

CBER CMC BLA Review Memorandum

BLA STN 125789

TECELRA

Afamitresgene autoleucel (afami-cel)

Reviewers

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1. BLA#: STN 125789

2. APPLICANT NAME AND LICENSE NUMBER

Adaptimmune LLC
License Number: 2315
DUNS: 078438854

3. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper/USAN:	afamitresgene autoleucel
Proprietary name:	TECELRA
Company Code:	ADP-A2M4
UNII Code:	CUY18BJ7BP
NDC Code:	83205-0001-2

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Pharmacological category:	MAGE-A4-directed genetically modified autologous T cell immunotherapy
Dosage form:	Cell suspension for infusion
Strength/Potency:	2.68E9 to 10E9 MAGE-A4 TCR positive T cells
Route of Administration:	Intravenous infusion
Indication:	Treatment of HLA-A*02:01P, HLA-A*02:02P, HLA-A*02:03P, or -A*02:06P positive adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, and whose tumor expresses the MAGE-A4 antigen as determined by an FDA-approved test.

5. MAJOR MILESTONES

Initial IND Submission (BB-IND 17235):	November 29, 2016
Orphan Drug Designation granted:	August 26, 2019
Regenerative Medicine Advanced Therapy Designation granted:	November 27, 2019
Pre-BLA Meeting:	October 13, 2022
BLA Submission (Rolling BLA Module 3):	December 5, 2023
Combination First Committee/Filing Meeting:	January 10, 2024
BLA Filed:	February 2, 2024
Mid-Cycle Meeting:	April 3, 2024
External Late-Cycle Meeting:	May 20, 2024
PDUFA Action Due Date:	August 2, 2024

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Elvira Argus, PhD; OTP/OGT/DGT2/GTB5	afami-cel manufacturing, process validation, controls, specification
Alan Baer, PhD; OTP/OGT/DGT2/GTIB	afami-cel and MAGE-A4-c1032 LVV assay validations
Laura DeMaster, PhD; OTP/OGT/DGT2/GTB4	MAGE-A4-c1032 LVV manufacturing, process validation, controls, specification, container closure
Y Nguyen, PhD; OTP/OGT/DGT1/GTB2	afami-cel and MAGE-A4-c1032 LVV control of materials, stability; afami-cel container closure
Andrey Sarafanov, PhD; OTP/OPPT/DH/HB2	afami-cel extractables and leachables assessment

7. INTER-CENTER CONSULTS REQUESTED

Not applicable

8. SUBMISSION(S) REVIEWED

Date Received	Submission/amendment	Comments/ Status
December 23, 2022	STN 125789/0.0	Initial submission (Unit 1 of 3) containing Modules 1, 2, 4
March 30, 2023	STN 125789/0.1	Unit 2 of 3 containing Module 5 and related portions of Modules 1 and 2
December 5, 2023	STN 125789/0.2	Unit 3 of 3 containing Module 3 and related portions of Modules 1 and 2
December 20, 2023	STN 125789/0.3	Updated lentiviral vector and DP stability data
January 18, 2024	STN 125789/0.4	Response to CMC IR #1
March 8, 2024	STN 125789/0.11	Response to CMC IR #2
April 5, 2024	STN 125789/0.21	Response to CMC IR #3
April 24, 2024	STN 125789/0.26	Response to DBSQC IR #3
April 24, 2024	STN 125789/0.27	Response to Form 483 Observations (Navy Yard facility)
April 26, 2024	STN 125789/0.28	Updated lentiviral vector and DP stability data
April 30, 2024	STN 125789/0.31	Follow up response to CMC IR #3 (Extractables & leachables)
May 15, 2024	STN 125789/0.39	Response to CMC IR #4
May 29, 2024	STN 125789/0.41	Response to DMPQ IR #2
June 10, 2024	STN 125789/0.46	Response to CMC IR #5
July 5, 2024	STN 125789/0.61	Response to CMC IR #6
July 9, 2024	STN 125789/0.66	Response to CMC IR #7
July 17, 2024	STN 125789/0.80	Response to CMC IR #8

July 29, 2024	STN 125789/0.88	Response to CMC IR #10
July 29, 2024	STN 125789/0.89	Response to CMC IR #9

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
(b) (4)	(b) (4)	(b) (4)	Yes	CMC: Mercy Quagraine (CBER/OTP/OCTHT/DCT1/CTB 1) <i>MF has been used in several GT BLAs. There are no outstanding issues with this MF.</i>
(b) (4)	(b) (4)	(b) (4)	Yes	CMC: Tania Rosen-Cheriyen (CBER/OTP/OGT/DGT1/GTC2) (b) (4) <i>were used in the manufacturing of the (b) (4). Appropriate safety testing was conducted and there are no current issues with this MF.</i>
(b) (4)	(b) (4)	(b) (4)	yes	(b) (4) <i>is of non-biological origin. There are no safety concerns regarding the use of this (b) (4) in the LV manufacturing.</i>
(b) (4)	(b) (4)	(b) (4)	yes	CMC: Archana Siddam (CBER/OTP/OCTHT/DCT1/CBT 1) <i>Adequate safety testing was performed to support the use of this (b) (4) in the DP manufacturing. No CMC issues with this DMF.</i>
(b) (4)	(b) (4)	(b) (4)	yes	CMC: Matthew Klinker (CBER/OCTHT/DCT1/CTB2) <i>There are no CMC concerns with this DMF.</i>
(b) (4)	(b) (4)	(b) (4)	Yes	CMC: Thomas Finn (CBER/OCTHT/DCT1/CTB2) <i>There are no CMC concerns with this MF.</i>

(b) (4)	(b) (4)	(b) (4)	Yes	CMC: Elizabeth Lessey-Morillon (CBER/OTP/OCTHT/DCT1/CTB 1) <i>In response to CMC IR #4, the sponsor provided the LOA to cross-reference the information. Currently, there are no outstanding CMC issues with this MF.</i>
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10. REVIEWER SUMMARY AND RECOMMENDATION

I. EXECUTIVE SUMMARY

The FDA CMC review team concludes that the manufacturing process, test methods, and control measures for afamitresgene autoleucel (afami-cel; TECELRA) are capable of yielding autologous products with consistent quality attributes determined acceptable for commercial manufacturing under this BLA.

Afami-cel is a genetically modified T cell immunotherapy indicated for the treatment of HLA-A*02:01P, HLA-A*02:02P, HLA-A*02:03P, or HLA-A*02:06P positive adult patients with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, and whose tumor expresses the Melanoma-associated antigen 4 (MAGE-A4) antigen. Afami-cel consists of autologous T cells transduced with a self-inactivating (SIN) replication-incompetent lentiviral vector (LV) MAGE-A4-c1032 to constitutively express an affinity-enhanced T cell receptor (TCR) specific for human MAGE-A4. The TCR has been genetically engineered to recognize the HLA-A*02-restricted MAGE-A4 peptide GVYDGREHTV. MAGE-A4 is a cancer/testis antigen expressed in immune-privileged sites and in solid tumors, including synovial sarcoma. The MAGE-A4 TCR coding sequence is comprised of TCR α and TCR β chains separated by a (b) (4)

The expression of MAGE-A4 TCR α and β chains is driven by a (b) (4). In T cells transduced with MAGE-A4-c1032 LV, the MAGE-A4 TCR α and β chains complex with the endogenous CD3 chains to form a functional TCR. Binding of afami-cel to MAGE-A4-expressing target cells leads to antigen-specific activation via the TCR-peptide-HLA-A*02 complex resulting in T cell proliferation, cytokine secretion, and killing of MAGE-A4/HLA-A*02-expressing cells.

Afami-cel is formulated at (b) (4) and is cryopreserved at $\leq -130^{\circ}\text{C}$ in cryopreservation (b) (4). The formulated cell suspension is filled into one or more (b) (4) Cryogenic Storage Container (b) (4) bags at fill volumes of (b) (4). The number of filled bags and fill volume depend on the number of MAGE-A4 TCR-positive T cells present in the lot, but all bags will contain the same fill volume for a given lot. The clinically approvable commercial dose range will be 2.68×10^9 to 10×10^9 MAGE-A4 TCR-positive T cells, provided as a single dose for infusion. The patient will receive the entire quantity of product shipped to the administration site. Afami-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 within a foam block inside the shipper. Following receipt at the administration site, afami-cel is stored in a vapor phase liquid nitrogen ($\leq -130^{\circ}\text{C}$) until the scheduled treatment time, when it is thawed and infused within 1 hour of thawing.

MAGE-A4-c1032 LV is a nonreplicating, SIN LV, based on (b) (4)

(b) (4) The LV is manufactured at
The LV is manufactured via (b) (4)

Afami-cel drug product (DP) is manufactured using patient apheresis material collected at qualified apheresis centers. The apheresis material is shipped to Adaptimmune's Navy Yard facility (Philadelphia, PA), where it is inspected, (b) (4), and stored until the initiation of DP manufacturing. The manufacturing process starts with apheresis (b) (4)

. The enriched T cells are transduced with MAGE-A4-c1032 LV and expanded in (b) (4)

to the DP (b) (4)
The cells are washed and formulated in (b) (4).

Afami-cel is manufactured from autologous leukapheresis material. The leukapheresis is shipped to the manufacturing site and processed within (b) (4) of collection: the material is (b) (4)

To manufacture afami-cel, leukapheresis material is (b) (4)

DS. An overview of the afami-cel DS and DP manufacturing process is provided in Figure 7. The final formulation calculation is performed based on (b) (4) tests. Filled bags are visually inspected, then placed in individual metal cassettes, cryopreserved in a (b) (4), and stored at $\leq -130^{\circ}\text{C}$ in vapor phase liquid nitrogen until lot release testing is complete. The DP bags required for administration are packaged into a vapor phase liquid nitrogen shipper and shipped to the administration site once the patient is scheduled for administration. Afami-cel stability at $\leq -130^{\circ}\text{C}$ in vapor phase liquid nitrogen was determined to be 6 months.

The afami-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 in-process and lot release testing are collected at the appropriate stages in manufacture. 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. The ability of the afami-cel manufacturing process to consistently manufacture product that meets predetermined product specifications is demonstrated by process validation studies. Chain of Identity/Chain of Custody (COI/COC) is established and validated at the collection site and maintained through the manufacturing process and administration.

J. RECOMMENDATION

K. APPROVAL

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of afamitresgene autoleucel (afami-cel, TECELRA). The CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, are capable of yielding a product with consistent quality characteristics. This information along with the postmarketing commitments (PMCs) and a post-marketing requirement (PMR) listed below satisfy 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 gathered during the pre-license inspections of the Adaptimmune LLC Navy Yard and (b) (4) facilities, the CMC review team recommends approval of this BLA.

Drug Substance and Drug Product Manufacturing Facilities:

1. Drug Product: Adaptimmune LLC; 351 Rouse Boulevard, Philadelphia, PA 19112. FEI: 3013525969; DUNS: 78438854
2. Lentiviral Vector: (b) (4)

PMCs:

1. Adaptimmune LLC commits to conduct a requalification of the (b) (4) sterility test using the (b) (4) method. The final qualification study report will be submitted as a PMC - Final Study Report by September 30, 2024.
2. Adaptimmune LLC commits to implement storage and shipping of (b) (4) sterility samples at (b) (4) and conduct a (b) (4) study. The final study report will be submitted as a PMC - Final Study Report by October 31, 2024.
3. Adaptimmune LLC commits to conduct a study measuring reduction of (b) (4) process-related impurities in the afami-cel manufacturing process. The final study report will be submitted as a PMC - Final Study Report by April 30, 2025.
4. Adaptimmune LLC commits to conduct a feasibility study to investigate potential negative controls for the (b) (4) assay. The final study report will be submitted as a PMC - Final Study Report by April 30, 2025.

PMR:

1. An adequate assessment of leachables in the DP including the contribution of (b) (4) major process components utilized in Step (b) (4) of the afami-cel manufacturing process, and an updated toxicological risk assessment once the study is completed.

Confirmed proposed study milestone dates:

- Initial Protocol Submission for FDA Review: August 9, 2024
- Final Protocol Submission: September 30, 2024
- Study Completion: October 1, 2025
- Final Study Report Submission: December 31, 2025

CBER Lot Release:

Afami-cel has been deemed exempt from CBER lot release testing or protocol review.

II. COMPLETE RESPONSE (CR)

Not applicable

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Elvira Argus, CMC Reviewer, Chair OTP/OGT/DGT2/GTB5	Concur	
Alan Baer, CMC Reviewer OTP/OGT/DGT2/GTIB	Concur	
Laura DeMaster, CMC Reviewer OTP/OGT/DGT2/GTB4	Concur	
Y Nguyen, CMC Reviewer OTP/OGT/DGT1/GTB2	Concur	
Kimberly Schultz, Division Director OTP/OGT/DGT2	Concur	
Denise Gavin, Office Director OTP/OGT	Concur	

Review of CTD

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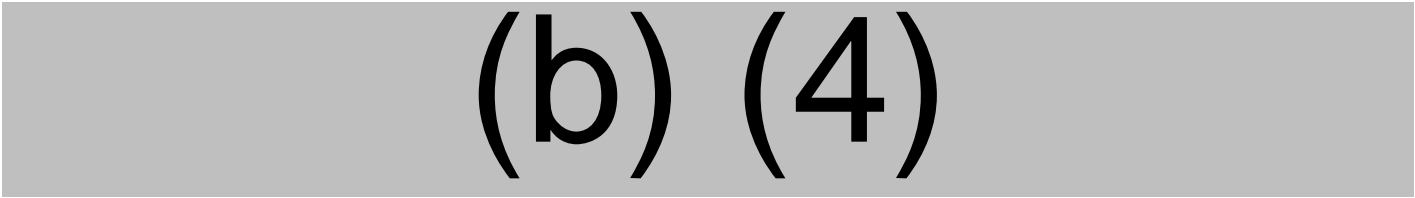
Module 3

3.2.S DRUG SUBSTANCE – MAGE-A4-c1032 LV


(b) (4)

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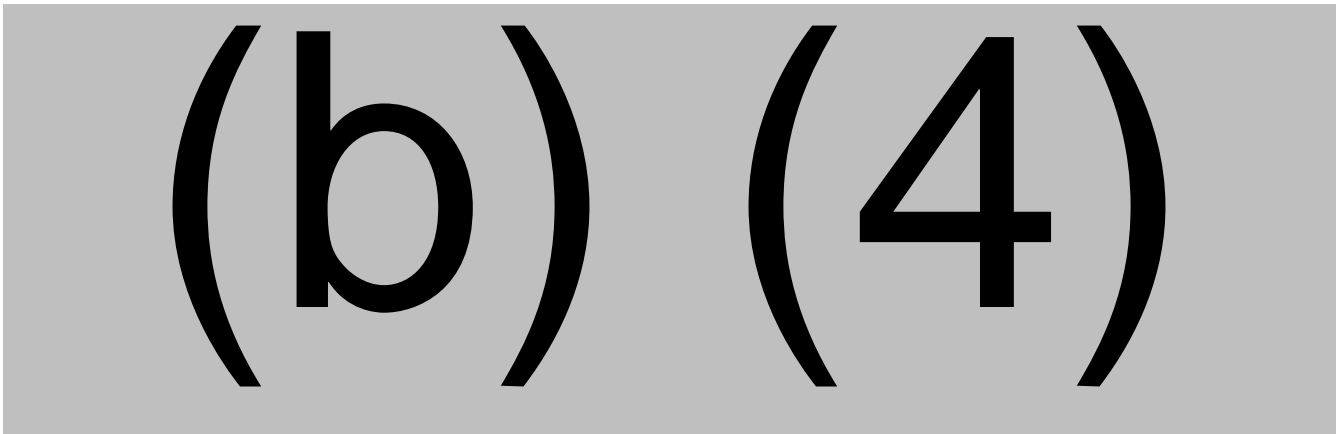
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105 pages determined to be not releasable: (b)(4)

(b) (4)

Government	Percentage
Current government	75%
Previous government	25%

[REDACTED]

Government	Percentage
Current government	85%
Previous government	15%

Reviewed by EA

administration at a target cell concentration of (b) (4), and filled into one or more bags. For any afami-cel batch, the same nominal fill volume is

targeted in all bags filled. A single dose of afami-cel contains $2.68 \times 10^9 - 10 \times 10^9$ MAGE-A4 TCR-positive T cells supplied in one or more bags. The filled DP is cryopreserved and stored in vapor phase of liquid nitrogen at $\leq -130^\circ\text{C}$.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The DS is afami-cel, a genetically modified T cell immunotherapy product consisting of autologous CD4 and CD8 T cells transduced with the self-inactivating MAGE-A4-c1032 LV encoding an enhanced affinity TCR specific for human MAGE-A4.

3.2.P.2.1.2 Excipients

Afami-cel is formulated with (b) (4) as the excipient. (b) (4) is supplied as a (b) (4) and contains 5% dimethyl sulfoxide (DMSO). None of the components of (b) (4) are materials of human or animal origin.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The current DP composition as described in 3.2.P.1 Description and Composition of the Drug Product was used throughout product development. (b) (4)

3.2.P.2.2.2 Overages

There are no overages used in the formulation of afami-cel DP.

3.2.P.2.2.3 Physicochemical and Biological Properties

The properties of afami-cel DP (b) (4)

The DP CQAs tested as part of lot release are described in 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s).

3.2.P.2.3 Manufacturing Process Development

Reviewed by EA

Manufacturing process development and comparability assessments performed during the product lifecycle are described in 3.2.S.2.6 Manufacturing Process Development. Information specific to the DP manufacturing process changes is described here.

Afami-cel DP Fill Procedure

The afami-cel DP manufacturing process begins after completion of (b) (4)

The concentration of transduced cells is variable between batches. The volume of formulated afami-cel is filled into a single bag or split between multiple bags, depending on the total number of harvested cells. The filled DP is

cryopreserved using a (b) (4) and transferred to long-term storage in the vapor phase of liquid nitrogen (-130°C).

(b) (4)

. The size and the number of cryobags was determined according to Table 76.

Table 75. Cryobag Size and Number Determination During Clinical Development

(b) (4)

(b) (4)

For commercial supply, the afami-cel dose range is 2.68×10^9 to 10×10^9 MAGE-A4 TCR-positive T cells. (b) (4)

A single cryobag size of 250 mL will be used for commercial afami-cel lots with a qualified fill capacity of (b) (4).

Reviewer Comments: If the total number of MAGE-A4 TCR-positive T cells is between 2.68×10^9 and (b) (4) and the (b) (4) is greater than (b) (4), the resulting volume could be less than (b) (4). The highest (b) (4) recorded for (b) (4) DP batches administered to date was (b) (4). Adaptimmune concludes that the risk of having a DP batch with a volume of (b) (4) is low. At the time of BLA review, the validated range of the (b) (4) assay is (b) (4) and the agreed upon commercial acceptance criterion is (b) (4). Based on the validated upper limit of (b) (4) and the minimum dose of 2.68×10^9 MAGE-A4 TCR-positive T cells, the minimum fill volume is (b) (4), which is within the qualified fill capacity. Adaptimmune's conclusion is acceptable.

To prevent exceeding the upper limit of the dose range for afami-cel supplied to the clinical site, the QA unit will follow a specific SOP on management and reconciliation of patient material. If the total product volume determined during (b) (4): Final Formulation exceeds the equivalent of (b) (4) MAGE-A4 TCR-positive T cells, all formulated product is filled into bags as described in 3.2.P.3.3 Description of Manufacturing Process. Bags are consecutively numbered, and the DP product bags are labeled “Bag X of Y”, where X represents the bag number and Y represents the total number of bags. The batch COA contains information on the number of bags, bag volume, and the number of MAGE-A4 TCR-positive T cells per bag. As part of batch disposition, a QA representative confirms that the DP batch meets the acceptance criterion for the minimum dose. When DP shipment is requested via an approved DP shipment request form, a QA representative determines the identity of DP bags for supply using the COA and confirms the total number of MAGE-A4 TCR-positive T cells does not exceed the maximum recommended dose.

For each DP batch intended for supply, the bag number, bag volume, and number of MAGE-A4 TCR-positive T cells per bag is recorded in a shipment authorization form by a QA representative and verified by a (b) (4) QA representative. Manufacturing or warehouse personnel use the completed shipment authorization form to determine which bag numbers to remove from the freezer and ensure that the bag number on the DP label matches the bag numbers on the shipment authorization form.

The cassettes containing the DP bags are placed onto (b) (4) for physical inspection and verification. During the physical inspection, the warehouse and QA personnel verify that the product matches the information on the shipment authorization forms by checking the bag numbers. The DP bags are then placed inside the cryoshipper for shipment. A T cell product shipment form and the DP COA are included in the cryoshipper.

Reviewer Comments: In response to CMC IR #5 sent on May 31, 2024, Adaptimmune indicated that each DP batch shipment will include the prescribing information, the DP COA, and the T cell product shipping form (MFG FRM 019). A copy of MFG FRM 019 is provided in the submission.

3.2.P.2.4 Container Closure System

The afami-cel container closure is the (b) (4) Cryogenic Storage Container (Bag) (b) (4) with 2 ethyl vinyl acetate (EVA) ports. These bags are made of animal-free materials, supplied pre-sterilized by (b) (4), FDA 510(k) cleared (b) (4)

E/L

To assess potential extractable and leachables in the DP originating from the contact with the DP CCS, an extractables simulation study was performed according to (b) (4) (b) (4). Briefly, labeled (b) (4) Cryogenic Storage Container was filled with (b) (4). The bags exposed to (b) (4). Following the (b) (4), the resulting

extraction samples were evaluated for trace inorganic elements by (b) (4), volatile organic extractables by (b) (4), volatile/semi-volatile organic extractables by (b) (4), and semi-volatile/non-volatile organic extractables by (b) (4). No elemental impurities were detected. Several organic extractables detected above the allowable limits were identified. Toxicology assessments were performed to establish the biological safety of these identified extractables.

Reviewer Comments: The E/L study is not adequate. The study represents accelerated study for storage and in use-hold. Therefore, may underestimate the leachables due to (b) (4) temperature stress of the bag comparing to actual conditions (e.g., -130°C). Importantly, according to (b) (4) accelerated conditions can be used in addition, but not instead of real-time study. The study also did not assess leachables originating from the (b) (4) high-risk process steps (e.g., starting from Step (b) (4) that involves product contact materials, (b) (4). Adaptimmune agreed to conduct an additional leachables study and to evaluate the cumulative effect on leachables in the DP as a PMR. For details on the deficiencies of the E/L study, please refer to consult review by Dr. Andrey Sarafanov.

3.2.P.2.5 Microbiological Attributes

Container Closure Integrity (CCI) of the (b) (4) Cryogenic Storage Container was tested by (b) (4) testing. For each study, a total of (b) (4)

All bags met prespecified acceptance criteria.

Reviewer Comments:

The sponsor provided the CCIT report in the submission. DMPQ determined that the CCIT of the (b) (4) Cryogenic Storage Container had deficiencies, which will be resolved through a PMC. Please refer to DMPQ review for details.


3.2.P.2.6 Compatibility

Reviewed by EA


Afami-cel DP is thawed and directly administered to the patient from the container closure system using an intravenous (IV) administration set. The procedure for afami-cel administration at the clinical site does not specify IV administration sets to be used, but indicates against the use of infusion pumps, and for filter pore sizes to be no smaller than 170 µm if a filter is used. Adaptimmune conducted a series of studies to evaluate afami-cel compatibility in the context of direct exposure to reference IV administration sets, and mixing with 0.9% Sodium Chloride used to prime, (b) (4) flush the administration set.

Compatibility with Reference Administration Sets


In this study, (b) (4) bags from each of (b) (4) healthy donor DP batches were used to evaluate the compatibility of afami-cel with (b) (4) reference IV administration sets. (b) (4) most commonly used administration sets, (b) (4), were chosen based on a survey conducted at the United States clinical sites: (b) (4)



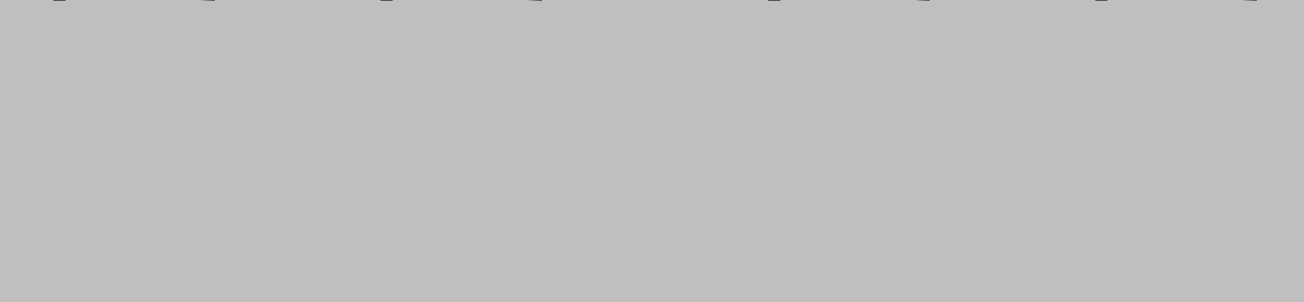
(b) (4), (b) (6)



(b) (4)



(b) (4), (b) (6)



(b) (4), (b) (6)

Reviewer Comments: Additional data for DP batches held in the IV set at room temperature for (b) (4) min is provided for the in-use stability study in 3.2.P.8 Stability and described below.

Study to Evaluate Priming, (b) (4) Flushing

Compatibility of afami-cel with 0.9% Sodium Chloride and the impact of (b) (4) flushing of the DP bag was evaluated using (b) (4) healthy donor DP batches. (b) (4) DP bags per batch were thawed and (b) (4) IV administration sets (with 170-micron filter) were prepared, (b) (4) primed with Sodium Chloride, (b) (4) not primed.

(b) (4)

(b) (4), (b) (6)

(b) (4), (b) (6)

(b) (4)

(b) (4), (b) (6)

In-Use Stability

Reviewer Comments: In-use stability studies were conducted using the same DP batches as those used in compatibility studies, and the study results are provided in 3.2.P.8 Stability section of the submission. As the study results are relevant to afami-cel compatibility with the IV administration set, the in-use stability study is described here.

The in-use stability study was conducted in two parts. In the first part of the study, (b) (4) healthy donor DP batches (b) (4), (b) (6) were thawed and held at (b) (4) for 0, 60, and (b) (4) minutes. Cell viability, (b) (4) T cells were evaluated at all time points. All samples met the release acceptance criteria. (b) (4) T cells remained stable at 60 and (b) (4) minutes. A consistent loss in cell viability was observed over the hold duration but the reduction was (b) (4) and the results were within the release acceptance criterion.

In the second part of the study, (b) (4) healthy donor DP batches (b) (4), (b) (6) IV administration set with a (b) (4) for 0 and (b) (4) minutes at room temperature. Cell viability and functional potency (cytotoxicity) were evaluated at both time points. There was a consistent decrease observed in both attributes compared to time T=0. An average decrease of 15% in functional potency was observed, but the magnitude of the decrease in each sample was within the assay variability and test results remained within the specification acceptance criterion for all (b) (4) batches. Cell viability decreased by 9.7% on average (worst case 14% reduction) and was still within the specification acceptance criterion in 2 out of (b) (4) batches for the (b) (4)-minute time point. One batch (b) (4), (b) (6) did not meet the acceptance criterion for cell viability (b) (4) with the result of 73.2%.

The results for cell viability are summarized in Table 81 and Figure 12. Despite the failure of one batch to meet the acceptance criterion for cell viability, Adaptimmune concluded that the totality of in-use stability data support the maximum in-use period of (b) (4) min post-thaw.

(b) (4), (b) (6)

(b) (4)

(b) (4), (b) (6)

Reviewer Comments: According to prescribing information, afami-cel DP should be administered within 1 hour post-thaw. Each cryobag will be thawed and the entire contents will be infused prior to thawing a consecutive DP bag. Given the difference in viability for matching donors in Part 1 and Part 2 of the study at the (b) (4)-min timepoint, the samples held in the IV set for 60 min would be expected to meet the cell viability acceptance criterion. The in-use stability data support an ambient hold of 1 hour. Based on the totality of the in-use stability data and the instructions in the prescribing information, the study conclusion is acceptable.

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

Pharmaceutical development of afami-cel DP is adequately described. Development studies demonstrate adequate compatibility of afami-cel with reference IV sets and with 0.9% Sodium Chloride solution. In-use stability studies support the stability of thawed

DP for 1 hour at room temperature as instructed in prescribing information or for (b) (4) hours based on the totality of the data.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Reviewed by EA

Afami-cel DP is manufactured at the Adaptimmune LLC site listed in Table 82.

Table 81. Afami-cel DP Manufacture, Testing, and Storage Sites

Site Name	Site Address	FDA Establishment Identifier (FEI)	Responsibilities
Adaptimmune LLC	Navy Yard Facility 351 Rouse Boulevard, Philadelphia, PA 19112, USA	3013525969	DP manufacture DP packaging and labeling DP release testing DP storage DP stability testing Approval of DP batch for release

3.2.P.3.2 Batch Formula

Each DP batch is used for only one patient (the autologous donor). The batch size for afami-cel is variable and depends on the number of MAGE-A4 TCR-positive T cells available for formulation and fill. A single dose of afami-cel contains a cell suspension of $2.68 \times 10^9 - 10 \times 10^9$ transduced T cells provided in one or more bags. The batch formula is provided in Table 83.

Table 82. Afami-cel Batch Formula

Component	Quality Standard	Quantity per Batch	Function
Drug substance	(In-house)	(as obtained)	active ingredient
(b) (4)	3.2.P.4.1 Specifications	q.s.	(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

The DP manufacturer and afami-cel batch formula information is adequately described.

3.2.P.3.3 Description of Manufacturing Process


Reviewed by EA

DP Manufacturing Process Steps

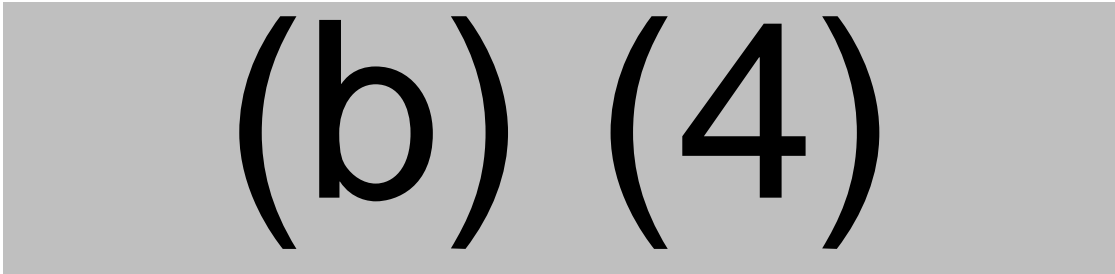
Afami-cel DS (b) (4) processed into DP with (b) (4) steps. The afami-cel manufacturing process flow diagram is shown in Figure 7.

(b) (4)




(b) (4)



(b) (4)



(b) (4)



DP Transportation

The number of DP bags required for dispatch to the clinical site is defined by comparing the quantity of MAGE-A4 TCR-positive T cells against the recommended dose range for afami-cel. If the quantity is insufficient for minimum dose, the DP batch is not released by QA. If the quantity is within dose range, all bags are dispatched for shipment. If the quantity is above the dose range, maximum number of bags within the dose range are indicated for shipment and the remaining bags are retained in storage.

The DP is shipped frozen using a qualified liquid nitrogen dry shipper. The DP bags and cassettes are inspected, secured, and placed into a fitted foam block that is lowered into the core of the shipper. The DP is transported by an experienced courier.

Reviewer Comments: In response to CMC IR #4 sent on May 8, 2024, Adaptimmune clarified that the DP is shipped to the authorized treatment center (ATC) (b) (4)

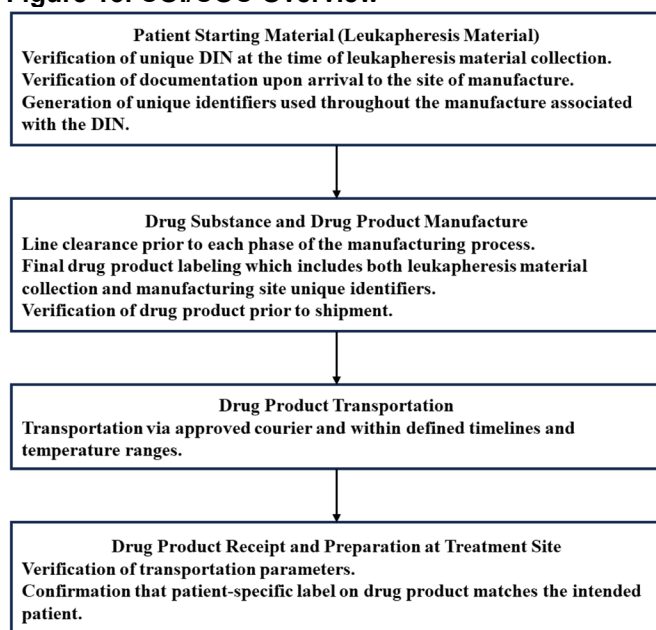
In response to CMC IR #5,

sent May 31, 2024, Adaptimmune further clarified the procedures to maintain COI/COC for the duration of product storage and provided information on qualification of ATCs. To ensure that the ATC can appropriately store and handle TECELRA, the Joint Commission accreditation of the treatment center will be verified prior to designating them as an ATC. The Joint Commission International Accreditation Standards for Hospitals include requirements that the medications are properly handled, stored, and dispensed. The response is acceptable.

DP Traceability System

A traceability system is in place to ensure that the DP, starting and raw materials, and all substances that come into contact with cells can be traced through the sourcing, manufacturing, packaging, storage, transport, and delivery to patient. The responsibilities for traceability with respect to COI/COC are outlined in Figure 13.

Figure 13. COI/COC Overview



A Production Order Form is initiated when a patient leukapheresis and manufacturing slot are scheduled. This form serves as the basis for coordinating the LM shipment, as well as creation and issuance of production batch numbers and MBRs. The COI/COC procedures are formally established at the time of leukapheresis and rely on verification of patient identifiers and assignment of the Donor Identification Number (DIN) at the time of collection. When the LM is received at the manufacturing site, the material and physical labels are inspected and verified with the accompanying documentation by ^{(b) (4)} personnel. The LM temperature can be tracked throughout the shipment process. During the receiving and verification process, the generated identifiers (batch numbers, chain of identity number (COID), and associated MBR number) are used in lieu of DIN for all manufacturing activities.

Traceability for DS and DP is further supported by a line clearance process, which is a pre-manufacturing safeguard activity that verifies COI before each phase of manufacturing begins. During this process, the production batch number, process phase, designated equipment, and printed labels are verified by (b) (4) personnel. The final DP label includes the identifiers assigned by the apheresis collection site (date of birth, DIN) and the generated identifiers (batch number and COID). SOPs are used to define the number of DP bags to be shipped to the clinical center or retained for storage, and for DP release. (b) (4) personnel verify and prepare the DP for pickup by the approved courier. The DP shipment temperature can be tracked throughout the shipment process.

Verification of the DP at the treatment site is performed following approved procedures specified in the prescribing information. In addition, T cell product shipment form will be used to 1) establish COC/COI within the ATC at the time of product receipt, 2) provide an opportunity to record details of receipt, inspection, and storage of the product at the appropriate temperature, and 3) allow Adaptimmune to finalize documentation and temperature data review to support product administration.

Reviewer Comments: The information regarding the T cell product shipment form was provided in response to the CMC IR #5 sent May 31, 2024. The response is acceptable.

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

The DP manufacturing process and DP traceability systems are adequately described.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Reviewed by EA

The CPPs and nCPPs for the DP manufacturing process are listed in Table 84. The criticality was established as described in 3.2.S.2.4 Controls of Critical Steps and Intermediates and PARs were supported by process characterization studies. There are no IPCs for the DP manufacturing process. However, in-process samples are taken for use in batch release testing in accordance with the DP release specification.

(b) (4)

(b) (4)

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

The proposed CPPs are supported by data and are adequate to ensure control of the DP manufacturing process.

3.2.P.3.5 Process Validation and/or Evaluation

Reviewed by EA

DP Shipper Validation

The packaging configuration was qualified by transporting (b) (4) batches of afami-cel for clinical use from Adaptimmune LLC to receiving sites in the United States by (b) (4)

The internal temperature in the (b) (4) dry vapor liquid nitrogen dewar was monitored for each shipment. The results demonstrate that the end-to-end shipping process from the manufacturing site to clinical sites in the US is controlled and performs as specified. All (b) (4) DP lots were administered to patients. Please refer to DMPQ review for additional details.

DP Transportation Validation

To qualify the DP transportation process, a simulated transportation study was conducted where the testing simulation conditions and duration simulated the actual movement required to complete the DP transportation steps. (b) (4)

. All other DP lots tested met the release acceptance criteria.

Reviewer Comments: DMPQ review concluded that the transportation qualification study was not sufficient to demonstrate that the process is adequately controlled. A PMC was requested to provide additional data and root cause assessments for the damage observed in the shipping study. Please refer to DMPQ review for additional details.

COI Evaluation

The COI procedures were evaluated by a retrospective review of the completed forms and batch production records detailed in Table 85 for (b) (4) clinical afami-cel batches. The review revealed no major inconsistencies with the process and documentation, supporting the COI process at Adaptimmune LLC.

(b) (4)

Labeling Evaluation

To demonstrate the DP label stability, the labeled container closure used for afami-cel was subjected to physical and functional testing as follows:

- (b) (4)

- (b) (4)

Based on the physical and functional testing, the product label was robust and durable and was determined to be fit for use.

Evaluation - Extractable and Leachable Risk Assessment:

Reviewed by AB and AS (primary reviewer)

Separate risk assessments were performed to evaluate the individual materials used in the (b) (4) DP manufacturing process(s) and for their potential to leach compounds during use, and to evaluate each material for the relative risk of leaching to occur. The results of this risk assessment will inform the overall control strategy for extractables and leachables in the P1.6.1 manufacturing process and for afami-cel. The manufacturing process(s) predominantly utilizes single-use systems, sterilized plastic materials. (b) (4) risk factors were assessed for each material:

(b) (4)

(b) (4)

Reviewer Comments: The (b) (4) cryogenic freezing bag, used as the final container closure for the DP, scored (b) (4). This material is used during (b) (4). The risk of this material leaching compounds into the drug product is mitigated by a leachable simulation study of this item, including the proposed commercial labeling (with color inks). The (b) (4), used during (b) (4) to allow (b) (4), used during (b) (4) for (b) (4), also scored high. Leachable simulation studies were performed to mitigate the risk of leachables in the DP.

A separate (b) (4) part study plan was also performed to assess the potential ingress of leachables across all phases of the manufacturing process, summarized in VAL 01158.

- (b) (4)

- (b) (4)

The maximum amount of each compound (any compound not within the cohort of concern) would be assessed per ICH M7 for a general once-in-a-lifetime dose of a parenteral product (120 µg/day permissible daily exposure or PDE) and a generalized margin of safety would be determined. If the worst-case scenario compound amount exceeded the ICH M7 recommendation, a compound specific PDE was calculated by a toxicologist. Then, a margin of safety would be determined based off that compound specific PDE. Elemental impurities detected above the reporting threshold would be evaluated against the (b) (4) daily permissible exposure limits.

The analytical methods used in this study are orthogonal and selected to target different classes of compounds, the targeted trace elements method was qualified by preparing (b) (4)

- (b) (4)

(b) (4) lots of (b) (4) were evaluated per the P1.6.1 manufacturing process for leachables. Organic extractables discovered with estimated concentrations at or above the analytical evaluation threshold (b) (4) based on volume are listed in Table 89.

(b) (4)

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

(b) (4)

Reviewer Comments: Compounds present in sufficient concentration at or above ICH M7 recommendations for 120 µg/day were identified and evaluated by a toxicologist (b) (4). Following an individual toxicology assessment, the maximum estimated amount of organic leachables was found to be lower than the ICH M7 recommendation for parenteral administration.

The only elemental impurity found to be higher than the recommended (b) (4) permissible daily exposure as a worst-case scenario carryover into the DP was (b) (4). (b) (4) trace elements, (b) (4), were detected at higher concentrations in the samples when compared to the test control. However, the worst-case amounts of both elements were lower than the established elemental parenteral PDE limits.

(b) (4)

Given that the adjusted short-term PDE for (b) (4) of (b) (4) is equal to the estimated single-day lifetime dose of (b) (4) as an impurity in the parenteral DP of (b) (4), the dose of (b) (4) in the DP is considered acceptable (i.e., no adverse health effects are expected).

Reviewer's Assessment of E&L Section (AS): *FDA did not agree that the initial extractables and leachables assessment for the afami-cel DP was adequate. Adaptimmune did not evaluate some of the high-risk process components, which may result in underestimation of the leachables profile in the final product. Following discussions during IRs, and Mid-cycle and Late-cycle meetings, analytical assessment of leachables in DP awaits an assessment of the overall leachables profile upon aligning it with extractables profile for (b) (4) major process components in (b) (4) of the afami-cel manufacturing process. These issues will be resolved through a PMR. Please refer to Dr. Andrey Sarafanov's review for additional details.*

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

- *The liquid nitrogen dewar shipment validation study was adequate.*
- *DMPQ review identified deficiencies in the DP transportation validation study. The deficiencies will be resolved via a PMC that Adaptimmune agreed to in Amendment 67 received on July 10, 2024.*
- *The COI and labeling procedures were demonstrated to be adequate.*
- *A PMR is included as part of approval because of missing E/L data.*

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

The procedure for releasing (b) (4) for use in DP manufacture includes COA confirmation and testing upon receipt according to the specification outlined in Table 91.

Table 90. Specification for (b) (4)

(b) (4)

Reviewer Comments:

CMC information for (b) (4) is cross referenced to BB-MF (b) (4). Currently, there are no CMC issues with the MF. Upon receipt, (b) (4) is visually inspected and tested for identity by (b) (4), endotoxin, (b) (4) using validated analytical methods. Validation reports for the in-house tests are provided in the BLA.

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

The following briefly describes non-compendial analytical methods used for batch release testing (in-house testing). Details of the specification used as part of quality control of (b) (4) is provided in the cross-referenced MF.

(b) (4)

(b) (4)

3.2.P.4.4 Justification of Specifications

Provided in the MF (b) (4).

3.2.P.4.5 Excipients of Human or Animal Origin

No components of the (b) (4) are of human or animal origin.

3.2.P.4.6 Novel Excipient

(b) (4) is not considered a novel excipient.

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

The information provided for the excipient is adequate.

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)

Afami-cel specifications are provided in Table 92. Justification for each specification is provided below.

Table 91. Afami-cel DP Commercial Lot Release Specifications

Attribute Type	Test	Method	Sample Type ¹	Acceptance Criteria
Appearance	Appearance – Visual Inspection	Visual inspection for (b) (4)	DP	(b) (4)
		Visual inspection for (b) (4)	DP	(b) (4)
	Appearance – Particulates	(b) (4)	DP	Absence of visible foreign particulates
	Appearance – Color	(b) (4)	DP	(b) (4)
	Appearance – Clarity	(b) (4)	DP	(b) (4)
Identity	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	DP	(b) (4)
Quantity	Number of MAGE-A4 TCR positive T cells	Calculated	-	$\geq 2680.0 \times 10^6$ cells ²
Potency	Cytotoxic activity	Cytotoxicity assay with flow cytometry	DP	(b) (4)
Purity	Cell viability	(b) (4)	DP	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Safety	Sterility	(b) (4)	DP	No growth

	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Endotoxin	(b) (4)	DP	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)

¹ (b) (4). "DP" indicates a sample taken (b) (4)

² The number of DP bags released for shipment to the clinical site is controlled by the QA unit to ensure that the number of MAGE-A4 TCR-positive T cells provided for patient administration does not exceed the upper limit of the recommended dose range.

(b) (4)

Reviewer Comments: During the review cycle, commercial DP specifications were modified from those originally submitted. The final agreed upon specifications are shown in Table 92. The specifications proposed in the original submission were supported by statistical analyses and clinical experience of up to (b) (4) afami-cel batches infused (b) (4)

In response to CMC IR #6 sent on June 28, 2024, and CMC IR #7 sent on July 5, 2024, Adaptimmune reassessed the acceptance criteria for quantitative tests using data from batches administered to (b) (4)

The lower limit for the potency acceptance criterion was further modified in response to the CMC IR #8 sent on July 12, 2024. The changes are acceptable.

Appearance

No statistical analyses are performed for appearance tests as these are qualitative parameters.

Visual Inspection – (b) (4)

Confirmation of (b) (4) in DP bags is required for batch release and serves as a measure to mitigate risks from microbiological and other contamination resulting from a container closure integrity failure.

Visual Inspection – (b) (4)

Confirmation of (b) (4) of the DP is required for batch release and serves as a measure to mitigate potential risks from manufacturing issues and batch misidentification.

Particulates

This is a qualitative (b) (4) assay. Confirmation of absence of visible foreign particulates in DP is required for batch release and serves as a measure to mitigate potential risks associated with particulates.

Color

This is a (b) (4) assay. The quantitative acceptance criterion for the color of the material is (b) (4) against color reference standards (b) (4) Based

on an analyst's ability to perceive color, the preceding hues were chosen to represent (b) (4).

Clarity

This is a (b) (4) assay. The acceptance criterion for clarity is (b) (4). The DP contains cells in formulation buffer and the DP is expected to be turbid due to the presence of cells. The acceptance criterion is based on the expected turbidity of the cell suspension.

Identity

The Identity tests, along with measures to ensure traceability (COI/COC), are used to mitigate the risk of misidentification of product type and batch.

(b) (4)

(b) (4)

Number of MAGE-A4 TCR-positive T cells

The specification is based on the available number of cells after sampling for release testing has been completed. The number of MAGE-A4 TCR-positive T cells is calculated using (b) (4).

The lower limit for the recommended DP dose of $\geq 2680.0 \times 10^6$ MAGE-A4 TCR-positive T cells was determined using results from (b) (4). The median dose was 8.00×10^9 MAGE-A4 TCR-positive T cells and range was 2.68×10^9 to 9.99×10^9 MAGE-A4 TCR-positive T cells, with positive clinical responses observed across the dose range administered. The proposed lower limit of 2.68×10^9 MAGE-A4 TCR-positive T cells is consistent with the minimum recommended dose. A maximum limit is not proposed. If more than the maximum recommended dose is manufactured, only the quantity of MAGE-A4 TCR-positive T cells within the recommended dose range will be supplied for administration. Controls to prevent overdose are described in 3.2.P.2.3 Manufacturing Process Development.

Cytotoxic Activity (Potency)

The assay measures the antigen-specific killing of target (T2) cells presenting the MAGE-A4 peptide by flow cytometry. The acceptance criterion for potency is established using statistical analysis of data from (b) (4).

(b) (4)

(b) (4), (b) (6)

¹ The proposed lower limit was revised in response to CMC IR #8

Reviewer Comments: The initially proposed acceptance criterion for potency was (b) (4). In response to CMC IR #7 sent on July 5, 2024, Adaptimmune revised the acceptance criterion to (b) (4) based on clinical experience. However, the lower limit of the acceptance criterion was based on a DP lot from a patient who did not respond to treatment. In response to CMC IR #8 sent on July 12, 2024, Adaptimmune agreed to revise the lower limit to (b) (4) based on the lowest observed value where there is a reasonable expectation of benefit to the patient and accounting for inter-assay variability. The proposed acceptance criterion for potency of (b) (4) is acceptable.

Purity

Percentage of Viable Cells

The percentage of viable cells in the DP is assessed using an (b) (4)

The acceptance criterion for cell viability is established using statistical analysis of data from (b) (4)

Based on the statistical analysis, the proposed acceptance criterion for percentage of viable cells is (b) (4). The distribution of batch release cell viability data for (b) (4) synovial sarcoma patient lots is shown in Figure 15.

(b) (4), (b) (6)

Reviewer Comments: The initially proposed acceptance criterion for cell viability was (b) (4) based on (b) (4) administered afami-cel batches. In response to CMC IR #7 sent on July 5, 2024, Adaptimmune revised the acceptance criterion to (b) (4) based on (b) (4) data. The revision is acceptable.

(b) (4)

(b) (4)

(b) (4)

Safety

Sterility

The test for sterility uses the (b) (4) system and mitigates the risk of adventitious microbial contamination. The sterility test was assessed for (b) (4) to (b) (4) and was concluded to be (b) (4) with respect to the probability of detection of microbial contamination. The acceptance criterion for the sterility method is "No Growth".

(b) (4)

Reviewer Comments: DBSQC reviewed the validation for the (b) (4) method and concluded that the assessment of (b) (4) with (b) (4) was not adequate. Adaptimmune agreed to provide additional method validation data in a PMC.

Endotoxin

The test for bacterial endotoxin is part of the overall control strategy for endotoxin contamination. Endotoxin is detected by the (b) (4) system that uses a (b) (4) method. The endotoxin test is performed in accordance with (b) (4). Based on the (b) (4)

(b) (4)

(b) (4)

Therefore, the proposed acceptance criterion for endotoxin is (b) (4).

(b) (4)

(b) (4)

(b) (4), (b) (6)

(b) (4)

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

Following interactions with the applicant, agreement on the commercial afami-cel release specifications has been reached.

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

Reviewed by AB

This section describes the analytical procedures for afami-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 are provided. For example, formulas for calculations needed to prepare solutions, determine appropriate cell concentrations and number of DP vials, and equipment settings are included in the analytical procedures.

Number of MAGE-A4 TCR positive T cells:

Calculation intended to determine the number of MAGE-A4 TCR-positive cells (final DP) and is determined using results from the (b) (4)

(b) (4)

Potency: Determines the ability of MAGE-A4 T-cell receptor (TCR) positive T cells to kill target (b) (4)

of the test sample to a reference. Minor changes were made to the potency assay, QC 079 R04 versus QC 079 R06, which are described in below.

Reviewer Comments: There have been no significant procedure changes between QC 079 R04 versus QC 079 R06, all batch data can be directly compared throughout clinical development.

Potency Validation: Summary of the validation studies performed for cytotoxic activity is provided, see Table 88 for Potency System Suitability and Table 96 for validation results. (b) (4)

(b) (4)

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

(b) (4)

Viability: Measurement of cell viability (%) using the (b) (4)

. Assay Validation in accordance with (b) (4)

The method is suitable for its intended purpose of determining viability (b) (4) and final formulated DP.

Viability Validation: Validation studies have been performed, consistent with ICH Q2

(b) (4). Samples used for testing include (b) (4)

The initial study VAL 02020, see Table 97, was subsequently updated by VAL 02111, see Table 98.

(b) (4)

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

(b) (4)

Reviewer Comments: The initial VAL 02020 protocol was for viability and (b) (4) method by the (b) (4) method using (b) (4) final DP along with (b) (4) VAL 02111 was subsequently performed to expand the range of the assay past (b) (4) for viability by re-assessing accuracy, intermediate precision, partial linearity assessment and range extension to ULOQ to determine whether the methods were suitable for their intended purpose.

(b) (4)

(b) (4)

(b) (4)

Appearance: Visual inspection of the container/closure and final DP is performed. The product is inspected for the absence of visible foreign particulates using a (b) (4) to assess the container closure, (b) (4) absence of visible particulates, color, and clarity of the final drug product. Visual inspection is consistent with guidance provided in (b) (4)

Changes were made to the appearance procedure during clinical development. Early clinical batches were tested using QC 119. The current appearance procedure, QC 189, intended to test commercial batches is described in Section 3.2.P.5.2 Analytical Procedures: Appearance. None of the revisions made to QC 119 altered the test procedure so no comparative studies were required.

Appearance Validation: Validation studies were performed for absence of visible particulates, color, and clarity, consistent with (b) (4) and FDA Guidance for Industry: *Analytical Procedures and Methods Validation for Drugs and Biologics* and Q2(R1) Validation of Analytical Procedures: Text and Methodology. *Assay is acceptable. Reviewed by DBSQC.*

Sterility: (b) (4) microbial method for sterility testing uses the (b) (4) system, which is a (b) (4) microbial method (not less than (b) (4)) that (b) (4)

. Validation studies have been performed in accordance with (b) (4)

Sterility Validation: Validation studies performed for the (b) (4) sterility method using the (b) (4) system have been performed in accordance with (b) (4)

Assay is acceptable. Reviewed by DBSQC.

(b) (4)

Assay is acceptable. Reviewed by DBSQC.

Endotoxin: Assesses safety with respect to the quantity of bacterial endotoxins detected in the (b) (4) DP per (b) (4) Bacterial Endotoxins Test using (b) (4).

Endotoxin Validation: Method validation results of (b) (4) to show that it can detect low levels of bacterial endotoxin (b) (4)

Assay is acceptable. Reviewed by DBSQC.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3: Lot release and characterization assays were appropriately presented and validated.

3.2.P.5.4 Batch Analyses

Batch analysis information for afami-cel lots administered to patients is summarized in Table 104. The data includes (b) (4) total lots (b) (4)

(b) (4) . Data from afami-cel lots manufactured for (b) (4) patients
(b) (4) were used to justify the commercial
afami-cel lot release acceptance criteria as described in 3.2.P.5.1 and 3.2.P.5.6
Specification(s) and Justification of Specification(s). All DP lots were manufactured at
Adaptimmune's Navy Yard facility.

(b) (4)

The supply failure rate was calculated for 52 subjects with synovial sarcoma who were enrolled and apheresed during clinical study ADP-0044-002 Cohort 1. Product manufacture was initiated for 52 subjects, with 44 subjects successfully treated. Seven subjects did not receive manufactured DP due to death (n=3), loss of eligibility prior to lymphodepleting chemotherapy (n=2), withdrawal by patient (n=1), and investigator decision (n=1). These were considered unrelated to successful manufacture. Four batches were considered failed:

- (b) (4), (b) (6) (subject (b) (6)) – batch aborted due to manufacturing failure.
- (b) (4), (b) (6) (subject (b) (6)) – batch did not meet current batch release specification.
- (b) (4), (b) (6) (subject (b) (6)) – batch aborted due to manufacturing issue.
- (b) (4), (b) (6) (subject (b) (6)) – lot damaged in transit.

The failure rate was calculated to be $(4 \text{ subjects} / 52 \text{ first batch manufacture}) \times 100\% = 7.7\%$.

3.2.P.5.5 Characterization of Impurities

Reviewed by AB and LKD

Refer to section 3.2.S.3.2 Impurities.

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

The batch analyses data provided are adequate. No major variability is observed in test results between clinical studies.

3.2.P.6 Reference Standards or Materials

Reviewed by AB

No references standards for afami-cel DP release and stability testing, other than for LV (b) (4), are used. Refer to LV Section 3.2.S.5 Reference Standards or Materials for (b) (4) standard stability testing results.

3.2.P.7 Container Closure System

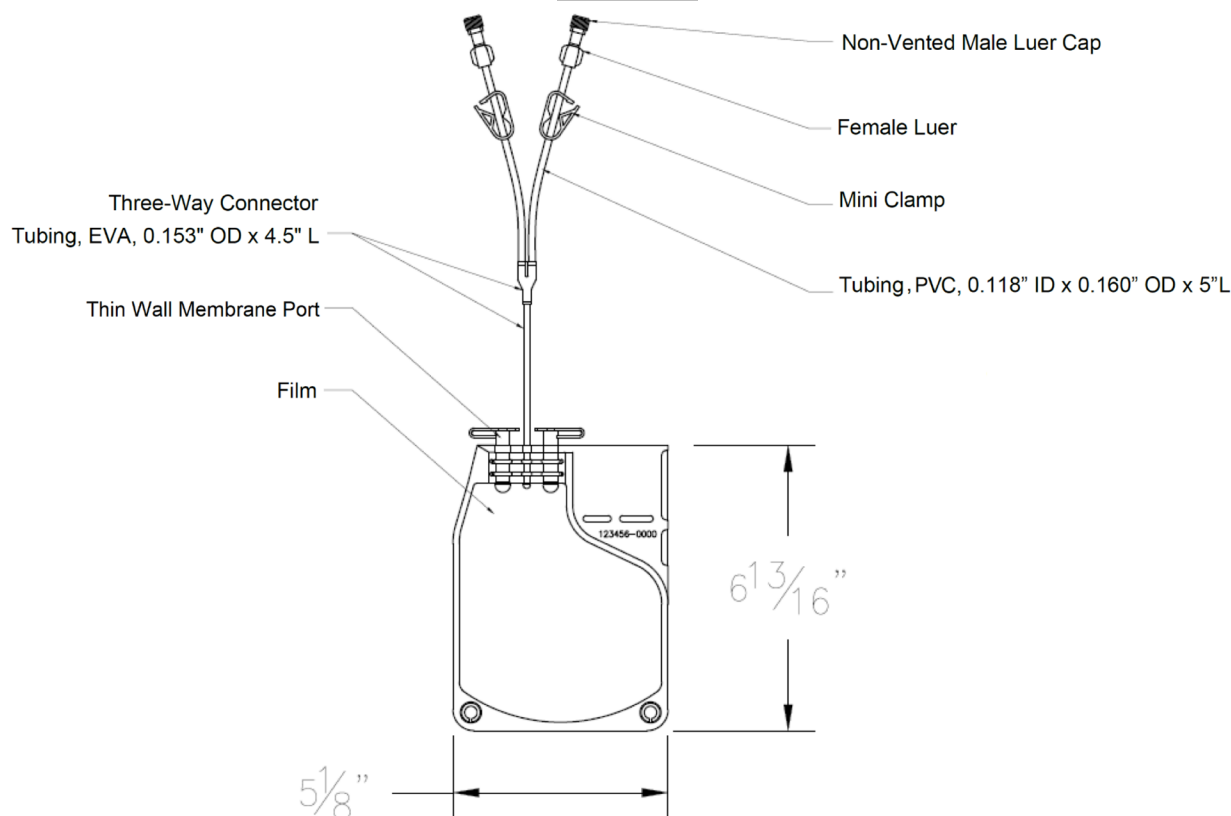
Reviewed by YN

The DP is stored in a (b) (4) Cryogenic Storage Container (Bag), (b) (4), supplied as pre-sterilized and read-to-use by (b) (4). The components for the bag are provided in (Table 105). Figure 22 shows the illustration of the bag.

Table 104. Primary Container Closure System Components

Component	Material(s) of Construction	Qualify Conformance
Bag Film (Container)	Polyolefins	ISO 10993
Thin Wall Membrane Port	Ethylene-vinyl acetate	
Ports	Ethylene-vinyl acetate	
Tubing	Ethylene-vinyl acetate and Polyvinyl chloride	
Luers	Acrylonitrile butadiene styrene	
Luer Caps	Polypropylene	
Mini Clamp	Polypropylene	
Three-Way Connector	Polyvinyl chloride	

Figure 22. Schematic Representation of the (b) (4) Cryogenic Storage Container



Abbreviations: EVA = Ethylene-vinyl acetate; ID = inner diameter; L = length; OD = outer diameter; PVC = Polyvinyl chloride made with DEHP-plasticizer.

Reviewer Comments:

The applicant provided an unlabeled figure of the bag in the original submission. In response to CMC IR #3, the applicant provided the updated Figure X and Table X above.

The primary packaging components are not derived from animal sources, but certain parts of the primary packaging (e.g., contact materials: bag film, tubing, port, 3-way connector, and female luer lock) may contain (b) (4) or may have been in contact with (b) (4). The applicant indicated that the supplier confirmed that the (b) (4) is unlikely to present any TSE risk and the container is manufactured using a rigorous process. However, the applicant did not provide details on this process. In response to CMC IR #3, the processing conditions for the primary packaging components include (b) (4). These steps are sufficient for mitigating the potential risk of TSE. Additionally, the applicant provided the updated animal material statement from (b) (4). The responses are adequate.

The filled and labeled bags are packaged in a labeled aluminum cassette for storage in the gas phase of liquid nitrogen before shipping. There is one bag per cassette, and one or more cassettes are packed in a foam block. A cryostrap is used to secure the foam

block and cassette to prevent movement during transportation. The loaded block is shipped in a liquid nitrogen dry shipper.

The specifications used to release the (b) (4) Cryogenic Storage Bags are in Table 106.

(b) (4)

Reviewer Comments:

The in-house identification and (b) (4) analysis assays have been validated. The SOPs and validation reports are provided in the submission. In response to CMC IR #4, the sponsor provided the acceptance criteria for lot release test methods: (b) (4)

Certificate of Conformance (COC) is provided for the (b) (4) Cryogenic Storage Container is provided in the submission (section 3.2.R). COC is from the cited manufacture (b) (4) that certifies the container are sterilized by (b) (4)

(b) (4) and the fluid path is sterile and non-pyrogenic. The containers are listed as passing the acceptance criteria for visual inspection, (b) (4), sterility, and endotoxin.

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

The (b) (4) Cryogenic Storage Container is 501(k) cleared under (b) (4) and is acceptable for use. The labeled container closure is reviewed in further details 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.

3.2.P.8 Stability

Reviewed by YN

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 long-term storage of DP. The stability data was generated with (b) (4) primary DP lots produced with the proposed commercial production process, Process Version P1.6.1. All DP lots were transduced with LV manufactured at (b) (4) and all DP lots were manufactured at the proposed commercial manufacturing facility. DP lots were stored in the same container closure system (e.g., (b) (4) bag) but at a (b) (4) volume (e.g., (b) (4)). Stability data is provided for different time points for primary DP lots stored in vapor phase of liquid nitrogen ($\leq -130^{\circ}\text{C}$). DP lots were assessed based on the proposed commercial DP lot release acceptance criteria using validated test methods. Based on the current data, Adaptimmune proposed a shelf-life of 6 months long-term storage at $\leq -130^{\circ}\text{C}$ for afami-cel.

Table 106. Stability Lots for afamitresgene autoleucel DP

Drug Product Lot Number	Date of Manufacture	Drug Product Container	Fill Vol. (mL)	Completed	Study Duration (Months) & Status
(b) (4), (b) (6)					

Accelerated Stability Study (b) (4)
(b) (4), (b) (6)

Table 107. Primary Stability Protocol for Long-term Storage

Test	Acceptance Criteria	Timepoint (months)							
		0	3	6	9	12	18	24	
Appearance: Visual inspection	(b) (4)	X	X	X	(b) (4)				
	(b) (4)	X	X	X					
Appearance: Particulates per (b) (4)	Absence of visible foreign particulates	X	X	X					
Appearance: Color per (b) (4)	(b) (4)	X	X	X					
Appearance: Clarity per (b) (4)	(b) (4)	X	X	X					
(b) (4)	(b) (4)	X	X	X					
(b) (4)	(b) (4)	X	X	X					
Cytotoxic Activity	(b) (4)	X	X	X					
Cell Viability	(b) (4)	X	X	X					
(b) (4)	(b) (4)	X	X	X					
(b) (4)	(b) (4)	X	X	X					
Sterility by (b) (4)	No growth	X	-	-					

Reviewer Comments:

Adaptimmune provided updated stability data during review in Amendment 28 (6 month long-term and accelerated). The updated data is included in this review. All lots met specification for identity, cytotoxic activity, (b) (4), and (b) (4). One batch (b) (4), (b) (6) had a leakage at the 6-month timepoint. Additionally, one batch (b) (4), (b) (6) was out of specification for cell viability (72%) at the 6-month timepoint, however not downward trend in the data. All other batches met acceptance criteria at all time points tested. Statistical evaluation will be performed when additional data are available.

Accelerated Stability Studies

(b) (4)

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

There is no post-approval commitment for DP stability. The primary stability batches currently included in the long-term stability study will continue to be tested. 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 the submission are met.

Reviewer Comments: This proposal is acceptable.

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

Other than the one lot (b) (4), (b) (6), which had a leakage at the 6-month timepoint, all primary stability lots ($n = (b) (4)$) met specification for the tested parameters for up to 6 months. No significant trends are observed. The current stability data supports a shelf-life of 6 months long-term storage at $\leq -130^{\circ}\text{C}$ for afami-cel.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Reviewed by DMPQ. Please refer to 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 [LV], Section 3.2.S.2.3 Control of Materials [afamitresgene autoleucel], and Section 3.2.S.4.1 Specifications_LV.

☐ Viral Clearance Studies

Not needed for this autologous product.

3.2.A.3 Novel Excipients

No novel excipients.

3.2.R Regional Information (USA)

Executed Batch Records

Master and executed batch records are provided and were reviewed in detail during inspection of Adaptimmune's Navy Yard and (b) (4), Inc. facilities. Please refer to EIR 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 (afami-cel).

Combination Products

Not applicable

Comparability Protocols

Comparability protocols were provided and reviewed under IND 17235. There are no comparability protocols for future changes.

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. Adaptimmune states that to their knowledge, no extraordinary circumstances exist; therefore, an environmental assessment was not prepared. The final afami-cel DP (DP) consists of human cells transduced with the lentivirus vector (LV). The LV used in the manufacturing of afami-cel DP is a non-replicating virus generated recombinantly and has negligible potential for release into the environment. The DP are human cells with stringent nutritional requirements for survival and replication and are unable to survive in the environment. Taken together, afami-cel DP consists of genetically modified human cells that “occur naturally in the environment”, 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.

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), Section 16 (How Supplied/Storage and Handling). The PI provided a detailed and accurate description of afami-cel, its mechanism of action, as well as the receipt and preparation procedures for afami-cel at the authorized treatment center.

Carton and Container Label:

Examples of the final bag (Figure 23), cassette (Figure 24), and common bag/cassette (Figure 25) labels are provided below. All labels contain the required text.

Figure 23. Tecelra Bag Label

afamitresgene autoleucel
Tecelra®  **VERIFY PATIENT IDENTIFIERS**






Patient MRN: MAX14CHARACTER
COID: MAX.18-CHARACTERS/

First Name MI: MAX.14CHARACTR
Last Name: MAX-14CHARACTR
DOB: 01-Jan-2000
DIN: MAX.16CHARACTERS

Exp: 31-Dec-2024
Lot: MAX.16-CHARACTER
LBL00035Rev00 Bag 01 of 01 

Figure 24. Tecelra Cassette Label

afamitresgene autoleucel
Tecelra® 


STOP
Confirm patient
identifiers prior
to infusion






Patient MRN: MAX14CHARACTER
COID: MAX.18.CHARACTERS/

First Name MI: MAX.14CHARACTR
Last Name: MAX-14CHARACTR
DOB: 01-Jan-2000
DIN: MAX.16CHARACTERS

LBL00036Rev00 Exp: 31-Dec-2024 Bag 01 of 01 Lot: MAX.16-CHARACTER 

Figure 25. Tecelra Common Label for Bag and Cassette


NDC 83205-0001-2

afamitresgene autoleucel
Tecelra® 

Rx ONLY **FOR AUTOLOGOUS & INTRAVENOUS USE ONLY**
No U.S. standard of potency

Contains: 2.68×10^9 to 10×10^9 MAGE-A4 TCR positive T cells in frozen suspension containing 5% DMSO (no preservative)


Gently mix by massaging post-thaw.
See full prescribing information for instructions for administration.
Store and transport at $\leq -130^\circ\text{C}$.

Suspension for intravenous infusion

GENETICALLY MODIFIED
DO NOT USE A LEUKODEPLETING FILTER OR IRRADIATE

Not evaluated for infectious substances

Manufacturer: Adaptimmune LLC, Philadelphia, PA 19112 USA
Phone: 1-855-24MYADAP (1-855-246-9232) U.S. Lic. #XXXX


LBL 00034 Rev 01

Reviewer Comments: During the review period, Adaptimmune modified the labels as requested by APLB, CMC, and the RPM Reviewer Tigist Assefa (OTP/DRPM). The final

version of labels was found acceptable and is provided here (Figures 23 - 25). For additional details, please refer to the label review by Tigist Assefa.

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

Reviewed by AB

VSV-G and Psi qPCR in Human (b) (4) PBMCs: Testing for RCL and afami-cel persistence utilizing qPCR to quantify VSV-G and Psi copy number in (b) (4) human PBMC samples. Validation was conducted at (b) (4) samples for precision and stability were prepared by (b) (4)

The parameters that were assessed include precision, stability, accuracy, specificity, linearity, carryover, and sensitivity (limit of detection). A (b) (4) study was performed and the limits of quantitation were established. Results indicate that acceptance criteria for precision, accuracy, specificity, linearity and carryover were met for PBMCs (b) (4)

. Recommended to use (b) (4) DNA. The ULOQ for both PBMCs (b) (4) for VSV-G and Psi. The LLOQ for both PBMCs (b) (4) is (b) (4) for VSV-G and Psi.

Insertional Oncogenesis Testing: Integration site analysis in subjects with > 1% persistence 1 year post-infusion. Assay is performed Using a (b) (4) analysis of integration site distributions named (b) (4)

. The method appears sound and is supported by the literature/citations, although no validation report was provided. Literature indicates that this pipeline accommodates analysis of integration in both single copy and repeated sequences. (b) (4)

(b) (4)

(b) (4)

Reviewer Comments: For assay development and validation, standard biopsy and IHC procedures were used to develop this assay with appropriate controls: MAGE-A4 expressing tumor cells (A375) and transduced and non-transduced T-cells using the engineered LVV, see Table 109.

Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5: Testing methodologies and data provided appear appropriate. For insertional oncogenesis, a reference is made to a published literature to support this method. This is reasonable.