DP lot release. The following lots administered in the the MM-001 trial, were not used in the analysis.

- (b) (4) DP lots (manufactured from the (b) (4) PBMC (b) (4)) being (b) (4) for infusion to meet the batch acceptance criteria for dosing: Lots (b) (4); and Lots (b) (4)
- (b) (4) cases of re-dosing with an (b) (4) DP lot (manufactured from the (b) (4) PBMC (b) (4)):
  - Lots (b) (4)
  - Lots (b) (4)
  - Lots (b) (4)
  - Lots (b) (4)
  - Lots (b) (4)
  - Lots (b) (4)
  - Lots (b) (4)
  - Lots (b) (4)
- (b) (4) lots were not infused because the patient was no longer eligible for treatment: Lots (b) (4).
- (b) (4) reported cases of patients being dosed more than once from the (b) (4) DP (b) (4): Lots (b) (4)
- (b) (4) that was out of specification for potency and released under an exception request.

Batch data were also provided for DP lots in the clinical trials CRB-401, MM-001, MM-002, and MM-003. However, only the the MM-001 lots were used to set specifications for ide-cel (see **Section**

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

CAR+ T Cell Percentage (Identity/Purity Test) Results Analysis
CAR positive T cells detection is used for identity and purity tests for DP lot release. The test is performed by (b) (4) that detects anti-BCMA02 CAR T cells. CAR+ T Cell Percentage is the percent CAR+ of unstimulated cells. The proposed acceptance criteria for lot release is (b) (4). Reviewer analysis was conducted to determine acceptability of this acceptance criteria. Data from the two manufacturing facilities (Celgene (b) (4), Celgene S12) used for the pivotal trial MM-001 are provided in Figure 23.



Reviewer Comments:
The CAR positive T cells data support setting a specific percentage of CAR positive T cells for the Identity test, and higher percentage of CAR T cells than the proposed acceptance criteria of (b) (4) *for purity. On average the percent of CAR positive T cells span* (b) (4) *across the four clinical trials, with a relatively even distribution. In the MM-001 trial, the CAR positive T cell percentage is evenly distributed and lies on average* (b) (4) *, with two outliers. The CAR positive T cell percentage is higher (ranging* (b) (4) *on average) in the data from the proposed commercial facility, Celgene S12, compared to the data from the Celgene* (b) (4) *facility where CAR positive T cell percentage ranges from* (b) (4) *. The mean CAR positive T cell percentage in the MM-001 trial is* (b) (4) *with a 95% confidence interval of* (b) (4) *. Overall, the data analysis supports setting an acceptance criteria of at least* (b) (4) *CAR positive T cells for the proposed commercial facility, Celgene S12, instead of simply detection of and* (b) (4) *percentage. The acceptance criteria for identity could be set lower than* (b) (4) *given it's an identity test for which a precise numerical is not necessary.*

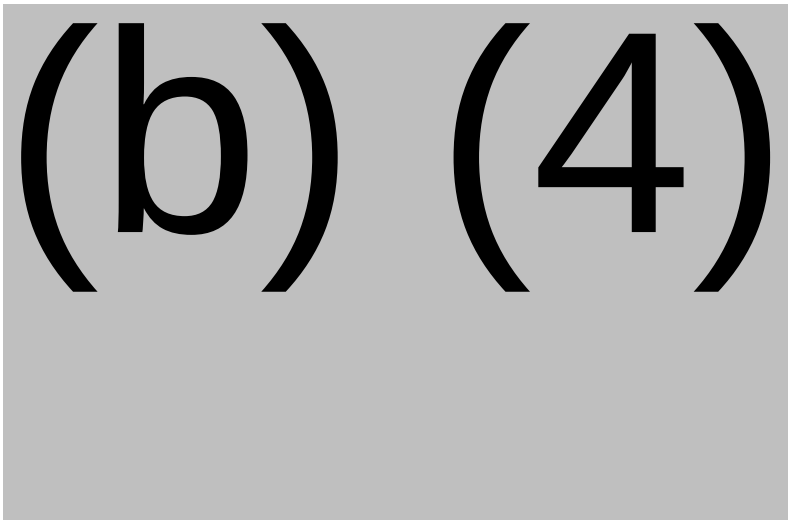
Celgene stated that the acceptance criterion for Identity is the LOQ of the assay ((b) (4) *). In response to IR#38, sent 12/28/2020, Celgene agreed to revise the acceptance criterion for Purity from a lower limit CAR T cell percentage* (b) (4) *to* (b) (4) *in Amendment 36. This is acceptable.*

In Amendment 36, Celgene also agreed to revise the acceptance criterion from (b) (4) *This request*

was made given (b) (4) *This is acceptable.*

Viability (Purity Test) Results Analysis

The viability test used as a purity test for DP lot release is performed with (b) (4). Viability results from the clinical trials was analyzed by the reviewer to assess acceptability of the proposed acceptance criteria (b) (4). The percentage of viable cells was compared between the two manufacturing facilities (Celgene (b) (4), Celgene S12) for MM-001 (**Figure 24**).



Reviewer Comments:
The viability data for DP lots in all four trials meets the acceptance criteria of (b) (4) *but supports ability to set higher acceptance criteria. The viability of cells in all four trials lies on average between* (b) (4) *with a few outliers below that. Viability of cells in the pivotal trial MM-001 are lower (on average between* (b) (4) *) than the other trials, although all lots are above* (b) (4) *viability. The mean viability for cells in the MM-001 trial is* (b) (4) *with a confidence interval of* (b) (4) *. In the MM-001 trial, the viability of cells in the proposed commercial facility, Celgene S12, are on average (*(b) (4)*) higher than cells from DP lots manufactured in the Celgene* (b) (4) *facility (*(b) (4)*). In response to IR#38, sent 12/28/2020, Celgene agreed to revise their acceptance criterion to* (b) (4) *viable cells in Amendment 36. This is acceptable.*

T Cell Percentage (Purity Test) Results Analysis

T cell percentage is performed as part of the purity tests for DP lot release, and is done by (b) (4). The results of the DP batch data were analyzed to determine acceptability of the proposed acceptance criteria (b) (4). The percentage of T cells in DP lots for the MM-001 trial were compared between the two facilities (Celgene (b) (4), Celgene S12) for MM-001 (**Figure 25**).

Figure 25. Percentage of T cells in Drug Product lots in MM-001 trial

(b) (4)

Reviewer Comments:
Analysis of the percentage of T cells data indicates the lots meet the proposed acceptance criteria (b) (4) *cells, but the analysis also support ability to set higher acceptance criteria. The percentage of T cells in the DP lots for all four clinical trials is on average between* (b) (4) *. The mean percentage of T cells in the DP lots in the pivotal trial MM-001 is* (b) (4) *with a confidence interval of* (b) (4) *. The percentage of T cells in the DP lots manufactured at the proposed commercial facility, Celgene S12, is slightly higher (closer to* (b) (4) *) compared to lots manufactured at Celgene* (b) (4) *(closer to* (b) (4) *). Within the MM-001 trial, even lots with T cell percentages outside the middle* (b) (4) *(interquartile range) are above* (b) (4) *, beginning around* (b) (4) *. In response to IR#38, sent 12/28/2020, Celgene agreed to revise the acceptance criteria from* (b) (4) *to* (b) (4) *in Amendmetn 36. This is acceptable.*

(b) (4) (Potency Test) Results Analysis
(b) (4) is performed as the potency test for CAR T cell activation for lot release. The assay uses (b) (4) Distribution of (b) (4) batch data was compared between the two manufacturing facilities for the pivotal trial, MM-001 (Celgene (b) (4), Celgene S12) (Figure 26). This data was analyzed by the reviewer to determine acceptability of the proposed acceptance criteria (b) (4) .

(b) (4)

Reviewer Comments:
The data meets the proposed acceptance criterion (b) (4) *for the potency test for DP lot release; however the data also indicates ability to set higher acceptance criterion. The distribution of percentage of* (b) (4) *falls on average between* (b) (4) *across the four clinical trials. DP lots in the pivotal trial MM-001 have on average between* (b) (4) *. In the pivotal trial, MM-001, DP lots manufactured at the proposed commercial manufacturing facility have on average higher percentage of* (b) (4) *compared to lots manufactured at Celgene* (b) (4) *. The mean* (b) (4) *in lots used in the pivotal trial, MM-001, is* (b) (4) *with a 95% confidence interval of* (b) (4) *. Overall, the average indicates a higher acceptance criterion than* (b) (4) *is possible. In response to IR#38, sent 12/28/2020, Celgene agreed to revise the lower limit acceptance criterion for* (b) (4) *to* (b) (4) *", and to add an upper limit of* (b) (4) *" based on 95/97 two-sided tolerance interval analysis in Amendment 36. This is acceptable.*

(b) (4)

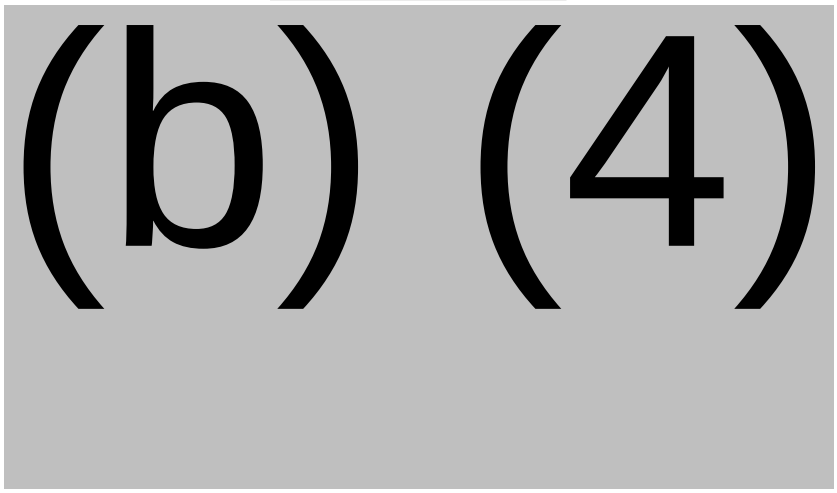
(b) (4)

(b) (4)

(b) (4)

Cell Concentration Results Analysis

Cell concentration test is used to calculate the dose. The cell concentration assay is done by T Cell counting in the (b) (4) analyzer instrument. Cell concentration batch data from the two manufacturing facilities used for the pivotal trial, MM-001 (Celgene (b) (4), Celgene S12) were analyzed by the reviewer to evaluate capacity to meet the proposed acceptance criteria (b) (4) CAR+T cell) for DP lot release (Figure 28).



Reviewer Comments:
The cell concentration batch data supports ability to generate sufficient cell concentration to achieve the lot release acceptance criteria for dose (b) (4) *CAR+T cell), especially if multiple bags of cellular DP is combined to achieve one dose per subject. The distribution of cell concentration in all four trials is on average* (b) (4) *. The distribution of cell concentration in the pivotal trial MM-001 is on average between* (b) (4) *, with a mean of* (b) (4) *and 95% confidence interval of* (b) (4) *. The cell concentration of DP lots is higher in lots manufactured at the proposed commercial facility, Celgene S12, compared to Celgene* (b) (4)*. However, the even distribution of lots manufactured at Celgene* (b) (4) *still support ability to meet the proposed acceptance criteria for lot release, given the comparability of the manufacturing processes used at both facilities. This is acceptable.*

Endotoxin Results Analysis

Endotoxin is performed as part of the safety lot release tests. Endotoxin results were evaluated to assess acceptability of the proposed acceptance criteria: (b) (4) . Lots for all four clinical trials were analyzed for percentage of lots with (b) (4) .

Reviewer Comments:
Overall Endotoxin results support an acceptance criterion of (b) (4) *. Most lots,* (b) (4)*, for all four trials reported Endotoxin levels* (b) (4) *. Only* (b) (4) *of lots (equivalent to* (b) (4) *lots) reported Endotoxin* (b) (4) *. Of the* (b) (4) *lots in the MM-001 trial, only* (b) (4) *lots had endotoxin* (b) (4) *and none of the lots reported Endotoxin levels* (b) (4) *. This is acceptable.*

3.2.P.5.5 Characterization of Impurities
Characterization of impurities is referenced to **Section 3.2.S.3.2 Impurities**.

3.2.P.6 Reference Standards or Materials
There are no reference standards for the DP.

3.2.P.7 Container Closure System
This section of the memo reviews the container closure system for the DP. The DP is stored in three sizes of (b) (4) bags: (b) (4) 50, (b) (4) 250, or (b) (4) 500 supplied by (b) (4). The components for the bags are provided (Table 87).

Table 87. Primary Container Closure System Components

Component of (b) (4) Bag	Material of Construction	Quality Conformance
Bag	(b) (4)	(b) (4)
Loading tube (stub tube)	(b) (4)	
Crimped ports	(b) (4)	

The loading tube is part of the tubing set used for DP filling and is sealed and removed with a tubing sealer after filling. Celgene describes the sealed loading tube as remaining connected to the DP bag. The crimped ports are also sealed to the bag, and one port is used to remove DP for administration. Drawings for the bags were provided for all cryobags. Pictures of these bags can be seen in Figure 15.

The filled and labeled (b) (4) cryopreservation bags are packaged in a labeled aluminum cassette for storage in the gas phase of liquid nitrogen before shipping. There is (b) (4) bag per cassette, and up to (b) (4) cassettes are packed in a rack to prevent movement during shipping. The loaded rack is shipped in a liquid nitrogen dry vapor shipping system which is a double-walled storage cylinder called a dewar. The submission reports that the walls of the dewar are composed of an absorbent material that absorbs liquid nitrogen when the dewar is charged. The dewar, which has an outer plastic shell layer with foam inserts, is closed with a foam vapor plug. The cylinder is reviewed in **Section 3.2.P.2.4 Container Closure System**.

The following specifications are used to release the (b) (4) bags (Table 88).

Table 88. (b) (4) Cryopreservation Bag Specifications

Test	Acceptance Criteria
Supplier Testing	
Biocompatibility	Vendor attestation to compliance with (b) (4) applicable test requirements
Sterilization by (b) (4)	Specification range (b) (4)
Integrity ((b) (4) test)	Vendor attestation passes established acceptance criteria
Sponsor Testing	
Identity ((b) (4))	The (b) (4) conforms to that of the reference standard

(b) (4)

Certificate of Conformance (COC) for each of the different sizes of (b) (4) bags ((b) (4) 50N, (b) (4) 250N, (b) (4) 500N) is provided in the submission (section 3.2.A.2). COC are from the cited manufacture ((b) (4)) that certifies the bags are sterilized by (b) (4) and the fluid path is sterile and non-pyrogenic. The COC states bags have been tested for integrity using a (b) (4) test. The bags are listed as passing the acceptance criteria for integrity and sterility. Further review of the bags is deferred to DMPQ.

Reviewer Comments:
The (b) (4) bags are 510(k) cleared under (b) (4) for blood component freezing (per 21CFR 864.9100). Testing for that included biocompatibility testing, thermal shock, durability in liquid nitrogen, and stability after sterilization. The labeled container closure is reviewed in further detail in ***Section* 3.2.P.2.4 Container Closure System***. Extractables and Leachables is reviewed in* ***Section* 3.2.S.2.5 Process Validation and/or Evaluation***, and stability for storage in the different sized bags reviewed in* ***Section* 3.2.P.8 Stability***.*

3.2.P.8 Stability

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

This section evaluates the stability data provided to support long-term cryogenic storage of the DP. The stability data was generated with (b) (4) primary DP lots produced with the proposed commercial manufacturing process, Process (b) (4) and (b) (4) secondary DP lots manufactured with a comparable process (Process (b) (4) ; Table 89). DP lots were stored in the container closure: (b) (4) cryopreservation bags ((b) (4) 50, (b) (4) 250, (b) (4) 500) and (b) (4) . Stability data is provided for different time points for primary and supportive DP lots stored in vapor phase of liquid nitrogen (≤-130ºC). DP lots were assessed based on the proposed commercial DP lot release acceptance criteria. Celgene states that assays were qualified and/or validated when the stability studies were performed.

Reviewer Comments:
Celgene provided updated stability data during review in Amendment 34. The updated data is included in this review.

Table 89. Stability Lots for Ide-cel DP

Designation	Drug Product Lot Number	Date of Manufacture	PBMC Manufacturing Facility	LVV Manu-facturing Facility	Drug Product Manufacturing Facility	Drug Product Container	Fill Vol. (mL)	Completed [and Planned] Test Intervals (months)	Study Duration (Months) & Status
Primary	(b) (4)	7 Oct 2019	Celgene S12[a]	(b) (4)	Celgene S12[a]	(b) (4) 50	(b) (4)	0,3,6,9,12	12, Completed
Primary		7 Oct 2019	Celgene S12[a]		Celgene S12[a]	(b) (4) 50		0,3,6,9,12	12, Completed
Primary		10 Oct 2019	Celgene S12[a]		Celgene S12[a]	(b) (4) 50		0,3,6,9,12	12, Completed
Primary		14 Nov 2019	(b) (4)		Celgene S12[a]	(b) (4) 250		0,3,12	12, Completed
Primary		21 Nov 2019	(b) (4)		Celgene S12[a]	(b) (4) 250		0,3,6,12	12, Completed
Primary		21 Nov 2019	(b) (4)		Celgene S12[a]	(b) (4) 250		0,6,9,12	12, Completed
Primary		10 Aug 2018	Celgene S12[a]		Celgene S12[a]	(b) (4) 250		0,3,6,12 (b) (4)	(b) (4) , Completed
Primary		17 Aug 2018	Celgene S12[a]		Celgene S12[a]	(b) (4) 250		0,3,6,12 (b) (4)	(b) (4) , Completed
Supportive		19 Jun 2018	Celgene (b) (4)		Celgene (b) (4)	(b) (4) 50		0,1,3,6,12 (b) (4)	(b) (4) , Completed
						(b) (4) 250		0,1,3,6,12 (b) (4)	(b) (4) , Completed
						(b) (4) 500		0,1	1, Completed

						(b) (4)	(b) (4)	0,1,3,6,12 (b) (4)	(b) (4), Completed
Supportive	(b) (4)	20 Jun 2018	Celgene (b) (4)	(b) (4)	Celgene (b) (4)	(b) (4) 50		0,1,3,6,12 (b) (4)	(b) (4) Completed
						(b) (4) 250		0,1,3,6,12 (b) (4)	(b) (4), Completed
						(b) (4) 500		0,1	1, Completed
						(b) (4)		0,1,3,6,12 (b) (4)	(b) (4), Completed
Supportive		23 Jun 2018	Celgene (b) (4)	(b) (4)	Celgene (b) (4)	(b) (4) 50		0,1,3,6,12 (b) (4)	(b) (4), Completed
						(b) (4) 250		0,1,3,6,12	12, Completed
						(b) (4) 500		0,1	1, Completed
						(b) (4)		0,1,3,6,12 (b) (4)	(b) (4), Completed

(b) (4); LVV = lentiviral vector;
a Clinical and Commercial manufacturing site
b Clinical manufacturing site
c Developmental grade LVV supplied by (b) (4)

Long term stability was assessed with the different cryopreservation bag sizes to account for the highest and lowest surface area to fill volume ratios used in the proposed commercial fill process (Table 90). The surface area to fill volume ratio is considered crucial because the rate of heat transfer is proportional to surface area and the total amount of heat extracted is proportional to the volume. Heat transfer capacity of the container closure during freezing and thawing directly impacts the heat transfer rate during cell solution temperature and phase changes that affect cell damage due to cryopreservation storage.

Table 90. Surface Area to Fill Volume Ratios of Cryopreservation Bags

(b) (4) Cryopreservation Bag	Surface Area (cm^2)	DP Fill Volume Range (mL)		Surface Area (cm^2) / Min Fill Volume (mL)	Surface Area (cm^2) / Max Fill Volume (mL)
		Min	Max		
(b) (4) 50[d]	(b) (4)				
(b) (4) 250					
(b) (4) 500					

Maximum surface area to fill volume ratio based on manufacturer's recommended fill volumes for (b) (4) 50, (b) (4) 250, and (b) (4) 500 bags
b Minimum surface area to fill volume ratio based on manufacturer's recommended fill volumes for (b) (4) 50, (b) (4) 250, and (b) (4) 500 bags
c Evaluated in lots (b) (4)
d Evaluated in lots (b) (4) with a (b) (4) mL fill volume and surface area (cm2) to fill volume (mL) ratio of (b) (4)
f Evaluated only for t = 1 month time point in lots (b) (4)

Reviewer Comments:
In response to IR#38, sent 12/28/2020), Celegene provided justification for the time points for which stability testing was omitted in Amendment 36. The stability study design was based on a matrix from (b) (4). The rationale for this is that there is not always enough of the larger (b) (4) bags ((b) (4) 250 and (b) (4) 500) to cover all stability time points (3,6,9,12 months) because an entire DP bag is needed for each time point. The amount of DP bags varies from lot to lot. Primary Lot (b) (4) is not tested at 6 and 9 months. All other primary stability lots are tested at 4 timepoints in the 0-12 months timespan. For supportive lots, the surface area to fill volume (SA:V) ratio is used to determine time points tested. The maximum and minimum SA:V ratio ((b) (4)) of the cryopreservation bags is tested, and determined to cover the (b) (4) 500 bag for Lots (b) (4). Celgene has committed to providing additional primary stability data for twelve months. Lastly, stability study for lots (b) (4)

(b) (4) for (b) (4) 500 cryopreservation bags was terminated after 1 month; these lots were not tested at (b) (4) months. This is acceptable.

Celgene also clarified the use of (b) (4) in Amendment 36 and provided vendor information. The (b) (4) are manufactured by (b) (4) . Celgene states that the (b) (4) This is acceptable.

In Amendment 36 Celgene disagreed with the recommendation to set a numerical limit for T cells instead of the proposed "report result" acceptance criteria. The justification is that only the stability indicating methods (cell viability, CAR+ T cell percentage, and (b) (4)) will be used for future stability studies.

Celgene performed a two-step regression analysis (analysis of covariance; ANCOVA) for the analytical methods: cell viability percentage, T cell percentage, CAR-positive T cell percentage, Cell concentration, and (b) (4) to determine stability trends. First, a common slope analysis was performed by ANCOVA modeling with two variables: Time and Lot or DP Configuration (bag size/fill volume combinations). This was used to assess differences between lots by maintaining DP configuration stable during this modeling . Common slope and regression analysis results are provided for each critical quality attribute assessed for stability.

<u>T cell Percentage Common Slope and Regression Analysis</u>
Independent trend analysis confirmed no significant changes in T cell percentage over time ((b) (4) months).

Reviewer Comments:
For lots (b) (4) at (b) (4) Celgene has concluded that the significant trend (difference) observed in T cell percentage at (b) (4) months is impractical because there is such a small change ((b) (4) in T cell expression) and low variability of the assay. This conclusion is supported by the data given the range of T cell percentage is within (b) (4) at (b) (4) months, and the slope analysis changes detected are within a (b) (4) change.

Overall, the regression analysis supports the conclusions that T cell percentage in the DP is maintained throughout storage, consistent within the surface area to fill volume of (b) (4) (which is the proposed commercial fill strategy), and comparable for DP lots in (b) (4) cryopreservation bags (b) (4) (supporting data provided but not presented here). In response o IR#43, sent 1/19/2021, Celgene agreed to set a numerical limit for T cell percentage stability ((b) (4)) based on the specification that is being used for DP lot release in Amendment 45.

<u>Cell Viability Common Slope and Percentage Regression Analysis</u>
Independent trend analysis confirmed no significant changes in cell viability over time ((b) (4) months).

Reviewer Comments:

The regression analysis supports Celgene 's conclusions that cell viability in the DP is maintained throughout storage, consistent within the surface area to fill volume of (b) (4) *(which is the proposed commercial fill strategy), and comparable for DP lots in* (b) (4) *cryopreservation bags* (b) (4) *(data provided but not included in review). Trends for viability of cell is well in excess of the FDA recommendation of* (b) (4)*; and lie within the* (b) (4) *range and range of variability for the analytical method. Therefore, the impracticality of the statistically significant trend (p=0.02) at t=* (b) (4) *months for lots* (b) (4) *filled at* (b) (4) *in* (b) (4) *250 bags is supported by the data.*

CAR-Positive T cell Percentage Common Slope and Percentage Regression Analysis

Though differences in CAR+ T cell percentage were observed between lots, Celgene attributes these differences to the use of different (b) (4) starting materials.

Reviewer Comments:
The regression analysis supports Celgene conclusions that CAR-Positive T cell Percentage in the DP is maintained throughout storage, consistent within the surface area to fill volume of (b) (4) *(which is the proposed commercial fill strategy), and comparable for DP lots in* (b) (4) *cryopreservation bags* (b) (4) *(data provided but not shown). The statistically significant change (p=0.05) over time for lots* (b) (4) *stored in cryopreservation* (b) (4) *was determined to be within normal assay variation. CAR-positive T cell percentage differences between lots is attributed to different* (b) (4) *starting materials; this is supported by the data as trends within lots from a single donor are consistent with no major changes or deviations.*

Cell Concentration Common Slope and Percentage Regression Analysis

Independent trend analysis confirmed no significant changes in cell concentration over time ((b) (4) months).

Reviewer Comments:
The regression analysis supports Celgene conclusions that cell concentrations in the DP are maintained throughout storage, consistent within the surface area to fill volume of (b) (4) *(which is the proposed commercial fill strategy), and comparable for DP lots in* (b) (4) *cryopreservation bags* (b) (4) *(supporting data provided but not shown). The statistically significant trend (p=0.02) observed for Lots* (b) (4) *filled at* (b) (4) *in* (b) (4) *50 bags was considered impractical because of assay variability. The statistically significant trend (p=0.07) observed for DP configuration over time for lot* (b) (4) *led to the slope trend analysis being performed individually which led to a statistically insignificant value (P=0.49). The cell concentration is considered stable up to 12 months.*

In response to IR#38, Celgene stated that cell concentration will not be included in future stability studies given cell concentration is used to calculate dose and in (b) (4) *calculations in Amendment 36. This is acceptable.*

(b) (4) Common Slope and Percentage Regression Analysis

Independent trend analysis confirmed no significant changes in (b) (4) over time ((b) (4) months).

Reviewer Comments:
The regression analysis supports that the (b) (4) *attribute in the DP lots is maintained throughout storage, consistent within the surface area to fill volume of* (b) (4) *(which is the proposed commercial fill strategy), and comparable for DP lots in* (b) (4) *cryopreservation bags* (b) (4) *(data provided but not shown). Although trends of increase in CD137 activation were statistically significant over time no decrease in* (b) (4) *was determined for all*

lots. One lot, (b) (4) , showed a decrease in (b) (4) between 3-12 months. However, this lot is an outlier compared to the other (b) (4) primary lots tested. Cumulatively the data supports 12 months of stability. In response to IR#43, Celgene agreed to revise the acceptance criteria (see long term stability study below) for stability protocol to be more congruent with specifications for DP lot release in Amendment 45. This is acceptable.

Long-term Cryogenic Stability Study Protocol for Future Studies

Long term stability studies will be conducted at T=0, 3 ,6 9 and 12 months. Tests include appearance, T cell percentage, % viable cells, %, CAR+ T cells, (b) (4) and sterility (t=0, 12 months only). All lots must meet commercial acceptance criteria.

Temperature Cycling Studies

Stressed conditions were used to further evaluate stability of the DP under conditions of routing (b) (4) (Table 91). Appearance, Cell concentration, Cell Viability Percentage, CAR+ T cell Percentage, T cell Purity, and (b) (4) were assessed for DP lots subject to temperature excursion (b) (4) °C (i.e. (b) (4)). Unstressed control kept at ≤-130°C was used for comparison. Lots used for the stressed temperature studies was provided. Celgene states that these lots passed all lot release acceptance criterion before being used in the temperature excursion studies. DP filled (b) (4) were used for the temperature cycling studies because of the limited quantity of DP in cryopreservation bags. The comparable stability of DP stored in cryopreservation bags versus (b) (4) in the stability studies above was provided as further rationale for using DP in (b) (4) .

Table 91. Temperature Cycling Stressed Study Results

Test	Acceptance Criteria for Unstressed Control	Cell Storage Condition	Drug Product Lot Number					
			bb2121-(b) (4)	DP-(b) (4)	bb2121-(b) (4)	DP-(b) (4)	DP-(b) (4)	DP-(b) (4)
Appearance	Liquid, colorless cell suspension	Control	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
		Stressed	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
T cell Percentage	(b) (4)	Control	(b) (4)					
		Stressed						
Cell Viability Percentage	(b) (4)	Control						
		Stressed						
CAR-positive T cell Percentage	(b) (4)	Control						
		Stressed						
(b) (4)	(b) (4)	Control						
		Stressed						

Cell Concentration (× 10^6 cells/mL)	Report Result	Control	(b) (4)
		Stressed	

N/A = not available

The temperature cycling studies results were analyzed with a least-squares mean analysis comparing unstressed control to stressed lots. p≤0.05 was considered statistically significant difference; and p>0.05 was considered not to be statistically significant. Appearance, T cell percentage, and cell concentration were not considered stability indicating assays given the lack of changes in these attributes under the stressed conditions (p>0.05 from least mean square analysis of unstressed control to stressed samples). Cell Viability, CAR-positive T cell Percentage, and (b) (4) were determined to be stability indicating given the changes in nature observed under temperature excursions (p ≤0.5 between control and stressed samples).

Overall Reviewer Summary for Section 3.2.P.8

The stability studies support the proposed commercial shelf life of 12 months when stored in the vapor phase of liquid nitrogen (≤ -130°C). All lots passed the proposed acceptance criteria, and in multiple cases well exceeded the numerical limits set for the time intervals tested up to (b) (4) *months. Regression analysis further supports stability of the DP attributes used for lot release safety and quality testing. No major deviations or changes in stability trends were found. In cases where lots could not be* (b) (4) *for the common slope analysis methods due to statistical significance, trends were assessed individually and not determined to be statistically significant. The surface area to fill volume ratio did not appear to impact stability of the DP lots, as tested in the regression analysis studies. Overall quality of the DP as evaluated by the specifications for lot release remained stable over time. Furthermore, stressed conditions tested in the temperature cycling study support that Cell Viability, CAR-Positive T cell percentage, and* (b) (4) *are stability indicating assays. Under stressed conditions, changes were observed for these attributes when DP lots were stressed by temperature excursion. This is acceptable.*

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

There is no post-approval commitment for DP stability. The stability data generated to date with cryopreservation storage conditions will be used for long-term stability. Celgene intends to provide real-time stability from on-going stability studies in the annual report. The shelf life of the DP will be updated based on the on-going stability data as long as the acceptance criteria established from the stability studies and data in this submission are met.

Reviewer Comments:
This proposal is acceptable.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Reviewed by DMPQ. Please see DMPQ review for details.

3.2.A.2 Adventitious Agents Safety Evaluation
Information in this section is integrated in the **Section 3.2.S.2.3 Control of Materials [LVV]** and **Section 3.2.S.2.3 Control of Materials [ide-cel].**

3.2.R Regional Information (USA)

- **Executed Batch Records**

One executed batch record is provided for the DP lot# (b) (4) which is manufactured at the proposed commercial facility, Celgene S12 (Summit). LOT (b) (4) was manufactured on October 7, 2019. Unexecuted batch records are provided for ide-cel DP – (b) (4) and ide-cel DP commercial process.

Reviewer Comments:
No changes were detected in comparing the executed batch records ide-cel (b) (4) and unexecuted batch records ide-cel-(b) (4) . No changes in testing were detected in the comparison of the unexecuted batch records ide-cel-U(b) (4) and unexecuted batch records ide-cel DP commercial. Batch records were reviewed further during inspection of the S12 facility for comparison with deviations. See EIR report for additional details.

- **Method Validation Package**

Full method validation reports were provided. Validations described in method validation sections (Sections 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures [LVV] 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures [ide-cel]).

Other eCTD Modules
Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

A categorical exclusion has been submitted under 21 CFR 25.31 (c) for substances occurring naturally in the environment. Celgene states that to their knowledge, no extraordinary circumstances exist; therefore, an environmental assessment was not prepared. The final ide-cel DP (DP) consists of human cells transduced with the lentivirus vector (LVV). The LVV used in the manufacturing of ide-cel DP is a non-replicating virus generated recombinantly. The ide-cel manufacturing process results in at least (b) (4) reduction of LVV in the DP. Additional (b) (4) steps further reduce the residual LVV in the ide-cel DP. No residual infectious LVV is detectable in the final DP. Furthermore, the DP are human cells, which are unable to survive outside the human body in the absence of complex solution and delicate environmental and physical controls. Taken together, the ide-cel product consists of genetically modified human cells that “occur naturally in the environment” and do not survive without complex nutritional and metabolic support and are degraded into naturally occurring substances in the environment.

Reviewer comments:
The categorical exclusion claim is acceptable. No FONSI review required.

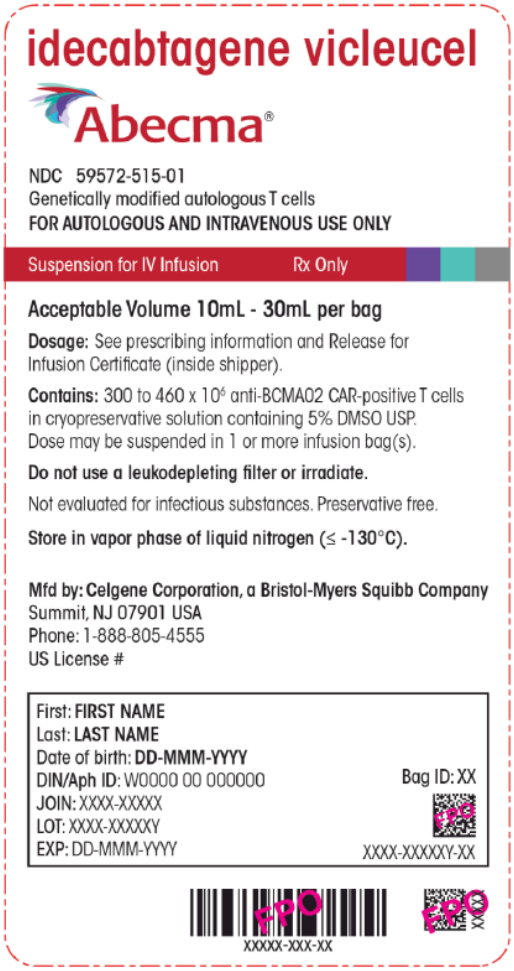
B. Labeling Review

Full Prescribing Information (PI):
The following sections of the PI were reviewed: Section 2 (Dose and Administration). Section 3 (Dosage Forms and Strengths), Section 11 (Description) and Section 16 (How supplied / storage and handling).

The PI provides a detailed and correct description of ide-cel and its mechanism of action. The PI also carefully and correctly describes the receipt and preparation procedures for ide-cel.

Reviewer comments:
There were multiple interactions with the Applicant during review of the PI where the Applicant was asked to include additional details on the receipt and administration preparation procedures of ide-cel. The applicant agreed to add the requested details and the included details were found to be adequate.

Carton and Container Label:
Examples of the (b) (4) 50 bag (left) and cassette (right) labels are provided below. All labels contain the required text.



Reviewer Comments:
The initial labels provided complied with 21 CFR 610.60-62 except the trade name (Abecma) appeared more prominent than the USAN/INN name (idecabtagene vicleucel). IR#63 was sent to Celgene on 3/11/2021 asking Celgene to address this issue and provide updated labels including the updated dose range and target bag volumes. Celgene provided updated labels in Amendment 64. The updated labels for the (b) (4) 50 bag and cassette are included above and are acceptable.

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

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

(b) (4)

(b) (4)

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