CBER CMC BLA Review Memorandum

BLA STN 125773

AMTAGVI
(Lifileucel)

Reviewer/Title/Affiliation
Karin Knudson, PhD │ Biological Reviewer │ CBER/OTP/OCTHT/DCT1/CTB2
Heba Degheidy, MD, PhD │ Biologist │ CBER/OTP/OCTHT/DCT1/CTTB
Iain Farrance, PhD│ Biologist │ CBER/OTP/OCTHT/DCT1/CTB1
Sukhanya Jayachandra, PhD │ Biologist │ CBER/OTP/OCTHT/DCT1/CTB1
Saravanan Karumbayaram, MPharm, PhD│ Biologist │ CBER/OTP/OCTHT/DCT1/CTB1
Elizabeth Lessey-Morillon, PhD │ Biologist │ CBER/OTP/OCTHT/DCT1/CTB1
Brian Niland, PhD │ Biologist │ CBER/OTP/OCTHT/DCT1/CTB2

1. BLA#: STN 125773

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

Submission Type & #	Holder	Referenced Item	LOA	Comments/Status
(b) (4)	(b) (4)	Letter dated 18Aug2022 authorize regulatory submission document, manufacture, and release capacity evaluation for (b) (4)	Yes	Information pertinent to (b) (4) Deferred to DMPQ reviewer. See review memo from Hector Carrero.
(b) (4)	(b) (4)	Letter dated 30Aug2022 authorize specific information for the (b) (4)	Yes	Information pertinent to (b) (4) . Deferred to DMPQ reviewer. See review memo from Hector Carrero.
(b) (4)	(b) (4)	Letter dated 29June2022 authorize all information for (b) (4) Interleukin-2	Yes	Information pertinent to (b) (4) Interleukin-2 (IL-2) was reviewed, assessed, and documented in the memo by Elizabeth Lessey-Morillon in section 3.2.S.2.3. Control of Materials – Ancillary Raw Materials and Consumables
(b) (4)	(b) (4) .	Letter dated 6July2023 authorize all information for CryoStor CS10	Yes	Information pertinent to CryoStor CS10 was reviewed, assessed, and documented in the memo by Elizabeth Lessey-Morillon in section 3.2.P.4 Control of Excipients
(b) (4)	(b) (4) .	Letter dated 6July2023 authorize all information for (b) (4)	Yes	Information pertinent to (b) (4) was reviewed, assessed, and documented in the memo by Karin Knudson in section 3.2.S.2.3. Control of Materials – Tumor Tissue
(b) (4)	(b) (4)	Letter dated 4July2023 authorize all information for (b) (4)	Yes	Information pertinent to (b) (4) Interleukin-2 (IL-2) was reviewed, assessed, and documented in the memo by Elizabeth Lessey-Morillon in section 3.2.S.2.3. Control of Materials – Ancillary Raw Materials and Consumables
(b) (4)	(b) (4)	Letter dated 29Jun2023 authorize all information for (b) (4)	Yes	Information pertinent to (b) (4) (b) (4) was reviewed, assessed, and documented in the memo by Elizabeth Lessey-Morillon in section 3.2.S.2.3. Control of Materials – Ancillary Raw Materials and Consumables
(b) (4)	(b) (4)	Letter dated 30Jun2023 authorize reference of Module 3.2.S. and specific (b) (4) related modules for (b) (4)	Yes	Information pertinent to (b) (4) was reviewed, assessed, and documented in the memo by Elizabeth Lessey-Morillon in section 3.2.S.2.3. Control of Materials – Ancillary Raw Materials and Consumables

(b) (4)	(b) (4)	Letter dated 24July2024 authorize reference of all information for (b) (4) (b) (4)	Yes	Information pertinent to (b) (4) (b) (4) reviewed, assessed, and documented in the memo by Elizabeth Lessey-Morillon in section 3.2.S.2.3. Control of Materials – Ancillary Raw Materials and Consumables and Karin Knudson in section 3.2.S.2.5. Process Validation and/or Evaluation.
(b) (4)	(b) (4)	Letter dated 14July2023 authorize all information for (b) (4)	Yes	Information pertinent to (b) (4) (b) (4) was reviewed, assessed, and documented in the memo by Wojtek Tutak in section 3.2.P.2.4 Container Closure System. See also consult review memo from Wojtek Tutak.

3. APPPLICANT NAME AND LICENSE NUMBER

Iovance Biotherapeutics, Inc., License #2298

4. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper/USAN: Lifileucel
Proprietary Name: AMTAGVI
Established Pharmacologic Class (EPC): autologous tumor-derived T cell immunotherapy
Company Code: LN-144
UNII Code: lifileucel: R0835E18NH
NDC Codes: 73776-001-11

5. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Description: Tumor-derived T cells
Dosage Form: Cell Suspension for Infusion
Strength/Potency: 7.5×10^9 to 72×10^9 total viable cells in (b) (4) (100-125 mL per container, one to four containers total) of cryopreservation solution containing 5% DMSO, 0.5% human serum albumin (HSA), and 300 IU/mL IL-2
Route of Administration: Intravenous infusion
Indication: Treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor.

6. MAJOR MILESTONES

Initial IND Submission (BB-IND 16317)	December 30, 2014
Orphan Drug Designation Granted	June 9, 2015
Fast Track Designation Granted	August 29, 2017
Regenerative Medicine Advanced Therapy Designation Granted	August 24, 2018
Pre-BLA Meeting	August 12, 2023
Non-Clinical Module (Rolling BLA Initial Module) Received	August 24, 2022
Clinical Module and Labeling Received	September 29, 2022
Quality Module (Final Module) Received	March 27, 2023
First Committee Meeting	April 17, 2023
Filing Meeting	May 11, 2023
BLA Filed	May 26, 2023
Mid-Cycle Meeting	July 27, 2023
Major Amendment Determination	September 8, 2023
Late-Cycle Meeting	November 20, 2023
Target Date	February 13, 2024
PDUFA Action Date	February 23, 2024

7. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Karin Knudson, PhD BLA Chair / CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB2	Environmental Analysis (1.12.14) Labeling (1.14) DS General Information (3.2.S.1) DS Manufacturer(s) (3.2.S.2.1) DS Description of Manufacturing Process (3.2.S.2.2) DS Control of Materials – Tumor Tissue (3.2.S.2.3) DS Process Validation and/or Evaluation (3.2.S.2.5) DS Manufacturing Process Development (3.2.S.2.6) DS Characterization (3.2.S.3) DS Specifications/Justification (3.2.S.4.1, 3.2.4.5) DS Analytical Procedures/Validation (3.2.S.4.2, 3.2.S.4.3) DS Batch Analyses (3.2.S.4.4) DS Reference Standards (3.2.S.5) DP Description and Composition (3.2.P.1) DP Pharmaceutical Development (3.2.P.2.1) DP Manufacture (3.2.P.3) DP Specifications/Justification (3.2.S.5.1, 3.2.5.6) DP Analytical Procedures/Validation (3.2.P.5.2, 3.2.P.5.3) DP Batch Analyses (3.2.P.5.4) DP Characterization of Impurities (3.2.P.5.5) DP Reference Standards (3.2.P.6) Facilities and Equipment (3.2.A.1) Executed Batch Records (3.2.R.1)
Heba Degheidy, MD, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTTB	DP Analytical Procedures/Validation (3.2.P.5.2, 3.2.P.5.3)
Iain Farrance, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	DP Analytical Procedures/Validation (3.2.P.5.2, 3.2.P.5.3)
Sukhanya Jayachandra, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	DP Analytical Procedures/Validation (3.2.P.5.2, 3.2.P.5.3) DP Reference Standards (3.2.P.6)
Saravanan Karumbayaram, MPharm, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	DP Analytical Procedures/Validation (3.2.P.5.2, 3.2.P.5.3) DP Stability (3.2.P.8)
Elizabeth Lessey-Morillon, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	DS Control of Materials (3.2.S.2.3) DP Control of Excipients (3.2.P.4) Adventitious Agents Safety Evaluation (3.2.A.2)
Brian Niland, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB2	Facilities and Equipment (3.2.A.1)
Andrey Sarafanov, PhD Consult Reviewer CBER/OTP/OPPT/DH/HB2	DP Container Closure System (3.2.P.2.4)
Wojtek Tutak, PhD Consult Reviewer CBER/OTP/OCTHT/DCT2/TEB2	DS Container Closure (3.2.S.6) DP Container Closure System (3.2.P.2.4) DP Container Closure (3.2.P.7)
Cinque Soto, PhD Consult Reviewer CBER/OTP/OCTHT/DCT1	Reports of Bioanalytical and Analytical Methods for Human Studies (5.3.1.4)

8. INTER-CENTER CONSULTS REQUESTED

None

9. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
8/24/2023	STN 125773 / 0.0	Preclinical Module
9/29/2023	STN 125773 / 0.1	Clinical Module, Labeling
3/27/2023	STN 125773 / 0.2	Quality Module and Completed Submission of Rolling BLA
5/3/2023	STN 125773 / 0.6	Response to CMC IR #1, dated 4/28/2023
6/20/2023	STN 125773 / 0.12	Response to CMC IR #2, dated 5/23/2023
6/22/2023	STN 125773 / 0.14	Response to CMC IR #3, dated 6/14/2023
7/10/2023	STN 125773 / 0.17	Response to CMC IR #4, dated 7/6/2023
7/19/2023	STN 125773 / 0.19	Response to CMC IR #5, dated 7/14/2023
7/25/2023	STN 125773 / 0.21	Response to CMC IR #6, dated 7/23/2023
7/25/2023	STN 125773 / 0.22	Additional response to CMC IR #2, dated 5/23/2023
8/16/2023	STN 125773 / 0.27	Response to CMC IR #7, dated 8/3/2023
8/10/2023	STN 125773 / 0.24	Response to CMC IR #8, dated 8/4/2023
8/17/2023	STN 125773 / 0.29	Response to Clinical IR #7, dated 8/16/2023 (labeling)
08/17/23	STN 125773 / 0.29	Response to CMC IR #9, dated 8/15/2023
8/24/2023	STN 125773 / 0.30	Response to CMC IR #10, dated 8/18/2023
8/28/2023	STN 125773 / 0.34	Response to CMC IR #11, dated 8/21/2023
9/1/2023	STN 125773 / 0.36	Additional response to CMC IR #9, dated 8/15/2023
09/06/2023	STN 125773 / 0.37	Response to CMC IR #12, dated 8/30/2023
09/21/2023	STN 125773 / 0.40	Response to CMC IR #13, dated 9/12/2023
09/19/2023	STN 125773 / 0.39	Response to CMC IR #14, dated 9/14/2023
10/30/2023	STN 125773 / 0.42	Response to CMC IR #15, dated 10/25/2023
11/3/2023	STN 125773 / 0.45	Additional response to CMC IR #10, dated 8/18/2023
11/15/2023	STN 125773 / 0.46	Response to CMC IR #16, dated 11/9/2023
11/21/2023	STN 125773 / 0.49	Response to CMC IR #17, dated 11/16/2023
11/20/2023	STN 125773 / 0.47	Response to CMC IR #18, dated 11/17/2023
12/7/2023	STN 125773 / 0.54	Additional response to CMC IR #17, dated 11/16/2023
12/13/2023	STN 125773 / 0.56	Response to CMC IR #19, dated 12/13/2023
12/15/2023	STN 125773 / 0.55	Response to CMC IR #20, dated 12/14/2023
12/18/2023	STN 125773 / 0.58	Additional response to CMC IR #20, dated 12/14/2023
1/3/2024	STN 125773 / 0.59	Response to CMC IR #21, dated 12/22/2023
1/10/2024	STN 125773 / 0.63	Response to CMC IR #22, dated 1/10/2023
1/19/2024	STN 125773 / 0.67	Response to CMC IR #23, dated 1/12/2024
1/22/2024	STN 125773 / 0.69	Response to CMC PMR IR #1, dated 1/19/2024
1/29/2024	STN 125773 / 0.71	Response to CMC IR #24, dated 1/24/2024
1/29/2024	STN 125773 / 0.73	Response to CMC IR #25, dated 1/26/2024
1/29/2024	STN 125773 / 0.72	Response to CMC PMC IR #2, dated 1/29/2024
1/30/2024	STN 125773 / 0.74	Response to Package Insert/Patient Information IR, dated 1/24/2024
2/6/2024	STN 125773 / 0.80	Response to CMC IR #26, dated 2/5/2024
2/8/2024	STN 125773 / 0.81	Response to Package Insert/Patient Information IR, dated 2/5/2024
2/9/2024	STN 125773 / 0.82	Additional response to CMC IR #24, dated 1/24/2024
2/13/2024	STN 125773 / 0.84	Response to Package Insert/Patient Information IR, dated 2/12/2024
2/14/2024	STN 125773 / 0.85	Response to Package Insert/Patient Information IR, dated 2/13/2024
2/14/2024	STN 125773 / 0.86	Response to CMC PMC IR #3 (DMPQ PMC), dated 2/13/2024

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Iovance Biotherapeutics, Inc. (i.e., the Applicant) submitted the biologics license application (BLA) 125773 to market lifileucel (AMTAGVI), an autologous tumor-derived T cell immunotherapy, for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. There is no FDA-approved second or subsequent line of therapy for patients with this indication, so there is a high unmet medical need.

Lifileucel (the drug product or DP) is an autologous product composed primarily of T cells collected from resected tumor material and expanded *in vitro*. The commercial manufacturing process, which is equivalent to the clinical manufacturing process, is continuous but occurs in two stages. In the first stage, also called the Pre-Rapid Expansion Phase or Pre-REP, resected tumors are shipped to (b) (4) manufacturing sites and fragmented and cultured for (b) (4) with interleukin-2 (IL-2) (b) (4) (b) (4) In the second stage, called the Rapid Expansion Phase or REP, the cultured cells (b) (4) cultured with IL-2, anti-CD3 antibody, (b) (4) (b) (4) the cultured cells are harvested, then washed and formulated with 48% Plasma-Lyte A, 2% human serum albumin (HSA)(b) (4) (final concentration 0.5% HSA), 50% CryoStor CS10 (final concentration 5% DMSO) and 300 IU/mL IL-2 (aldesleukin). The final formulated DP containing 7.5 x 10^9 to 72 x 10^9 viable cells is filled into(b) (4) to 4 cryopreservation bags (100 mL to 125 mL each bag), cryopreserved, and stored at ≤ 150°C. The DP release testing consists of tests for product safety (i.e., sterility, mycoplasma, and endotoxin testing), dose, purity (viability and product-related cellular impurities), and potency. After successful completion of manufacturing and release testing, the cryopreserved DP is shipped to an Applicant-qualified treatment center in a liquid nitrogen dry shipper. Lifileucel is then thawed and administered by intravenous infusion without additional manipulation.

Establishing meaningful potency-related critical quality attributes (CQAs) for complex biological products is challenging. The lifileucel manufacturing process is designed to expand T cells without enriching for reactivity toward specific tumor antigens, and without selecting for specific T cell phenotypes. As a result, each lot contains a heterogenous polyclonal T cell population with antigen specificity that is defined by the T cells present in the patient-specific starting material. Therefore, lifileucel is inherently highly variable from lot-to-lot. Additionally, the attributes that define an effective T cell response against human tumors are not well-understood, and anti-tumor activity is not restricted to a specific T cell subset or phenotype. The Applicant evaluated multiple attributes during product development but has not established a specific mechanism of action (MOA) for lifileucel. The potency-related CQAs tested for lot release are (b) (4)

(b) (4) The Applicant was not able to demonstrate any meaningful correlation between these potency-related CQAs and clinical efficacy and none of these potency-related CQAs have an established relationship to clinical efficacy. However, these attributes were selected as potency-related CQAs based on their well-established relationship to T cell function and are supported by a sound scientific rationale. Based on the current manufacturing process and process control established by the Applicant, these potency-related CQAs are therefore sufficient to ensure the continued potency of the commercial product.

All release assays have been appropriately validated. However, the (b) (4) assays for determining T cell expression of (b) (4) (b) (4) do not include analysis of (b) (4) controls. The validation studies showed sufficient control of these assays, and the commercial release acceptance criteria are based on samples analyzed with the current control strategy. However, the accuracy of the release test results may be negatively affected by the (b) (4) controls. To ensure appropriately controlled analysis of these potency-related CQAs for product release, the Applicant agreed to conduct a study to evaluate a (b) (4) control strategy as a Post-Marketing Commitment (PMC). This study will include a comparative analysis of the original control strategy and the (b) (4) control strategy, and re-evaluation of the (b) (4) release acceptance criteria upon study completion.

The real-time stability data from (b) (4) batches supports storage of the DP at ≤ 150°C for up to six months. The shelf life of the DP is up to three hours at room temperature after thawing. The product is stored in 510(k) cleared cryopreservation bags for freezing cells. The bags are evaluated and tested, including for extractables and leachables with (b) (4) DP (i.e., (b) (4) However, the Applicant has not performed a (b) (4) assessment of all organic and elemental leachables for the DP over its manufacturing, storage, and in-use period (i.e., cumulative leachables in the final DP). Therefore, we require the assessment of cumulative organic and elemental leachables in a (b) (4) study as a PMC.

To demonstrate the clinical effectiveness of lifileucel, the Applicant provided results from Study C-144-01, a single-arm, multi-cohort Phase 2 study. The lifileucel product used in this study was manufactured at (b) (4) The (b) (4) facility manufactured the majority of lots (b) (4) infused in Study C-144-01. Analytical comparability between (b) (4) were not demonstrated prior to submission of the BLA. Review of the analytical comparability studies under the BLA determined that neither comparability between (b) (4) have been established. Thus, the primary efficacy analysis and release acceptance criteria are based only on (b) (4)-manufactured lots.

The commercial lifileucel product is to be manufactured in its entirety at (b) (4) and Iovance Cell Therapy Center (iCTC), (b) (4) located in Philadelphia, PA. The iCTC facility was (b) (4) used as a manufacturing site for study C-144-01 clinical lots. Analytical comparability between (b) (4) iCTC was not demonstrated prior to submission of the BLA. The analytical comparability studies submitted with the BLA, with reanalysis requested by the FDA, were sufficient to establish analytical comparability between (b) (4) iCTC and support commercial lifileucel production at iCTC. The manufacturing differences between the (b) (4) sites are minimal and statistical assessment based on two independent reference populations both supported comparability. However, the analytical comparability studies were limited to assessment of routine quality controls, which generally would not be adequate to assess the impact of major manufacturing changes. In addition, as previously described, the MOA for the DP is not well characterized, and the Applicant has not established meaningful product attributes relevant to DP efficacy. Thus, it will be very challenging for the Applicant to complete a convincing comparability exercise to support a major manufacturing change post-licensure without performing additional clinical studies, as any comparability exercise will be limited by the inherent variability of the product without the identification of meaningful and relevant CQAs. While the Applicant has been informed of the challenges surrounding execution of future comparability exercises during the BLA review, this concern will be reiterated in a formal communication as an Advisory Comment to the Applicant in the Approval Letter.

The iCTC facility was inspected on August 21 to 25, 2023, and no observations were identified during the pre-licensure inspection (PLI). The (b) (4) facility was inspected on (b) (4) One 483 observation was issued on (b) (4) (b) (4) for the (b) (4) facility concerning deficient aseptic manufacturing personnel qualification. (b) (4) sufficiently addressed the 483 issue. All records will be available for review (b) (4)

Lifileucel is manufactured in a (b) (4) process system with appropriate controls to maintain product quality and safety. The raw materials, product contacting materials, and reagent qualification programs are acceptable. Raw materials derived from animals and humans are controlled to ensure the absence of microbial contaminants and adventitious agents. The manufacturing process has been adequately validated. The Chain of Identity/Chain of Custody (COI/COC) is appropriate for a patient-specific product and is maintained through the manufacturing and shipping process, until administration at the treatment center using multiple product specific identifiers.

On August 28, 2023 (STN 125773/.034), the Applicant provided a substantial amount of revised or new CMC information pertaining to the process controls, release specifications and product CQAs, and the (b) (4)/iCTC comparability study. This required the FDA to independently assess the substantial changes to the CMC information and re-evaluate the identified major review issues. Therefore, the Amendment was determined to be a Major Amendment, and the review timeline was revised accordingly.

The following major CMC concerns were raised during the review of this submission and were resolved through information requests:

1. Insufficient process controls to ensure manufacturing control and consistency.
2. Insufficient justification for the selected potency-related CQAs.
3. Insufficient justification for the release potency-related, potency, and dose acceptance criteria.
4. Lack of appropriate statistical assessment of the (b) (4) iCTC comparability study results.
5. Insufficient justification for the assay control strategy for potency-related CQA (b) (4)

The following CMC concerns were raised during review of this submission that require a PMC:

1. A study to assess a (b) (4) control strategy for (b) (4) (b) (4) as determined by (b) (4), to address the lack of appropriate assay control strategy to assess these potency-related CQAs.
2. A leachables study to assess the organic and elemental leachables in a (b) (4) study over the product's manufacturing and storage.
3. A study for container closure integrity testing (CCIT) using an appropriate positive control (issue identified by DMPQ and described in review memo by Hector Carrero).

The following CMC concern will be provided to the Applicant in an advisory comment:

1. The current analytical comparability study strategy will not be sufficient to perform a successful analytical comparability exercise following a future major manufacturing change. Additional clinical studies may be necessary to establish comparability after a major manufacturing change, if comparability cannot be established using an analytical comparability exercise alone.

The CMC review team recommends approval, with PMCs.

B. RECOMMENDATION

I. APPROVAL

Manufacturing Facilities

The following facilities are used to manufacture lifileucel (b) (4) DP (b) (4) facilities independently manufacture lifileucel DP in its entirety):

(b) (4)

The following facilities are used for testing of the lifileucel (b) (4) DP:

(b) (4)

- Iovance Cell Therapy Center (iCTC), 300 Rouse Blvd., Philadelphia, PA 19112, USA

(b) (4)

Post-Marketing Commitments (PMCs)

1. Iovance Biotherapeutics, Inc. commits to perform a study to develop and evaluate the suitability of (b) (4) controls for (b) (4) (b) (4) of (b) (4) on the drug product. This study is designed to include a comparative analysis of performance characteristics of the original control strategy (using (b) (4) to the (b) (4) control strategy for (b) (4) in a statistically meaningful number of clinical batches manufactured at (b) (4) and Iovance Cell Therapy Center (iCTC) facilities. Iovance Biotherapeutics, Inc. also commits to re-evaluation of the (b) (4) commercial release acceptance criteria after completion of a statistically powered study. Iovance Biotherapeutics, Inc. will submit the study protocol, including justification for the number of batches to be used in the comparative analysis and re-evaluation of the commercial release acceptance criteria, for review and feedback as a product correspondence supplement by April 30, 2024. Iovance Biotherapeutics, Inc. will submit the final study report, which includes the validation report and justification for change to the commercial release acceptance criteria (if changes are necessary), as a Prior Approval Supplement by April 30, 2025.

   Study Protocol Submission: April 30, 2024

   Final Report Submission: April 30, 2025

2. Iovance Biotherapeutics, Inc. commits to execute a (b) (4) organic and elemental leachables study for lifileucel over the manufacturing, storage, and in-use period (i.e., for cumulative leachables in the drug product). Given the complexity of the biological product, this can be a simulated study [i.e., (b) (4) (b) (4) performed at (b) (4) and Iovance Cell Therapy Center (iCTC) manufacturing facilities. This study is designed to start at the manufacturing process step with high-risk for leachables (i.e., (b) (4) and evaluate respective maximal hold times for the drug product during manufacturing, long-term storage including freezing up to 6 months and thawing of the bag for use, and in-use conditions. The analytical data will be assessed for safety using at least a (b) (4) safety margin, considering analytical uncertainty of the methods. Iovance Biotherapeutics, Inc. will submit the final study report as a Postmarketing Commitment – Final Study Report by February 28, 2025.

   Final Study Report Submission: February 28, 2025

3. Iovance Biotherapeutics, Inc. commits to performing the container closure integrity testing with a positive control with an established sensitivity, (i.e., a (b) (4)
Iovance Biotherapeutics, Inc. will submit the final report as a Postmarketing Commitment – Final Report by February 28, 2025.

   Final Report Submission: February 28, 2025.

Advisory Comment (Included in Approval Letter)

As previously communicated, the protocol and product quality attributes used to establish comparability between (b) (4) and Iovance Cell Therapy Center (iCTC) manufactured drug product will not be sufficient to establish analytical comparability after implementation of a major manufacturing change. We recommend you perform additional (b) (4) to (b) (4) and elucidate the specific mechanism of action of your drug product (b) (4) (b) (4) We recommend you request a formal meeting with us prior to incorporating new product quality attributes, implementing a major manufacturing change, and/or executing a comparability exercise. Your executed comparability study report(s) should be submitted as a Prior Approval Supplement. If product comparability cannot be established based on analytical comparability studies alone, additional clinical study(ies) with your drug product, AMTAGVI, may be required.

Inspectional Follow-Up
None

CBER Lot Release
Lifileucel is exempt from lot release.

II. COMPLETE RESPONSE

Not applicable

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Karin Knudson, PhD BLA Chair / CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB2	Concur	
Heba Degheidy, MD, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTTB	Concur	
Iain Farrance, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Sukhanya Jayachandra, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Saravanan Karumbayaram, MPharm, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Elizabeth Lessey-Morillon, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Brian Niland, PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTB2	Concur	
Matt Klinker, PhD Chief, Cell Therapy Branch 2 (CTB2) CBER/OTP/OCTHT/DCT1/CTB2	Concur	
Melanie Eacho, PhD Division Director CBER/OTP/OCTHT/DCT1	Concur	
Heather Lombardi, PhD Office Director CBER/OTP/OCTHT	Concur	

Review of CTD

Table of Contents

TABLE OF FIGURES

TABLES

Module 3

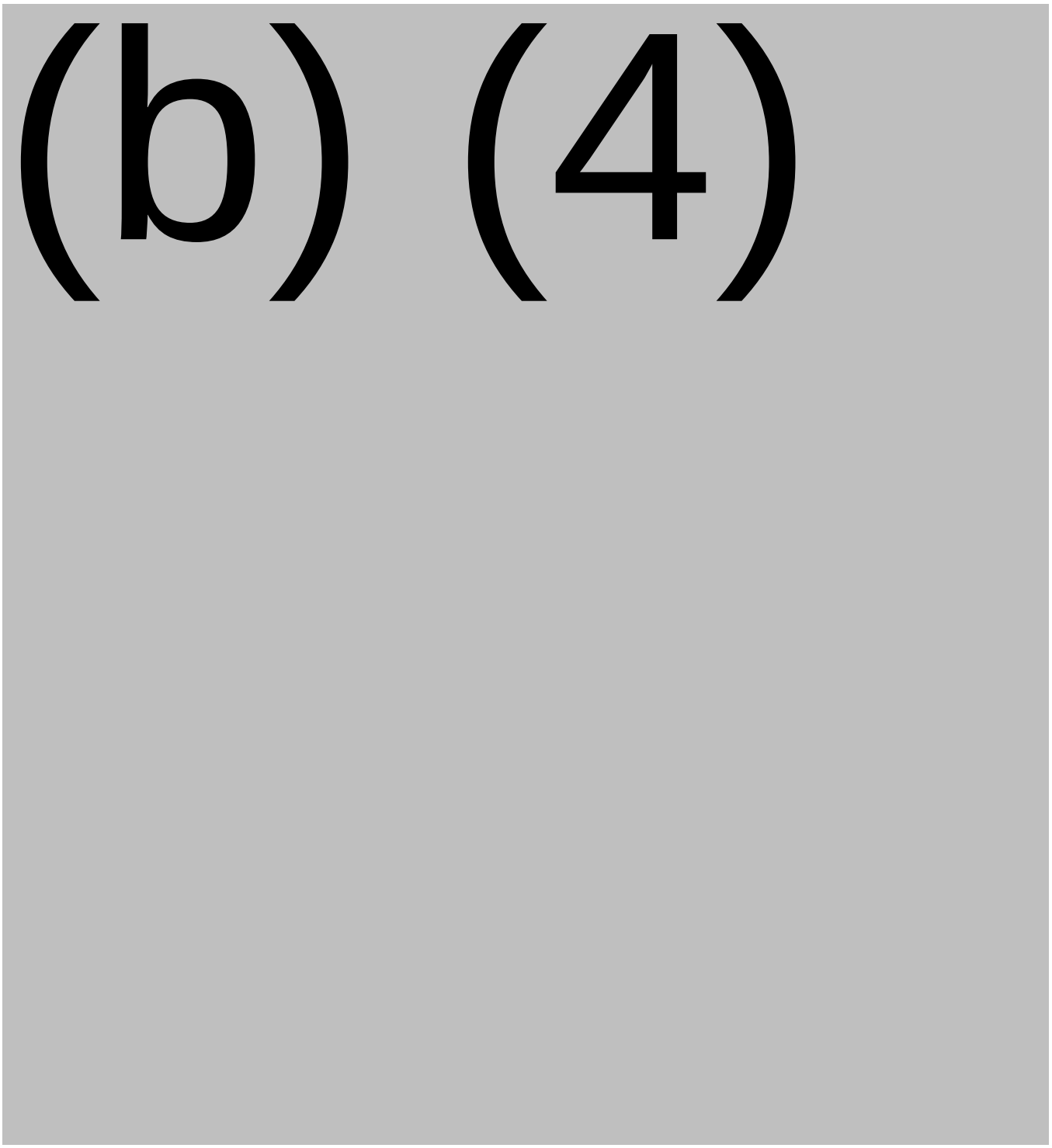
3.2.S. DRUG SUBSTANCE

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

Section reviewed by KK.

(b) (4)

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



3.2.P. DRUG PRODUCT

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

Section reviewed by KK.

The DP is formulated in (b) (4) suitable for intravenous infusion (b) (4) (b) (4) and filled into cryogenic freezing bags cleared by FDA (510(k) (b) (4) One dose of lifileucel consists of 7.5 x 10^9 to 72 x 10^9 total viable cells (TVC) in a total volume of (b) (4) filled into (b) (4) or 4 cryogenic bags (100-125mL per bag). No reconstitution diluents are used with the final DP.

Table 80. Composition of Lifileucel

Component	Quantity per 100 mL[1]	Function	Quality Standard
Lifileucel	(b) (4)	Active Ingredient	In-house
CryoStor® CS10 [2]	(b) (4)	(b) (4)	
Plasma-Lyte A	(b) (4)		
Albumin (Human) 25%	(b) (4)		
Interleukin-2 [3,5]	(b) (4)		

[1] *Target final volume per bag is dependent on the number of cryopreservation bags filled which may vary between individual patient batches* (b) (4)
[2] *CryoStor CS10 contains* (b) (4) *dimethylsulfoxide (DMSO) for* (b) (4) *The nominal concentration of DMSO in the DP is 5% (v/v).*
[3] *Aldesleukin (Proleukin®), an IL-2 product, is approved for therapeutic use.*
[4] *Plasma-Lyte A meets the* (b) (4)
[5] (b) (4)
Adapted from Table 1 in eCTD section 3.2.P.1

3.2.P.2 Pharmaceutical Development

Section reviewed by KK.

3.2.P.2.1 COMPONENTS OF THE DRUG PRODUCT

3.2.P.2.1.1 Drug Substance

(b) (4) The manufacturing process is continuous with no distinct (b) (4) DP. The compatibility between the (b) (4) and the excipients are described in 3.2.P.2.2 Drug Product of this memo.

3.2.P.2.1.2 Excipients

Table 81. Excipients for Lifileucel

Component	Concentration	Final Concentration	Function
CryoStor® CS10 [1]	(b) (4)	50% (v/v) 5% DMSO (v/v)	(b) (4)
Plasma-Lyte A [2]		48% (v/v)	
Albumin (Human)		2% (v/v) 0.5%	
Interleukin-2 [3,4]		300 IU/mL	

[1] *CryoStor CS10 contains 10% (v/v) dimethylsulfoxide (DMSO) for cryopreservation. The nominal concentration of DMSO in the DP is 5% (v/v).*
[2] *Aldesleukin (Proleukin®), an IL-2 product, is approved for therapeutic use.*
[3] *Plasma-Lyte A meets the* (b) (4)
[4] (b) (4)
Adapted from Table 1 in eCTD section 3.2.P.1

Plasma-Lyte A: Plasma-Lyte A (b) (4)

Human Serum Albumin (HSA): (b) (4)

CryoStor CS10: CryoStor CS10 (b) (4)
(b) (4) DMSO (b) (4)

(b) (4) Lifileucel is composed of 50% CryoStor CS10, which results in a total of 5% DMSO in the final formulation.

IL-2: IL-2 is added in the final formulation to support the survival and expansion of T cells after DP infusion.
Reviewer comment: CMC IR #5 (14July2023) asked the Applicant to address whether the IL-2 included in the DP will have a clinical effect and thus should be considered an active ingredient instead of an excipient. In Amendment 19 (19July2023), states that the maximum IL-2 dose administered as part of the DP is (b) (4) (b) (4) *. This dose is approximately 0.01% of the clinically-effective cumulative dose administered during a single course of therapeutic IL-2 monotherapy:*

(b) (4)

IL-2 monotherapy has a modest overall response rate of 10%, so it is unlikely a lower concentration would have a clinical effect. In addition, the dose of IL-2 in the DP is at least (b) (4) *lower than what is administered to patients as part of the regimen after the administration of lifileucel:*

- *600,000 IU/kg every 8-12 hours for up to 6 doses: total up to* (b) (4)

An increase of IL-2 doses administered to the subjects is not correlated with greater clinical efficacy of the DP. Finally, it is unlikely that there is any contribution to disease control by IL-2, independent of the DP, when administered after nonmyeloablative lymphodepletion (NMA-LD) during the phase of significant peripheral lymphopenia, as was observed in clinical study investigating the effect of high dose IL-2 in combination with NMA-LD. The clinical reviewer Dr. Lianne Hu reviewed the response and agrees that the IL-2 in the formulated DP is unlikely to have a clinical response.

Inclusion of IL-2 as an excipient and not an active ingredient is acceptable. No additional CMC concerns identified.

3.2.S.4.1. AND 3.2.S.4.5. SPECIFICATION(S) AND JUSTIFICATION OF SPECIFICATION(S)
The manufacture of the (b) (4) DP is a continuous process with no distinct (b) (4) The in-process specifications and justifications are reviewed in 3.2.S.2.4. Controls of Critical Steps and Intermediates in this memo.

3.2.P.2.2 DRUG PRODUCT
Section reviewed by KK.
3.2.P.2.2.1 Formulation Development
Early clinical studies of lifileucel (i.e., Study C-144-01 Cohort 1 not evaluated under BLA) used the Gen 1 formulation which allowed the DP to be shipped at (b) (4) (b) (4) The registrational study (Study C-144-01, Cohorts 2 and 4) used the Gen 2 formulation, which enables cryopreservation of the product and a prolonged shelf life. The Gen 2 formulation is the same as the intended commercial formulation (Table 82). See 3.2.S.2.6.2.1. History of Manufacturing Sites and Process Used During Clinical

Development of this memo for a description of the Gen 1 and Gen 2 manufacturing processes.

Table 82. Formulations Used During Clinical Development

Characteristic	Gen 1 Formulation	Gen 2 Formulation (Commercial Formulation)
Composition	(b) (4)	Cells suspended in 50% CryoStor 10, 48% Plasma-Lyte A, 2% Human Albumin (25%), and supplemented with 300 IU/mL IL-2
Storage Temperature		≤ -150°C
Container Closure System		Cryogenic freezing bag
Usage		C-144-01 Cohort 2 and Cohort 4

Reproduced from Table 1 in eCTD section 3.2.P.2.2 of the submission.

3.2.P.2.2.2 Overages
This section is not applicable.

3.2.P.2.2.3 Physicochemical and Biological Properties
Reviewed in section 3.2.S.1.3. General properties of this memo.

3.2.P.2.3 MANUFACTURING PROCESS DEVELOPMENT
Section reviewed by KK.
Reviewed in section 3.2.S.2.6. Manufacturing Process Development of this memo.

3.2.P.2.4 CONTAINER CLOSURE SYSTEM
This section is copied from consult review and review summary by Wojtek Tutak (CBER/OTP/OCTHT/DCT2/TEB2).

Primary Packaging:
DP is placed in sterile (b) (4) cryopreservation bags manufactured by (b) (4) (b) (4) All materials are biocompatible and meet either (b) (4) or (b) (4) VI applicable test requirements. The (b) (4) cryopreservation bags are unclassified, pre-amendment devices with 510(k)-clearance number (b) (4) intended to hold blood components in the cryogenic state. Each (b) (4) bag is equipped with an (b) (4) and the (b) (4) are certified as sterile and non-pyrogenic.

Table 83. General Information for the (b) (4) Cryopreservation Bag

Attribute	Target
Dimensions	(b) (4)
Freeze (b) (4)	(b) (4)
Materials	Bag: (b) (4) (b) (4)

(b) (4)

Secondary Packaging:
Each filled and labeled (b) (4) bag is placed in a labeled, protective (b) (4) cassette from (b) (4) made to contain (b) (4) bags. A sterile (b) (4) is used as a protective (b) (4) Product labels are affixed to the outside of each cassette. (b) (4) to four cassettes, each containing one (b) (4) bag, will be shipped to the treatment center.

Table 84. General Information for the Cassette (Secondary Packaging)

Attribute	Target
Dimensions	(b) (4)

Reproduced from Table 2 in eCTD section 3.2.P.7.

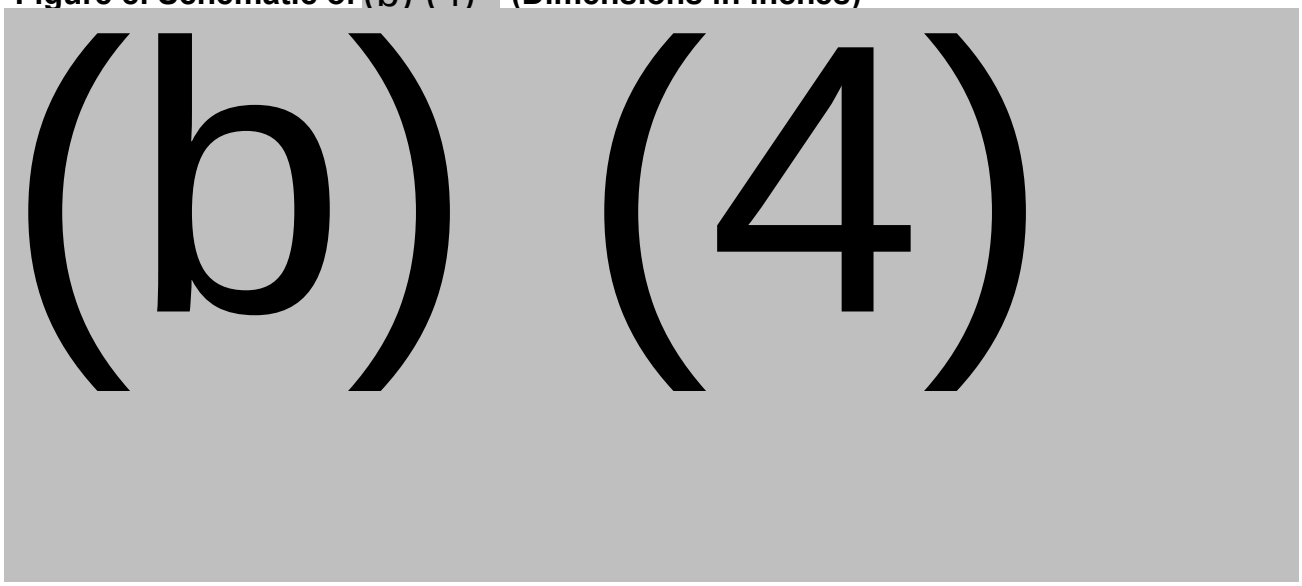
Figure 7. Schematic of Cassette

(b) (4)

Reproduced from Figure 2 in eCTD Section 3.2.P.7.

Tertiary Packaging:
Up to four cassettes, each containing one (b) (4) bag, can be placed in a (b) (4) (b) (4) Shipper (b) (4) for shipment to a treatment center.

Figure 8. Schematic of (b) (4) (Dimensions in Inches)



Performance Analysis:
The Applicant evaluated the (b) (4) cryopreservation bags with acceptable results for: (b) (4) Other relevant information not provided in this BLA submission was leveraged from the 510(k) submission such as: (a) sterilization validation, (b) biocompatibility, (c) shelf life, and (d) performance testing (i.e. (b) (4) cryobags have been in use for approximately 20 years without any major issues recorded.

Stability:
The Applicant proposes a 6-month shelf life for the DP when stored in the original packaging at ≤ -150°C, (b) (4) (b) (4) Because the (b) (4) (b) (4) the Applicant intends to (b) (4) of shelf-life remains on the (b) (4) bag expiration at the date of DP manufacture.

Extractables and Leachables:
This section is copied from consult review and review summary by Dr. Wojtek Tutak (CBER/OTP/OCTHT/DCT2/TEB2). The review of extractables and leachables (E/L) analytical and toxicological risk (TRA) assessments was completed by consult reviewer

Dr. Andrey Sarafanov (CBER/OTP/OPPT/DH/HB2) and Dr. Yongjie Zhou (CBER/OTP/OPT/DPT2/PTB2), respectively.

An extractables and leachable (E/L) study on the container closure system was performed by the Applicant to only analyze the potential E/L components released from the bags (b) (4) filled with the (b) (4) DP (i. e. (b) (4) In general, the Applicant's analytical assessment of E/L was found to be acceptable by the E/L consult reviewer (Dr. Sarafanov), even though the E/L data were marked with relatively large Analytical Evaluation Threshold (AET) due to the used for calculation too low analytical uncertainty factor (AUF) values, which were insufficiently justified. Specifically, the leachable study reported values for (b) (4) (b) (4) were below the reporting limit of (b) (4) but the Applicant did not explain how far or close these values were to the reporting limit (AET). Additional information provided by the Applicant explained that the originally submitted analytical values were "actual recorded value" for the (b) (4) using an (b) (4) (b) (4) for AET calculation, implying that no excessive approximations or estimates were used to establish the AET. The analytical values for the (b) (4) in the simulated DP were found to not raise questions of safety by Dr. Yongjie Zhou during the toxicological assessment review.

Consult reviewer comment (Dr. Andrey Sarafanov): During review, I determined that the overall (cumulative) leachables in the DP, originating from other components of the manufacturing process (b) (4) were not assessed, thus could be underestimated. I reviewed the manufacturing process description to identify the specific process step and respective intermediate contact components of the process from which leachables accumulate in the DP. Upon my review, I determined that the analytical assessment of leachables in DP was insufficient, and the Applicant agreed performing that study post-approval. The Applicant's commitment to assess cumulative leachables in a (b) (4) study post-marketing study is acceptable. A PMC related to this study is recommended.

PMC: Cumulative Leachables Study

This section is adapted from consult review by Dr. Andrey Sarafanov (CBER/OTP/OPPT/DH/HB2).

In Amendment 21 received 25July2023, the Applicant states they intend to evaluate a cumulative leachables study covering the manufacturing process, entirety of the product shelf life, and in-use conditions of the DP. This intention was affirmed in Amendment 40 received 21Sep2023 and at the Applicant Late Cycle Meeting on 20Nov2023. At the Applicant Late Cycle Meeting on 20Nov2023, the Applicant stated they plan to perform a (b) (4) simulated cumulative leachables study starting with the (b) (4) (b) (4) All subsequent processing steps including the full shelf life of the product, (b) (4) will be tested in the study. They also stated both organic and elemental leachables would be assessed in the cumulative leachables study, and they will assess the analytical data with (b) (4) safety margin (due to unjustified AUF used for calculation of AET).

To obtain confidence in the safety of the manufacturing process and the product during long-term storage in the container closure, the cumulative leachables study became a PMC. The Applicant agreed to perform a (b) (4) cumulative leachables study as a PMC in Amendment 69 (22Jan2024). The final report will be submitted to the FDA as a Postmarketing Committment by 28Feb2025.

Overall Consult Reviewer's Assessment of Section 3.2.P.7:
Multiple IRs were sent during the review of the container closure system and extractables and leachables assessment. Based on the reviewed information and additional consult reviewer's feedback, the container closure is acceptable for the proposed use.

The analytical assessment of cumulative leachables in the DP is insufficient. In Amendment 21 (25July2023) in response to CMC IR #6 (26July2023), the Applicant committed to performing an analytical cumulative leachables study. This commitment was reaffirmed at the Applicant Late Cycle Meeting on 20Nov2023. In Amendment 69 (22Jan2024), the Applicant agreed to conduct a PMC study evaluate cumulative leachables in a (b) (4) simulated study covering the high-risk manufacturing steps and storage and in-use shelf life.

We agree with the consult review's assessment. See consult review memos by Dr. Wojtek Tutak and Dr. Andrey Sarafanov for complete review of the container closure system and extractables and leachables assessment.

3.2.P.2.5 MICROBIOLOGICAL ATTRIBUTES
Assessment of the container closure integrity of the (b) (4) bags by (b) (4) (b) (4) is deferred to DMPQ. Please refer to the review memo by Hector Carrero.

PMC: Container Closure Integrity Testing (Final DP Container)
This section is adapted from DMPQ review by Hector Carrero (CBER/OCBQ/DMPQ/MRB2).
The container closure integrity testing (CCIT) performed on the final DP container did not include an adequate positive control to demonstrate the sensitivity of the method. Thus, the sensitivity of the CCIT assay was not established appropriately.

To address the noted deficiency regarding the CCIT positive control, a new final DP container CCIT study with an appropriate established positive control (b) (4) (b) (4) became a PMC. The Applicant agreed to perform a new CCIT study with an appropriate positive control as a PMC in Amendment 86 (14Feb2023). The final report will be submitted to the FDA as a Postmarketing Commitment by 28Feb2025.

Reviewer comment: We defer to DMPQ's assessment. See DMPQ review memo by Hector Carrero for a complete assessment of the container closure integrity testing.

3.2.P.2.6 COMPATIBILITY

Compatibility of (b) (4) DP lots with (b) (4) infusion sets from (b) (4) different suppliers (b) (4) (b) (4) were tested with the (b) (4) (b) (4) to represent the commonly used infusion sets at treatment centers. To represent conditions expected during administration of the DP at treatment centers, each (b) (4) bag containing DP was (b) (4)

Table 85. Summary Results of Compatibility Study with (b) (4) Infusion Sets

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.2:
Information provided is acceptable, with no deficiencies identified.

3.2.P.3 Manufacture
Section reviewed by KK.
3.2.P.3.1 MANUFACTURERS
Manufacturing is a continuous process, with (b) (4) DP. Reviewed in section 3.2.S.2.1. Manufacturer(s).

3.2.P.3.2 BATCH FORMULA
Manufacturing is a continuous process, with (b) (4) DP. Reviewed in sectio3.2.P.1. Description and Composition of the Drug Product of this memo.

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:
Information provided is acceptable, with no deficiencies identified.

3.2.P.3.3 DESCRIPTION OF MANUFACTURING PROCESS

Manufacturing is a continuous process, with (b) (4) DP. Reviewed in 3.2.S.2.2. Description of Manufacturing Process and Process Controls of this memo.

3.2.P.3.4 CONTROLS OF CRITICAL STEPS AND INTERMEDIATES
Manufacturing is a continuous process, with (b) (4) DP. Reviewed in 3.2.S.2.4. Controls of Critical Steps and Intermediates of this memo.

3.2.P.3.5 PROCESS VALIDATION AND/OR EVALUATION
Manufacturing is a continuous process, with (b) (4) DP. Reviewed in 3.2.S.2.5. Process Validation and/or Evaluation of this memo.

3.2.P.4 Control of Excipients
Section reviewed by EL.
Four excipients are used to formulate the product: Plasma-Lyte A, 25% Albumin (Human), CryoStor CS10, and IL-2. Plasma-Lyte A, 25% Albumin (Human), and IL-2 are all FDA-approved materials. The (b) (4) FDA-approved excipients are listed in Table 86. The (b) (4) excipients are listed in Table 87.

Table 86. (b) (4) **Excipients**

Excipient	Grade	Manufacturer	Quality Documentation
Plasma-Lyte A (b) (4)	(b) (4)	(b) (4)	COA
Albumin (Human) 25%	(b) (4)	(b) (4)	COA

Adapted from Table 1 in eCTD section, 3.2.P.4.1

Table 87. (b) (4) **Excipients**

Excipient	Human or Animal Origin	Grade	Manufacturer	Quality Documentation
CryoStor CS10	(b) (4)	(b) (4)	(b) (4)	COA
Interleukin-2	(b) (4)	(b) (4)	(b) (4)	COA

Adapted from Table 2 in eCTD section 3.2.P.4.1

3.2.P.4.1. AND 3.2.P.4.4. SPECIFICATIONS AND JUSTIFICATION OF SPECIFICATIONS
3.2.P.4.1.1.1. Plasma-Lyte A
Plasma-Lyte A, (b) (4) material approved for intravenous administration in the U.S (NDC 0338-0221-04). Plasma-Lyte A meets the (b) (4). Each lot is dispositioned in accordance with written procedures upon meeting the release criteria described in Table 88.

(b) (4)

3.2.P.4.1.1.2. Albumin (Human)
Albumin (Human) 25% is approved for therapeutic use (b) (4) This product is a derivative of human plasma collected exclusively from U.S. donors in accordance with applicable regulations for the manufacture of human biological products. The COA states all donations of plasma were individually tested and non-reactive to (b) (4) as described in Section 3.2.P.4.2.

(b) (4)

Adapted from Table 4 in eCTD section 3.2.P.4.1
Reviewer Comment: Representative COA from (b) (4) was provided in eCTD Section 3.2.P.4.1. The (b) (4) database provided (b) (4) for albumin, human. Testing is adequate.

3.2.P.4.1.1.3. CryoStor CS10
CryoStor CS10 is a (b) (4) (b) (4) Each lot is dispositioned based on the manufacturer's COA and review of additional incoming raw material (b) (4) test results meeting the specification for release of CryoStor CS10 (Table 90).

(b) (4)

Adapted from Table 5 in eCTD section 3.2.P.4.1

Reviewer Comment: Representative COA from (b) (4) was provided in eCTD Section 3.2.P.4.1. (b) (4) has been reviewed and used to support commercial applications. The (b) (4) database provided (b) (4) for CryoStor CS10. The (b) (4) database provided (b) (4) (b) (4) for (b) (4) in CryoStor CS10. Testing is adequate

3.2.P.4.1.1.4. Interleukin-2 (IL-2)

IL-2 is supplied as a sterile lyophilized powder that is approved for intravenous administration (Proleukin [aldesleukin] NDC 76310-022-01) and reconstituted in the container. Each lot is dispositioned based on the manufacturer's COA and additional test results that meet specification (Table 91). The additional incoming raw material testing is (b) (4) except for the (b) (4) test, as described in 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures. (b) (4) For justification of classifying IL-2 (aldesleukin) as an excipient instead of active ingredient, see section 3.2.P.2.1 Components of the Drug Product.

(b) (4)

Adapted from Table 6 in eCTD section 3.2.P.4.1

Reviewer Comment: Representative COA from (b) (4) was provided in eCTD Section 3.2.P.4.1. The (b) (4) database provided (b) (4) (b) (4) for Interleukin-2. Testing is adequate.

3.2.P.4.2 AND 3.2.P.4.3 ANALYTICAL PROCEDURES AND VALIDATION OF ANALYTICAL PROCEDURES

(b) (4)

(b) (4)

3.2.P.4.5 EXCIPIENTS OF HUMAN OR ANIMAL ORIGIN

Table 95. Excipients of Human or Animal Origin

Excipient	Function	Quality Standard	Source/Component	Manufacturer	Quality Documents
CryoStor CS10	(b) (4)				

Adapted from Table 1 in eCTD section 3.2.P.4.5

Table 96. Excipients of Human or Animal Origin

Excipient	Function	Quality Standard	Source/Component	Manufacturer	Quality Documents
CryoStor CS10	(b) (4)				
Albumin (Human) 25%					

Adapted from Table 1 in eCTD section 3.2.P.4.5

3.2.P.4.6 NOVEL EXCIPIENT
None

Overall Reviewer's Assessment of Section 3.2.P.4:
No information requests or additional information was necessary for the review of eCTD section 3.2.P.4. No CMC concerns identified.

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)
Section reviewed by KK.

3.2.P.5.1 Specifications
The final agreed upon lifileucel lot release specifications, which were formalized under the submission in Amendment 73 (29Jan2024), are summarized in Table 97. The Applicant's selection of CQAs is reviewed in 3.2.S.2.6.3.2. Critical Quality Attributes Designation and 3.2.S.2.6.3.2.1. Critical Quality Attributes Designation for Potency/Identity Matrix.

The product is cryopreserved and stable for the duration of all product release testing. The release of the commercial product will be performed after completion of all testing.

Table 97. Final Commercial Release Specifications

Attribute	Test	Analytical Method	Acceptance Criteria	Testing Facility
Appearance	DP	Visual inspection	No sign of clumps	(b) (4) iCTC
	DP	Visual inspection	Colorless to Dark Yellow	(b) (4) iCTC
	Container	Visual inspection	Intact Bag [1]	(b) (4) iCTC
Identity	(b) (4)	(b) (4)	(b) (4)	iCTC
Potency-Related				iCTC
				iCTC
				iCTC
				iCTC
				(b) (4) iCTC
				(b) (4) iCTC
				iCTC
Purity				(b) (4) iCTC
				iCTC
				iCTC
Safety	Endotoxin (EU/mL)	(b) (4)		(b) (4) iCTC
	Mycoplasma	(b) (4)	Not detected	(b) (4)
	Sterility	(b) (4)	No growth	(b) (4) iCTC

[1] Each bag is without visible defects or leaks
[2] Updated in Amendment 46 (15Nov2023).
[3] Updated in Amendment 63 (12Jan2024).
[4] Established in Amendment 56 received 18Dec2023.
Adapted from Table 1 in eCTD section 3.2.P.5.1 and Table 1 in eCTD section 1.11.1 (Response to FDA Request for Information [Date of Questions: 10January2024]) in Amendment 63 (12Jan2024).

3.2.P.5.6. Justification of Specifications

A summary of the justification for the commercial release specifications is shown in Table 98. Release specifications removed during review of the BLA and justifications for removal are summarized in Table 99.

In the original submission, the proposed commercial release acceptance criteria were based on statistical analysis of the total product batches manufactured for clinical use in the C-144-01 Cohort 2 and Cohort 4 at (b) (4) after excluding outliers. This data set included OOS batches and clinical batches that met release specifications but were not infused. In general, the acceptance criteria were

based on the minimum and maximum value observed for each attribute from the data set, and clinical responses were observed across the range. The original methodology for establishing the acceptance criteria was not acceptable as comparability has not been established between (b) (4) Inclusion of the (b) (4) (b) (4) lots in setting release acceptance criteria may introduce additional variability, leading to less control of the final product.

The possibility of, in part, using clinical response (i.e., overall response rate (ORR)) to establish release acceptance criteria was addressed by the Applicant in response to CMC IR #11 (21Aug2023) and CMC IR #16 (9Nov2023). In Amendments 34 (28Aug2023) and 46 (15Nov2023), the Applicant states that there is an overlapping distribution of product attributes in batches from responding and non-responding subjects. In addition, other than dose (discussed below), there is no correlation between product CQAs and clinical response. Thus, the Applicant concludes the product CQAs are not predictors of clinical response. In addition, the Applicant states that to fully reflect batches that have a meaningful clinical response, batches with stable disease (SD) should be included in the data set. Overall, the Applicant concludes that clinical response should not be used to establish release acceptance criteria for this product.

As (b) (4) is the only proposed commercial manufacturing site used during the clinical study, in CMC IR #22 (10Jan2024), the Applicant was informed that (b) (4) lots should only be used to establish the release acceptance criteria. Except for dose (discussed below), the final agreed release acceptance criteria from Amendment 63 (12Jan2024) are based on the range of the attribute in Cohort 2 and Cohort 4 clinical batches manufactured at (b) (4) with outliers removed (according to the Applicant's analysis). A summary of the data used to generate the release acceptance criteria is in Table 100. Distribution of (b) (4) Cohort 2 and 4 attribute results is shown in Figure 9.

To determine product commercial dosing range, dose of (b) (4) Cohort (b) (4) batches (i.e., primary efficacy set) and the corresponding Best Overall Response (BOR) were assessed by CMC, clinical, and clinical pharmacology. It was determined that the lowest dose where a clinically meaningful response (i.e., complete response (CR) or partial response (PR)) was observed is 7.5E9. (b) (4) batches with dose < 7.5E9 were administered in Cohort 4. Of note, dose was the only product attribute that correlated with BOR and demonstrated a statistically significant difference between responding and non-responding subjects. However, this trend was weak. (b) (4) of (b) (4) batches produced a BOR of stable disease (SD) and (b) (4) of (b) (4) produced a BOR of progressive disease (PD). Batches with a BOR SD were not included in determining the commercial dosing range as the Applicant performed a single arm study where SD cannot be appropriately assessed without a randomized trial (per FDA guidance). The upper end of the dosing range was determined by the highest (b) (4) batch dose administered in Cohort 4 without a safety signal, which was 72E9. Thus, the commercial dosing range was established as 7.5E9 – 72E9 total viable cells in CMC IR #22 (10Jan2024). The Applicant agreed to the dosing range in Amendment 63 (12Jan2024).

See the clinical review memo for additional discussion of the dosing range, including limitations of this assessment.

(b) (4)

he Applicant agreed to the dose acceptance criteria in Amendment 63 (12Jan2024) and acknowledged the maximum infused dose of the DP is ≤ 72E9 total viable cells.

Table 98. Summary of Justification for Final Commercial Release Specifications

Test	Acceptance Criteria	Justification
DP	No sign of clumps	Product safety
DP	Colorless to Dark Yellow	(b) (4)
Container	Intact Bag [1]	Product safety. Ensures sterility of DP.

(b) (4)

Test	Acceptance Criteria	Justification
Dose (TVC)	(b) (4)	(b) (4) (b) (4)
Cell viability (%)	(b) (4)	(b) (4)
(b) (4) (b) (4)	(b) (4) (b) (4)	
Endotoxin (EU/mL)	(b) (4)	Product safety. (b) (4)
Mycoplasma	Not detected	Product safety. (b) (4) (b) (4)
Sterility	No growth	Product safety. (b) (4) (b) (4)

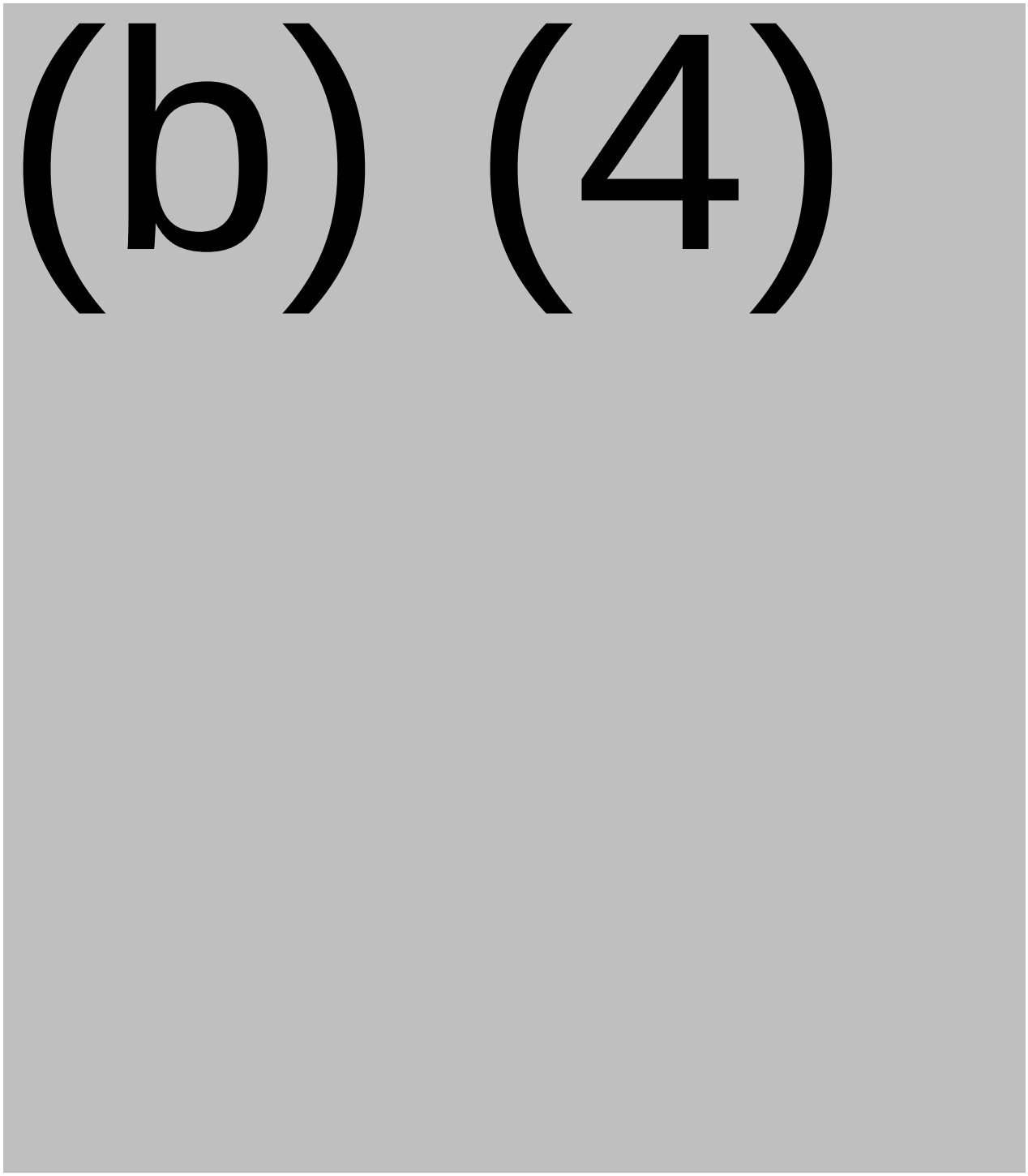
BOR = best overall response
[1] Each bag is without visible defects or leaks
[2] Updated in Amendment 46 (15Nov2023).
[3] Updated in Amendment 63 (12Jan2024).
[4] Established in Amendment 56 received 18Dec2023.
Adapted from Table 1 in eCTD section 3.2.P.5.1 and eCTD section 3.2.P.6, Table 1 in REP-0398 in eCTD section 3.2.P.5.1, and eCTD section 1.11.1 (Response to FDA Request for Information [Date of Questions: 21August2023]) in Amendment 34 (28Aug2023))

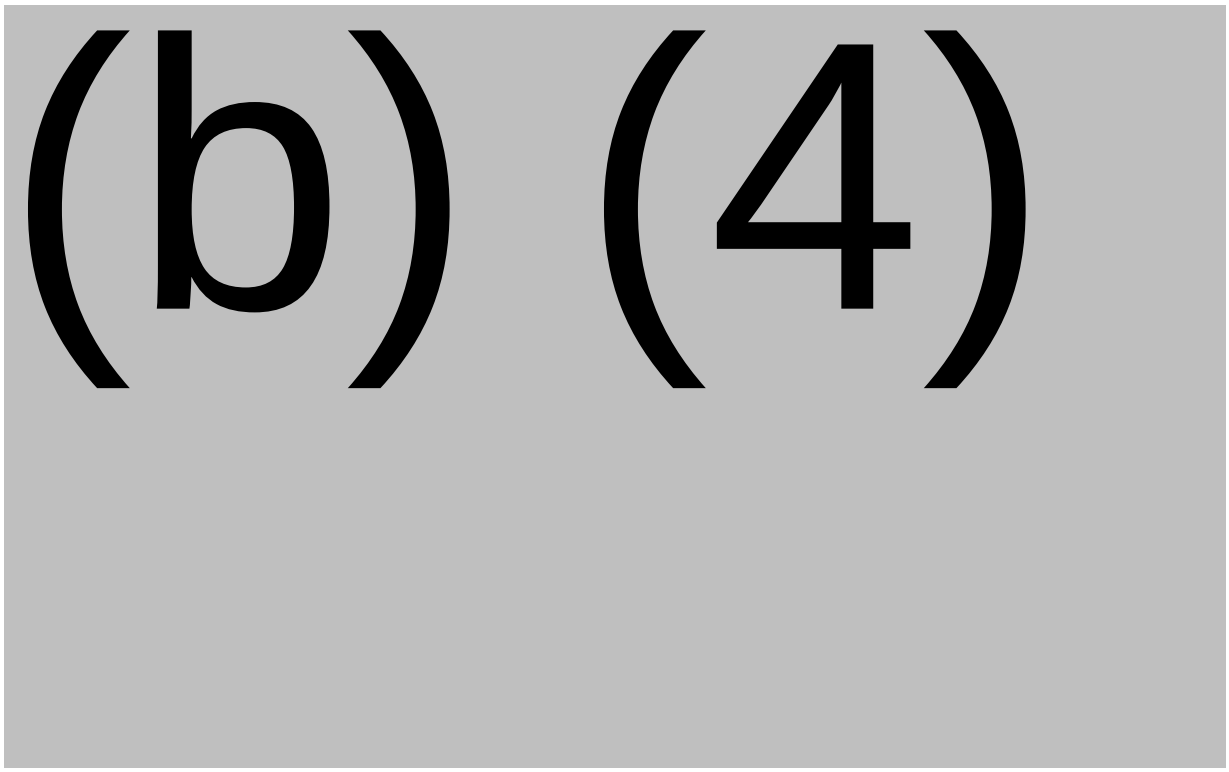
2 pages have been determined to be not releasable: (b)(4)

Adapted from from Attachment: C-144-01 IPC Manufacturing Reference Data of eCTD section 1.11.1 (Response to FDA Request for Information [Date of Questions: 10November2023]) in Amendment 46 (15Nov2023).

Reviewer comment: Multiple information requests were sent to address issues identified with the release specifications and justification for release specifications:

- *Justification of release specifications: In Amendment 34 (28Aug2023), the Applicant provided additional justification for the release specifications, including acceptance criteria in response to CMC IR #11 (21Aug2023). This is acceptable.*





The release specifications were not agreed to prior to the BLA submission. During the BLA review, concerns with the ability of the release specifications to determine and control product quality and potency were communicated to the Applicant at the Midcycle Meeting (dated 27Aug2023) and in CMC IR #11 (dated 21Aug2023). While it does not appear that the current release specifications are able to discriminate a quality and potenty batch due to uncertainty surrounding the product CQAs (discussed in 3.2.S.2.6.3.2. Critical Quality Attributes Designation) and product variability, the release specifications do ensure consistency of the commercial product with the clinical product, which showed clinical efficacy across the product specification ranges.

3.2.P.5.6.2. Correlation of Product Attributes to Clinical Outcome

Potential associations between the clinical response and the measured (b) (4) (b) (4) were examined in Cohort 2 and Cohort clinical lots from Study C-144-01 in (b) (4) (b) (4) to Clinical Response in Study C-144-01 (Cohorts 2 and 4)." The data generated by the (b) (4) DP batches were evaluated for potential association of BOR, which includes (b) (4) (b) (4) test was used to evaluate the association between BOR and the measured attributes. The analysis was exploratory in nature and hypothesis generating, since multiplicity is not adjusted for, and variables such as patient attributes are not controlled in the statistical testing. The analysis showed:

- (b) (4)

- (b) (4)

(b) (4)

Reviewer comment: In response to CMC IR #11 (21Aug2023), the Applicant provided additional analysis of product CQAs to response (responders vs. non-responders), duration of response (DOR), and time to confirmed response (TTR) in Amendment 34 (28Aug2023) to potentially provide additional justification for the product CQAs, in particular the potency-related attributes. A multiplicity adjustment was implemented for each cohort separately. The applicant states that these data help provide justification for inclusion of a CQA but overlapping distributions in responders vs. non-responders means these results cannot be used to exclude CQAs based on the clinical response alone. The analysis showed:

(b) (4)

Overall, this analysis provides support that the dose is currently the only clinically meaningful product attribute but does not preclude inclusion of the other selected attributes as CQAs for release testing. This is acceptable.

3.2.P.5.1.2. Release of Product Batches

Prior to commercial batch release, batches should meet the established process parameters, IPC, and final product specifications. Product batches that do not meet criteria for a process parameter or an IPC (b) (4)

A summary of the process control strategy and requirements for release of product batches is in Table 101.

Table 101. Requirements for Disposition of Product Batches

(b) (4)

Reviewer comment: The Applicant provided details on batch disposition for release in Amendment 49 (21Nov2023) in response to CMC IR #17 (16Nov2023). This is acceptable.

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:
Multiple information requests were sent during the review of the product specifications. The current release acceptance criteria are based on the manufacturing experience at (b) (4)*, a commercial manufacturing site, to ensure consistency of the commercial product to the clinical product. The wide acceptance criteria are acceptable as the product is highly variable due to the autologous nature of the product and clinical responses were observed across the specification ranges. See detailed reviewer comment in this section for more information.*

OOS commercial batches (b) (4)

No remaining CMC deficiencies identified.

3.2.P.5.2 AND 3.2.P.5.3 ANALYTICAL PROCEDURES AND VALIDATION OF ANALYTICAL PROCEDURES
Section reviewed by KK, HD, SK, IF, SJ.

Appearance by Visual Inspection
Section reviewed by KK.

(b) (4)

Reviewer comment: The Applicant did not provide the full visual inspection assay validation or description of operator training for visual inspection in the original submission. In response to CMC IR #5 (14July2023), the applicant submitted a description of the assay validation in Amendment 19 (19July2023). Further discussions

concerning the visual inspection validation, development of the (b) (4) *and operator training occurred during the iCTC PLI (21Aug2023 to 25Aug2023). The information provided by the Applicant is adequate to address concerns regarding the visual inspection validation. No additional CMC concerns identified.*

Overall Reviewer's Assessment of Visual Inspection Validation: *The visual inspection is an objective measurement of product quality, so appropriate validation and operator training regarding this assay is critical. One CMC IR was sent during review of the visual inspection method and its validation:*

- *The original submission did not provide complete information regarding the visual inspection validation or operator training. Information regarding the validation and operator training were provided in Amendment 19 (19July2023) in response to CMC IR #5 (14July2023). Additional clarification of the validation and operator training was provided during the during the iCTC PLI (21Aug2023 to 25Aug2023).*

The applicant addressed all concerns. No remaining CMC concerns identified. Assay determined to be appropriate for its intended use.

Viable Cell Count and Cell Viability
Section reviewed by SK.

(b) (4)

(b) (4)

Summary results of the viable cell count validation provided in Table 102. Summary results of the viability validation provided in Table 103.

Reviewer Comment: The Applicant provided the method procedure (b) (4) *method validation protocol* (b) (4) *and validation final report (VFR –* (b) (4) *They provided data from their validation parameters* (b) (4)

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

All assays have been adequately validation and determined appropriate for intended use. See reviewer's assessment under (b) (4) (b) (4) *for information regarding and justification of* (b) (4) *PMC.*

3.2.P.5.4 BATCH ANALYSES
Section reviewed by KK
The Applicant provides the following data sets in the submission and in Amendment 34 (28Aug2023):

1. All product batches manufactured and infused for clinical Study C-144-01 for Cohort 2 and Cohort 4
2. QC results from product (b) (4) testing using the (b) (4) (b) (4) parameters for product batches manufactured for clinical Study C-144-01 for Cohort 2 and Cohort 4
3. All product batches that were manufactured for clinical Study C-144-01 but were not infused in patients due to changes in patient health status (quantitative measures only)
4. Non-clinical batches used for PPQ and comparability studies

Reviewer comment: The initial batch analysis records were not complete and did not include all infused/non-infused clinical batches and non-clinical batches. In response to CMC IR #11 (21Aug2023), the Applicant submitted Amendment 34 (28Aug2023) with updated batch records. This is acceptable.

Summary of Clinical Batches Infused:
Of the (b) (4) batches initiated for Study C-144-01 Cohort 2 and Cohort 4, (b) (4) clinical batches were manufactured and infused. (b) (4) OOS lots were (b) (4) (b) (4) The number of batches manufactured at each site is:

- Cohort 2 (b) (4) total): (b) (4)
- Cohort 4 (b) (4) total): (b) (4)

Summary of Clinical Batches Not Infused:
Of the (b) (4) batches initiated for Study C-144-01 Cohort 2 and Cohort 4, a total of (b) (4) batches from Study C-144-01 Cohort 2 and Cohort 4 were manufactured but not infused. (b) (4) batch was OOS for endotoxin. (b) (4) batches were terminated early due to in-process sterility and/or mycoplasma failure. (b) (4) batches were terminated due to patient withdrawal. (b) (4) batches were manufactured but not infused due to change in patient health status.

- Cohort 2 ((b) (4) total): (b) (4)
- Cohort 4 (b) (4) total): (b) (4)

There is a low rate (b) (4) of complete manufacturing failure. All lots terminated prior to release testing had in-process (b) (4) with a root cause of (b) (4) An IPC for sterility is established (b) (4) (b) (4) to identify contaminated product (b) (4) in manufacturing. For commercial batches that are OOS for any release specification(s),

other than safety testing, the Applicant intends to (b) (4)

Batch analysis from (b) (4) lots only was used to establish commercial release acceptance criteria, as comparability was not established between (b) (4) (b) (4) See 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s) for justification of release specifications. A summary of release testing results up to (b) (4) clinical batches not terminated prior to release testing (no outliers removed), including (b) (4) batches, is in Table 121.

Table 121. Summary of Clinical Batch Release Analysis

(b) (4)

Summary of Non-Clinical Batches:
In Amendment 34 (28Aug2023), the Applicant provided the batch results from (b) (4) batches used for process validation and compatibility studies at (b) (4) and iCTC. These batches were not for clinical use. At (b) (4) iCTC, (b) (4) batches were manufactured for both PPQ and comparability studies, (b) (4) batches were manufactured for PPQ study only, and (b) (4) batches were manufactured for comparability study only. Results and deviations pertaining to the non-clinical batches were reviewed in 3.2.S.2.5. Process Validation and/or Evaluation and 3.2.S.2.6. Manufacturing Process Development – Comparability.

Overall Reviewer's Assessment of Sections 3.2.P.5.4:
In CMC IR #11 (21Aug2023), complete batch analysis records, including all infused/non-infused batches and non-clinical batches, were requested. The Applicant provided updated batch records in Amendment 34 (28Aug2023). The information provided is acceptable with no additional CMC issues or deficiencies identified.

3.2.P.5.5 CHARACTERIZATION OF IMPURITIES
Section reviewed by KK.
Reviewed in 3.2.S.3.2. Impurities of this memo.

3.2.P.6 Reference Standards or Materials
Section reviewed by SJ.
(b) (4)

Reviewer comment: In response to CMC IR #22 (10Jan2024), the Applicant provided information comparing the (b) (4)
(b) (4) *This information is acceptable. The establishment and qualification of the DP* (b) (4) *lots for lot release testing of the final DP is acceptable. The Applicant agreed to the agency advice comments from 16Dec2022 and*

generated (b) (4) *DP lots to be used as* (b) (4) (b) (4) *No CMC concerns are noted.*

3.2.P.7 Container Closure System

Section reviewed by consult Wojtek Tutak (CBER/OTP/OCTHT/DCT2/TEB2)

Reviewed in 3.2.P.2.4 Container Closure System of this memo.

3.2.P.8. Stability

Section reviewed by SK.

3.2.P.8.1. AND 3.2.P.8.3. STABILITY SUMMARY AND CONCLUSION AND STABILITY DATA

To characterize long-term and in-use DP stability, the Applicant conducted a study on (b) (4) PPQ batches manufactured at (b) (4) PPQ batches manufactured at iCTC. These batches were manufactured from (b) (4) (b) (4) . The stability data are considered representative of worst-case conditions, given that the (b) (4) The stability protocol includes assessment after (b) (4) (b) (4) however, data from the (b) (4) month timepoint is not yet available. In-use stability is assessed at (b) (4) (b) (4) timepoints by testing (b) (4) samples of each DP batch (b) (4) (b) (4) See Table 122.

Reviewer comment: The Applicant assessed stability at a 3-month timepoint on DP cryopreserved in (b) (4) *Only* (b) (4) (b) (4) *was analyzed, and all samples passed the acceptance criteria. While the Applicant argues that storage of DP in* (b) (4) *cryobags does not affect product characteristics, these data are not included in the stability assessment due to use of a non-representative container closure, limited product testing, and successful completion of the 6-month timepoint.*

(b) (4)

3.2.P.8.1.2. Long Term Stability Study

The cryopreserved < -150°C DP was stored for 0, 1, and 6 months in (b) (4) cryopreservation bags, which is representative of the container closure used for the commercial product. Results of the (b) (4) long-term stability timepoint, which will

include all tests performed for the 6-month timepoint listed in Table 123, are pending. At each timepoint, the cryopreserved DP was thawed to reach 18-25ºC and tested using the for product release testing analytical methods. The Applicant indicates that all the analytical methods were validated at the time of testing except for the (b) (4) assays, which were qualified but not validated at the 0-month and 1-month study timepoints. The 6-month stability study was performed using validated (b) (4) assays.

Reviewer comment: The Applicant used qualified (b) (4) *assays for the 0- and 1-month study, which were then validated in time for use during the 6-month study. The duration of product stability will be based on the later timepoint, so this is acceptable.*

(b) (4)

Adapted from Table 2 in eCTD section 3.2.P.8.1. and Tables 1-7 in eCTD section 3.2.P.8.3.

In Amendment 56 (18Dec2023), the applicant provided additional justification for the use of the release acceptance criteria for the stability study by providing an assessment of the (b) (4) for all batches and stability-indicating assays (b) (4)

Table 124. Stability and Shelf-Life Analysis

(b) (4)

Reviewer Comment: The parameters and acceptance criteria listed in Table 123 are identical to the DP release specifications provided in Table 1 of eCTD section 3.2.P.5.1. In addition, the stability acceptance criteria do not include a comparison to the timepoint (b) (4) *In CMC IR #19, dated 13Dec2023, the Applicant was asked to address whether the stability AC, which are wide, are able to establish a meaningful shelf life for all DP batches as: (1) DP batches with values at the higher end of the allowable range can degrade significantly before failing to meet the stability AC, (2) the stability results may not establish a relevant shelf life for lots with values near the minimum acceptance criteria at release. In Amendment 56 (18Dec2023), the Applicant assessed the* (b) (4) (b) (4) *for the stability-indicating assays. Briefly, the results demonstrate that* (b) (4) *do not incur a significant loss in stability over 6 months. For* (b) (4) (b) (4) *loss over 6 months. Batches released with results at the lower end of the specification are expected to remain within specification limits through the proposed shelf life. The statistics consult, Dr. Tianjiao Dai, reviewed these results and the Applicant's justification for the current acceptance criteria and found them to be acceptable. However, it is noted that* (b) (4) *month stability may be difficult to demonstrate for low potency batches given the results of this analysis. No additional CMC concerns identified.*

All the tested batches passed the long-term stability acceptance criteria for the 6-month timepoint. The Applicant proposes a 6-month shelf life for the cryopreserved DP when maintained at temperature of ≤-150°C, and the data provided support this proposed maximum hold time.

3.2.P.8.1.3. In-Use Stability Study

The Applicant evaluated the stability of either 1-month or 6-month cryopreserved DP (b) (4) stability timepoint are pending. Results are shown only for the 6-month timepoint in Table 125, as similar results were observed at the 1-month timepoint.

Table 125: Summary of In-Use Stability Data (6-Month Cryopreserved DP)

(b) (4)

The Applicant proposes 3-hour maximum hold time for the post-thaw/in-use DP when maintained at temperature between 18-25°C, and the data provided support this proposed maximum hold time.

3.2.P.8.1.4. Accelerated Stability Study

(b) (4)

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

(b) (4)

3.2.P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT
The Applicant's plan is to continue the on-going stability studies to completion. Results of the stability studies will be reported to the application as per the applicable regulatory requirements.

Given the autologous nature of the product and that the sample volume required for stability testing would have an impact on the final dose available for patient infusion, post-approval stability testing is not planned.

Overall Reviewer's Assessment of Section 3.2.P.8:
In Amendment 56 (18Dec2023), the Applicant provided justification for their stability specifications, which are the same as the product release specifications in response to CMC IR #19 (13Dec2023). The applicant addressed all concerns; however, it should be noted that the applicant may have difficulties establishing stability of the product at the (b) (4)-month timepoint. No additional CMC concerns identified.

The proposed 6-month shelf-life for cryopreserved DP and 3-hour post-thaw/in-use DP shelf-life are acceptable and supported by the provided stability results.

3.2.A APPENDICES
3.2.A.1 Facilities and Equipment
Assessment of the facilities and equipment is deferred to DMPQ. Please refer to the review memo by Hector Carrero.

3.2.A.2 Adventitious Agents Safety Evaluation
Section reviewed by EL.
3.2.A.2.1. NON-VIRAL ADVENTITIOUS AGENTS
3.2.A.2.1.1. (b) (4)
The Applicant's microbial control strategy consists of elements of facility design and controls, raw materials controls, and process controls.

1. Facility design and controls: The product is manufactured in a controlled environment using single-use, sterile (b) (4) except for process manipulations that are executed aseptically in a qualified Grade (b) (4) (b) (4) within a Grade (b) (4) suite. The process from Day (b) (4) on Day (b) (4) occurs within a (b) (4) system in the Grade (b) (4) suite. Product contact equipment is sterile and 100% disposable. Facility cleaning includes the use of appropriate disinfectants to control contamination. Facility cleaning also occurs

between products in a suite to prevent cross contamination. Cleaning processes and frequencies are procedurally-controlled. Environmental monitoring of the Grade (b) (4) and Grade (b) (4) suite and associated airlocks is performed throughout the manufacturing process. Environmental monitoring of manufacturing personnel is performed on all individuals working in the Grade (b) (4) (b) (4) and Grade (b) (4) suite. Environmental monitoring results are analyzed according to the microbial detection limits during operation per (b) (4)

2. Raw materials controls: All components and non-biological raw materials used in the lifileucel manufacturing process are certified sterile by their vendors. Safety measures are put in place for materials that are used in the process, such as sterile filtration of (b) (4) and the use of antimicrobial agents.
3. Process controls: Aseptic controls and technique are employed in the manufacture of the product. The lifileucel manufacturing process successfully completed (b) (4) consecutive aseptic process validation (APV) runs prior to the commencement of GMP manufacturing, and APV runs are completed at periodic intervals. The final product and stability samples are tested for sterility.
   Reviewer Comment: Review of the adequacy about the aseptic process validation is deferred to the DMPQ reviewer.

3.2.A.2.1.2. Identification of Materials Derived from Sources of Animal, Human or Cellular Origin

As part of the Applicant's adventitious agents safety evaluation, Table 128 and Table 129 sumarizies all raw materials and excipients that are materials of animal, human or cellular origin, or had indirect contact with materials of animal or human origin. Each identified material was then subject to adventitious agent safety evaluation.

Table 128. Raw Materials Derived from Sources of Animal, Human, or Cellular Origin

(b) (4)

(b) (4)

Table 129. Excipient Materials Derived from Sources of Animal, Human or Cellular Origin

Material	Source	Quality Standard	Country of Component origin	Manufacturer	Representative Quality Documents
Albumin (Human) 25% (b) (4) IL-2) CryoStor CS10	(b) (4)				

Adapted from Table 2 and 3 in eCTD section 3.2.A.2

3.2.A.2.2. VIRAL ADVENTITIOUS AGENTS

The product is manufactured using aseptic manufacturing. No viral clearance studies were completed on the (b) (4) DP. Raw materials are reviewed for the risk of introducing viral adventitious agents. The product is a single lot product. No additional product viral adventitious agents testing is conducted.

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

Section 3.2.S.2.3. Control of Materials of this memo provides additional adventitious agent safety evaluation information for each reagent individually. The Applicant's approach to controlling risks associated with adventitious agents is adequate.

3.2.A.3 Novel Excipients

None

3.2.R REGIONAL INFORMATION (USA)

3.2.R.1 Executed Batch Records

This section contains: (1) the Master Batch Record and two Executed Batch Records (PPQ lots (b) (4) from

(b) (4) and (2) Master Batch Record and two Executed Batch Records (PPQ lots (b) (4) from iCTC.
Reviewer comment: Executed batch records were reviewed at the (b) (4) *iCTC PLIs. No deficiencies identified.*

3.2.R.2 Method Validation Package
This section contains analytical assay validation reports. All analytical assay validation reports found in the regional information section are discussed under the relevant section in 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.

Comparability Protocols
Comparability protocols are discussed in 3.2.S.2.6 Manufacturing Process Development – Comparability of this memo.

OTHER ECTD MODULES
Module 1
ENVIRONMENTAL ANALYSIS OR CLAIM OF CATEGORICAL EXCLUSION
Section reviewed by KK.
The Applicant requests that lifileucel be granted a categorical exclusion under the provision of the 21 CFR Part 25.31(c). The requested action is in compliance with the categorical exclusion criteria. To the Applicant's knowledge, per the requirements of 21 CFR 25.15, no extraordinary circumstances exist.
Reviewer Comment: A claim of categorical exclusion has been submitted under 21 CFR 25.31(c). FDA concludes that this product occurs naturally in the environment, and approval of this BLA does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. No extraordinary circumstances exist. The categorical exclusion claim is accepted.

LABELING REVIEW
Section reviewed by KK.
Full Prescribing Information (PI)
Prescribing information was reviewed and revisions were made to the draft provided by the Applicant in Amendment 28 (17Aug2023). The revised PI was provided to the Applicant on 24Jan2024, 5Feb2024, 12Feb2024, and 13Feb2024. The Applicant provided their response to the PI revisions in Amendment 74 (30Jan2024), Amendment 81 (8Feb2024), Amendment 84 (13Feb2024), and Amendment 85 (14Feb2024).

Container and Package Label
The applicant provided draft labeling for the product bag (container) and cassette (package). Each label is 3 by 5 inches. Each product bag is packaged in a metal cassette, and the bag label cannot be viewed while stored in the cassette. The bag and cassette labels were reviewed, and revisions were provided to the Applicant in CMC IR #23 (12Jan2024), CMC IR #24 (24Jan2024), and CMC IR #25 (26Jan2024). The Applicant submitted final revised label for both the bag (container) and cassette (package) in Amendment 82 (9Feb2024) in response to CMC IR #24 (24Jan2024).

There will be specific labels for the (b) (4) manufactured product and for the iCTC manufactured product, which will be identical except for the site-specific manufacturing information. The bag and cassette labels will contain unique NDC numbers. All bag and cassette labels are shown in Figure 15,
Figure 16, Figure 17, and Figure 18.

Of note, while the final product is filled into (b) (4) to four bags (100mL to 125mL DP per bag), the final product may be shipped to the treatment center in one to four bags (100mL to (b) (4) DP total) due to issues observed with the product or container closure integrity post-cryopreservation. The Applicant includes a packing slip with each shipped lot that indicates how many total bags/cassettes are actually in the shipment. A copy of this packing slip is provided in Amendment 80 (6Feb2024) in response to CMC IR #26 (5Feb2024).

The Applicant's Drug Supply Chain Security Act exemption request was granted.

Figure 15. iCTC Bag (Container) Label

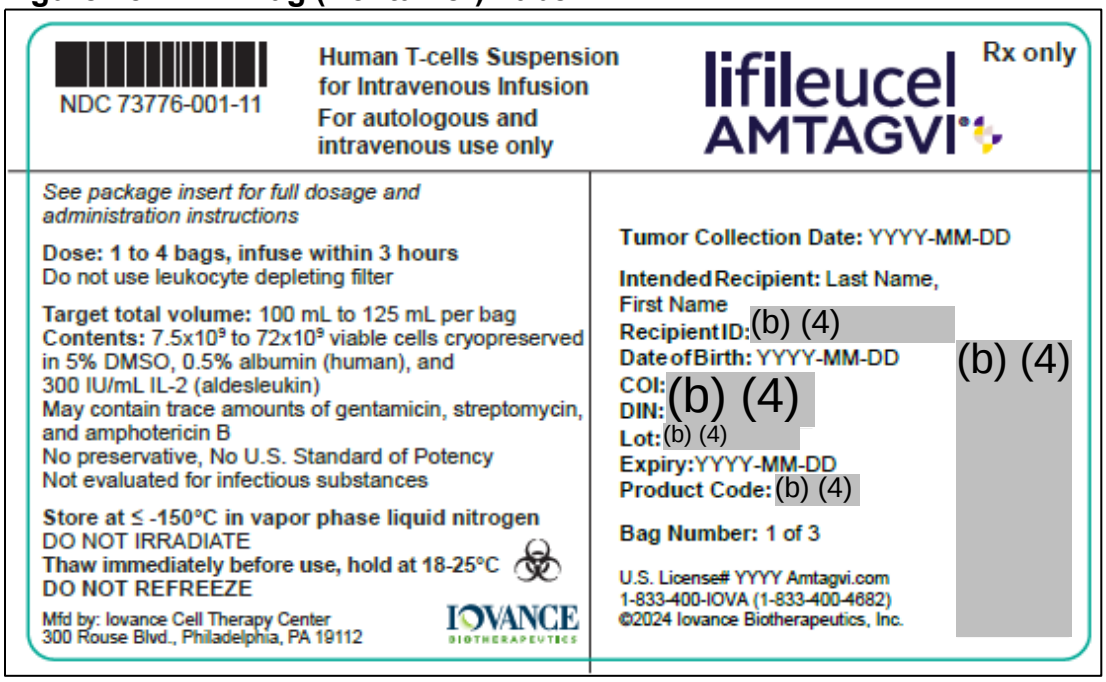
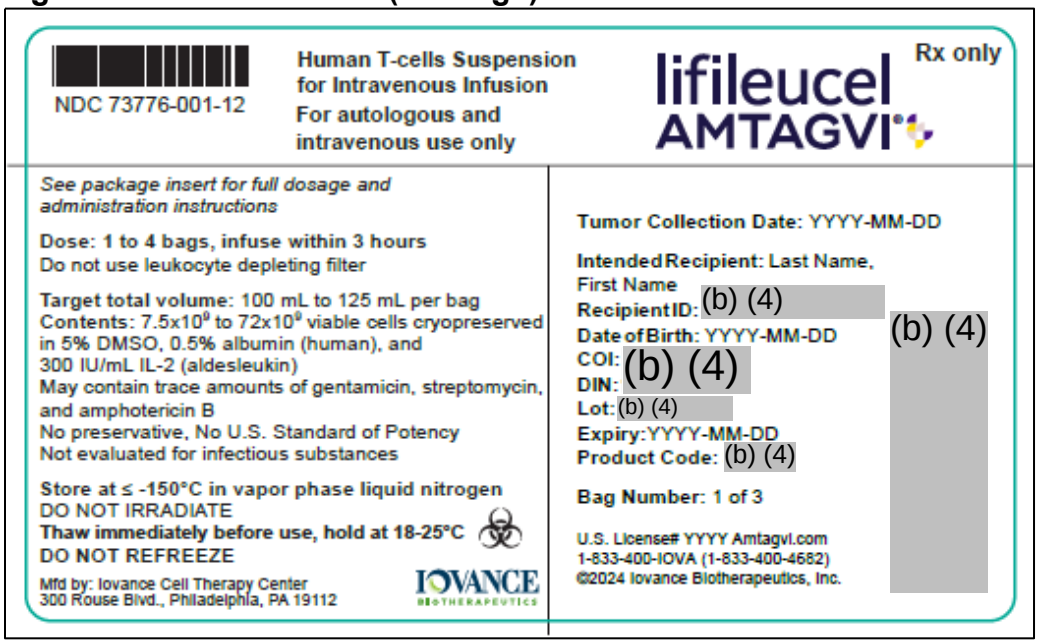


Figure 16. iCTC Cassette (Package) Label



(b) (4)

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

Starting Material and In-Process Labels

Tumor Starting Material Labels

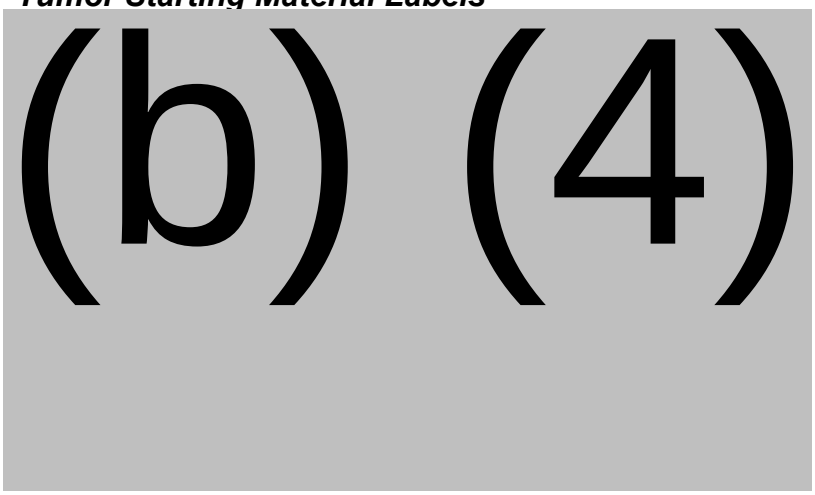
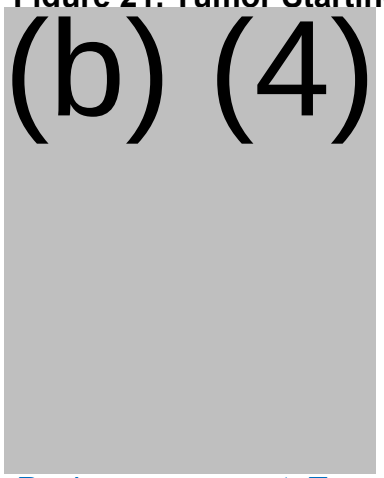
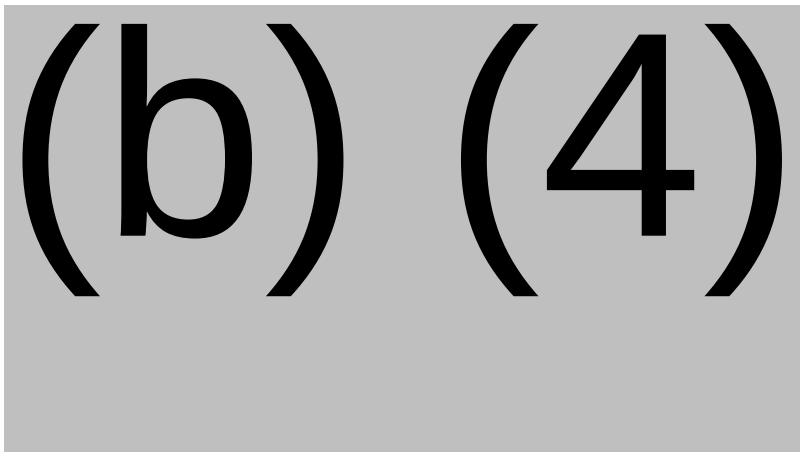


Figure 21. Tumor Starting Material Shipping Label (COI/COC)



Reviewer comment: Tumor starting material labels were provided in Amendment 34 (28Aug2023) in response to CMC IR #11 (21Aug2023). All starting tumor material labels are acceptable.

In-Process Labels



(b) (4)

(b) (4)

Reviewer comment: In-process labels were provided in Amendment 34 (28Aug2023) in response to CMC IR #11 (21Aug2023). All in-process labels are acceptable.

Module 5

(b) (4) *ASSAY VALIDATION*

This assay is not used for product release or to make clinical decisions regarding patient treatment. This section is copied from bioinformatics consult review memo by Dr. Cinque Soto (CBER/OTP/OCTHT/DCT1).

Purpose: (b) (4)

(b) (4)

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