

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

CBER CMC BLA Review Memorandum

BLA STN 125868

**Allogeneic regulatory T cell-based immunotherapy with HSPC and T cells-vldq
(TREGZI)**

Reviewer/Title/Affiliation

Elizabeth Lessey-Morillon, Chair, CMC Reviewer, CBER/OTP/OCTHT/DCT1/CTB1

Karin Knudson, CMC Reviewer, CBER/OTP/OCTHT/DCT1/CTB2

Saravanan Karumbayaram, CMC Reviewer, CBER/OTP/OCTHT/DCT1/CTB1

Ruipeng Wang, CMC Reviewer, CBER/OTP/OCTHT/DCT1/CTB2

BLA#: STN 125868

APPLICANT NAME AND LICENSE NUMBER

Orca Biosystems Inc.
License No. 2404

PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper Name: Allogeneic regulatory T cell-based immunotherapy with HSPC and T cells-vldq
Proprietary Name: TREGZI

GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological Category: Allogeneic regulatory T cell-based immunotherapy with hematopoietic stem and progenitor cells and T cells
- b. Dosage form:
Regulatory T cell (Treg) Drug Product (DP): 1.3×10^6 to 3.5×10^6 cells per patient kg in 100 mL Multiple Electrolytes Injection and 2% HSA, stored at $5 \pm 3^\circ\text{C}$
Hematopoietic stem and progenitor cell (HSPC) Drug Product (DP): $\geq 1.0 \times 10^6$ cells per patient kg in 100 mL Multiple Electrolytes Injection and 2% has, stored at $5 \pm 3^\circ\text{C}$
Conventional T cell (Tcon) Drug Product (DP): 1.3×10^6 to 6.9×10^6 cells per patient kg in 15 mL cryoprotective media (Multiple Electrolytes Injection, 3% to 4% HSA, 7.5% DMSO, and 1.8% Hetastarch), stored cryopreserved at $< -125^\circ\text{C}$
Tcon Diluent: 38 mL of multiple electrolyte injection with 2%HSA, stored at (b) (4) $^\circ\text{C}$
- c. Route of Administration: Intravenous Infusion
- d. Indication: For use in matched donor hematopoietic stem cell transplantation with myeloablative preparative regimen, for hematopoietic and immunologic reconstitution and to improve chronic graft vs host disease (cGVHD)-free survival, in the treatment of adults with hematological malignancies

MAJOR MILESTONES

Application Receipt Date:	06Aug2025
BLA filed:	01Oct2025
Internal Mid-Cycle Meeting:	20Nov2025
Mid-Cycle Meeting with Applicant:	Applicant Cancelled
Proprietary Name Review:	03Dec2025
Internal Late-Cycle Meeting:	06Jan2026
Late-Cycle Meeting with Applicant:	23Jan2026
Major Deficiencies Communication:	26Mar2026
Major Amendment:	27Mar2026
Internal Target Action:	30Jun2026
PDUFA Action:	6Jul2026

CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Elizabeth Lessey-Morillon, PhD OTP/OCTHT/DCT1/CTB1	Drug Substance (Tcon DS, HSPC DS); Batch Records, Process Validation (Treg DP, HSPC DP, Tcon DP); Drug product (HSPC DP, Tcon DP, Tcon Diluent DP)
Karin Knudson, PhD OTP/OCTHT/DCT1/CTB2	Drug Substance (Treg); Analytical Procedures and Validation of Analytical Procedures (Treg DP, HSPC DP, Tcon DP), Drug product (Treg)
Saravanan Karumbayaram, PhD OTP/OCTHT/DCT1/CTB1	Control of Materials (Treg DS, HSPC DS, Tcon DS), Control of Excipients (Treg DP, HSPC DP, Tcon DP, Tcon Diluent)
Ruipeng Wang, PhD OTP/OCTHT/DCT1/CTB2	Stability (Treg DP, HSPC DP, Tcon DP)
Simone Porter and Safa Karandish OTP/OCTHT/DHT/HTRS	Consult review of Donor eligibility
Mona Mansouri, PhD Consult Reviewer OTP/OCTHT/DCT1/CTTB	Consult review of delivery device
Haarin Chun, PhD Consult Reviewer OTP/OPPT/DH/HB2	Consult review of Toxicology Risk Assessment for the Container Closure
Andrey Sarafanov, PhD Consult Reviewer OTP/OPPT/DH/HB2	Consult review of extractables and leachables
Fang Chen, PhD Consult Reviewer CBER/OBPV/DB/DNCE	Consult review of CMC statistics

INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Qibing Zhou, PhD CDER/OPQ/OPQAIII/DPQAXV	ICCR# 01116769 - (b) (4) Reagent CR/GMP, GMP (b) (4) and GMP (b) (4)	Yes

SUBMISSION REVIEWED

Date Received	Submission	Comments/ Status
6Aug2025	STN 125868/0	Original Submission
18Sep2025	STN 125868/0.05	Applicant Response to CMC Information Request (IR) #1 dated 16 Sep 2025
7Oct2025	STN 125868/0.07	Applicant Response to CMC IR #2 dated 29 Sep 2025
14Oct2025	STN 125868/0.08	Applicant Response to CMC IR #3 dated 07 Oct 2025
23Oct2025	STN 125868/0.12	Applicant Response to CMC IR #5 dated 20 Oct 2025 and CMC IR #4 dated 17 Oct 2025
28Oct2025	STN 125868/0.13	Applicant Response to CMC IR #6 dated 24 Oct 2025
4Nov2025	STN 125868/0.15	Applicant Response to DBSQC IR #1 dated 23 Oct 2025
7Nov2025	STN 125868/0.16	Applicant Response to CMC IR #7 dated 31 Oct 2025
21Nov2025	STN 125868/.018	Applicant Response to DBSQC IR #2 dated 07 Nov 2025
26Nov2025	STN 125868/0.20	Applicant Response to DBSQC IR #3 dated 14 Nov 2025
2Dec2025	STN 125868/0.21	Applicant Response to CMC IR #8 dated 21 Nov 2025

5Dec2025	STN 125868/0.23	Additional Response to CMC IR #7 dated 31 Oct 2025 - BLA Commitment in Response to CMC IR #7 (DE)
11Dec2025	STN 125868/0.24	Additional Response to CMC IR #7 dated 31 Oct 2025 - BLA Commitment in Response to CMC IR #7 (Leachable Study)
15Dec2025	STN 125868/0.25	Applicant Response to CMC IR #9 dated 01 Dec 2025
17Dec2025	STN 125868/0.27	Applicant Response to CMC IR #12 dated 16 Dec 2025
31Dec2025	STN 125868/0.31	Applicant Response to CMC IR #14 dated 22 Dec 2025 and CMC IR #13 dated 19 Dec 2025
9Jan2026	STN 125868/0.32	Additional Response to CMC IR #8 dated 02 Dec 2025 - BLA Commitment in Response to CMC IR #8 (PPQ Protocol for PS 3/4)
12Jan2026	STN 125868/0.33	Applicant Response to CMC IR #10 dated 16 Dec 2025
16Jan2026	STN 125868/0.34	Applicant Response to CMC IR #15 dated 11 Jan 2026; Additional Response to CMC IR #9 dated 01 Dec 2025 (Request for Clarification); Sponsor Response to DBSQC IR #4 dated 12 Jan 2026
30Jan2026	STN 125868/0.37	Additional Response to CMC IR #10 dated 16 Dec 2025 (Treg (b) (4)) Additional Response to DBSQC IR #2 dated 07 Nov 2025 (VI)
6Feb2026	STN 125868/0.38	Additional Response to CMC IR #10 dated 16 Dec 2025 (Treg (b) (4) Validation); Additional Response to DBSQC IR #3 dated 14 Nov 2025 (Bioburden)
6Feb2026	STN 125868.039	Applicant Response to Form 483 Issued 15 Jan 2026
13Feb2026	STN 125868/0.40	Additional Response to CMC IR #9 dated 01 Dec 2025, CMC IR #14 dated 22 Dec 2025, and CMC IR #15 11 Jan 2025 (Preliminary Data for Cell Count Validation and Validation Protocols)
20Feb2026	STN 125868/0.41	Applicant Response to CMC IR #16 dated 13 Feb 2026
26Feb2026	STN 125868/0.43	Additional Response to DBSQC IR #2 dated 07 Nov 2025 (VI)
2Mar2026	STN 125868/0.44	Applicant Response to CMC IR #17 dated 27 Feb 2026
13Mar2026	STN 125868/0.45	Additional Response to CMC IR #9 01 Dec 2025, CMC IR #10 16 Dec 2025, CMC IR #14 22 Dec 2025, and CMC IR#16 13 Feb 2026; Additional Response to DBSQC IR #1 dated 05 Nov 2025 (B&F)
17Mar2026	STN 125868/0.47	Applicant Response to Late Cycle Meeting Memorandum 19 Feb 2026
20Mar2026	STN 125868/0.48	Additional Response to CMC IR #8 21Nov2025
27Mar2026	STN 125868/0.49	Additional Response to CMC IR #9 15 Dec 2025, CMC IR #14 31 Dec 2025, and CMC IR#16 20 Feb 2026; BLA Commitment in Response to CMC IR dated 26 March 2026 (Major Deficiencies, no IR #)
31Mar2026	STN 125868/0.50	Additional Response to CMC IR #7 17 Nov 2025 and CMC IR #9 15 Dec 2025
16Apr2026	STN 125868/0.51	Applicant Response to the Comment 6 from CMC IR (no #) dated 26 March 2026
24Apr2026	STN 125868/0.52	Applicant Response to CMC IR (no #) dated 26 March 2026 and CMC IR #18 dated 13 Apr 2026
28Apr2026	STN 125868/0.53	Applicant Response to CMC IR (no #) dated 27 Apr 2026
30Apr2026	STN 125868/0.54	Applicant Response to CMC IR #19 dated 29 Apr 2026
5May2026	STN 125868/0.55	Applicant Response to CMC IR #20 dated 30 Apr 2026
7May2026	STN 125868/0.56	Applicant Response to CMC IR #21 dated 5 May 2026
11May2026	STN 125868/0.57	Applicant Response to CMC IR #22 dated 5 May 2026 (DE)
14May2026	STN 125868/0.58	Applicant Response to CMC IR #23 dated 12 May 2026
15May2026	STN 125868/0.59	Applicant Response to CMC IR #24 dated 14 May 2026

20May2026	STN 125868/0.60	Applicant Response to CMC IR #26 dated 19 May 2026
29May2026	STN 125868/0.61	Applicant Response to CMC IR #27 dated 28 May 2026
29May2026	STN 125868/0.62	Applicant Response to CMC IR #25 dated 15 May 2026; Additional Response to CMC IR #26 dated 19 May 2026
1Jun2026	STN 125868/0.63	Applicant Response to CMC IR #28 dated 29 May 2026
3Jun2026	STN 125868/0.64	Applicant Response to CMC IR #29 dated 1 Jun 2026
9Jun2026	STN 125868/0.66	Applicant Response to CMC IR #30 dated 5 Jun 2026
16Jun2026	STN 125868/0.67	Applicant Response to CMC IR #31 dated 12 Jun 2026
18Jun2026	STN 125868/0.68	Applicant Response to CMC IR #32 dated 16 Jun 2026
23Jun2026	STN 125868/0.69	Correspondence Regarding Anticipated CMC PMCs dated 18 Jun 2026
26Jun2026	STN 125868/0.70	BLA Commitments in Responses to CMC IR #32 dated 16 June 2026 and CMC IR #34 dated 24 June 2026

REFERENCED REGULATORY SUBMISSIONS

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
CBER MF2 (b) (4)	[REDACTED]	[REDACTED]	Y	The sampling for adventitious agent testing for (b) (4) [REDACTED] was resolved through interactive communications with the MF holder. No outstanding safety concerns with the cross reference file.
IND 18873	Orca Biosystems Inc.		NA	Good standing; contains BLA supporting clinical study development information; also contains expanded access protocol to treat patients should commercial product be OOS to prevent treatment delays
MF (b) (4)	[REDACTED]	List of Centers HPC viability data	Y	A complete review of the MF has not occurred. The Applicant references the MF to the list of centers and HPC stability data. The list of Center is acceptable. While not review, the HPC stability data is not directly applicable to address the Applicant's stability studies of the Apheresis material. The only information from MF to support this BLA is the list of centers in MF.

REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Orca Biosystems Inc. (iOrca Biosystems Inc. (the Applicant) submitted BLA 125868 to market TREGZI (allogeneic regulatory T cell-based immunotherapy with HSPC and T cells-vldq) for use in 8/8 HLA-matched-donor hematopoietic stem cell transplantation (HSCT) with a myeloablative preparative regimen. The proposed indication is hematopoietic and immunologic reconstitution and improvement of chronic graft-versus-host disease (cGVHD)-free survival in adults with hematological malignancies. There are currently no FDA-approved therapies for the prevention of cGVHD, representing a significant unmet medical need for an effective and well-tolerated preventive therapy.

Product Description

TREGZI consists of three distinct cellular drug product (DP) components derived from a single matched donor following Granulocyte-Colony Stimulating Factor (G-CSF) mobilization and apheresis collection:

- Hematopoietic stem and progenitor cell (HSPC) DP – stem cells that create new blood and immune cells, administered fresh on day 0.
- Regulatory T cell (Treg) DP – Treg cells that help prevent graft versus host disease (GVHD), administered fresh on day 0.
- Conventional T cell (Tcon) DP – T-cells that provide immediate immune function and allow the graft to fight infections and leukemia, administered on day 2-3.

All three DP components contribute to the therapeutic benefit of TREGZI. The sequential administration of Tregs prior to Tcon is hypothesized to reduce Tcon inflammatory activity while preserving immune reconstitution capacity.

Manufacturing

All three drug products are derived from a single matched donor peripheral blood apheresis material through (b) (4). Upon arrival at the manufacturing site, donor apheresis material is (b) (4)

Following final formulation and fill of all three DPs and a Tcon diluent, the products are shipped to the treatment center. Release tests include sterility, endotoxin, appearance, identity, purity, viable cell dose, (b) (4), and potency. Because the Treg and HSPC DPs must be administered within 72 hours post-apheresis collection (PAC), they are released based on a negative (b) (4) result, with final 14-day sterility results available only after product administration.

Stability

The Applicant conducted stability studies for three cellular products using engineering run batches manufactured at the commercial site (SAC-02) from healthy donor apheresis material. The studies evaluated storage stability, in-use stability, and compatibility with administration sets.

Treg and HSPC DPs were stored at $5 \pm 3^{\circ}\text{C}$ with a 72-hour shelf life PAC and (b) (4). Tcon DP was cryopreserved at $< -125^{\circ}\text{C}$ with a 7-day shelf life and 4-hour in-use stability at $5 \pm 3^{\circ}\text{C}$ post-thaw. Clinical experience supports the product remains effective up to 72 hr.

HSPC DP appears to maintain critical quality attributes (CQAs) throughout the proposed shelf life and in-use period. The stability study provided only weak support that Treg potency is maintained at 72 hours, and the minimum (b) (4) potency level required for clinical efficacy has not been established. The minimum Treg (b) (4) potency level required to remain potent has not been demonstrated. The study showed Treg (b) (4) potency declines with time. This decline is not specific to post fill stability as Treg (b) (4) Potency declines with time from apheresis collection. Currently, the impact of this drop on Treg Potency is unknown. The results from the (b) (4) assay in the stability study support show Treg remain functional, but due to study design, this data alone is insufficient fully support Treg stability without clinical experience. Reanalysis of Treg DP (b) (4) potency data submitted in the Major Amendment showed a percent difference ranging from (b) (4) between original and revised results, though the overall declining trend was consistent. In the Tcon DP stability studies, cell aggregates were observed in all (b) (4) batches and in (b) (4) of (b) (4) apheresis-derived batches after cell thawing and dilution. Tcon DP derived from apheresis showed an increasing trend for cell aggregation post-thaw over time. Nevertheless, Treg DP and Tcon DP cell dose and viability appear to be stable.

Manufacturing Facility

The commercial TREGZI will be manufactured at the SAC-02 facility. SAC-02 is a (b) (4) facility that began manufacturing clinical batches of TREGZI on (b) (4). For Phase 1 to Phase 3 clinical studies, TREGZI was manufactured at (b) (4) under IND 18873. The commercial site, SAC-02, was inspected as part of the Pre-License Inspection (PLI) from 8Jan2026, to 15Jan2026. One observation was issued regarding lack of control over analytical methods, as detailed in the issued Form 483. These analytical deficiencies had cascading effects throughout the application, compromising the Chemistry, Manufacturing, and Controls (CMC) review team's ability to assess product quality, ensure patient safety, and establish commercial product equivalence to the Phase 3 product.

Initial Determination

Although the Phase 3 Precision-T study met its primary endpoint with a statistically significant improvement in the TREGZI arm compared to standard of care, the CMC review team initially determined that the Applicant had not demonstrated reasonable

assurance of manufacturing control. Specifically, the CMC review team could not confirm that the methods, processes, and controls at SAC-02 were designed to ensure product safety, purity, and potency, nor could it determine whether the drug product manufactured at (b) (4), and used in Phase 3 studies, was equivalent to the proposed commercial product at SAC-02. These unresolved issues would have precluded assurance that the commercial product would be as safe and efficacious as the Phase 3 product.

CMC identified major deficiencies that were unresolved at the time of declaring a major amendment. These deficiencies were communicated to the Applicant on 26Mar2026, relating to the following:

1. (b) (4) based assay methods lack appropriate scientific controls leading to serious patient safety implications.
2. Unsuccessful validation of analytical methods to ensure that future commercial batches meet acceptable standards for quality and purity and maintain consistency over time
3. Downward trends for Treg product attributes and an increase in out-of-specification (OOS) lots for commercial products manufactured at SAC-02 compared to Phase 3 products manufactured at (b) (4), which can result in exposing patients to unsafe or ineffective products
4. Unable to demonstrate that manufacturing process can consistently identify and select a consistent Treg population while excluding harmful impurities like (b) (4), which can affect patient safety and product efficacy
5. Insufficient safety information regarding residual (b) (4) in the final Treg DP
6. Apheresis products from ineligible donors, including those with risk factors of communicable diseases, cannot be used to manufacture licensed drug product

Declaring Major Amendment

On 13Mar2026, 24 days before the PDUFA action date, the Applicant submitted 66 study reports (2,347 pages) containing new (b) (4) control strategies, process revalidation reports, and method validation reports in Amendment 45. These were significant amounts of new data and comprehensive review could not be conducted in this review cycle. However, in initial review of approximately 41 key reports, substantial CMC concerns remained. The nature of these deficiencies—specifically, the current failures in method validation studies demonstrating that the methods cannot provide reliable and accurate results—precluded resolution through a PMC/PMR, as these are essential manufacturing control and validation data required to ensure the continued safety, purity, and potency of the DP manufactured at the intended commercial facility as required by 21 CFR 601.2(d). Failure to demonstrate these essential manufacturing controls and method validations would also fail to ensure the intended commercial products are as safe and efficacious as the Phase 3 clinical products supporting the clinical outcomes data in the BLA. These outstanding deficiencies would preclude approval even after extending the review time by declaring a major amendment, and the CMC review team initially recommended issuing a Complete Response Letter for the BLA in order for the Applicant to have adequate time to address these major concerns and resubmit the BLA.

However, the OTP review committee proposed a unique opportunity to the Applicant for a one-time extension to the review clock, given the clinical efficacy of TREGZI shown in the BLA. This would allow additional time to submit any outstanding study reports, manufacturing and control data reanalysis, and justifications required to address the outstanding major CMC deficiencies noted above. The Applicant committed in writing “to fully address all of the deficiencies as outlined in the Information Request (IR) received on 26Mar2026 and provide all additional data by 26Apr2026” and OTP issued a Major Amendment letter dated 27Mar2026, extending the action due date to 06Jul2026.

Final Assessment

The Applicant provided additional information addressing the above major CMC deficiencies in Amendment 52 (received 24Apr2026) and in responses to subsequent IRs needed to complete the CMC review. While the responses resolved many concerns, certain outstanding issues require resolution under Post-Marketing Commitments (PMCs). The assessment applied regulatory considerations by balancing the criticality of unresolved CMC information against the safety risk and delaying patient access to TREGZI, a patient-matched, time-sensitive cellular therapy. The regulatory considerations also took into account the manufacturing processing controls needed to demonstrate product consistency with the Phase 3 product, which demonstrated clinical efficacy and the manufacturing process that should not negatively impact the intrinsic characteristics of the donor cells as a minimally manipulated DP. We considered available options including post-market regulatory options to resolve the outstanding issues without delaying patient access, while ensuring product quality. A total of 16 PMCs, falling under the umbrella of four unresolved deficiency topics, are summarized at the end of the Executive Summary.

Contextually Appropriate Regulatory Considerations

The CMC team took multiple regulatory considerations into account during the development under IND and review of this BLA, which posed regulatory challenges as a fresh, donor-matched, single lot product for each patient. The approval of this BLA balances pre- and post-approval CMC expectations, enabling timely access to a product addressing significant unmet medical need with clear clinical benefits, while also balancing patient access with generation of evidence to be gathered in the post-marketing setting.

Key regulatory considerations for CMC in the review of TREGZI include:

- Given the favorable clinical benefit, the Agency agreed to accept and review significant CMC information after the designation of a major amendment late in the review cycle. This allowed the applicant to address major CMC deficiencies not addressed in the major amendment submission. In addition, the CMC review team used the PMC pathway as a structured approach to finalize the requested studies. This adjustment reflected the clinical significance of the program and

required extraordinary CMC team effort to complete review within the mandated timelines.

- The specifications for all three DP components were based on the Phase 3 efficacy study (Precision-T study) but also leveraged prior knowledge of HSPCs and related stem cell transplant experience, as applicable. The CMC review team also considered the logistical constraints of infusing the fresh DP components to the patient within 72 hours from end of first apheresis collection in assessing the product lot release tests. All three cellular DPs are released based on (b) (4) (b) (4) detection for an interim sterility assurance before obtaining the final 14-day (b) (4)-based sterility test results and based on demonstrated manufacturing controls. The Treg Potency assay was accepted for lot release despite known limitations compared to direct biological function assessment (e.g., (b) (4) assay). The (b) (4) is included in stability and PPQ studies and is performed as extended characterization testing every (b) (4) lots. The canonical (b) (4) used to identify Tregs was not required for release given logistical constraints (e.g., sample volume, assay timing) and supplemental supportive data.
- Regulatory considerations also included the amount of clinical experience demonstrating product efficacy for up to 72 hours to support the shelf life, as stability data alone were insufficient to confirm Treg potency stability at 72 hours. The (b) (4) Potency decline is not specific to post fill stability but is also observed based on time from apheresis collection and manufacturing time. There was no data to support minimum (b) (4) potency amount to remain effective outside the lowest level administered in the Phase 3 study. The stability study included the (b) (4) assay, which supported Treg product is functional, but the assay was not validated and only intended for extended characterization.
- The Agency exercised regulatory consideration to allow a shortened product sample retain duration based on feasibility and stability concerns of a fresh product, and not requiring the applicant to retain product samples for the standard six-month period after expiration per 21 CFR 600.13.
- Regulatory consideration was exercised in reviewing (b) (4) during manufacturing. The Applicant described that under certain circumstances, the (b) (4) may experience (b) (4) (b) (4) requiring adjustments to instrument parameters, including the (b) (4). Such parameter changes may (b) (4) (b) (4) necessitating a corresponding (b) (4) to ensure Treg DP purity. While (b) (4) are generally not ideal for process consistency, (b) (4) (b) (4) under these specific circumstances is necessary and appropriate given the complex, donor-variable nature of this manufacturing process.

Major CMC Deficiencies: Pre-Approval Resolutions and Post-Marketing Commitments

Major Deficiency 1: (b) (4) Assay Controls

What was Submitted: Redesigned (b) (4) assays with improved (b) (4)

- Enhanced SOPs with detailed work instructions and operator training programs using representative data sets including:
(b) (4)
- Comparison study of original and redesigned methods demonstrating consistency under controlled conditions to support use of historical CMC data
- Historical reanalysis of Phase 3 batch records using revised method (b) (4) approach using available in process data to replicate as closely as possible, the revised methodology, to provide assurance Phase 3, stability, and PPQ batch record data.

What remains unresolved: Implementation of reference material controls for the (b) (4) methods.

Rationale for PMC: These controls are essential to the life cycle of the assay to ensure long term consistency and use in studies to support post-marketing changes. Reference material control qualification requires substantial time to implement, and the Applicant has not yet done so. The lack of these controls poses manageable risk when paired with substantial improvements in the assay. A PMC allows the Applicant to complete this implementation and qualification of reference material post-approval while enabling earlier patient access to a therapy that now incorporates material improvements to assay rigor.

Major Deficiency 2: Analytical Method Validation

What was submitted:

- Revalidation data for:
(b) (4)

What Remains Unresolved:

- Complete validation data sets with adequate sample sizes and study design
- Intermediate precision (IP) assessment with sufficient replicates per analyst/equipment combination
- Expanded validated ranges to support range possible, and future CMC studies
- Resolution of sample failures and study design limitations identified during review
- Complete data sets not provided in study reports

Rationale for PMC:

The analytical methods validation study for (b) (4) support the analytical methods for approval based on manufacturing experience. However, the number of replicates to support validation was (b) (4) due to failures and specific analytes not meeting pre-determined acceptance criteria across batches. The Applicant also previously agreed to assess IP (b) (4) which requires qualification and implementation of relevant reference material. However, this assessment remains outstanding. Regulatory consideration took into account the risk of delaying patient access to an effective DP and continuing to ensure adequate analytical method validations in the post-approval space (e.g., full range possible based on acceptance criteria observed manufacturing ranges, future comparability studies). PMCs requiring root cause assessment and corrective actions, supplemental validation studies with adequate sample sizes and broader ranges, and intermediate precision assessments across antibody lots and days will establish a more robust analytical foundation post-approval, while allowing the natural passage of time necessary to complete these studies.

MAJOR DEFICIENCY 3: Manufacturing Consistency and Trending Concerns

What Was Submitted:

- Batch Record Reanalysis to address Major Deficiency #1 supports the leveraging of historical batch records collected with the deficit analytical method
- Trending Investigation into the trending for Treg viability, Treg potency, and Tcon viability identified correlation of (b) (4) time before conducting release testing at SAC-02.
- Trending Investigation into increased Tcon viability OOS events to demonstrate Tcon viability OOS cluster has not continued as expected, correlation with (b) (4) in time from apheresis to Tcon formulation at SAC-02
- Implementation corrective action to reduce time to release testing to be consistent with (b) (4) and additional of hold times for continue process verifications
- Interim data of (b) (4) lots from pending study supports effectiveness of corrective measures

What Remains Unresolved:

- Sufficient post-change manufacturing data to fully demonstrate that corrective measures prevent recurrence of observed trends
- Confirmation that manufacturing measures remain effective over extended production

Rationale for PMC: The corrective measures are scientifically sound and supported by interim data from (b) (4) lots demonstrating their effectiveness. Although (b) (4) lots represent a small dataset, this is reasonable given the low production frequency of a (b) (4). While all released lots remained within specification, the potential for future OOS events exists if underlying issues

are not fully resolved. A PMC requiring continued batch record monitoring, trending analysis, and (b) (4) comparison to (b) (4) data for the first two years post-approval will provide assurance that corrective measures remain effective while allowing the natural passage of time necessary to accumulate sufficient post-approval manufacturing experience. This approach balances the need for manufacturing assurance against the benefit of timely patient access

DEFICIENCY 4: Manufacturing Process Control of Treg (b) (4) at SAC-02

What was submitted:

- Updated SOPs with detailed work instructions and operator training programs with representative data sets to improve (b) (4) consistency
- Treg characterization study of sort process poorly designed (b) (4) assay method

What remains unresolved:

- Qualification of the (b) (4) assay method used to characterize the Treg population is required before repeating the Treg characterization study.
- Comprehensive Treg characterization study at SAC-02 demonstrating consistent Treg identity and purity

Rationale for PMC: Treg purity is a critical quality attribute and essential data for evaluating manufacturing consistency and supporting future comparability studies. The improved SOP and historical (b) (4) characterization provide sufficient current assurance for approval. Qualification of the (b) (4) method and completion of the characterization study require additional analytical work that need not delay patient access. A PMC requiring extended characterization at SAC-02 will establish the necessary data foundation while allowing time for assay development. The Applicant's commitment to improve the characterization assay and the availability of historical (b) (4) data provide reasonable assurance of consistency in the Treg sort process for approval. Given the risk of delaying effective therapy, regulatory consideration allowing completion of characterization studies under a PMC is appropriate.

MAJOR DEFICIENCY 5: Donor Eligibility Screening

What was submitted:

- Revised donor eligibility screening and testing to reduce the risk of transmissible disease transmission from ineligible donors.

The applicant resolved all concerns by following 12 CFR 1271.

MAJOR DEFICIENCY 6: Residual (b) (4) Quantification

What was submitted:

- Study data to quantify (b) (4) [REDACTED]
[REDACTED] in drug product supernatants using (b) (4)
- Risk assessment and safety margin analysis

The applicant resolved all concerns by providing adequate data and risk assessment.

B. RECOMMENDATION

I. APPROVAL

The CMC review team concludes that BLA 125868, with the agreed post-marketing commitments (PMCs), satisfies the CMC requirements for biological product licensure under Section 351(a) of the Public Health Service Act. The Applicant has resolved the major CMC deficiencies communicated on 26Mar2026 and agreed on 25Jun2026 to, address the remaining CMC concerns through PMCs.

Manufacturing facility:

Orca Biosystems Inc: SAC-02 Facility, 7910 Metro Air Parkway, Sacramento, CA 95837
FEI: 3035546696, DUNS 119463419

CBER Lot release:

TREGZI is exempt from CBER lot release testing and protocol review.

Post-Marketing Commitments:

The Applicant agreed to the following CMC PMCs on June 25, 2026:

(Numbering consistent with Final PMCs Letter)

2. Orca Biosystems, Inc. commits to revise and update all method validation reports for (b) (4) [REDACTED] based on the revisions requested in information requests sent April 24, 2026 to June 18, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by August 31, 2026.

Final Report Submission: August 31, 2026

3. Orca Biosystems, Inc. commits to establish a system to improve the quality and integrity of data handling for future study data. Orca Biosystems, Inc. will submit the proposal as a Product Correspondence by August 31, 2026. Orca Biosystems, Inc. will submit the implementation report as a Product Correspondence by July 31, 2027.

Proposal Submission: August 31, 2026

Final Implementation Report: July 31, 2027

4. Orca Biosystems, Inc. commits to perform a full risk assessment of the (b) (4) [REDACTED] Assay procedures and controls to evaluate the root cause of the repeatability validation parameter failures during the method validation studies performed under VAL-0178 and reported in VAL-0212. After completion of the risk and root cause assessments, as necessary, corrective actions will be proposed, justified, and implemented. Orca Biosystems, Inc. will submit the risk

assessment and, if necessary, proposed corrective actions as Prior Approval Supplement by September 30, 2026. Orca Biosystems, Inc. will submit a final study report summarizing the implemented corrective actions and, as needed, updated assay Standard Operating Procedures and/or Work Instructions as a Prior Approval Supplement by July 31, 2027.

Risk Assessment Submission: September 30, 2026

Final Report Submission: July 31, 2027

5. Orca Biosystems, Inc. commits to perform supplemental validation of the (b) (4) Assay assessing all validation parameters using a statistically justified number of new batches. The validation study will incorporate any method procedure and control changes deemed necessary by the risk assessment in PMC #3. Orca Biosystems, Inc. will submit the study protocol as Product Correspondence by December 31, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

Study Protocol Submission: December 31, 2026

Final Report Submission: July 31, 2027

6. Orca Biosystems, Inc. commits to perform supplemental validation of the (b) (4) Assays using (b) (4) to evaluate intermediate precision of the assay when (b) (4) Orca Biosystems, Inc. will submit the study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

Study Protocol Submission: September 30, 2026

Final Report Submission: July 31, 2027

7. Orca Biosystems, Inc. commits to perform supplemental validation of the following (b) (4) for the (b) (4) Assay:

(b) (4)

(b) (4)

Orca Biosystems, Inc. will submit study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

Study Protocol Submission: September 30, 2026

Final Report Submission: July 31, 2027

8. Orca Biosystems, Inc. commits to perform supplemental validation to assess all validation parameters for the (b) (4) across the range of (b) (4) unless otherwise indicated, using a (b) (4) Orca Biosystems, Inc. will establish a LOD. Orca Biosystems, Inc. will submit study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

Study Protocol Submission: September 30, 2026

Final Report Submission: July 31, 2027

9. Orca Biosystems, Inc. commits to perform supplemental validation of the (b) (4) for the (b) (4) Assay:

(b) (4)

Orca Biosystems, Inc. will submit study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

Study Protocol Submission: September 30, 2026

Final Report Submission: July 31, 2027

10. Orca Biosystems, Inc. commits to perform supplemental validation of the (b) (4) [REDACTED] to evaluate intermediate precision of the assay when (b) (4) [REDACTED] Orca Biosystems, Inc. will submit the study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

Study Protocol Submission: September 30, 2026

Final Report Submission: July 31, 2027

11. Orca Biosystems, Inc. commits to perform supplemental validation of the (b) (4) [REDACTED] to evaluate intermediate precision of the assay when (b) (4) [REDACTED] Orca Biosystems, Inc. will submit the study protocol(s) as Product Correspondence by September 30, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by July 31, 2027.

Study Protocol Submission: September 30, 2026

Final Report Submission: July 31, 2027

12. Orca Biosystems, Inc commits to the following for the first two years of commercial manufacturing:
- Submit batch production records, including in-process test results, lot release data, and characterization data quarterly.
 - Conduct extended characterization testing for (b) (4) [REDACTED] commercial-scale lots.

Orca Biosystems, Inc. will provide interim reports as Product Correspondence quarterly for 2 years after the start of commercial manufacturing. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by November 30, 2028.

Interim Report Submission: Quarterly for 2 years after start of commercial manufacturing

Final Report Submission: November 30, 2028

13. Orca Biosystems, Inc commits to conduct the following concerning the (b) (4) characterization assay:

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Orca Biosystems, Inc. will submit the revised SOPs and/or WIs as Prior Approval Supplement by September 30, 2026. Orca Biosystems, Inc. will submit the study protocol(s) as Product Correspondence by October 31, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by September 30, 2027.

Revised SOPs/Wis Submission: September 30, 2026

Study Protocol Submission: October 31, 2026

Final Report Submission: September 30, 2027

14. Orca Biosystems, Inc. commits to perform the following concerning the use of reference materials in their release assays:

- a. Qualification of reference materials for the (b) (4) [REDACTED]
[REDACTED] to establish defined operating ranges, release criteria, and acceptance limits.
- b. Revise the release method standard operating procedures (SOPs) and/or Work Instructions (WIs) to include use of the reference material for the (b) (4) [REDACTED]
[REDACTED]

Orca Biosystems, Inc. will submit the revised SOPs and/or WIs, and the final study report(s) as a Prior Approval Supplement by December 31, 2026.

Final Report Submission: December 31, 2026

15. Orca Biosystems, Inc. commits to performing a study evaluating (b) (4) [REDACTED]
[REDACTED] to revise the (b) (4) [REDACTED] assay acceptance criteria of critical (b) (4) [REDACTED] manufacturing (b) (4) [REDACTED]
[REDACTED] and release testing (b) (4) [REDACTED]

[REDACTED] Orca Biosystems, Inc. will submit the study protocol(s) as Product Correspondence by October 31, 2026. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by August 31, 2027.

Study Protocol Submission: October 31, 2026

Final Report Submission: August 31, 2027

16. Orca Biosystems, Inc. commits to providing full leachables study results using validated analytical methods for compounds identified as extractables with high-risk levels. Orca Biosystems, Inc. will submit the final study report(s) as a Prior Approval Supplement by November 30, 2026.

Final Report Submission: November 30, 2026

17. Orca Biosystems, Inc. commits to update all eCTD Module 3 sections in BLA 125868, as applicable, to incorporate changes to your submission resulting from

the interactive review process from the original BLA submission review period. The Module 3 update will include a detailed summary table of all changes with hyperlinks. Orca Biosystems, Inc. will submit the revised Module 3 as a PMC-Final Study Report by August 31, 2026.

Full Module 3 Update: August 31, 2026

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Elizabeth Lessey-Morillon, Ph.D. CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Karin Knudson, Ph.D. CBER/OTP/OCTHT/DCT1/CTB2	Concur	
Saravanan Karumbayaram, PharmD CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Ruipeng Wang, Ph.D. CBER/OTP/OCTHT/DCT1/CTB2	Concur	
Irina Tiper, Ph.D. CBER/OTP/OCTHT/DCT1/CTB1	Concur	
Melanie Eacho, Ph.D CBER/OTP/OCTHT/DCT1	Concur	

Review of CTD

Table of Contents

Module 3	32
3.2.S DRUG SUBSTANCE [T _{REG}]	33
3.2.S.1.1 – 1.3 Nomenclature, Structure, and General Properties	33
3.2.S.2 Manufacture	34
3.2.S.2.3 Control of Materials	34
3.2.S.3 Characterization	51
3.2.S.3.1 Elucidation of Structure and Other Characteristics	51
3.2.S DRUG SUBSTANCE [HSPC]	60
3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties	60
3.2.S.3 Characterization	61
3.2.S.3.1 Elucidation of Structure and Other Characteristics	61
3.2.S DRUG SUBSTANCE [T _{con}]	64
3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties	64
3.2.S.2.3 Control of Materials	65
3.2.S.3 Characterization	65
3.2.S.3.1 Elucidation of Structure and Other Characteristics	65
3.2.P DRUG PRODUCT [T _{reg}]	68
3.2.P.1 Description and Composition of the Drug Product	68
3.2.P.2 Pharmaceutical Development	68
3.2.P.2.1. Components of the Drug Product	68
3.2.P.2.2 Drug Product	69
3.2.P.2.2.2 Overages	69
3.2.P.2.3 Manufacturing Process Development	69
3.2.P.2.4 Container Closure System	110
3.2.P.2.5 Microbiological Attributes	111
3.2.P.3 Manufacture	112
3.2.P.3.1 Manufacturer(s)	112
3.2.P.3.2 Batch Formula	112
3.2.P.3.3 Description of Manufacturing Process	113
3.2.P.3.4 Controls of Critical Steps and Intermediates	123
3.2.P.3.5 Process Validation and/or Evaluation	131
3.2.P.4 Control of Excipients	145
3.2.P.4.1 Specifications	145
3.2.P.4.3 Validation of Analytical Procedures	146
3.2.P.4.6 Novel Excipient	146
3.2.P.5 Control of Drug Product	146
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)	146
3.2.P.5.1 Specifications	146
3.2.P.5.6 Justification of Specifications	148
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	154
3.2.P.5.4 Batch Analyses	190
3.2.P.5.5 Characterization of Impurities	207
3.2.P.6 Reference Standards or Materials	216

3.2.P.7 Container Closure System.....	217
3.2.P.8 Stability.....	217
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data	217
3.2.P DRUG PRODUCT [HSPC].....	224
3.2.P.1 Description and Composition of the Drug Product.....	224
3.2.P.2 Pharmaceutical Development.....	224
3.2.P.2.1. Components of the Drug Product.....	224
3.2.P.2.2 Drug Product	225
3.2.P.2.2.2 Overages	225
3.2.P.2.3 Manufacturing Process Development.....	225
3.2.P.2.4 Container Closure System	242
3.2.P.2.5 Microbiological Attributes	242
3.2.P.2.6 Compatibility	242
3.2.P.3 Manufacture	242
3.2.P.3.1 Manufacturer(s).....	242
3.2.P.3.2 Batch Formula	242
3.2.P.3.3 Description of Manufacturing Process.....	242
3.2.P.3.4 Controls of Critical Steps and Intermediates	247
3.2.P.3.5 Process Validation and/or Evaluation.....	249
3.2.P.4 Control of Excipients	253
3.2.P.5 Control of Drug Product.....	254
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s).....	254
3.2.P.5.1 Specifications.....	254
3.2.P.5.6 Justification of Specifications	256
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	261
3.2.P.5.4 Batch Analyses.....	281
3.2.P.5.5 Characterization of Impurities.....	288
3.2.P.6 Reference Standards or Materials.....	288
3.2.P.7 Container Closure System.....	288
3.2.P.8 Stability.....	289
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data	289
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment	294
3.2.P DRUG PRODUCT Tcon.....	294
3.2.P.1 Description and Composition of the Drug Product.....	294
3.2.P.2 Pharmaceutical Development.....	294
3.2.P.2.1. Components of the Drug Product.....	294
3.2.P.2.2 Drug Product	295
3.2.P.2.2.2 Overages	295
3.2.P.2.3 Manufacturing Process Development.....	295
3.2.P.2.4 Container Closure System	311
3.2.P.2.5 Microbiological Attributes	312
3.2.P.2.6 Compatibility	312
3.2.P.3 Manufacture	312
3.2.P.3.1 Manufacturer(s).....	312
3.2.P.3.2 Batch Formula	312

3.2.P.3.3 Description of Manufacturing Process.....	312
3.2.P.3.4 Controls of Critical Steps and Intermediates	319
3.2.P.3.5 Process Validation and/or Evaluation.....	322
3.2.P.4 Control of Excipients	326
3.2.P.4.1 Specifications	327
3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures	327
3.2.P.4.4 Justification of Specifications.....	327
3.2.P.4.5 Excipients of Human or Animal Origin.....	328
3.2.P.4.6 Novel Excipient.....	328
3.2.P.5 Control of Drug Product.....	328
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s).....	328
The final commercial acceptance criterion for Viable T Cell Dose is is	330
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	331
3.2.P.5.4 Batch Analyses.....	343
3.2.P.5.5 Characterization of Impurities.....	349
3.2.P.6 Reference Standards or Materials.....	349
3.2.P.7 Container Closure System.....	349
3.2.P.8 Stability.....	350
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data	350
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment	357
3.2.P DRUG PRODUCT [T _{con} Diluent]	358
3.2.P.1 Description and Composition of the Drug Product.....	358
3.2.P.2.2 Drug Product	358
3.2.P.2.2.2 Overages	358
3.2.P.2.3 Manufacturing Process Development.....	359
3.2.P.2.4 Container Closure System	359
3.2.P.2.5 Microbiological Attributes	360
3.2.P.2.6 Compatibility	360
3.2.P.3 Manufacture	360
3.2.P.3.1 Manufacturer(s).....	360
3.2.P.3.2 Batch Formula	360
3.2.P.3.3 Description of Manufacturing Process.....	360
3.2.P.3.4 Controls of Critical Steps and Intermediates	362
3.2.P.3.5 Process Validation and/or Evaluation.....	363
3.2.P.4 Control of Excipients	364
3.2.P.5 Control of Drug Product.....	364
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s).....	364
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures	367
3.2.P.5.4 Batch Analyses.....	370
3.2.P.5.5 Characterization of Impurities.....	370
3.2.P.6 Reference Standards or Materials.....	370
3.2.P.7 Container Closure System.....	371
3.2.P.8 Stability.....	372

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data	372
3.2.P.8.2 Post-Approval Stability Protocol And Stability Commitment [Tcon Diluent]	374
3.2.A APPENDICES	375
3.2.A.1 Facilities and Equipment	375
3.2.A.2 Adventitious Agents Safety Evaluation	375
3.2.A.3 Novel Excipients	378
3.2.R Regional Information (USA)	378
C. Labeling Review	378
Bag Label, primary Label	379
Carton Labels	388
Shipment Info Card	392
Full Prescribing Information (PI):	395

Tables:

Table 1. Location for Cross-Referenced DS Information	32
Table 2. Treg Nomenclature	33
Table 3. Raw Materials of Non-Biological Origin – (b) (4) Compliant	34
Table 4. Raw Materials of Non-Biological Origin – (b) (4)	34
Table 5. Raw Materials of Biological Origin	37
Table 6. Quality Criteria for (b) (4)	38
Table 7. Quality Criteria for (b) (4)	38
Table 8. Quality Criteria for (b) (4) Reagent, HUD and CR/GMP	39
Table 9. Quality Criteria for (b) (4) Reagent CR/GMP	39
Table 10. (b) (4)	43
Table 11. Samples and Reagents	44
Table 12. Method Acceptance Criteria – (b) (4)	44
Table 13. Summary of Prepared Solutions Formulated for Use in the Manufacturing of HSPC, Treg, and Tcon DPs	45
Table 14. Specifications for Incoming Apheresis	47
Table 15. CQA Analysis of Treg DP	52
Table 16. Immunophenotypic Analysis of Treg DP	54
Table 17. HSPC Nomenclature	60
Table 18. Tier 1 CQAs for the HSPC DP	61
Table 19. Tcon Nomenclature	65
Table 20. Prepared Solutions Formulated for Use in the Manufacturing of Tcon DP	65
Table 21. Extended Characterization of Tcon DP Cell Types	67
Table 22. Statistical Summary of the Tcon DP CBC Results	67
Table 23. Excipients for Treg DP	68
Table 24. Treg QTPP Elements Relevant to DP Manufacturing	70
Table 25. Treg DP Impact and Uncertainty Scoring Methodology	71
Table 26. Treg Quality Attribute Criticality and Classification	72
Table 27. Process Parameter Impact and Control Score Criteria	78
Table 28. Summary of Process Parameter Risk Assessment (Rev2.0) for Treg DP Manufacturing	79

Table 29. Summary of Process Development Studies and Established PAR for Treg DP Manufacturing Process Parameters	80
Table 30. (b) (4) Used for CD4/CD127 (b) (4)	82
Table 31. Treg DP Purity as Determined by Release Testing	87
Table 32. Summary of (b) (4) from (b) (4) Target and Non-target Populations	92
Table 33. CD4/CD127 (b) (4) Material Stability Study	96
Table 34. Summary of Hold Time Historical Data for Treg Manufacturing	99
Table 35. Summary of Treg Process Versions During Clinical Production	100
Table 36. Summary of Treg Process Versions Between Clinical and Comparability/Commercial Processes	102
Table 37. General Process Changes Between Comparability Runs and Process PPQ Runs at SAC-02	104
Table 38. Treg Manufacturing Process Changes Between Comparability Runs and PPQ Runs at SAC-02	105
Table 39. Treg DP Quality Attributes for Comparability Assessment	108
Table 40. Treg Drug Product Tier 2 Attribute Results	109
Table 41. Manufacturing and Testing Facilities	112
Table 42. Batch Formula for Treg DP	112
Table 43. CPP in Treg DP Manufacturing	123
Table 44. IPCs in Treg Manufacture	125
Table 45. PCPs in Treg DP Manufacturing	125
Table 46. Non-CPPs in Treg DP Manufacturing	126
Table 47. Control of Pre-Batch Solutions and Reagents	130
Table 48. Pre-Batch Consumables	131
Table 49. PPQ Study Conditions	132
Table 50. Treg Drug Product Quality Attributes	133
Table 51. Difference In Reported Results Treg Drug Product Quality Attributes from Legacy Method and Redesigned Method	134
Table 52. Treg Critical Process Parameters	134
Table 53. Treg In-Process Controls	135
Table 54. Revised Acceptance Criteria Compared to PPQ Criteria	135
Table 55. VAL-0427 Study Protocol Summary	138
Table 56. VAL-0428 Acceptance Criteria	138
Table 57. Summary of FACS Aria Fusion Instrument Equivalence Study Results	139
Table 58. Treg Quality Attributes Included in CPV ¹	141
Table 59. Critical Process Parameters in CPV	141
Table 60. In-Process Controls in CPV	142
Table 61. Additional Process Parameters in CPV	142
Table 62. Treg Key Performance Indicators	143
Table 63. Solution (b) (4) Validation Summary	143
Table 64. In-Process (b) (4) Validation Summary	144
Table 65. (b) (4) Excipients Used in Treg and HSPC DP	145
Table 66. Treg DP Release Specifications	147
Table 67. Changes to Proposed Treg DP Commercial Specifications	147
Table 68. Summary of Tolerance Intervals with Original and Revised Phase 3 Batch Records	148

Table 69. Potential Responses for Treg Clinical Outcomes	149
Table 70. Phase 3 OOS Batches for Treg DP Cell Count ($\times 10^6$ cells/kg).....	150
Table 71. Phase 3 OOS Batches for Treg DP (b) (4) ($\times 10^6$ cells/kg)	150
Table 72. (b) (4) Used for (b) (4) Method	156
Table 73. (b) (4) Method Performance Requirements.....	157
Table 74. Treg DP (b) (4) Assay Validation Study Results.....	159
Table 75. (b) (4) Used for Treg (b) (4) Assay	163
Table 76. Controls Used in Treg (b) (4) Method.....	164
Table 77. Cell (b) (4) Used for Treg (b) (4) Assay Validation	173
Table 78. Cell (b) (4) for Linearity, Accuracy, and Precision Assessments for Treg (b) (4) Assay.....	173
Table 79. Summary of Treg DP (b) (4) Assay Validation Protocol.....	173
Table 80. Treg DP (b) (4) Validation Study Results (1/2)	174
Table 81. Treg DP (b) (4) Validation Study Results (2/2)	175
Table 80. (b) (4) Used for (b) (4) Potency Assay	178
Table 81. Controls Used in Treg (b) (4) Potency Assay.....	179
Table 82. (b) (4) Acceptance Criteria for Treg (b) (4) Potency Assay	181
Table 83. Method Performance Requirements.....	181
Table 84. Cell (b) (4) Used for (b) (4) Potency Assay Validation	184
Table 85. Cell (b) (4) for Linearity, Accuracy, and Precision Assessments for (b) (4) Potency Assay Validation.....	184
Table 86. Summary of Treg DP (b) (4) Potency Assay Validation Protocol	185
Table 89. Treg DP (b) (4) Potency Validation Study Results (1/2).....	185
Table 90. Treg DP (b) (4) Potency Validation Study Results (2/2).....	186
Table 87. Summary Batch Records Timeline	191
Table 88. Summary of all failed lots and failures of Treg DP to meet specifications ...	192
Table 89. Treg Potency (b) (4)	203
Table 90. Treg DP Product-Related Impurities.....	208
Table 91. Theoretical Process-Related Impurity Clearance for Treg DP	210
Table 92. Summary of Process-Related Impurities Assessment for Treg DP	211
Table 93. Theoretical (b) (4) Levels.....	213
Table 94. Updated Theoretical Cumulative (b) (4) Impurities per Dose	214
Table 95. (b) (4) per cell	215
Table 95. Summary of (b) (4) Process-Related (b) (4) in Orca-T Drug Products by (b) (4) Analysis	215
Table 96. Primary Stability Batches	217
Table 97. Summary of Treg DP Storage Stability Data at $5 \pm 3^\circ\text{C}$	218
Table 98. Summary of Treg DP In-Use Stability Data at (b) (4) $^\circ\text{C}$	219
Table 99. Summary of Treg DP In-Use Compatibility Data	221
Table 100. Excipients for HSPC DP.....	224
Table 101. HSPC QTPP Elements Relevant to DP Manufacturing	225
Table 102. HSPC DP Impact and Uncertainty Scoring Methodology	226
Table 103. HSPC Quality Attribute Criticality and Classification	227

Table 104. Summary of Process Parameter Risk Assessment (Rev2.0) for HSPC DP Manufacturing	230
Table 105. Summary of Process Development Studies and Established PAR for HSPC DP Manufacturing Process Parameters	230
Table 106. Summary of Hold Time Historical Data for HSPC DP Manufacturing	231
Table 107. Summary of HSPC Process Versions During Clinical Production	231
Table 108. Summary of HSPC DP Manufacturing Process Changes Between Clinical and Comparability/Commercial	233
Table 109. Comparison of Attributes Between (b) (4) Process	236
Table 110. HSPC Quality Attributes for Comparability Assessment	238
Table 111. HSPC DP Tier 1 Attributes TOST Results	239
Table 112. (b) (4) Dose	241
Table 113. CPP in HSPC DP Manufacturing	247
Table 114. IPCs in HSPC DP Manufacturing	248
Table 115. Non-CPPs in HSPC DP Manufacturing	248
Table 116. HSPC Drug Product Quality Attributes	249
Table 117. Difference In Reported Results Treg Drug Product Quality Attributes from Legacy Method and Redesigned Method	250
Table 118. HSPC Critical Process Parameters	251
Table 119. HSPC In-Process Controls	251
Table 120: Revised Acceptance Criteria Compared to PPQ Criteria	252
Table 121. HSPC Release Specifications Additional Treg Quality Attributes be Included in CPV ¹	253
Table 122: HSPC DP Release Specifications	255
Table 123. Changes to Proposed HSPC DP Commercial Specifications	256
Table 124. Phase 3 OOS Batches for HSPC DP % Viable HSPC Cells	258
Table 125. Additional OOS Attributes for Lot (b) (4)	259
Table 126. Phase 3 OOS Batches for HSPC DP (b) (4) (b) (4) cells/kg)	259
Table 127 Phase 3 OOS Batches for HSPC DP Viable HSPC Cell Dose ($\times 10^6$ cells/kg)	260
Table . HSPC DP (b) (4) Assay Validation Study Results	262
Table 128. (b) (4) Used for (b) (4) Assay	266
Table 129. Controls Used in HSPC (b) (4) Method	267
Table 130. Method Performance Requirements	268
Table 131. Cell (b) (4) Used for HSPC DP and Tcon DP (b) (4) Assay Validation	276
Table 132. Cell (b) (4) for Linearity, Accuracy, and Precision Assessments for HSPC DP and Tcon DP (b) (4) Assay	276
Table 133. Summary of HSPC DP and Tcon DP (b) (4) Assay Validation Protocol	277
Table 140. HSPC DP and Tcon DP (b) (4) Study Results	277
Table 134. Summary of all failed lots and failures of HSPC DP to meet specifications	282
Table 135. Primary HSPC DP Stability Batches	289

Table 136. Summary of HSPC DP Storage Stability Data at $5 \pm 3^{\circ}\text{C}$	289
Table 137. Summary of HSPC DP In-Use Stability Data at (b) (4)C.....	291
Table 138. Summary of In-Use Compatibility Data	292
Table 139: Excipients for Tcon DP	295
Table 140. Tcon QTPP Elements Relevant to Drug Product Manufacturing	296
Table 141. Tcon Impact Scoring Criteria	297
Table 142. Tcon Quality Attribute Criticality and Classification	297
Table 143. Summary of Process Parameter Risk Assessment (Rev2.0) for Tcon DP Manufacturing	299
Table 144. Summary of Process Development Studies and Established PAR for Tcon DP Manufacturing Process Parameters	300
Table 145. Summary of Hold Time Historical Data for Tcon DP Manufacturing.....	301
Table 146: Summary of Tcon Process Versions During Clinical Production	302
Table 147: General Differences in Potential Tcon Source Materials	305
Table 148. Longitudinal Average Change Relative to Tcon DP, Pre-Cryopreservation	308
Table 149. Summary of Manufacturing Process Changes Between Clinical and Comparability/Commercial	308
Table 150. Tcon Quality Attributes Comparability Assessment.....	310
Table 151: Historical Data Relevant to Deriving Tcon DP PSDs.....	310
Table 152. Tcon Drug Product Tier 1 Attributes TOST Results.....	310
Table 153. Tcon Drug Product Tier 2 Attribute Results	311
Table 154. CPP in Tcon DP Manufacturing.....	319
Table 155. IPCs in Tcon DP Manufacture	320
Table 156. PCPs in Tcon DP Manufacturing.....	320
Table 157. Non-CPP for Tcon DP Manufacturing	321
Table 158: Tcon Drug Product Quality Attributes	323
Table 159. Difference In Reported Results Tcon Drug Product Quality Attributes from Legacy Method and Redesigned Method.....	323
Table 160. Tcon Critical Process Parameters	323
Table 161. Tcon In-Process Controls	324
Table 162. Revised Acceptance Criteria Compared to PPQ Criteria	325
Table 163. Tcon Release Specifications Additional Quality Attributes be Included in CPV ¹	325
Table 164. (b) (4) Excipients Used in Tcon DP	326
Table 165. (b) (4) Excipient Used in Tcon Drug Product.....	326
Table 166: Tcon DP Release Specifications	328
Table 167. Changes to Proposed Tcon DP Commercial Specifications.....	329
Table 168. Phase 3 OOS Batches for Tcon DP Viable T-cell Dose ($\times 10^6$ cells/kg)....	330
Table 169. Summary Statistics of (b) (4) Cell Count Across Analytical Method Versions	332
Table 173. Tcon DP (b) (4) Cell Count Assay Validation Study Results	333
Table 170. Controls Used in Tcon (b) (4) Method	336
Table 171. Method Performance Requirements.....	338
Table 175. Summary of all failed lots and failures of Tcon DP to meet specifications.	343

Table 176. Overlay of Original Method and Redesigned Method Data – Tcon Viability	345
Table 177. Overlay of Original Method and Redesigned Method Data – Tcon Viable T Cell Dose.....	345
Table 178. Number of Tcon OOS by Attribute,.....	346
Table 179. Theoretical Clearance for Tcon DP from (b) (4) Material	349
Table 180. Primary Tcon DP Stability Batches	350
Table 181. Summary of Storage Stability Data at < -125°C Using (b) (4) Source	351
Table 182. Summary of Storage Stability Data at < -125°C Using (b) (4) Source.....	352
Table 183. Summary of Tcon DP In-Use Stability Data at 5 ± 3°C from (b) (4) Source	354
Table 184. Summary of In-Use Stability Data at 5 ± 3°C from (b) (4) Source	354
Table 185. Summary of In-Use Compatibility Data from (b) (4) Source	355
Table 186. Summary of In-Use Compatibility Data from (b) (4) Source.....	356
Table 187. Tcon Diluent Formulation	358
Table 188. Comparison of Clinical and Commercial Material 3.2.P.2.3 Manufacturing Process Development [Tcon Diluent]	359
Table 189. Tcon Diluent Drug Product Manufacturing and Testing Facilities	360
Table 190. Batch Formula for Tcon Diluent Drug Product.....	360
Table 191. Tcon Diluent DP Preparation Process Parameters	362
Table 192. Quality Attributes (Average Values Bold in Parentheses)	362
Table 193. Critical Process Parameter.....	363
Table 194. In-Process Controls.....	364
Table 195. Specifications for Tcon Diluent Drug Product.....	364
Table 196. Summary of Method Controls.....	366
Table 197. Summary of Method Acceptance Criteria	366
Table 198. Compendial Analytical Method	366
Table 199. Summary of Validation Studies Results for Protein Concentration Determination by (b) (4) Method.....	368
Table 200. Summary of Accuracy Data from (b) (4) Standards, HSA Spiked MEI, and HSA Spiked (b) (4)	369
Table 201. Stability Conditions and Time Points	372
Table 202. Tcon Diluent Drug Product Stability Study Results.....	373
Table 203. Tcon Diluent Drug Product Stability Study Results at Accelerated Conditions (b) (4)	373
Table 204. Tcon Diluent Drug Product Stability Study Results at Optional Storage Conditions (5°C ± 3°C).....	374
Table 205. (b) (4) Specifications	376
Table 206. (b) (4) Specifications	376
Table 207. (b) (4) Specifications	376
Table 208. (b) (4) Specifications	376

Figures:

Figure 1. Results of (b) (4) for Precision-T Batches	52
--	----

Figure 2. Results of Viability for Precision-T Batches.....	52
Figure 3. Results of % Viable Treg for Precision-T Batches.....	53
Figure 4. Results of % (b) (4) Tregs for Precision-T Batches	53
Figure 5. Results of Viable Treg Cell Dose for Precision-T Batches	53
Figure 6. (b) (4) Between Treg DP and Blood from Orca-T Recipients on Day 14.....	55
Figure 7. Percent (b) (4) Tregs During Accelerated Degradation Study	56
Figure 8. (b) (4) T Cells by Treg DP but Not (b) (4) ...	57
Figure 9. (b) (4) Levels from (b) (4) Assay (b) (4) Comparing Treg DP vs. (b) (4)	57
Figure 10. (b) (4) of Treg DP during Accelerated Degradation Study	58
Figure 11. (b) (4) of Treg DP Lots.....	58
Figure 12. Survival Based on Treg DP Dose.....	59
Figure 13. Overall Survival Data for the xenoGVHD Study using Treg DP from Accelerated Degradation Study.....	60
Figure 14. Historical Data HSPC DP (b) (4) Dose (cells/kg)	62
Figure 15. Historical Data HSPC DP Viability.....	62
Figure 16. Historical Data HSPC DP % Viable HSPC Dose.....	62
Figure 17. Historical Data HSPC Drug Product (b) (4) Performance	63
Figure 18. Correlation Between Viable (b) (4) and (b) (4) Cell Dose	64
Figure 19. Historical Data Tcon DP Viability.....	66
Figure 20. Historical Data Tcon DP Viable T Cell Dose (cells/kg)	67
Figure 21. Correlation of Frequency of (b) (4) Tregs vs. (b) (4)	76
Figure 22. Correlation of Normalized Treg (b) (4) Potency vs. Hazard Ratio (Logrank Method).....	77
Figure 23. Example of (b) (4) of (b) (4) Sample	84
Figure 24. Treg Sort Process Development Methods.....	86
Figure 25. Example of Treg Purity, as Determined by (b) (4), in (b) (4), (b) (4), and Treg DP Samples.....	87
Figure 26. Correlation of (b) (4) Method for Treg Cells in (b) (4), and Treg DP Material	87
Figure 27. (b) (4)	89
Figure 28. (b) (4) Robustness and Effect on Treg DP Purity and Yield	89
Figure 29. Non-Treg T Cell Impurity Data from CPV.....	91
Figure 30. (b) (4) for (b) (4) for (b) (4) Characterization	92
Figure 31. (b) (4) Expression in (b) (4) vs. (b) (4) in (b) (4) Cells	93
Figure 32. (b) (4) Example from SOP-0431	94
Figure 33. Example of (b) (4)	98
Figure 34. Setting Target (b) (4) Population Threshold.....	99
Figure 35. Treg DP Tier 1 Attribute Equivalence Analysis.....	109
Figure 36. (b) (4) Process Flow	114
Figure 37. (b) (4) Process Flow (Part 1).....	116
Figure 38. (b) (4) Process Flow (Part 2).....	117
Figure 39. Example of (b) (4)	120

Figure 40. Setting Target (b) (4) Population Threshold.....	120
Figure 41. Treg Conditioning Process Flow	121
Figure 42. Treg Drug Product Formulation and Fill Process Flow.....	122
Figure 43. Standard (b) (4) Scheme for Analysis of (b) (4)	158
Figure 44. Treg (b) (4) Control using (b) (4) Cells.....	165
Figure 45. Example of (b) (4) for Treg DP	165
Figure 46. (b) (4) Strategy for (b) (4) Assay for Treg DP	167
Figure 47. Viability (b) (4) of Treg DP	169
Figure 48. (b) (4) Plots	170
Figure 49. Adjusting the (b) (4) on the Treg DP (b) (4)	170
Figure 50. (b) (4) Copied from (b) (4) and Final (b) (4)	171
Figure 51. (b) (4) Strategy using (b) (4) and (b) (4) for Treg (b) (4) Potency Assay	182
Figure 52. Treg Longitudinal data trending.....	193
Figure 53: Control Chart of Treg DP (b) (4) Potency.....	195
Figure 54. Control Chart for original and revised method for Treg Viability	198
Figure 55. Control Chart for original and revised method for % Treg Cells (Viable)....	199
Figure 56. Control Chart for original and revised method for Viable Treg Cell Dose...	199
Figure 57. Control Chart for original and revised method for Treg (b) (4) Potency	200
Figure 58. Comparison of Processing Times at Manufacturing Sites.....	201
Figure 59. Interim Control Chart Analysis of Treg (b) (4) Potency	202
Figure 60. Interim Control Chart Analysis of Treg Viability	203
Figure 61. Correlation of Total Process Time to Treg (b) (4) Potency.....	204
Figure 62. Correlation of Total Process Time to Treg Viability	204
Figure 63. Correlation of Process Time from End of (b) (4) to DP Sampling with (b) (4) Potency	204
Figure 64. Correlation of Process Time from End of (b) (4) to DP Sampling with Viability	205
Figure 65. Correlation of Process Time from Apheresis Collection to Process Start with (b) (4) Potency	205
Figure 66. Correlation of Process Time from Apheresis Collection to Process Start with Treg Viability	206
Figure 67. Run Chart of % viable Treg Cells	206
Figure 68. (b) (4) Strategy for (b) (4) Impurities.....	208
Figure 69. Oneway Analysis of Vein to Vein Times Versus Clinical Outcome Phase 3 Study	222
Figure 70. Oneway Analysis of Vein to Vein Times Versus Clinical Outcome Phase 1 Study	223
Figure 71. Study Results Reported by (b) (4) ANOVA.....	235
Figure 72. Study Results Reported by (b) (4) ANOVAs Formed ANOVA.....	235
Figure 73. Comparison of (b) (4)	236
Figure 74. HSPC Tier 1 Attributes Equivalence Analysis Chart	240
Figure 75. (b) (4) Analysis from Updated (b) (4) for (b) (4) Cell Dose.....	241
Figure 76: (b) (4) Process Flow.....	244
Figure 77: (b) (4) Process Flow	246

Figure 78. Fit Y by X analysis of HSPC (b) (4) vs HSPC Clinical Outcomes	257
Figure 79. (b) (4) Strategy of (b) (4) Assay for HSPC DP ...	270
Figure 80. (b) (4) of HSPC DP Using (b) (4) as a (b) (4) Control Material ...	271
Figure 81. Positive Predictor – (b) (4) of HSPC DP Using (b) (4) as a (b) (4) Control Material Place Holder	272
Figure 82. (b) (4) Adjustments of the Positive Predictor – (b) (4) for HSPC DP Purity and Viability Gating Using (b) (4) As a (b) (4) Control Material	273
Figure 83. (b) (4) Adjustments of the Positive Predictor – (b) (4) for HSPC DP Purity and Viability Gating Using (b) (4) as a (b) (4) Control Material	273
Figure 84. (b) (4) of HSPC DP Using (b) (4) as a (b) (4) Control Material	274
Figure 85. Summary of residual T cells in HSPC DP over time	282
Figure 86. HSPC Drug Product (b) (4) (cells/kg) over time	283
Figure 87. HSPC Drug Product HSPC Cell Dose over time	283
Figure 88. HSPC Drug Product Viability over time	284
Figure 89 HSPC Drug Product % Viable HSPC over time	284
Figure 90. Overlay of Original Method and Redesigned Method Data – HSPC Viability	286
Figure 91. Overlay of Original Method and Redesigned Method Data – % Viable HSPC Cells	286
Figure 92. Overlay of Original Method and Redesigned Method Data – Viable HSPC Cell Dose	287
Figure 93. Overlay of Original Method and Redesigned Method Data – HSPC (b) (4)	287
Figure 94: Distributions of (b) (4) Cellular Attributes	306
Figure 95: Equivalence of Tcon DP from (b) (4) Source Material.	307
Figure 96. Tcon Drug Product Tier 1 Equivalence Analysis	311
Figure 97: Apheresis Intake Process Flow	313
Figure 98: Overall Tcon Process Flow Diagram – Primary Pathway	314
Figure 99. Overall Tcon Process Flow Diagram – Alternative Pathway	315
Figure 100: (b) (4) Process Flow	316
Figure 101: Tcon Conditioning Process Flow	317
Figure 102: Tcon Formulation, Fill, and Cryopreservation Process Flow	318
Figure 103. Overall Freezing Program Reference	320
Figure 104. Phase 3 OOS Batches for Tcon DP Viability	329
Figure 105. Graft to Graft Performance (b) (4) Across Method Versions	332
Figure 106. (b) (4) Strategy of (b) (4) Assay for Tcon DP ...	339
Figure 107. Source Material for Manufacturing Tcon	343
Figure 108. Correlation of Process Time from Apheresis Collection to Tcon Process Start with Tcon Viability	347
Figure 109. Control Chart of Duration Between Apheresis Collection and Tcon Process Start	347
Figure 110. Statistical Analysis of Tcon Viability After Interim Action Implementation	348
Figure 111. Tcon Diluent Process Flow Diagram	361

Figure 112. Calculation of reported % Recovery	365
Figure 113: Packaging Makeup for Tcon and Diluent	379

Module 3

This memo has been updated to include the information provided in the April 24, 2026, response to Major Deficiencies (Amendment 52) and after. While not finalized, the original memo is provided in Appendix A for the complete assessment leading to identification of the Major Deficiencies and is only summarized, as needed, within this memo.

Due to the continuous manufacturing process of all three DS into DP, some of the DS information is referenced to either the Treg DS section or the corresponding DP section. See **Table 1**

Table 1. Location for Cross-Referenced DS Information

eCTD Module	Treg DS Information Location	HSPC DS Information Location	Tcon DS Information Location
3.2.S.2.1 (Manufacturers)	3.2.P.3.1 (Treg)	3.2.P.3.1 (Treg)	3.2.P.3.1 (Tcon)
3.2.S.2.2 (Description of Manufacturing Process and Process Controls)	3.2.P.3.3 (Treg)	3.2.P.3.3 (HSPC) and 3.2.P.3.3 (Treg)	3.2.P.3.3 (Tcon)
3.2.S.2.3.1 (Apheresis Starting Material)	3.2.S.2.3.1 (Treg)	3.2.S.2.3.1 (Treg)	3.2.S.2.3.1 (Treg)
3.2.S.2.3.2 (Raw Materials)	3.2.S.2.3.2 (Treg)	3.2.S.2.3.2 (Treg)	3.2.S.2.3.2 (Treg)
3.2.S.2.4 (Control of Critical Steps and Intermediates)	3.2.P.3.4 (Treg)	3.2.P.3.4 (HSPC) and 3.2.P.3.4 (Treg)	3.2.P.3.4 (Tcon)
3.2.S.2.5 (Process Validation and/or Evaluation)	3.2.P.3.5 (Treg)	3.2.P.3.5 (Treg)	3.2.P.3.5 (Tcon)
3.2.S.2.6 (Manufacturing Process Development)	3.2.P.2.3.2 (Treg)	3.2.P.2.3.2 (HSPC)	3.2.P.2.3.2 (Tcon)
3.2.S.3.2 (Impurities)	3.2.P.5.5 (Treg)	3.2.P.5.5 (HSPC)	3.2.P.5.5 (Tcon)
3.2.S.4.1 (Specifications)	3.2.P.5.1 (Treg)	3.2.P.5.1 (HSPC)	3.2.P.5.1 (Tcon)
3.2.S.4.2 (Analytical Procedures)	3.2.P.5.2 (Treg)	3.2.P.5.2 (HSPC)	3.2.P.5.2 (Tcon)
3.2.S.4.3 (Validation of Analytical Procedures)	3.2.P.5.3 (Treg)	3.2.P.5.3 (HSPC)	3.2.P.5.3 (Tcon)
3.2.S.4.4 (Batch Analysis)	3.2.P.5.4 (Treg)	3.2.P.5.4 (HSPC)	3.2.P.5.4 (Tcon)
3.2.S.4.5 (Justification of Specifications)	3.2.P.5.5 (Treg)	3.2.P.5.5 (HSPC)	3.2.P.5.5 (Tcon)
3.2.S.5 (Reference Standards or Materials)	3.2.P.6 (Treg)	3.2.P.6 (HSPC)	3.2.P.6 (Tcon)
3.2.S.6 (Container Closure)	3.2.P.7 (Treg)	3.2.P.7 (HSPC)	3.2.P.7 (Tcon)
3.2.S.7.1 (Stability Summary and Conclusions)	3.2.P.8.1 (Treg)	3.2.P.8.1 (HSPC)	3.2.P.8.1 (Tcon)
3.2.S.7.2 (Post Approval Stability Protocol and Stability Commitments)	3.2.P.8.2 (Treg)	3.2.P.8.2 (HSPC)	3.2.P.8.2 (Tcon).
3.2.S.7.3 (Stability Data)	3.2.P.8.3 (Treg)	3.2.P.8.3 (HSPC)	3.2.P.8.3 (Tcon)

Reviewer generated table

3.2.S DRUG SUBSTANCE [T_{REG}]

Due to the continuous manufacturing process of all three DS into DP, some of the DS information is referenced to the corresponding DP section. See **Table 1** for the location of Treg DS information not provided within this section.

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

This section is reviewed by KK.

Table 2. Treg Nomenclature

Company code	Orca-T Regulatory T Cells (Treg)
Proper name/ Non-proprietary name:	Allogeneic regulatory T cell-based immunotherapy with HSPC and T cells-vldq
Proprietary name:	TREGZI
Other names:	Regulatory T cell, Treg, Treg drug substance, (b) (4) CD3+CD4+CD25+CD127-/low cells, (b) (4)
UNII:	Leukocyte antigen matched allogeneic human regulatory T cells: UU6Y78RSG6

Reviewer generated table

Reviewer comment:

- **Proper name/Non-proprietary name:** A USAN was not assigned to TREGZI, as it is a minimally-manipulated product. CBER has assigned a multi-word non-proprietary name of “allogeneic regulatory T cell-based immunotherapy with HSPC and T cells-vldq.” CMC review team does not object to APLB’s determination that the suffix “-vldq” is acceptable.
- **Proprietary name:** CMC review team does not object to APLB’s determination that “TREGZI” is acceptable.
- **Established pharmacologic class (EPC):** The Applicant’s proposal of “allogeneic stem cell and T-cell immunotherapy derived from an HLA-matched donor” is overly broad and not specific enough for a Treg product with HSPC and Tcon components. The CMC review team recommends the following for the EPC: “Allogeneic regulatory T cell-based immunotherapy with hematopoietic stem and progenitor cells and T cells.”

(b) (4)

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

(b) (4)

3.2.S.3.1.3. Immunophenotyping of the Treg DP

The critical findings in this section are related to **Major Deficiency #4**.

Treg subset phenotyping by evaluation of (b) (4) was obtained during the analytical comparability study, summarized in section 3.2.P.2.6 [Treg]. (b) (4) were considered Tier 2 attributes and provide a profile of Tregs' developmental state and functionality.

Table 16. Immunophenotypic Analysis of Treg DP

Attribute	(b) (4): Comparability Batches (n= (b) (4)) Mean (Range, %CV)
(b) (4) (% of Viable Treg)	(b) (4)
(b) (4) (% of Viable Treg)	(b) (4)
(b) (4) (% of Viable Treg)	(b) (4)

Reviewer generated table based on data in Table 7 "Treg Drug Product Tier 2

Attribute Results" in eCTD section 3.2.P.2.3.3 Comparability Assessments

Reviewer comment: Given the identified issues with the conduct of (b) (4) assays for product release, the reliability/accuracy of these data is not known. As (b) (4) is the canonical (b) (4) used to identify Treg cells, and it is necessary for product characterization, this assay should be, at minimum, qualified.

In the Major Deficiency communication sent 26Mar2026, the Applicant was informed that the (b) (4) process and resulting (b) (4) population (i.e., the population that will be formulated into the Treg DP) were not adequately characterized. The deficiency comment specified that the Applicant should qualify the (b) (4) assay prior to further characterization of the (b) (4) process and (b) (4) material. The Applicant submitted the (b) (4) assay qualification results and (b) (4) assay SOPs/WIs in Amendment 52 (24Apr2026) in response to the Major Deficiency email sent 26Mar2026 and Amendment 59 (15May2026) in response to CMC IR #24 sent 12May2026, respectively. However, review of the (b) (4) assay SOPs/WIs identified critical issues with the sample (b) (4) and data analysis protocols. Thus, the (b) (4) assay qualification results were not reviewed, as they cannot be assessed until the fundamental flaws in the assay methodology are resolved. Appropriate characterization of the Treg DP, which is necessary to evaluate of manufacturing consistency post-licensure, remains unresolved.

PMC #13 establishes the Applicant's commitment to (1) revise the (b) (4) assay SOPs/WIs, (2) appropriately qualify the (b) (4) assay, and (3) perform extended characterization of the Treg DP throughout the manufacturing process.

PMC #12 establishes the Applicant's commitment to perform extended characterization testing, including evaluation of (b) (4), for (b) (4) commercial-scale lots.

3.2.S.3.1.4. Functional Characterization of the Treg DP

(b) (4) methods were used to interrogate Treg DP function: (b) (4)

How each assay contributes to the functional characterization of the Treg DP is summarized below.

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

3.2.S.3.1.1 Historical Data Analysis of HSPC Critical Quality Attributes (CQAs)

The Applicant's characterization of HSPC quality attributes is provided in Table 18. The characterization is based on (b) (4) lots manufactured between (b) (4) (b) (4) which includes (b) (4) grafts from Phase 1b and (b) (4) grafts manufactured at the (b) (4) and (b) (4) facilities for the Phase 3 clinical studies. The following attributes are also depicted graphically for (b) (4) (Figure 14), Viability (Figure 15), % Viable HSPC (Figure 16), (b) (4) (Figure 17).

Reviewer Comment: The characterization to support use of (b) (4) related attributes and HSPC DP is adequate.

Table 18. Tier 1 CQAs for the HSPC DP

Category	Attribute
Identity	HSPC Phenotype
Strength	(b) (4)
Purity	Viability
Purity	% Viable HSPC
Potency	Viable HSPC Cell Dose (b) (4)
Potency	(b) (4)

Reviewer generated table based on Table 1 in eCTD section 3.2.S.3.1 Elucidation of Structure and Other Characteristics [HSPC]

HSPC Phenotype

HSPCs conventional molecular phenotype is defined as (b) (4) and CD34+ by (b) (4) (b) (4), which distinguishes the cells as being (b) (4)

(b) (4)

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

Figure reproduced from Figure 4 in eCTD 3.2.S.3.1 Elucidation of Structure and Other Characteristics [HSPC]

Reviewer comment: The analysis of historical clinical lot CQAs indicates a consistent manufacturing process and efficient control systems.

3.2.S.3.1.2 Extended Characterization

The primary MOA of HSPCs is driven by their capacity for self-renewal and differentiation into all blood cell lineages, including erythroid, myeloid, and lymphoid cells, to repopulate bone marrow microenvironment. The functional potential of HSPCs is determined based on their ability to proliferate and differentiate, as measured by (b) (4) Assays and total number viable HSPCs per kilogram of recipient body weight (viable HSPCs/kg dose). The (b) (4) was used for lot release during the Phase 3, Precision -T study, shown in Figure 17. Correlation of (b) (4) with dose is shown in Figure 18.

(b) (4)

(b) (4)

Figure reproduced from Figure 10 in eCTD 3.2.S.3.1 Elucidation of Structure and Other Characteristics [HSPC]

(b) (4)

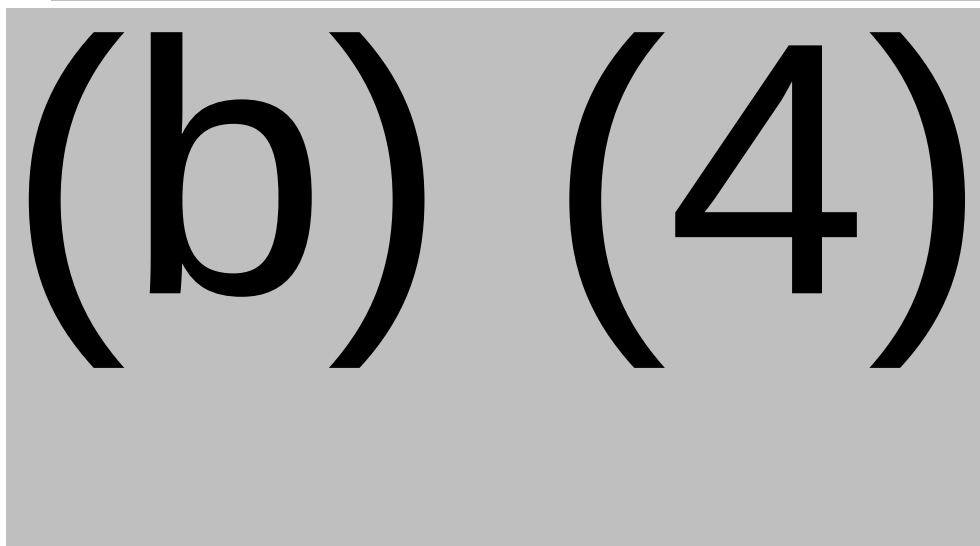


Figure reproduced from Figure 11 in eCTD 3.2.S.3.1 Elucidation of Structure and Other Characteristics [HSPC]

Reviewer Comment: The Applicant's justification for removing (b) (4) as a post-release measurement for HSPC is based on these data, historical knowledge of HSPC DP dosing and clinical outcomes for (b) (4) cells in transplant settings, and manufacturing using the (b) (4) system without further processing that impacts (b) (4) cell behavior or function. (b) (4) results are only available post-administration. Removal of this post-release test after the Phase 3 study was agreed to during the IND. Because the results would only be obtained post release, and the manufacturing is considered minimal manipulation using an FDA-approved device without required product testing before administration, removal of this assay for commercial product is acceptable.

Overall Reviewer's Assessment of Section 3.2.S.3.1:

While the historical data provided is impacted by the (b) (4) -based deficiencies, the data here are acceptable for use as characterization data. See section 3.2.P.5.4 [HSPC] of this memo for discussion concerning the reanalysis of Phase 3 batch records.

(b) (4)

[Redacted text block]

[Redacted text block]

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and Other Characteristics

This section is reviewed by EL.

See section 3.2.P.2.3.2.1 [Tcon] for a detailed comparison of the Tcon DP from apheresis material and (b) (4)

Tcon DP is defined based on its molecular phenotype of (b) (4) CD3+. The Tcon is comprised of (b) (4). The characteristics of Tcon are based on their ability to provide a donor-derived immune T-cell repopulation to mediate graft-versus-infection (GVI), and possibly graft-versus-leukemia (GVL) effects.

3.2.S.3.1.1 Historical Data Analysis of Tcon Critical Quality Attributes (CQAs)

The characterization of quality attributes of the Tcon DP was performed by analyzing a total of (b) (4) grafts manufactured between (b) (4), which included (b) (4) grafts from Phase 1b and (b) (4) grafts from Phase 3 clinical studies. The quality attributes are also depicted graphically for viability (Figure 19) and Viable T Cell Dose (Figure 20).

Tcon Phenotype

Tcons conventional molecular phenotype is defined as (b) (4) and CD3+ by (b) (4).

Viability

The historical data analysis showed low variability, with (b) (4) of the batches having viability above the established acceptance criterion. Historical data shown in Figure 19.

(b) (4)

(b) (4)

Figure reproduced from Figure 2 in eCTD section 3.2.S.3.1 Elucidation of Structure and Other Characteristics [Tcon]

Viable T Cell Dose

Only (b) (4) of (b) (4) clinical batches analyzed (less than (b) (4) of manufactured batches) did not meet the viable T cell dose acceptance criterion during clinical production.

(b) (4)

(b) (4)

Figure reproduced from Figure 4 in eCTD section 3.2.S.3.1 Elucidation of Structure and Other Characteristics [Tcon]

Reviewer comment: The analysis of historical clinical lot CQAs indicates a consistent manufacturing process and efficient control systems.

3.2.S.2.3.1.2 Extended Characterization of Tcon DP Cell Types

The Applicant evaluated (b) (4) Tcon DP batches from the Phase 1b and Phase 3 Precision T study. The characterization data in Table 21 is expected, given that the starting material from apheresis material from G-CSF mobilized donors. The Tcon DP is comprised of immune cells with low frequency of HSPCs, supporting the need to enrich the HSPC for generation of the HSPC DP.

Table 21. Extended Characterization of Tcon DP Cell Types

(b) (4)

Table reproduced from Table 2 in eCTD section 3.2.S.3.1 Elucidation of Structure and Other Characteristics [Tcon]

Reviewer Comment: The Applicant's extended characterization for the Tcon is reasonable.

(b) (4)

(b) (4) of Tcon DP prior to cryopreservation was performed on (b) (4) clinical Tcon DP batches using a (b) (4). The results are in in Table 22 and indicate general hematological health and immune competence of the Tcon DP.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.S.3.1:

While the historical data provided is impacted by the (b) (4) -based deficiencies, the data here is sufficient to support characterization of the Tcon DP. For discussion of the reanalysis of Phase 3 batch records, see section 3.2.P.5.4 [Tcon] of this memo.

3.2.P DRUG PRODUCT [T_{reg}]

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

This section is reviewed by KK.

Treg DP is a single cell suspension of purified Treg cells (surface phenotype: (b) (4) CD4+CD25+CD127-/low cells) formulated in multiple electrolytes injection, Type 1, (b) (4) (MEI) + 2% (w/v) human serum albumin (HSA) at a (b) (4) of approximately (b) (4). Treg DP is formulated in a volume of approximately 100 mL to contain enough cells for a patient dose of 1.3×10^6 to 3.5×10^6 Tregs cells/kg. Treg DP is filled into industry standard (b) (4) (b) (4) bags, stored at 2-8°C, and shipped fresh to be administered IV in its entirety on day 0. The Treg DP is administered immediately after the HSPC DP.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1. Components of the Drug Product

This section is reviewed by KK.

This information is provided in eCTD section 3.2.P.2 [Treg] and document 3.2.P.2.1 of the submission.

3.2.P.2.1.1 Drug Substance

The active ingredient in the Treg DS and DP is the same, live Treg cells (surface phenotype: (b) (4) CD4+CD25+CD127-/low) purified from G-CSF-mobilized peripheral blood from an HLA-matched donor. The Treg DS composition is provided in section 3.2.S.1.3 [Treg] and the Treg DS characterization is in section 3.2.S.3.1 [Treg].

Treg DS is immediately formulated into Treg DP, eliminating the need for DS storage.

Reviewer comment: The identified phenotype of the Treg cells aligns with the scientific literature. This is acceptable.

3.2.P.2.1.2 Excipients

Table 23. Excipients for Treg DP

Component	Concentration	Final Concentration	Function
-----------	---------------	---------------------	----------

Albumin (Human) (b) (4) Solution, (b) (4)	(b) (4)	2% (v/v)	Stabilizer
Multiple Electrolytes Injection (MEI) Type 1, (b) (4)	1X	To 100 mL	Isotonic Solution

Reviewer generated table based on Table in eCTD section 3.2.P.3.2 Batch Formula [Treg]

□ 3.2.P.2.1.2.1 Excipient Selection Rationale

Multiple Electrolytes Injection (MEI) Type 1, (b) (4): MEI, Type 1, (b) (4) grade, is a sterile, nonpyrogenic, isotonic solution of balanced electrolytes in water for injection. The solution is administered by IV infusion for parenteral replacement of acute losses of extracellular fluid. The electrolyte composition closely reflects normal human plasma (extracellular fluid). (b) (4) can be used for Treg formulation.

Human Serum Albumin (HSA), (b) (4) HSA is used as an excipient to protect the cells in the DP by (b) (4)

It acts as a (b) (4)

. It effectively mimicks the natural conditions of the bloodstream, where albumin is naturally present in high concentrations.

Reviewer Comment: The excipients selected are supported by similar usages for other cell therapy products. The excipients are acceptable.

□ 3.2.P.2.1.2.2 Compatibility of the DP with Excipients

The compatibility of the DP to the excipients is reviewed in the stability studies in section 3.2.P.8 [Treg].

3.2.P.2.2 Drug Product

This section is reviewed by KK.

This information is provided in eCTD 3.2.P.2 [Treg] and document 3.2.P.2.2 of the submission.

3.2.P.2.2.1 Formulation Development

Treg DP is formulated by delivering the appropriate volume of Treg DS into the final container closure system and adding MEI, Type 1, (b) (4) + 2% (w/v) HSA to a final volume of 100 mL. No significant changes have been made to the Treg DS or DP formulation, dosage, or primary container closure during product development, and the proposed commercial formulation is the same as used in the pivotal clinical study.

3.2.P.2.2.2 Overages

No overage is provided for Treg DP. Treg DP is provided in a single dose infusion bag intended to be delivered in its entirety.

3.2.P.2.2.3 Physicochemical and Biological Properties

Reviewed in section 3.2.S.3.1 [Treg] of this memo.

3.2.P.2.3 Manufacturing Process Development

3.2.P.2.3.1 Control Strategy Development

This section is reviewed by KK.

This information is provided in eCTD 3.2.P.2 [Treg] and document 3.2.P.2.3.1 [Treg] of the submission.

The goal of the process control strategy is to identify and control the quality attributes which impact the quality target product profile (QTPP). The process control strategy includes control of parameters which impact the quality attributes, in-process controls (IPCs), and attribute testing to directly measure and monitor the quality attributes of the manufactured DPs.

□ 3.2.P.2.3.1.1 Identification of Critical Quality Attributes

3.2.P.2.3.1.1.1 Treg DP Quality Target Product Profile (QTPP)

A QTPP was created based on the intended effects of the Treg DP and describes attributes that ensure the quality, safety, and efficacy of the product. Elements that were considered to create the QTPP include: the target efficacy, composition, intended use, route of administration, dosage forms, delivery systems, mechanism of action, dosage strength, container closure system, pharmacokinetics, stability requirements, quality attributes, safety profile, and other physical attributes.

Table 24. Treg QTPP Elements Relevant to DP Manufacturing

Category	Description
Dosage	Between a specified lower and upper bound of viable Treg cells per kg delivered intravenously, once, on Day 0, after HSPC infusion
Active Ingredient Composition	The specific target cell population of the Treg DP is: (b) (4) CD4+ CD25+ CD127low/-
Description	Treg DP is provided as single-dose in (b) (4) (b) (4) bags with a fill volume of 100 mL
Formulation	Selected cells, MEI (Type 1, (b) (4)), and 2% (w/v) HSA, at a (b) (4)
Cell Viability	(b) (4) cells must be substantially viable at the time of administration
Purity	No less than minimum specified % viable Tregs of (b) (4) CD4+ CD25+ CD127-/low phenotype (% of viable Treg within (b) (4) fraction)
Potency	• Within a specified range of (b) (4) cells per kg; AND • Within a specified range of viable Treg (product of % viable Treg and (b) (4) cells/kg); AND • Within a specified range of (b) (4) Treg stimulation (b) (4)
Identity	Positively identified via appropriate cell phenotyping
Appearance	No obvious visual anomalies and conforms to pre-determined color, opacity, packaging, and labels
Product-related cellular impurities and apheresis residuals	(b) (4)
Process-related impurities and reagent residuals	(b) (4) • Leachables at levels justified or determined to be safe
Particulates	• Cellular debris from (b) (4) at levels determined or justified to be safe. • Visible and subvisible particles at levels determined to be safe

Table adapted from Table in eCTD section 3.2.P.2.3.1 Control Strategy Development [Treg]

Reviewer comments: The Treg DP attributes are based on general scientific knowledge of Tregs and (b) (4) transplants. This is acceptable.

3.2.P.2.3.1.1.2 Treg DP Critical Quality Attribute Risk Assessment and Designation

A comprehensive risk ranking and filtering exercise was performed to rank each quality attribute to create a comprehensive list of Tier 1, Tier 2, and Tier 3 quality attributes for the Treg DP. The tiering system is used to inform, including but not limited to, the comparability strategy, process validation, process control strategy, and attribute testing strategy.

- Tier 1: Critical to the QTPP (high criticality, CQA) and must be controlled. Certain attributes related to general composition, appearance, and safety are considered obligatory Tier 1 quality attributes.
- Tier 2: Lower impact to the QTPP than Tier 1 and should be assessed to determine the appropriate control and testing strategies.
- Tier 3: Minimal/negligible impact to the QTPP and low criticality.

To evaluate the list of potential quality attributes and rank them for criticality, a CQA risk assessment was performed using impact scores (potential severity of impact to safety and efficacy) and uncertainty scores (level of information on the attribute at the time of assessment). The impact and uncertainty scores were based on platform/product knowledge, in vitro data, non-clinical in vivo data, and/or clinical experience.

Table 25. Treg DP Impact and Uncertainty Scoring Methodology

Impact Score	Impact to Immune Tolerance Prevention of GVHD and Safety	Uncertainty Score ¹	Minimum Level of Information Available for Attribute
16 (High)	• Acute GVHD (Steroid Refractory Grade 3-4) • Severe chronic GVHD • Irreversible adverse events	5 (High)	No information available.
8 (Medium)	• Acute GVHD (Steroid Responsive Grade 3-4) • Moderate chronic GVHD • Moderate but reversible adverse events	4 (Medium)	Some relevant peer-reviewed literature leveraging <i>in vitro</i> data.
4 (Low)	• Minor impact to Treg functionality, but GVHD is not expected • Minimal or manageable adverse events	3 (Low)	• Internal non-clinical or <i>in vitro</i> data • Peer-reviewed literature leveraging <i>in vitro</i> data with broad consensus • Emerging clinical data across a moderate range but no edge of failure elucidated
2 (Lowest)	• No changes observed • No impact to patient outcome		

¹ Uncertainty scores may be further modified (e.g., reduced) in the presence of substantial information or data from any source that can be considered relevant in the absence of clinical data, as justified by subject matter experts.

Adapted from Tables 2 and 3 in eCTD section 3.2.P.2.3.1 Control Strategy Development [Treg]

Reviewer comment: Scoring CQA impact separately for each drug product (HSPC, Tcon, Treg) likely underestimates overall risk, given the complexity of the treatment

regimen and undefined interactions among the three products. For example, HSPC CQAs may affect Treg efficacy, and Treg:Tcon dose ratios may influence GVHD development; however, these cross-product effects on clinical response are not adequately addressed in the assessment.

The overall criticality score (“Impact” x “Uncertainty”) was used to classify each quality attribute into the three tiers (Tier 1 (high) = >24, Tier 2 (medium) = 10-24, Tier 3 (low, negligible) = <10). High impact quality attributes are always classified as Tier 1 regardless of uncertainty score, while the lower impact quality attributes can be classified as Tier 2 or Tier 3 depending on uncertainty score. There was no ranking for safety attributes, including sterility, endotoxin adventitious agents, as they are required to be Tier 1 attributes.

Table 26. Treg Quality Attribute Criticality and Classification

NOTE: Criticality Score = Impact × Uncertainty. Tier 1 (score >24): High criticality, must be controlled. Tier 2 (score 10-24): Medium criticality. Tier 3 (score <10): Low criticality.

Category	Attribute	Criticality Score ¹ (Impact x Uncertainty) / Tier	Classification Rationale
Safety	Sterility	NA / Tier 1	Obligatory safety attribute
	Endotoxin	NA / Tier 1	Obligatory safety attribute
	Adventitious Agents	NA / Tier 1	Obligatory safety attribute
Identity	Treg phenotype	NA / Tier 1	Obligatory attribute
	Donor/patient match	NA / Tier 1	Obligatory attribute
Appearance	Physical State	NA / Tier 1	Obligatory attribute
	Clarity	NA / Tier 1	Obligatory attribute
	Color	NA / Tier 1	Obligatory attribute
	Cell Aggregates	NA / Tier 1	Obligatory attribute
	Visible Foreign Particles	NA / Tier 1	Obligatory attribute
	Headspace	NA / Tier 1	Obligatory attribute
	Container Integrity	NA / Tier 1	Obligatory attribute
Composition	MEI Concentration	NA / Tier 1	Obligatory attribute
	HSA Concentration	NA / Tier 1	Obligatory attribute
	(b) (4)	NA / Tier 1	Obligatory attribute
	Cell Concentration	NA / Tier 1	Obligatory attribute
	Volume	NA / Tier 1	Obligatory attribute
Potency	Activation of Tregs (b) (4)	32 (16 x 2) / Tier 1	• (b) (4)

	Potency Method)		(b) (4)
	Viable Treg Dose (Viable Tregs/kg)	32 (16 x 2) / Tier 1	- See section 3.2.P.2.3.1.1.3 [Treg] for additional information. - Viable Treg dose directly correlates with total potent cell dose - Attribute is a combination of purity (Treg phenotype) and strength (total (b) (4) cell dose).
	Treg (b) (4)	32 (16 x 2) / Tier 1	See section 3.2.P.2.3.1.1.3 [Treg] for additional information.
Strength (Dose)	(b) (4) Dose	32 (16 x 2) / Tier 1	(b) (4) cell dose likely correlates with total potent cell dose in Treg DP - Correlation observed between (b) (4) dose, potency, and purity
Purity – Non-Target Apheresis	% Viability relative to all (b) (4)	32 (16 x 2) / Tier 1	- Cell viability recognized as indicator of cell health - Low viability decreases the available dose and increases the number of non-viable cells dosed
	Non-Treg T cell Impurity	32 (16 x 2) / Tier 1	- Residual viable donor conventional T cells are necessary for development of GVHD 1:1 ratio of Treg to Tcon required to prevent GVHD (i.e., dose dependent control of GVHD). - Minimizing the number of viable Tcons in the Treg DP minimizes the risk of GVHD in Treg/Tcon supplemented HSPC transplants
Purity – Target Cells	% Viable Treg Purity (% Viable Treg Cells)	24 (8 x 3) / Tier 2	- Key attribute for calculation of target cell dose but more critical to control specific impurities % viable Treg purity is not as meaningful since efficacy is greater modulated by potency and dose - No correlations between % viable Treg (b) (4) and clinical efficacy observed - See reviewer comment below.
	(b) (4)	16 (8 x 2) / Tier 2	(b) (4)
	(b) (4)	12 (4 x 3) / Tier 2	(b) (4)

Purity – Non-Target Apheresis	(b) (4)	12 (4 x 3) / Tier 2	(b) (4)
	(b) (4)	24 (8 x 3) / Tier 2	(b) (4)
	(b) (4)	16 (8 x 2) / Tier 2	(b) (4)
	(b) (4)	12 (4 x 3) / Tier 2	(b) (4)
	(b) (4)	16 (8 x 2) / Tier 2	(b) (4)
	(b) (4)	12 (4 x 3) / Tier 2	(b) (4)
	(b) (4)	24 (8 x 3) / Tier 2	(b) (4)
	(b) (4)	12 (4 x 3) / Tier 2	(b) (4)

Purity – Process Related	Extractables and Leachables	16 (4 x 4) / Tier 2	- Compounds identified in the extractables study are Tier 2 attributes if the calculated theoretical worst-case dose is above the PDE - Classification is re-assessed after a leachables study is conducted and assessed against the PDE
--------------------------	-----------------------------	---------------------	---

¹ No scoring is performed for obligatory Tier 1 attributes (i.e., general composition, appearance, and safety)

Table adapted from Table 4 in eCTD section 3.2.P.2.3.1 Control Strategy Development [Treg].

Reviewer comment: The obligatory Tier 1 attributes are acceptable. Frequency of (b) (4) Treg (activation of Treg), viable Treg dose, (b) (4) dose, frequency of viable (b) (4) cells, and frequency of viable Treg cells are important measurements of product identity, quality, and potency and should be included as Tier 1 attributes and as a part of release testing.

The severity scores of the product-related impurities (e.g., (b) (4)) are acceptable. Both product- and process-related impurities are reviewed under section 3.2.P.5.5 [Treg] of this memo.

The Applicant states that frequency of viable Treg is a Tier 2 attribute since, based on clinical development, there is no correlation between the result and clinical efficacy. However, it is logical to expect that a less pure Treg DP could impact the development of GVHD, as the resulting cellular impurities are more likely to be conventional T cells which are the main drivers of GVHD. Of note, the same markers used to identify Tregs (i.e., (b) (4) CD4+CD25+CD127-/lo) may also identify (b) (4) . To fully evaluate the frequency of Tregs in the DP, an assessment of (b) (4) which is the canonical (b) (4) essential for Treg development, lineage commitment, and immunosuppressive function, is necessary. After further optimization and qualification of the (b) (4) assay, as agreed to under PMC #13, the Applicant should reassess the correlation between frequency of viable Treg and clinical efficacy.

It is acceptable that the (b) (4) (b) (4), and frequency of (b) (4), which are identified as Tier 1 or Tier 2 attributes, are not included in routine release testing, due to limited sample availability and time constraints. However, these assessments should be included as a part of process qualification or comparability studies, due to their potential effect on Treg DP quality and potency.

In addition, due to ongoing concerns questions regarding SAC-02 manufacturing consistency, which were included as a Major Deficiency in the communication sent 26Mar2026, PMC #12 establishes the Applicant's commitment to perform extended characterization testing, including evaluation of (b) (4), for (b) (4) commercial-scale lots.

3.2.P.2.3.1.1.3 Treg DP Potency CQA and Assay Selection

This information is provided in eCTD 3.2.S.3.1 [Treg] of the submission. This information is included in this memo section as it applies to potency-associated CQA

justification and potency testing included as a part of Treg DP release (i.e., use of post-stimulation CD69 expression for Treg DP potency release testing).

Three methods were used to interrogate Treg DP function and potency, as described in detail in section 3.2.S.3.1.4 [Treg] of this memo:

- (b) (4)

Figure 1. The effect of the number of trials on the mean accuracy of the responses. The error bars represent the standard error of the mean. The asterisks indicate significant differences between the two conditions ($p < .05$, Wilcoxon signed rank test).

(b) (4)

(b) (4)

(b) (4)

A large rectangular area of the document is redacted with a solid gray fill. The redaction covers approximately the top half of the page content.

(b) (4)

(b) (4)

A large rectangular area of the document is redacted with a solid gray fill. The redaction covers approximately the bottom half of the page content, starting below the first redacted block and ending above the footer.

□ **3.2.P.2.3.1.2 Process Parameter Risk Assessment**

After quality attribute classification was performed for the three cellular DPs (see memo section 3.2.P.2.3.1.1.2 [Treg], section 3.2.P.2.3.1.1.2 [HSPC], and section

3.2.P.2.3.1.1.2 [Tcon]), a list of all process parameters (PP) was created. A risk assessment was performed to determine the variability of (b) (4) PP and potential impact of each PP to each Tier 1 and Tier 2 quality attribute (i.e., both Tier 1 and Tier 2 attributes considered CQAs for the risk assessment). Potential critical process parameters (CPP) were identified. No parameter impact was assessed for Tier 3 attributes, as they were deemed to have negligible risk to DP safety or quality.

In addition to work instructions (WIs), standard operating procedures (SOPs), and subject matter expert (SME) knowledge, a failure modes and effects analysis (FMEA) risk assessment was performed to evaluate the severity, occurrence, and detection of potential failure modes. The identification of failure modes was performed by systemic evaluation of process instructions, past deviations, SME discussions, and failure to meet PP ranges.

Table 27. Process Parameter Impact and Control Score Criteria

Impact Score	Impact of PP to Tier 1 or Tier 2 CQA ¹	Control Score ²	Control Score Criteria
16 (High)	• Severe effect	4 (None/Minimal)	• Poorly controlled • Expected to be outside the desired, meaningful range (b) (4) batches OR no controlled range has been determined.
8 (Medium)	• Moderate effect	3 (Low)	• Moderately controlled AND/OR no direct process data available • Expected to be outside the desired, meaningful range (b) (4) batches.
4 (Low)	• Minimal effect	2 (Medium)	• Well controlled, not directly supported with process data • All “2” scores of 2 must be justified with clear rationale for why it is expected to be well controlled (e.g., industry knowledge, indirect process data supporting level of control). Indirect vs. direct process data may be acceptable.
2 (None/Minimal)	• No effect	1 (High/Effective)	• Well controlled, directly supported with process data from (b) (4) batches • A well-controlled parameter is expected to be outside the desired, meaningful range (b) (4) batches ^b

¹ Both Tier 1 and Tier 2 attributes are considered CQAs for the purposes of the parameter classification assessment

² If process instructions only list a target for the parameter, the approximate range is (b) (4) from that target, unless otherwise justified.

Table adapted from Table 2 and Table 3 in eCTD section 3.2.P.2.3.1 Control Strategy Development [Treg]

The overall criticality score (“Impact” x “Control”) was used to classify each quality attribute into potential (p)CPP (≥ 16) or non-CPP (<16), noting:

- The impact to Tier 1/2 quality attributes carries more weight than control in this analysis.
- The cutoff of total criticality score (16) was determined to ensure all parameters with high impact to Tier 1/2 quality attributes are classified as pCPPs.

- A parameter with low control score and medium or low impact is not deemed necessary to hold the pCPP classification.
- Parameters with high control score and low impact are classified as pCPPs.
- Parameters with no or minimal impact are always non-CPPs.

A total of (b) (4) PP were analyzed in the initial assessment (Revision 1.0), with (b) (4) PP designated as pCPPs (b) (4) and (b) (4) PP as non-CPP (b) (4). After development work and historical data analysis (summarized in [section 3.2.P.2.3.1.3 \[Treg\]](#), the initial risk assessment was reviewed to rescore all of the pCPPs and create a list of confirmed CPPs and non-CPPs (Revision 2.0). The final risk assessment evaluated a total of (b) (4) PP, with (b) (4) PP designated as CPP (b) (4) and (b) (4) PP as non-CPP (b) (4). A summary of the final PP risk assessment and PP classification is shown in Table 28.

Reviewer comment: Table 28 is a list of all pCPP that were further investigated for establishment as CPP or Non-CPP. It is a non-inclusive list of Non-CPP and thus may not recapitulate the Non-CPP listed in [section 3.2.P.3.4.1 \[Treg\]](#) and [section 3.2.P.3.4.4 \[Treg\]](#).

Table 28. Summary of Process Parameter Risk Assessment (Rev2.0) for Treg DP Manufacturing

Unit Operation	Process Parameter	Criticality Score Rev 2.0 (Impact x Control)	PP Criticality
----------------	-------------------	--	-------------------

(b) (4)

(b) (4)

□ **3.2.P.2.3.1.3 Process Development and Characterization by Unit Operation**

Process characterization studies were conducted to better understand the process and confirm the criticality of various pCPPs. The characterization studies either confirmed the PP as critical or non-critical, depending on the observed impact to product CQAs. The proven acceptable range (PAR) was established based on study data or historical data analysis of ^(b) ₍₄₎ Phase 1b/Phase 3 batches manufactured between ^(b) ₍₄₎ ^(b) ₍₄₎ using tolerance intervals, as required.

Table 29. Summary of Process Development Studies and Established PAR for Treg DP Manufacturing Process Parameters

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

❑ **3.2.P.2.3.1.4 In-Process Hold Times**

The DP process has no defined hold points due to continuous manufacturing, but in-process materials may be transiently held during the manufacturing process. (b) (4)

(b) (4)

(b) (4)

□ **3.2.P.2.3.1.5 Process Control Strategy**

The Treg DP process control strategy involves control of:

- Critical process parameters (CPPs) – see [section 3.2.P.3.4.1 \[Treg\]](#)
- Non-critical process parameters (Non-CPPs) - [section 3.2.P.3.4.4 \[Treg\]](#)
- In-process controls (IPCs) – see [section 3.2.P.3.4.2 \[Treg\]](#)
- Key performance indicators (KPIs) – see [section 3.2.P.3.4.3 \[Treg\]](#)
- DP release testing – see [section 3.2.P.5.1 and 3.2.P.5.2 \[Treg\]](#)
- Continued process verification (CPV) testing – see [section 3.2.P.3.5.3 \[Treg\]](#).

The process control strategy was assessed for robustness through the performance of PPQ studies, as described in [section 3.2.P.3.5.2 \[Treg\]](#).

3.2.P.2.3.2 Process History and Process Changes

This section reviewed by KK.

This information is provided in eCTD 3.2.P.2 [Treg] and document 3.2.P.2.3.2 [Treg] of the submission.

□ **3.2.P.2.3.2.1 Treg DP Process Development at (b) (4) During Phase 1b and Phase 3 Trials**

The initial Treg DP manufacturing process was based on protocols from (b) (4)

(b) (4). The manufacturing process was initiated at the (b) (4) (Process Version (b) (4)), and then (b) (4)

(b) (4) to support IND 18873. (b) (4) were used during the clinical manufacture of Treg DP (Phase 1b and Phase 3) under IND 18873.

(b) (4) SAC-02, the proposed commercial manufacturing facility. A summary of the clinical process versions and changes to Treg DP manufacturing is in Table 35.

Table 35. Summary of Treg Process Versions During Clinical Production

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

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

(b) (4)



Adapted from Table 1 in eCTD section 3.2.P.2.3.2 Process History and Process Changes [Treg].

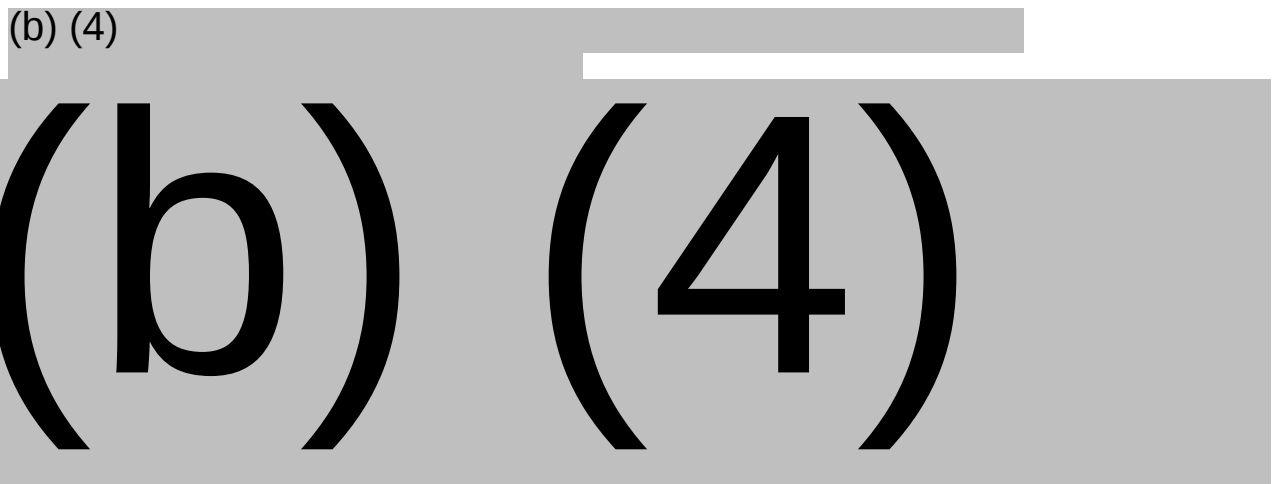
□ **3.2.P.2.3.2.2 Treg DP Commercial Process Development at SAC-02**

The DP manufacturing process^{(b) (4)}
commercial manufacturing facility SAC-02. In general, the process improvements implemented at SAC-02 pertain to the facility or are operational in nature. (b) (4)

There are no major changes to collection and shipment of apheresis starting materials, process flow/steps, reagents, process volumes, cell concentrations, or process temperatures. A summary of the clinical^{(b) (4)} and proposed commercial SAC-02^{(b) (4)} processes, specifically those processes that were changed, is shown in Table 36.

A comparability study between the two sites was completed. See section 3.2.P.2.3.3 [Treg].

(b) (4)



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

(b) (4)

(b) (4)

□ **3.2.P.2.3.2.3 Post-Comparability Process Development**

A gap assessment was conducted post-comparability to document additional modifications to the SAC-02 GMP process. All changes were documented using the change control system. Table 37 describes the general changes to the electronic batch record (eBR) between comparability and process performance qualification (PPQ) runs. These changes are applicable to all three cellular DPs. Table 38 includes Treg manufacturing process changes.

Reviewer Comment: The Applicant refers to post-comparability changes, which does not mean (b) (4) manufacturing at SAC-02, as it was initially assumed. These are changes that were included after completion of the (b) (4) comparability study in late Phase 3 lots and once manufacturing was initiated (b) (4).

Table 37. General Process Changes Between Comparability Runs and Process PPQ Runs at SAC-02

(b) (4)

(b) (4)



*Table adapted from Table in eCTD section 3.2.P.2.3.2 Process History and Process Changes [Treg]
Reviewer comment: Most general process changes are related to process improvement and compliance with CGMP for commercial manufacturing. All post-comparability general process changes are acceptable.*

Table 38. Treg Manufacturing Process Changes Between Comparability Runs and PPQ Runs at SAC-02

(b) (4)



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

(b) (4)

Table adapted from Table 5 in eCTD section 3.2.P.2.3.2 Process History and Process Changes [Treg]

Reviewer Comment: All Treg process changes are unlikely to affect the quality of the final Treg DP, with the exception of the introduction of the (b) (4) step (see section 3.2.P.2.3.2.2.2 [HSPC] of this memo. In addition, the established process changes are unlikely to affect comparability between clinical and commercial DP. The reanalysis of Phase 3 batch records with the revised method is reasonable, and there are no additional concerns regarding product comparability (b) (4).

□ 3.2.P.2.3.2.4 Treg DP Analytical Development History

The following changes were made (b) (4) prior to initiation of the Phase 3 study:

- Percent Viable Treg Cells: % Treg cells, without accounting for viability, was reported during the Phase 1b study. For the Phase 3 study purity specification, % Viable Treg cells was calculated by multiplying the % Treg Purity by (b) (4). (b) (4) is a comparable measure of Treg viability because of the high purity of target cells in the Treg drug product.
- Treg Cell Dose: Treg Cell Dose, without accounting for viability, was reported during the Phase 1b study. For the Phase 3 study purity specification, Viable Treg Cell Dose was calculated by multiplying the Treg Cell Dose by (b) (4). (b) (4) is a comparable measure of Treg viability because of the high purity of target cells in the Treg drug product.

Reviewer comment: Inclusion of a measurement of viability in the calculation of Treg DP purity and dose is justified. The changes to the analytical methods for purity and dose are acceptable.

As part of the Phase 3 filing submitted to IND 18873, following changes were made to the specifications for Treg DP:

- Visual inspection was included in the lot release
- A specification for strength as (b) (4) Cell Dose was added with acceptance criterion of $1.6 - (b) (4) \times 10^6$ cells/kg.
- The Total Treg Cell Dose was updated to Viable Treg Cell Dose to account for percent viability and acceptance criterion was updated from $(b) (4) \times 10^6$ cells/kg to $1.6 - (b) (4) \times 10^6$ cells/kg.
- The Purity specification of % Treg Cells was updated to account for % viability and changed to be % Viable Treg Cells with the same acceptance criterion of (b) (4).
- The acceptance criterion for (b) (4) potency was updated from (b) (4) (b) (4) after a review of data from (b) (4) manufactured lots.
- Treg DP expiry was updated from 72 hrs to (b) (4) hrs after end of apheresis collection to reduce the likelihood that the infusion would be delayed.

Reviewer comment: The acceptability of these changes are discussed [section 3.2.P.5.6 \[Treg\]](#) and [section 3.2.P.5.8 \[Treg\]](#) of this memo

3.2.P.2.3.3 Comparability Assessments

This section is reviewed by EL. This information is provided in eCTD 3.2.P.2 [Treg] and document 3.2.P.2.3.3 [Treg] of the submission.

Manufacturing of the product (b) (4) SAC-02 to meet the anticipated commercial demand. To establish comparability, the Applicant conducted a prospective (b) (4) evaluation of (b) (4) SAC-02 using (b) (4) batches of (b) (4), representative of the apheresis starting material for the DP manufacturing process. All three cellular products were evaluated in the study. (b) (4) of ancillary materials and excipients were used for each (b) (4) manufacturing run. Test samples were transferred to (b) (4) for testing.

An equivalence test with matched-pairs two one-sided test (TOST) was used to establish equivalence. The Tier 1 CQAs selected include release criteria CQAs and Tier 2 characterization attributes. The prospective acceptance criteria were based on practically significant difference limits (PSDs) of these selected attributes and consider both manufacturing history and safety/efficacy of the DPs. The PSD for each comparability attribute represents a difference of two standard deviations from the mean of historical clinical manufacturing experience. The results are provided in Table 39.

Table 39. Treg DP Quality Attributes for Comparability Assessment

Category	Comparability Attribute	Assay
Safety (Tier 1)	14-Day Sterility	(b) (4)
	(b) (4)	
	Endotoxin	
Tier 1 Attributes (PSD criteria)	(b) (4) Viability	(b) (4)
	% Viable Treg Cells	
	(b) (4)	
	(b) (4)	
	(b) (4)	
	Potent Treg Dose	
	(b) (4)	(b) (4)
Tier 2 Attributes (Report only)	(b) (4)	(b) (4)

Table adapted from Table 1 in eCTD section 3.2.P.2.3.3 Comparability Assessments [Treg]

(b) (4)

(b) (4)

Figure reproduced from Figure 1 in eCTD section 3.2.P.2.3.3 Comparability Assessments [Treg]

Reviewer Comment: The Applicant's approach to establishing comparability is acceptable. The approach uses (b) (4) manufacturing of a single lot and then lot release testing at (b) (4) samples. The Applicant is assessing (b) (4) lots, which is reasonable for a matched one-lot product, which is consistent with current regulatory considerations. The study protocol was determined to be acceptable under the IND.

The impact of the deficiencies in (b) (4) analytical methods, as outlined in section 3.2.P.5.2 and 3.2.P.5.3 [Treg] of this memo, on the comparability has been considered. The reanalysis of Phase 3 batch records with the revised method is reasonable and does not raise additional concerns regarding product comparability between (b) (4) SAC-02.

(b) (4)

(b) (4)

(b) (4)

Table reproduced from Table 7 in eCTD section 3.2.P.2.3.3 Comparability Assessments [Treg]
Reviewer Comment: This extended panel provides additional data evaluating the isolated populations at (b) (4) SAC-02. This provides supportive data that the overall purity of the populations remains the same. The Applicant will need to collect extended characterization data as a PMC in addition to reporting under CPV.

See PMC #12.

3.2.P.2.4 Container Closure System

This section is copied from consult review and review summary by Dr. Mona Mansouri (CBER/OTP/OCTHT/DCT1/CTTB).

The Treg DP is filled into (b) (4) 150 mL (b) (4) (b) (4) bags (b) (4), catalog number (b) (4) at a target fill volume of 100 mL. This Class II medical device, manufactured by (b) (4) received FDA 510(k) clearance (b) (4) in (b) (4) as a container for collection and processing of blood and blood components. The container is constructed of (b) (4) (b) (4) and holds approximately 100 mL of product that appears off-white, white, yellow, orange, to red in color with a (b) (4). The container closure system was selected based on its compatibility with the DP formulation (MEI Type 1, (b) (4) + 2% HSA), suitability for refrigerated storage at 2-8°C, and established use in similar cell therapy products. The bag features integrated tubing with a luer lock connector that is heat-sealed after product filling and sampling. The vendor has (b) (4) tested the bag following ISO (b) (4) standards, demonstrating it (b) (4) and maintains sterility throughout the 72-hour shelf-life post-apheresis collection. The filled bag is packaged in a secondary sterile resealable (b) (4) bag for protection during refrigerated storage and shipment in validated (b) (4) temperature-controlled shippers. Storage stability at 5 ± 3°C has been demonstrated by monitoring cell concentration, viability, (b) (4) potency, (b) (4) assay, and sterility; viability ranges from (b) (4) at formulation and declines to (b) (4) at 72 hours post-apheresis collection (PAC), with an in-use stability of (b) (4) after removal from cold storage. Extractable/leachable data and container closure integrity testing are discussed in Module 3.2.P.2.4 (Treg).

Reviewer's Comment: The information provided regarding Treg's container closure system is adequate. Additional details are provided in the consult reviewer's memo.

3.2.P.2.5 Microbiological Attributes

Assessment of the microbiological attributes is deferred to DMPQ. Please refer to the review memo by Hector Carrero (CBER/OCBQ/DMPQ/MRB2).

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

The reanalysis of Phase 3 batch records with the revised method is reasonable and no additional concerns regarding control strategy development were identified.

(b) (4)



(b) (4)

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

This section is reviewed by KK. This information is provided in eCTD 3.2.P.3.1 [Treg] of the submission.

Commercial Treg DP will be manufactured in its entirety and tested at Orca Biosystems, Inc. SAC-02 Facility.

Table 41. Manufacturing and Testing Facilities

Name	Address	FEI	DUNS	Responsibility
Orca Biosystems Inc. SAC-02 Facility	7910 Metro Air Parkway Sacramento, CA 95837	3035546696	119463419	DS and DP Manufacturing DP Packaging and Labeling DP Release and Stability Testing

DUNS = Data Universal Numbering System

FEI = FDA Establishment Identifier

Adapted from Table 1 in eCTD section 3.2.P.3.1. Manufacturer(s) [Treg]

3.2.P.3.2 Batch Formula

This section is reviewed by KK. This information is provided in eCTD 3.2.P.3.2 [Treg] of the submission.

Table 42. Batch Formula for Treg DP

Component	Quality Standard	Amount
Treg DS	In house	1.3E6 to 3.5E6 viable Treg per patient kg
Albumin (Human) (b) (4) Solution	(b) (4)	2% (v/v)

Multiple Electrolytes Injection (MEI) Type 1	(b) (4)	To 100 mL
--	---------	-----------

Adapted from Table 1 in eCTD section 3.2.P.3.2 Batch Formula [Treg]

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

The information provided is acceptable. No CMC deficiencies identified.

3.2.P.3.3 Description of Manufacturing Process

This section is reviewed by EL or KK, as indicated below. This information is provided in eCTD 3.2.P.3.3 [Treg] of the submission.

The Treg DP is manufactured from a (b) (4) apheresis material from a single donor. The Treg DP manufacturing begins after the Tcon DP and HSPC DP manufacturing steps, outlined in section 3.2.P.3.3 [HSPC] and section 3.2.P.3.3 [Tcon].

□ 3.2.P.3.3.4.3 Apheresis Intake

This section is reviewed by EL. This information is provided in eCTD 3.2.P.3.3.4.3 [Treg] of the submission.

(b) (4) apheresis bags are shipped to the manufacturing and refrigerated until manufacturing begins. See section 3.2.P.3.3.4.3 [Tcon] of this memo for detailed summary of the apheresis intake.

(b) (4)

(b) (4)

(b) (4)

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

□ 3.2.P.3.3.4.9. Treg Formulation and Fill

This section is reviewed by KK. This information is provided in eCTD 3.2.P.3.3.4.9 [Treg] of the submission.

Figure 42. Treg Drug Product Formulation and Fill Process Flow

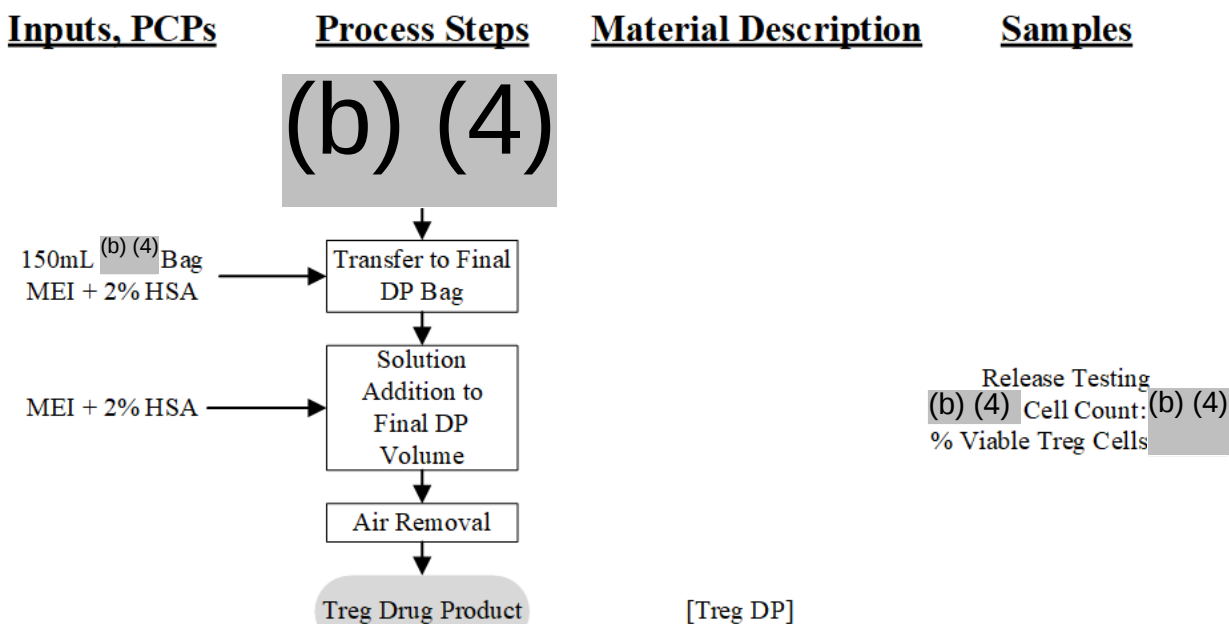


Figure reproduced from Figure 11 in eCTD section 3.2.P.3.3 Description of Manufacturing Process and Process Controls [Treg]

1. The [Treg DS] material is transferred (b) (4) into the 150 mL transfer bag, which is the final DP container closure.
2. The final volume in the bag is brought to a target volume with MEI + 2% HSA and confirmed by (b) (4). Air is removed from the Treg DP container using (b) (4), and all samples for testing are removed using a (b) (4). Lastly, the tubing of the Treg DP container is heat sealed closed.
3. The Treg DP is visually inspected. (b) (4)
 - a. If (b) (4) are still visible, a note is added to the batch record and chain of custody form with details of the visual observation.
4. Labels are applied, and the final container (primary bag) is placed into a secondary sterile resealable (b) (4) bag.

3.2.P.3.4 Controls of Critical Steps and Intermediates

This section is reviewed by KK. This information is provided in eCTD 3.2.P.3.3 [Treg] and 3.2.P.3.4 [Treg] of the submission.

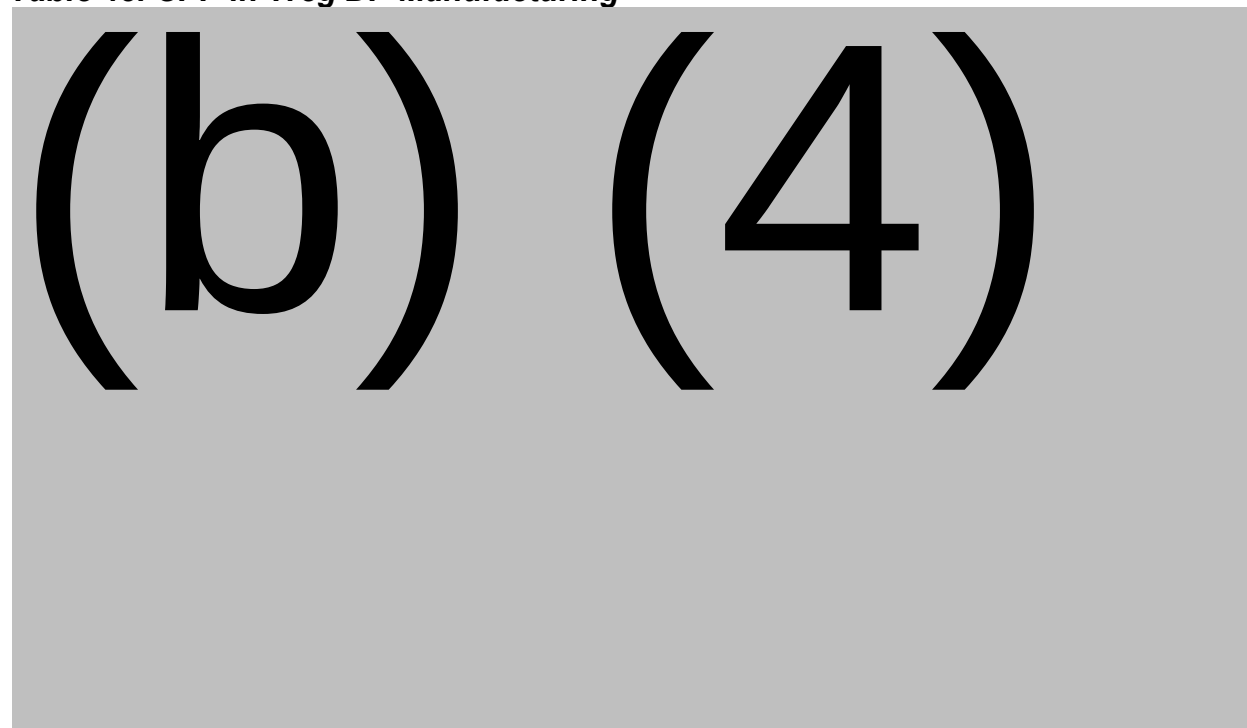
The manufacturing of Treg DP is a continuous process from initiation to formulation with limited hold times. The process control strategy involves the use of:

- Critical process parameters (CPPs): Process parameters whose variability has an impact on CQAs and should be monitored or controlled to ensure the process produces the desired product quality.
- In-process controls (IPCs): Checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the product conforms to its specifications.
- Process control points (PCPs): Points in the manufacturing process when an individual step within a unit operation has multiple defined processing scenarios. PCPs are primarily used to determine which process scenario best fits the material, given expected variability in the starting apheresis material, through use of a controlling measurement from the same or prior unit operation.
- Key performance indicators (KPIs): KPIs are used to track the performance of the process but are not tied to product quality.
- DP quality attribute testing: See [section 3.2.P.5.1 \[Treg\]](#).

3.2.P.3.4.1 Critical Process Parameters (CPPs)

Treg DP CPPs were determined using a quality risk ranking and filtering approach (see [section 3.2.P.2.3.1.2 \[Treg\]](#)) and are summarized in Table 43.

Table 43. CPP in Treg DP Manufacturing

A large gray rectangular area covering the table content, indicating that the information has been redacted. The redaction is marked with the text "(b) (4)" in large black font.

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

(b) (4)

(b) (4)

3.2.P.3.4.4 Non-Critical Process Parameters (Non-CPPs)

Non-CPP are not established conditions (ECs) but are included as supportive information to describe the manufacturing information at an appropriate level of detail. For most non-CPPs, a normal operating range (NOR) is used, which represents the region around the target operating conditions that contain common operation variability.

(b) (4)

(b) (4)

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

□ (b) (4)
(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.3.5 Process Validation and/or Evaluation

This section is reviewed by EL and KK. This information is provided in eCTD 3.2.P.3.5 [Treg] of the submission.

The Applicant evaluated all three components as part of their process validation strategy. The process validation studies provided by the Applicant are:

- Process performance qualification (PPQ)
- Continued Process Verification (CPV)
- (b) (4) validation
- Solution and consumables hold validations
- Aseptic process simulation (APS)
- Shipping validation of the HSPC DP with the Treg DP

3.2.P.3.5.2 Process Performance Qualification

This section is reviewed by EL.

Reviewer comment: This section has been updated to include reanalysis results reported in eCTD 1.11.1 Quality Information Amendment from Amendment 52 (24Apr2026).

The critical findings in this section are related to **Major Deficiency #4**, as communicated on 26Mar2026.

(b) (4)

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

(b) (4)

3.2.P.4 Control of Excipients

This section is reviewed by SK.

All DPs are formulated with multiple electrolytes injection (MEI), Type 1, and human serum albumin (HSA). List of compendial excipients is shown in Table 65.

Table 65. Compendial Excipients Used in Treg and HSPC DP

Excipient	Supplier	(b) (4)	Reference
HSA (Human) (b) (4) Solution, (b) (4)	(b) (4)	(b) (4)	Manufactured from human plasma units collected in US plasmapheresis centers licensed by FDA
Multiple Electrolytes Injection, Type 1, (b) (4) (MEI)	(b) (4)	(b) (4)	

Table adapted from Table 1 in eCTD sections 3.2.P.4.1 Specifications [Treg] and 3.2.P.4.1 Specifications [HSPC]

^a (b) (4) are considered equivalent and have both been qualified as a DP excipient.

The Treg DP contains only (b) (4) excipients. The Treg and HSPC DPs contain the same (b) (4) excipients.

(b) (4) is approved by FDA for clinical use (intravenous infusion).

Human Albumin (b) (4) Solution (b) (4) is FDA licensed (US License Number (b) (4) to manufacture and prepare plasma derivatives for sale and usage as an excipient.

(b) (4) (Multiple Electrolytes Injection, Type 1, (b) (4)) is a FDA approved sterile, nonpyrogenic isotonic solution for intravenous administration. It contains no antimicrobial agents.

(b) (4) is indicated for replacement of acute extracellular fluid volume losses in surgery, trauma, burns or shock and as an adjunct to restore a decrease in circulatory volume in patients with moderate blood loss.

3.2.P.4.1 Specifications

Multiple Electrolytes Injection: Identity testing is performed by (b) (4), and the excipient meets (b) (4) identity tests for (b) (4). The Applicant verifies the labeling for (b) (4).

3.2.P.4.2 Analytical Procedures

All excipients used in the manufacture Treg are compendial.

3.2.P.4.3 Validation of Analytical Procedures

The (b) (4) excipients conform to the standards outlined in the (b) (4). No validation of the analytical procedures is needed.

3.2.P.4.4 Justification of Specifications

Multiple electrolytes injection (MEI) is a (b) (4) excipient, manufactured under cGMP guidelines and testing conforms to (b) (4).

Human serum albumin (HSA) is a (b) (4) excipient, manufactured under cGMP guidelines and testing conforms to (b) (4).

DMSO is a (b) (4) excipient, manufactured under cGMP guidelines and testing conforms to (b) (4).

Reviewer Comment: The justification of specification for (b) (4) excipients is acceptable.

3.2.P.4.5 Excipients of Human or Animal Origin

Except for HSA, none of the other excipients are sourced from human or animals. HSA is a (b) (4) excipient, manufactured under cGMP guidelines and testing conforms to (b) (4).

3.2.P.4.6 Novel Excipient

There are no novel excipients used in the Treg or HSPC DPs.

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

The information provided is acceptable, with no deficiencies 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)

This section is reviewed by EL.

Reviewer comment: This section has been updated using data from eCTD section 3.2.R Regional Information document "RPT-0342- JUSTIFICATION OF COMMERCIAL SPECIFICATION FOR ORCA-T" in Amendment 52 (24Apr2026).

3.2.P.5.1 Specifications

The Treg DP specifications are listed in Table 66. The specifications from the Phase 3 study and the PPQ study for the following parameters were adjusted based on clinical data: (b) (4) Cell Dose, Viable Treg Cell Dose, % Viable Treg Cells and (b) (4) Potency.

Table 66. Treg DP Release Specifications

Test Attribute	Analytical Method	Commercial Acceptance Criteria	Clinical Acceptance Criteria	PPQ Acceptance Criteria
(b) (4) Viable Cell Dose	(b) (4) Cell Count	1.3E6 to 3 ^{(b) (4)} E6 cells/kg	(b) (4) cells/kg	(b) (4) cells/kg
Treg Phenotype	Treg (b) (4) Method	Treg detected	Treg detected	Treg detected
Viability	Treg (b) (4) Method	(b) (4)		
% Viable Treg Cells	Treg (b) (4) Method	(b) (4)		
Viable Treg Cell Dose	Calculation: Product of % Viable Treg Cells and (b) (4) Cell Dose	1.3E6 to 3.5E6 cells/kg	(b) (4) cells/kg	(b) (4) cells/kg
(b) (4) Potency	(b) (4) Potency	(b) (4)		
Appearance	(b) (4) Visual Inspection of Injection	Clear to opaque liquid Color is off-white, white, yellow, orange, to red No visible foreign particles No defects	Clear to opaque liquid Color is off-white, white, yellow, orange, to red No visible foreign particles No defects	Clear to opaque liquid Color is off-white, white, yellow, orange, to red No visible foreign particles No defects
Interim Sterility Assurance	(b) (4) Microbial Characterization, Identification, and Strain Typing – (b) (4)	No organisms detected	No organisms detected	No organisms detected
Sterility ^a	(b) (4) Sterility Tests (14-Day)	No organisms detected (Post administration results)	No organisms detected (Post administration results)	No organisms detected (Post administration results)
Endotoxin	(b) (4) Bacterial Endotoxins Test	(b) (4)		

Reviewer generated table

^a The product is released based on interim assurances of sterility with final (b) (4) -based sterility results available after administration

The proposed changes to Treg DP specifications are provided in Table 67. The determination of the final acceptance criterion is discussed below with the justification of specifications.

Table 67: Changes to Proposed Treg DP Commercial Specifications

Test Attribute	Final Acceptance Criterion	(b) (4)
(b) (4) Cell Dose	1.3E6 to 3 ^{(b) (4)} E6 cells/kg	

% Viable Treg Cells	(b) (4)	(b) (4)
Viable Treg Cell Dose	1.3E6 to 3.5E6 cells/kg	
(b) (4) Potency	(b) (4)	

Reviewer Generated Table

Reviewer Comment: In Amendment 68 (16Jun2026), the Applicant agreed to the proposed specifications sent in CMC IR #32 (16Jun2026). This is acceptable. See discussion of the final acceptance criteria for each specification below.

3.2.P.5.6 Justification of Specifications

Release testing data from all Treg DP lots produced over the course of development were analyzed. This includes batches for the Precision T Phase 1b and Phase 3 studies ((b) (4) Batches), as well as lots produced for other physician-led clinical studies based out of Stanford, with a total of (b) (4) batches with the original batch reported results. The Treg DP Potency measurement was implemented for Phase 3 and therefore has fewer lots.

Following method update to address Major Deficiency #1, described in QCCR-2026-0065 in Amendment 52 (24Apr2026), the historical data was reanalyzed. See [section 3.2.P.5.4 \[Treg\]](#). The Applicant provides a comparison of the original and reanalyzed historical data in Table 68. The Applicant chose not to revise the justification for specification because of overlap with the original range.

Table 68. Summary of Tolerance Intervals with Original and Revised Phase 3 Batch Records

Drug Product	Attribute	Original Methods Tolerance Interval	Updated Methods Tolerance Interval
Treg	Viability (%)	(b) (4)	(4)
	% Viable Treg Cells (%)		
	(b) (4) Cell Dose (x1E6 cells/kg)		
	Viable Treg Cell Dose (x1E6 cells/kg)		
	Potency (%)		
HSPC	Viability (%)		
	% Viable HSPC Cells		
	(b) (4)		
	(b) (4) Cell Dose		
	Viable HSPC Cell Dose		
Tcon	Viability		
	Viable T-cell Dose		

Table reproduced Table 9 "Summary of Differences Between Original and Updated Method Data" in eCTD section 3.2.R Regional Information document "RPT-0342 rev. 04" from Amendment 52 (24Apr2026)

Reviewer Comment: See [section 3.2.P.5.4 \[Treg\]](#) for discussion of the reanalysis of the historical data.

(b) (4)

□ **Treg Cell Dose**

The tolerance interval is $1.3 - 3.5 \times 10^6$ cells/kg. The total range of data analyzed for clinical outcome correlations was (b) (4) $- 3.5 \times 10^6$ cells/kg. With no correlation with

clinical outcomes observed, the Applicant's proposed acceptance criterion is based on the tolerance interval analysis results of (b) (4) – 3.5×10^6 cells/kg.

(b) (4)

The final commercial acceptance criterion for Treg Cell Dose is $1.3 - 3.5 \times 10^6$ cells/kg.

Reviewer Comment: Based on clinical experience to demonstrate effectiveness, the acceptance criterion should be $1.3 \times 10^6 - 3.5 \times 10^6$ based on Phase 3 data. The Applicant proposed 3.5×10^6 for the upper limit, they have experience up to (b) (4) $\times 10^6$. In Amendment 68 (16Jun2026) the Applicant agreed to use 1.3×10^6 as the lower limit as sent in CMC IR #32 (16Jun2026), which is acceptable. Early negotiations mistakenly proposed an upper limit of (b) (4) $\times 10^6$, which was revised to 3.5×10^6 in Amendment 70 (received 26Jun2026).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

□ Treg Phenotype

The purpose of the Treg phenotype assay is to confirm the identity of the active cells of interest in the DP by molecular phenotype. The cell surface markers used to identify the Treg phenotype are (b) (4) CD4+CD25+CD127-/low. The acceptance criterion is based on Treg cells being present.

COI/COC is also used to establish product identity, which is appropriate for a patient-specific product. COI/COC starts with the identification of the donor starting material and is maintained through the manufacturing and shipping process, until administration at the transplant center using product specific identifiers.

Reviewer Comment: This specification is redundant because Treg dose and % viable Treg cells provide a quantitative measurement of the total number and % Treg population. While this specification will distinguish the Treg DP from the HSPC and Tcon DPs, it is not able to differentiate between independent Treg lots. No other products are manufactured at the SAC-02 facility.

To ensure identity, the Applicant also relies on COI/COC. The COI/COC applies to all three DPs. The patient identifiers used for COI are consistent with those already in use with tracking HSCT. The COI/COC was reviewed during PLI inspection with no concerns identified.

□ Viability

The tolerance interval using both the original and updated methods is (b) (4). The total range of data analyzed for clinical outcome correlations was (b) (4). There was no correlation observed between viability and the Treg clinical outcomes (cGVHD, cGFS, and aGVHD34). However, there was a significant difference between Death vs Grade 3 or 4 aGVHD outcome when correlated with viability, seen in **Error! Reference source not found.** The Applicant provides rationale as to why higher Treg DP viability is unlikely to increase the risk of death over aGVHD. In addition, they state that the observed significance is more likely a result of small number of subjects in each group and the range of viability observed in the clinical studies. The proposed acceptance criterion is (b) (4) to align with the Phase 3 specifications.

The final commercial acceptance criterion for Viability is (b) (4).

Reviewer comment: The proposed acceptance criterion is below the experience from the Phase 3 study. However, we agree that there is not a significant safety risk to establish the acceptance criterion at (b) (4), and this lower acceptance criterion is not a stability concern. The Treg DP dosing is based on viable cells and the risk from non-viable cells in the DP is balanced against the benefit of the product. Also, due to limited alternative treatments and with the patients undergoing myeloablative conditioning, we

agree to set the commercial acceptance criterion beyond the range used in the Phase 3 study.

❑ **% Viable Treg Cells**

The original tolerance interval is (b) (4) and for the updated methods is (b) (4). The total range administered for Phase 3 study was (b) (4). After the release data was correlated against the three Treg clinical outcomes (cGVHD, cGFS, and aGVHD34), the proposed acceptance criterion is based highest tolerance interval analysis at (b) (4).

The final commercial acceptance criterion for % Viable Treg Cells is (b) (4).

Reviewer Comment: We agree to (b) (4) specification based on clinical lot range of (b) (4) after the reanalysis, which was previously (b) (4). The Phase 1 study includes lots as low as (b) (4) for subjects that responded. Extending the range by (b) (4) beyond the range observed in Phase 3 clinical study is acceptable.

(b) (4)

❑ **Visual Inspection**

Reviewed by DBSQC. See DBSQC memo by Salil Ghosh (CBER/OCBQ/DBSQC/LAC).

(b) (4)

❑ **Sterility**

Reviewed by DBSQC. See DBSQC memo by Claire Wernly (CBER/OCBQ/DBSQC/LMIVTS).

(b) (4)

Action Plan For Positive Sterility Test Result

Sterility testing results under (b) (4) (14-day testing) are not available prior to release of the product for administration. Interim sterility reads occur after the start of (b) (4) at the following intervals: (b) (4) to provide a more rapid notification, if needed, of positive results.

Treating physicians will be promptly notified as part of the action plan to ensure patient safety and transparency. The treating physician is notified to evaluate the subject for any signs of infection that may be attributable to the product sterility failure. The sterility action plan includes a comprehensive root cause analysis process, incorporating microbial identification to understand potential contamination sources. The investigation and proposed corrections for a failure of lot release or CPV sterility testing will include: identification of the microorganism(s) and anti-microbial agent sensitivity testing; evaluation of the current procedures for collecting and processing the investigational cell products to determine the step at which contamination could be introduced; development of changes in the procedures that will assist in preventing sterility lapses in the future; and implementation of appropriate testing to ensure that such changes to the procedures produce a sterile product. Corrective and preventive actions are documented and reviewed to ensure any identified sources of contamination are effectively addressed before resuming production.

Reviewer comment: The Applicant will have an expanded access IND, and all recipients will enrolled and undergo informed consent to be informed of the risk associated with an out-of-specification (OOS) product. Due to the rapid administration of the products, high medical need and clinical benefit, this is acceptable.

□ Endotoxin

Reviewed by DBSQC. See DBSQC memo by Claire Wernly (CBER/OCBQ/DBSQC/LMIVTS).

(b) (4) Bacterial Endotoxins

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

There are overarching safety concerns regarding Applicant's proposal of widening the acceptance criteria for all three DP at once. The entire MOA of this product is to reduce the GVHD risk of the HSPC DP and Tcon DP. By moving the Treg acceptance criteria outside the dosing, purity, and potency ranges demonstrated to be effective during the clinical studies, there is greater uncertainty about the product's ability to remain effective. Our concerns were communicated to the Applicant in CMC IR #32 (16Jun2026), in which we asked the applicant to agree to our proposed acceptance criteria. In Amendment 68 (16Jun2026), the Applicant agreed to our proposal. This is acceptable.

Regulatory judgment allowed the Treg Viability acceptance criterion to be (b) (4) despite there being no clinical experience at Viability lower than (b) (4). However, additional widening of other attribute acceptance criteria is not acceptable, as there is limited knowledge of the impact of those acceptance criterion changes to product safety and efficacy.

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

Section reviewed by KK.

The critical findings in this section are related to **Major Deficiency #1 and 2.**

(b) (4)



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

Sterility

Sterility is performed per (b) (4) Sterility Test (b) (4) and (b) (4) Microbial Characterization, Identification, and Strain Typing.

Reviewed by DBSQC. See memo by Claire Wernly

Endotoxin

Endotoxin testing is performed per (b) (4) Bacterial Endotoxins Test (b) (4) , using FDA-licensed (b) (4)

Reviewed by DBSQC. See memo by Claire Wernly.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

The release assays are acceptable for commercial use, with PMC.

See individual assessment under each release analytical method.

See DBSQC reviewer memos for assessment of the Appearance, Sterility, and Endotoxin methods and method validations.

3.2.P.5.4 Batch Analyses

The critical findings in this section are related to **Major Deficiency #3**.

Initial Assessment Leading to MAJOR DEFICIENCY #3

There are the following manufacturing issues for product and Treg batches manufactured at SAC-02, discussed in more detail below:

(b) (4)

(b) (4)

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

(b) (4)



3.2.P.5.5 Characterization of Impurities

The critical findings in this section are related to CR deficiency #5.

Impurities representing any components of a biological or chemical origin that do not have the desired properties such as those attributable to DP, are included as impurities.

3.2.P.5.5.1 Product-Related Impurities

The purity of Treg DP is defined as target viable Treg (b) (4) CD4+/CD25+CD127-/lo], and manufacturing experience from the Phase 1b and Phase 3 clinical studies have demonstrated that the final Treg DP consists of (b) (4) target cells. Cell-based impurities in the Treg DP consist of (b) (4) including:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)



Reviewer comment: The provided cellular impurity data supports that the final Treg DP contains approximately less than (b) (4) and approximately less than less than (b) (4). With exception of the measurements of (b) (4), the cellular impurity data were generated with (b) (4) methods. Due to deficiencies with the (b) (4) methods, especially those used to determine (b) (4), the accuracy and reliability of these data are in question. Product-related impurities should be reassessed after resolution of the (b) (4) method control issues.

3.2.P.5.5.2 Process-Related Impurities

The critical findings in this section are related to **MAJOR** Deficiency #5.

Initial Assessment Leading to Major Deficiency #5

The potential process-related impurities that may be present in Treg DP are categorized as:

(b) (4)



(b) (4)

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

(b) (4)

(b) (4)

MAJOR AMENDMENT: MAJOR DEFICIENCY #5 Assessment:

Data from eCTD 1.11.1.2.4 "Agency Comment 5" and 3.2 RPT-0316 ORCA-TTM
EXTENDED CHARACTERIZATION re received 24Apr2026 in Amendment 52

The Applicant provide direct analytical measurements of (b) (4) impurities and concludes data demonstrates that the manufacturing process consistently clears these impurities to levels well below established safety thresholds, and do not require routine release testing or monitoring.

The Applicant used a (b) (4) -based method to quantify (b) (4) remaining on the cell surface after manufacturing. They also utilized (b) (4) to quantify (b) (4) in the drug product (b) (4) .

(b) (4) derived from process reagents were characterized using a (b) (4) -based method to assess (b) (4) through (b) (4) .

Reviewer comment: The approach is reasonable to quantify residual (b) (4) impurities

Residual (b) (4) impurities are evaluated across (b) (4) independent grafts and expressed as (b) (4) per dose under maximum dosing conditions in Table .

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Quantification of Worst-Case Exposure Using these new methods, the sponsor directly measured the impurities across independent grafts and calculated the total worst-case exposure ((b) (4)) for a 100 kg patient at maximum dosing.

The total exposures were calculated as:

(b) (4)

Integrated Risk Assessment and Safety Margins The sponsor contextualized these direct measurements by comparing them to conservative safety thresholds derived from other FDA-approved products, demonstrating substantial safety margins:

(b) (4)

Reviewer comment: The only item close to the limit is (b) (4). The Applicant is using conservative acceptable limits based on therapeutic doses, not toxicity. The (b) (4) are the same as FDA approved (b) (4). There are no concerns regarding (b) (4). However, amount of (b) (4) in (b) (4) has not been seen before and is also product specific. The provided calculations based on quantified residual amounts per cell is critical to provide a robust assessment of (b) (4) residual. The estimated maximum exposure does not raise any safety concerns and further supports the safety profile from the clinical studies. This is acceptable.

3.2.P.6 Reference Standards or Materials

This section is reviewed by KK.

Analytical method controls including instrument calibration and performance verification standards, microbiological control standards, and quantitative analytical reference materials are used for the analytical methods.

Reviewer Comment: The reference materials used as part of the analytical method is reviewed with the methods, see [section 3.2.P.5.1 and 3.2.P.5.6 \[Treg\]](#).

3.2.P.7 Container Closure System

The Treg DP container closure system is described in [section 3.2.P.2.4 \[Treg\]](#).

Reviewer's Comment: The information provided regarding Treg's container closure system is adequate. Additional details are provided in the consult reviewer's memo.

3.2.P.8 Stability

This section is reviewed by RW.

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

The Applicant proposes a shelf life of 72 hours post-apheresis collection (PAC) when maintained at $5 \pm 3^{\circ}\text{C}$, with an in-use stability of (b) (4) at (b) (4) after removal from refrigerated storage. To characterize storage stability and in-use stability, the Applicant conducted studies on engineering run batches manufactured at the commercial site (SAC-02) using the commercial manufacturing process described in section 3.2.P.3.3 [Treg]. The batches were manufactured from healthy donor apheresis starting material that underwent the same mobilization regimen (b) (4) of G-CSF treatment), collection device and protocol, and transportation conditions as used for commercial product production. The stability protocol includes assessment at the time of formulation (approximately 48 hours PAC), 60 hours PAC, and 72 hours PAC for storage stability. In-use stability is assessed at 72 hours PAC (time of removal from cold storage), (b) (4) at (b) (4) (b) (4) (b) (4) In-use compatibility with a standard administration set including a (b) (4) was evaluated for a gravity infusion at (b) (4) using product at (b) (4) hours PAC as a worst-case scenario.

Table 101. Primary Stability Batches

Batch Number	Manufacturing Site	Date of Manufacture	Storage Stability Available Time Points - Hours PAC (Hours post formulation)	In-Use Stability Available Time Points -Hours PAC (Hours at (b) (4))
--------------	--------------------	---------------------	--	--

(b) (4)

Table reproduced from Table 3, eCTD 3.2.P.8.1 Stability Summary and Conclusions [Treg, Orca Bio] and Tables 2 and 3, eCTD 3.2.P.8.3 "Stability Data [Treg, Orca Bio] from original submission (no change in the MA)

Reviewer comment: The Applicant assessed storage stability at 72 hours PAC (Post-Apheresis Collection) and in-use stability at up to (b) (4) PAC. (b) (4) Potency, (b) (4) Assay, and Viable Treg Cell Dose had been evaluated but listed as "Report Results".

Storage Stability Study

For the storage stability study, samples were held in a calibrated $5 \pm 3^{\circ}\text{C}$ refrigerator to mimic the (b) (4). Testing samples and time points are listed in Table . The container closure system and formulation used for the stability studies was the same as used for the commercial product. Acceptance criteria and summary of storage stability data are list in Table .

Table 102. Summary of Treg DP Storage Stability Data at $5 \pm 3^{\circ}\text{C}$

Test Parameter	Acceptance Criteria	Time of Formulation Mean (Range)	60-61hr PAC Mean (Range)	72hr PAC Mean (Range)
Appearance	Conforms	Conforms (b) (4)	Conforms (b) (4)	Conforms (b) (4)
(b) (4)	Report Results	(b) (4)		
Cell Concentration ($\times 10^6$ cells/mL)	Report Results	(b) (4)		
Sterility ((b) (4))	NGD	NGD (b) (4)	Not tested	NGD (b) (4)
Treg Phenotype	Report Results	Treg detected (3/3)	Treg detected (3/3)	Treg detected (3/3)
(b) (4) Cell Dose ($\times 10^6$ cells/kg)	Report Results	(b) (4)		
Viable Treg Cell Dose ($\times 10^6$ cells/kg)	Report Results	(b) (4)		
(b) (4) Potency (%)	Report Result (b) (4)	(b) (4)		
(b) (4) Assay	Report Results	(b) (4)		
Viability (%)	(b) (4)			
(b) (4)	Report Results	(b) (4)		
Viable Treg Cells (%)	(b) (4)			
Viable Treg (b) (4) of Viable CD45+)	Report Results	(b) (4)		
(b) (4)	Report Results	(b) (4)		

(b) (4); NGD = no growth detected; PAC = post-apheresis collection

Table reproduced from Table 2, eCTD 3.2.P.8.3 Stability Data [Treg, Orca Bio] from original submission. The revision in the MA only affected % Viability of Treg DP, % Viable Treg, and (b) (4) Treg / (b) (4). The revised data has been reviewed; it did not affect the conclusion.

Reviewer Comment:

Stability assessment at $5\pm3^{\circ}\text{C}$ (formulation, 60hr, 72hr PAC) showed all attributes met acceptance criteria. However, (b) (4) potency declined (b) (4) falling below the proposed (b) (4) commercial specification at 72hr. Viability and viable Treg percentages showed modest declines but remained well above (b) (4) criterion. The Applicant excluded (b) (4) potency from the Treg DP stability acceptance criteria. Therefore, the data met acceptance criteria for storage stability set by the Applicant. In the Major Amendment, (b) (4)

(b) (4). Even though the Agency agreed that the Applicant may use the (b) (4) assay as one of the potency CQAs along with viability of cells, the Agency did ask the Applicant to establish a correlation between the (b) (4) assay and the Treg (b) (4) assay (Meeting ID: 20952). The (b) (4) assay is one of the traditional measurements of Treg function, and it was deemed not feasible for use in Treg DP release assays due to the complexity of assay qualification and the length of the assay, especially for this freshly administered product. Instead, the Applicant agreed to evaluate the Treg (b) (4) assay as part of the process validation, stability, and comparability. (b) (4)

(b) (4) according to data submitted by the Applicant. However, (b) (4) Treg (b) (4) Assay has not been qualified, and therefore this data alone is insufficient to fully support Treg stability without clinical experience. As discussed below in the review of clinical experience, it appears that longer storage up to around 70 hours PAC had no clinical impact for Treg DP. Since viability of cells (another potency CQA) is stable and storage up to around 70 hours PAC in clinical experience had no clinical impact for Treg DP in Phase 1b/3 studies, it is reasonable to believe that Treg DP is stable up to 72 hours at $5\pm3^{\circ}\text{C}$.

3.2.P.8.1.2 In-Use Stability Study

For the in-use stability study, after the drug product was held for 72 hours PAC at $5\pm3^{\circ}\text{C}$, the DP was removed from cold storage, sampled, and placed at (b) (4) to simulate (b) (4) conditions during administration. Study samples were collected on time points described in Table . The Pre-PPQ (b) (4) batch was not tested at (b) (4) PAC and moved directly to compatibility testing at the (b) (4) PAC timepoint as a protocol modification after prior lots showed results below acceptance criteria at (b) (4) . The acceptance criteria and summary of results for in-use stability are shown Table .

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer Comment:

The in-use stability data indicate that critical quality attributes decline when Treg DP is held at (b) (4) following removal from refrigerated storage. At the (b) (4) PAC timepoint (b) (4) (b) (4), all (b) (4) batches tested met all acceptance criteria, with viability and % viable Treg cells remaining above (b) (4) of the 72-hour PAC values. However, at (b) (4) PAC (b) (4) (b) (4), both viability and % viable Treg cells fell below the specification of (b) (4) of the 72-hour PAC value for both batches tested (b) (4). Additionally, (b) (4) potency showed marked (b) (4) from a mean of (b) (4) at 72 hours PAC to (b) (4) at (b) (4) PAC, and (b) (4) the limit of quantification for (b) (4) batches at (b) (4) PAC. This represents a critical loss of functional activity at (b) (4) after removal from storage condition, which would be expected to impact clinical efficacy. These results demonstrate that the Treg DP should not be held at ambient temperature for extended periods and support the Applicant's proposed in-use (b) (4) after removal from $5 \pm 3^{\circ}\text{C}$ storage.

3.2.P.8.1.3 In-Use Compatibility Study

Administration of Treg DP to a recipient is accomplished by connecting the DP bag to a representative infusion set and procedure with the use of a (b) (4) that is a worst case.

The DP remaining from the in-use stability study was selected for the study of compatibility with the administration set, representing a worst case for the age of the material that could be used for clinical administration. Samples from each step and testing results are listed in Table .

Table 104. Summary of Treg DP In-Use Compatibility Data

Test Parameter	Acceptance Criteria
Appearance	Conforms
(b) (4)	Report Results
Cell Concentration ($\times 10^6$ cells/mL)	Report Results
Sterility ((b) (4))	NGD
Treg Phenotype	Report Results
(b) (4) Cell Dose ($\times 10^6$ cells/kg)	See recovery of (b) (4)
(b) (4)	of pre-administration testing
Viable Treg Cell Dose ($\times 10^6$ cells/kg)	Report Results
(b) (4) Potency (%)	Report Results
(b) (4) Treg (b) (4) Assay	Report Results
Viability (%)	See relative viability
Relative Viability	(b) (4) of pre-administration testing
(b) (4)	Report Results
Viable Treg Cells (%)	See relative viable Treg cells
Relative Viable Treg Cells (%)	(b) (4)
Viable Treg (b) (4)	Report Results
(b) (4)	Report Results

(b) (4) ; NGD, No growth detected; NT, Not tested; (b) (4)

Table reproduced from Tables 5 and 6, eCTD 3.2.P.8.3 Stability Data [Treg, Orca Bio] from original submission. The revision in the MA only affected % Viability of Treg DP, % Viable Treg, and (b) (4) (b) (4) The revised data has been reviewed; it did not affect the conclusion.

Reviewer Comment:

The in-use compatibility study demonstrates that Treg DP is physically and chemically stable during administration through a standard infusion set with a (b) (4) according to the Applicant's acceptance criteria. All (b) (4) batches tested met the primary acceptance criterion of (b) (4) recovery for (b) (4) cell dose, with a mean recovery of (b) (4) (range (b) (4) across individual batches). This indicates that most cells (b) (4), with minimal loss due to (b) (4). Viability and % viable Treg cells remained (b) (4) of pre-administration values, demonstrating that the cells maintain their viability during the administration process. The viable Treg cell dose showed (b) (4) recovery, which is consistent with the (b) (4) cell dose recovery and indicates that the functional cell population is preserved during administration.

(b) (4)

Under normal clinical use, where Treg DP would be administered within (b) (4) of removal from cold storage and at earlier timepoints in the shelf life, the (b) (4) potency would be substantially higher, and the impact of the administration process would be proportionally less significant.

No substantial losses in cell number or viability were observed during the compatibility study, supporting the conclusion that Treg DP is compatible with standard administration components including infusion sets and (b) (4). The data demonstrate consistent delivery of the DP and compatibility with device components and materials used at transplant centers is further validated by the Phase 3 data.

3.2.P.8.1.4 Clinical Data Analysis

The Applicant analyzed clinical data to provide supportive evidence for the proposed shelf life by correlating clinical outcomes with the vein-to-vein time (elapsed time from end of donor apheresis collection to start of Treg DP infusion to the patient). The Applicant selected chronic GVHD (cGVHD), survival free from chronic GVHD (cGFS), and acute GVHD grade 3 or 4 (aGVHD34) for analysis and concluded that there were no correlation exists between the clinical outcomes and the vein-to-vein times.

Figure 69. Oneway Analysis of Vein to Vein Times Versus Clinical Outcome Phase 3 Study

(b) (4)

(b) (4)

Figure 70. Oneway Analysis of Vein to Vein Times Versus Clinical Outcome Phase 1 Study

(b) (4)

(b) (4)

Reviewer Comment:

Using the clinical data analysis as supportive evidence that Treg DP maintains efficacy throughout the proposed 72-hour shelf life had been agreed by FDA through a Type B CMC Meeting (IND 18873, CRMTS #15135, dated 18 August 2023). The Applicant claims that the lack of correlation between vein-to-vein time and clinical outcomes (cGVHD, cGFS, aGVHD34) in both Phase 3 (n=88) and Phase 1b (n=154) studies suggests that product quality and potency are maintained within the proposed storage period. It is reasonable to believe that failure of efficacy of the Treg DP would confound the clinical outcomes. However, Treg efficacy or potency is not the only factors that could contribute to the clinical outcomes. (b) (4) from HSPC drug product and administering significant less T cell dose comparing standard of care (SOC) could also help to achieve favorable clinical outcomes. Among (b) (4) patients (~(b) (4) of total patients) in both Phase 1b and 3 studies with Treg DP administration time over 60 hours PAC (mostly around 70 hours PAC), approximately (b) (4) of patients suffered from death or moderate/severe cGVHD during the evaluated time period, which is very close to the number for all patients (b) (4) and patients with Treg DP administration time within 60 hours PAC. It appears that longer storage up to around 70 hours PAC had no clinical impact for Treg DP.

The replacement of (b) (4) with (b) (4) was questionable with (b) (4). Since the CR-issue with the (b) (4) potency assay validation, the exclusion of lot (b) (4) may or may not be appropriate. In Amendment [SN 0022] received 02Dec2025, the Applicant clarified the discrepancy regarding the exclusion of lot (b) (4) in response to CMC IR #4 (21Nov2025). The Applicant explained that at the time of study execution, the Phase 3 specification of (b) (4) potency was in use, and (b) (4) did not meet this specification. The commercial release specification was subsequently revised to (b) (4) as justified in Module 3.2.P.5.6 (Treg). It is unclear what the impact of (b) (4) potency on Treg DP is. With the known decline of Treg (b) (4) potency, the clinical data showed that there is no indication of extended storage leading to higher death and

moderate/severe cGVHD based on Phase 3 and 1b studies. Therefore, it is a minor concern for Treg DP stability.

OVERALL REVIEWER'S ASSESSMENT OF SECTION 3.2.P.8 [Treg DP]

The information provided is acceptable.

3.2.P DRUG PRODUCT [HSPC]

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

Section reviewed by EL.

HSPC DP is a single cell suspension of purified hemopoietic stem cells (surface phenotype: (b) (4) CD34+) formulated in multiple electrolytes injection, Type 1, (b) (4) (MEI) + 2% (w/v) human serum albumin (HSA) at a (b) (4) of approximately (b) (4). HSPC DP is formulated in a volume of approximately 100 mL to contain enough cells for a patient dose of at least 1×10^6 HSPCs/kg. HSPC DP is filled into industry standard (b) (4) transfer bags, stored at 2-8°C, and shipped fresh to be administered IV in its entirety on day 0.

3.2.P.2 Pharmaceutical Development

Section reviewed by EL.

3.2.P.2.1. Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The active ingredient in the Treg DS and DP are the same, live hematopoietic stem and progenitor cells (surface phenotype: (b) (4) CD34+) purified from G-CSF-mobilized peripheral blood from an HLA-matched donor. The HSPC DS composition and the HSPC DS characterization are assessed in section 3.2.S.1.3 [HSPC] of this memo. HSPC DS is immediately formulated into Treg DP, eliminating the need for storage of the DS.

Reviewer Comment: The HSPC DP is purified CD34+ using the (b) (4) system which is a well characterized cell population for both their attributes and clinical benefit for engraftment. This is acceptable.

3.2.P.2.1.2 Excipients

The excipients in the HSPC DP are provided in Table and justification for the selection of the excipients is provided in section 3.2.P.2.1.2 [Treg]. An assessment of the compatibility of the DP with the excipients please see section 3.2.P.8.3 [HSPC] of this memo.

Table 105. Excipients for HSPC DP

Component	Concentration	Final Concentration	Function
Albumin (Human) (b) (4) Solution, (b) (4)	(b) (4)	2% (v/v)	Stabilizer
Multiple Electrolytes Injection (MEI) Type 1, (b) (4)	Undiluted	To 100 mL	Isotonic Solution

Reviewer generated table based on Table 1 in eCTD 3.2.P.3.2 Batch Formula [Treg, Cell Suspension for Infusion]

Reviewer Comment: The excipients selected are supported by similar usages for other cell therapy products. This is acceptable.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

This section reviewed by EL.

HSPC DP is formulated in multiple electrolytes injection (MEI), Type 1, (b) (4) + 2% human serum albumin (HSA) at approximately 100 mL for the phase 3 study and the intended commercial product.

3.2.P.2.2.2 Overages

No overage for HSPC DP.

3.2.P.2.2.3 Physicochemical and Biological Properties

Reviewed in section 3.2.S.3.1 [HSPC] of this memo.

Reviewer Comment: The properties are consistent with known properties of CD34+ cells in HSCT.

3.2.P.2.3 Manufacturing Process Development

The HSPC related manufacturing process and development was provided in eCTD 3.2.P.2.3 Manufacturing Process Development [Treg, Cell Suspension for Infusion] with some additional information in eCTD 3.2.P.2.3 Manufacturing Process Development [HSPC, Cell Suspension for Infusion]. The relevant information for the HSPC DP from both sections is summarized here.

3.2.P.2.3.1 Control Strategy Development

A QTPP was created as described in section 3.2.P.2.3.1.1.1 [Treg].

□ 3.2.P.2.3.1.1 Identification of Critical Quality Attributes

3.2.P.2.3.1.1.1 HSPC DP Quality Target Product Profile (QTPP)

A QTPP was created as described in section 3.2.P.2.3.1.1.1 [Treg]. The identified QTPP elements relevant to HSPC DP are provided in Table .

Table 106. HSPC QTPP Elements Relevant to DP Manufacturing

Category	Description
Dosage	Greater or equal to a specified minimum number of viable HSPC cells per kg delivered intravenously, once, on Day 0 (the first day of treatment)
Active Ingredient Composition	HSPC DP: (b) (4) CD34+
Description	HSPC DP is provided in a single-dose (b) (4) bag with a fill volume of 100 mL
Formulation	Selected cells, MEI (Type 1, (b) (4)), and 2% (w/v) HSA, at a (b) (4)
Cell Viability	(b) (4) cells must be substantially viable at the time of administration
Purity	No less than the specified minimum % viable (b) (4) cells (% of viable CD34+ (b) (4))
Potency	• No less than minimum specified (b) (4) cells per kg; AND • No less than minimum number specified of viable CD34+ cells per kg (product of % viable CD34+ (b) (4) cells/kg); AND • (b) (4) potential above specified limit. Limits must consider potential losses in potency during storage, shipment, and administration
Identity	Positively identified via HSPC cell phenotyping

Appearance	No obvious visual anomalies and conforms to pre-determined color, opacity, packaging, and labels.
Product related cellular impurities and apheresis residuals	• Healthy donor erythrocytes, leukocytes (particularly Tcons), granulocytes, (b) (4) platelets (b) (4) are either generally regarded as safe (GRAS) or at levels justified to be safe • (b) (4) T cell dosage per kg in HSPC DP (% of viable (b) (4) (b) (4) are at levels justified to be safe • Non-target cells are present at a significantly reduced proportion compared to their natural abundance in the original blood product. Consider erythrocyte HLA types in matched donor/patient pairs.
Process related impurities and reagent residuals	• (b) (4) at levels determined or justified to be safe. • Leachables at levels determined or justified to be safe.
Particulates	• (b) (4) at levels determined or justified to be safe. • Visible and subvisible particles at levels determined to be safe.

Table adapted from Table 1 “QTPP Elements Relevant to Drug Product Manufacturing” in eCTD
3.2.P.2.3.1 Control Strategy Development [Treg, Cell Suspension for Infusion]

Reviewer Comment: The HSPC DP attributes very much align with the historical knowledge of CD34+ Cells. The assessment is adequate and largely based on scientific knowledge of CD34+ and transplant medicine. This is acceptable.

3.2.P.2.3.1.1.2 HSPC DP Critical Quality Attribute Risk Assessment and Designation

A comprehensive risk ranking and filtering exercise was performed to rank each quality attribute to create a comprehensive list of Tier 1, Tier 2, and Tier 3 quality attributes for the HSPC DP:

- Tier 1: Critical to the QTPP (high criticality, CQA) and must be controlled. Certain attributes related to general composition, appearance, and safety are considered obligatory Tier 1 quality attributes.
- Tier 2: Lower impact to the QTPP and should be assessed to determine the appropriate control and testing strategies.
- Tier 3: Minimal/negligible impact to the QTPP, low criticality and are instead noted as obligatory in the final risk ranking.

To evaluate the list of potential quality attributes and rank them for criticality, a CQA risk assessment was performed using impact scores (potential severity of impact to safety and efficacy) and uncertainty scores (level of information on the attribute at the time of assessment). The impact and uncertainty scores were based on platform/product knowledge, in vitro data, non-clinical in vivo data, and/or clinical experience. The assessment is provided in Table .

Table 107. HSPC DP Impact and Uncertainty Scoring Methodology

Impact Score ¹	Engraftment, Blood Reconstitution
16(High)	• Graft Failure • Neutrophils not reconstituted
8(Medium)	• Significant delay in engraftment • Neutrophils not fully reconstituted
4(Low)	• Minor delay in engraftment

	Neutrophils reconstituted however observable impact or delayed engraftment
2(Lowest)	- No changes observed to engraftment - No impact to patient outcome

¹ Uncertainty scores may be further modified (e.g., reduced) in the presence of substantial information or data from any source that can be considered relevant in the absence of clinical data, as justified by subject matter experts.

Adapted from Tables 2 and 3 in eCTD 3.2.P.2.3.1 Control Strategy Development [Treg, Cell Suspension for Infusion]

As with the Treg DP (see section 3.2.P.2.3.1.1.2 [Treg] of this memo), overall criticality score classified each quality DP attribute. The HSPC related scoring is in Table .

There was no ranking for safety attributes, including sterility, endotoxin adventitious agents, as they are required to be Tier 1 attributes. Additionally, HSPC phenotype and donor/patient match are required as Tier 1 identity attributes.

Table 108. HSPC Quality Attribute Criticality and Classification

Category	Attribute	Criticality Score ¹ (Impact x Uncertainty) / Tier	Classification Rationale
Safety	Sterility	NA / Tier 1	Obligatory safety attribute
	Endotoxin	NA / Tier 1	Obligatory safety attribute
	Adventitious Agents	NA / Tier 1	Obligatory safety attribute
Identity	HSPC phenotype	NA / Tier 1	Obligatory attribute
	Donor/patient match	NA / Tier 1	Obligatory attribute
Appearance	Physical State	NA / Tier 1	Obligatory attribute
	Clarity	NA / Tier 1	Obligatory attribute
	Color	NA / Tier 1	Obligatory attribute
	Cell Aggregates	NA / Tier 1	Obligatory attribute
	(b) (4)	NA / Tier 1	Obligatory attribute
	Headspace	NA / Tier 1	Obligatory attribute
	Container Integrity	NA / Tier 1	Obligatory attribute
Composition	MEI (Type 1 (b) (4) Concentration	NA / Tier 1	Obligatory attribute
	HSA Concentration	NA / Tier 1	Obligatory attribute
	(b) (4)	NA / Tier 1	Obligatory attribute
	Cell Concentration	NA / Tier 1	Obligatory attribute
	Volume	NA / Tier 1	Obligatory attribute
Potency	(b) (4)	32 (16 x 2) / Tier 1	- The (b) (4) potency is a well characterized analytical method for prediction of successful HSPC engraftment - The Applicant justify releasing based on cell CD34+ cell dose based on correlation with clinical experience and manufacturing history. (see section 5.3.1.4 HSPC of this memo)
Strength (Dose)	Viable HSPC Dose (Viable HSPC/kg)	32 (16 x 2) / Tier 1	Risk of engraftment failure if decrease below (b) (4) CD34+ cells/kg dose
	(b) (4) Dose	32 (16 x 2) / Tier 1	(b) (4) cell dose correlates directly with total potent cell dose

			Given the correlations between (b) (4) dose, Potency, and Purity, (b) (4) cell dose (Strength) is considered highly impactful since it directly contributes to potent cell dose.
Purity – Non-Target Apheresis	% Viability relative to (b) (4)	32 (16 x 2) / Tier 1	Cell Viability is a generally recognized critical indicator of cell health.
Purity – Non-Target Apheresis	Tcells (Residual Viable T-cell Dose)	32 (16 x 2) / Tier 1	Minimizing the number of viable (b) (4) cells, known to mediate the development of GVHD to minimize the risk of GVHD
Purity – Target Cells	% Viable HSPC Purity	24 (8*3) / Tier 2	% purity of target cells controls for all impurities, including those not at increasing risk of GVHD and is not directly associated with clinical outcome, unlike dose or residual T cells - Phase three clinical experience with product 39% to 96% (CV of 10.95%).
Purity – Target Cells	(b) (4)	12 (4*3) / Tier 2	(b) (4) HSPC associated with greater engraftment, but no accepted optimal subpopulation has been identified for bone marrow derived CD34+ cells - CD34 measures include all HSPC progenitors present
Purity – Non-Target Apheresis	(b) (4)		

(b) (4)

	Extractables and Leachables	12 (4*4) / Tier 2	• Compounds identified in the extractables study are Tier 2 attributes if the calculated theoretical worst-case dose is above the PDE. • Classification is re-assessed after a leachables study is conducted and assessed against the PDE.
--	-----------------------------	-------------------	--

Adapted from Table 5 in eCTD section 3.2.P.2.3.1 Control Strategy Development [Treg, Cell Suspension for Infusion]

Reviewer Comment: The rankings do highlight the criticality of removing viable T-cells from the HSPC DP. The Applicant's assessment is reasonable and base largely on historical knowledge regarding stem cell transplants. This is acceptable.

□ 3.2.P.2.3.1.2 Process Parameter Risk Assessment

A process parameter risk assessment was performed as described in section 3.2.P.2.3.1.2 [Treg], specifically for the process used to generate the HSPC DP. The assessment of the criticality of the process parameters is shown in Table .

Reviewer comment: Table is a list of all pCPP that were further investigated for establishment as CPP or Non-CPP. It is a non-inclusive list of Non-CPP and thus may not recapitulate the Non-CPP listed in section 3.2.P.3.4.1 [HSPC] and section 3.2.P.3.4.4 [HSPC].

Table 109. Summary of Process Parameter Risk Assessment (Rev2.0) for HSPC DP Manufacturing

Unit Operation	Process Parameter	Criticality Score Rev 2.0 (Impact x Control)	PP Criticality
----------------	-------------------	--	-------------------

(b) (4)

HSPC Formulation / Fill	HSPC DP Formulation: HSPC DP Final Volume	16 (16 x 1)	CPP
----------------------------	--	-------------	-----

(b) (4)

Table adapted from Table 27 "Summary of Parameter Classification Changes from Revision 2.0 Assessment" in eCTD section 3.2.P.2.3.1 Control Strategy Development [Treg]

Reviewer Comment: This is consistent with process parameters when using HDE approved (b) (4) system. This is acceptable.

3.2.P.2.3.1.3 Process Development and Characterization by Unit Operation

Process characterization studies were conducted as described in section 3.2.P.2.3.1.3 [Treg], specifically for the process used to generate the HSPC DP are provided in Table . See Table 29 for shared processes with the Treg DP including (b) (4)

Table 110. Summary of Process Development Studies and Established PAR for HSPC DP Manufacturing Process Parameters

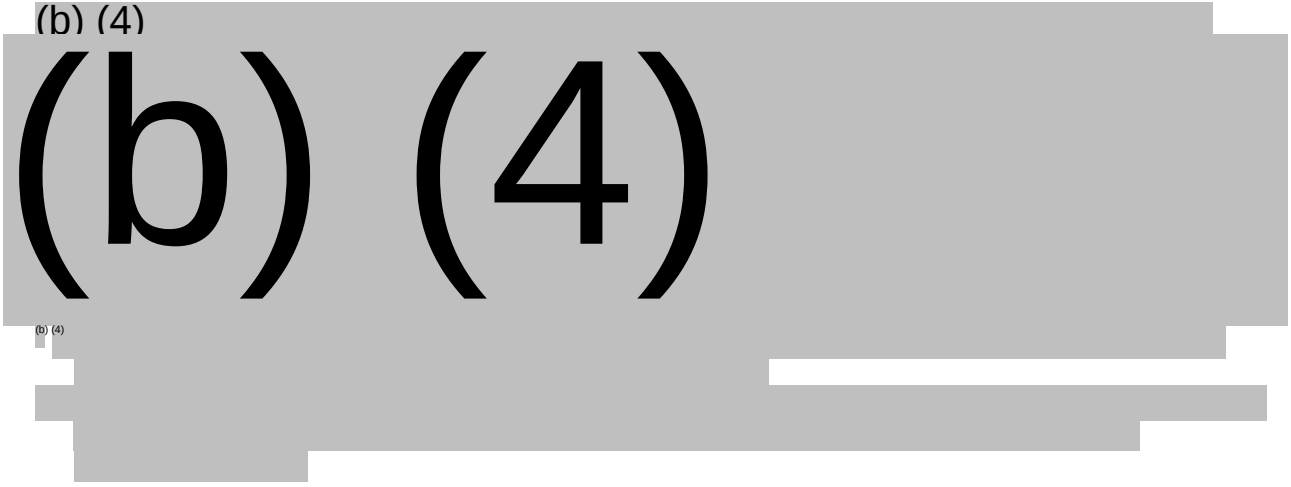
Unit Operation	Process Parameter	Characterized Range	Target	Criticality	Rationale
HSPC Formulation/ Fill	HSPC DP Final Volume (mL)	(b) (4) (PAR)	100	CPP	Lower cell conc. had shorter shelf life. Cell conc. tested up to (b) (4) mL not affected.

Reviewer generated table from information in eCTD sections 3.2.P.2.3.1 Control Strategy Development [Treg], 3.2.P.3.3 Description of Manufacturing Process and Process Controls [Treg], and 3.2.P.3.3 Description of Manufacturing Process and Process Controls [HSPC]

□ 3.2.P.2.3.1.4 In-Process Hold Times

In-process hold times were assessed as described in [section 3.2.P.2.3.1.4 \[Treg\]](#) and are provided in Table 111 for the HSPC DP. For more information about the hold time tracking in the planned Continued Process Verification (CPV), including justification, see [section 3.2.P.3.5.3 \[HSPC\]](#).

(b) (4)



□ 3.2.P.2.3.1.5 Process Control Strategy

The HSPC DP process control strategy involves control of:

- Critical process parameters (CPPs) – see [section 3.2.P.3.4.1 \[HSPC\]](#)
- Non-critical process parameters (Non-CPPs) -see [section 3.2.P.3.4 \[HSPC\]](#)
- In-process controls (IPCs) – see [section 3.2.P.3.4.2 \[HSPC\]](#)
- Key performance indicators (KPIs) – see [section 3.2.P.3.4.3 \[HSPC\]](#)
- DP release testing – see [section 3.2.P.5.1 and 3.2.P.5.2 \[HSPC\]](#)
- Continued process verification (CPV) testing – see [section 3.2.P.3.5.3 \[Treg\]](#)

The process control strategy was assessed for robustness through the performance of PPQ studies, as described in [section 3.2.P.3.5.2 \[Treg\]](#).

3.2.P.2.3.2 Process History and Process Changes

□ 3.2.P.2.3.2.1 HSPC Drug Product Process Development at (b) (4) During Phase 1b and Phase 3 Trials

For summary information on the initial process development, see [section 3.2.P.2.3.2.1 \[Treg\]](#). The changes that apply to the HSPC DP during the Phase 1b and Phase 3 study are outlined in Table .

(b) (4)



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

(b) (4)

Table adapted from Table 1 in 3.2.P.2.3.2 Process History and Process Changes [Treg, Cell Suspension for Infusion] and eCTD 3.2.P.2.3.2 Process History and Process Changes [HSPC, Cell Suspension for Infusion]

Reviewer Comment: The changes during though Phase 3 are acceptable.

□ **3.2.P.2.3.2.2 Commercial Process Development at SAC-02**

The changes from the Phase 3 study to the intended commercial HSPC product are outlined in

Table These include changes after Phase 3 and those occurring after comparability study.

See section 3.2.P.2.3.2.2 [Treg] and section 3.2.P.2.3.2.3 [Treg] for a summary of commercial process development and post-comparability process development including general process changes applicable to all three cellular DPs, respectively.

Reviewer Comment: The Applicant refers to post-comparability changes which does not mean (b) (4) SAC-02, as it was initially assumed. These are changes that are included in late Phase 3 lots and as well as once manufacturing initiated at SAC-02.

Table 113. Summary of HSPC DP Manufacturing Process Changes Between

(b) (4)

(b) (4)



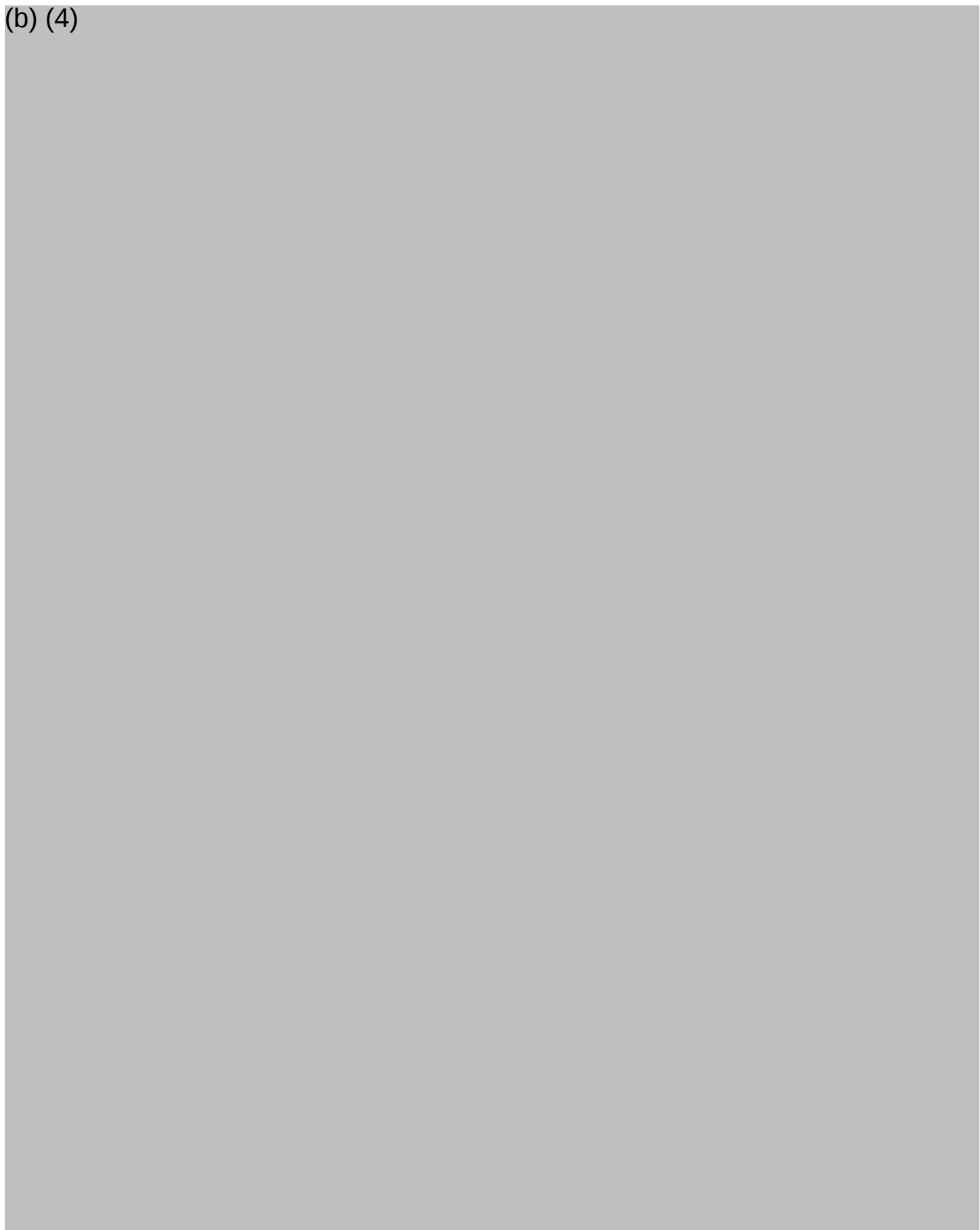
Table adapted from Table 2 in 3.2.P.2.3.2 Process History and Process Changes [HSPC, Cell Suspension for Infusion]

Reviewer Comment: The Applicant did not include the (b) (4) step in the table. However, this is a change occurring after comparability was established between (b) (4) SAC-02. The change also occurred with the late Phase 3 data, which is not addressed within eCTD 3.2.P.2.3.2 Process History and Process Changes [HSPC, Cell Suspension for Infusion]. This was revealed from Applicant's response received 2Dec2025 to CMC IR#8 (21Nov2025) and is concluded above. See 3.2.P.2.3.2.2.2 [HSPC] of this memo for additional discussion of the (b) (4).

(b) (4)



(b) (4)



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

(b) (4)

3.2.P.2.3.3 Comparability Assessments

A comparability study assessed the change of from (b) (4). All three drug products were included in the study and the methodology is review in section 3.2.P.2.3.3 [Treg] of this memo. The HSPC attributes evaluated are provided in Table . A description of the source of historical batch data, the matched-pairs TOST/equivalence approach, derivation of PSDs, and data transformations used to normalize data is provided in section 3.2.P.2.3.3 [Treg] of this memo. The results in Table and Figure .

Table 115. HSPC Quality Attributes for Comparability Assessment

Comparability Attribute		Assay
Safety (Tier 1)	14-Day Sterility	(b) (4)
	(b) (4)	(b) (4)
	Endotoxin	(b) (4)
Appearance (Tier 1)	Appearance	Visual Inspection
Tier 1 Attributes (PSD criteria)	(b) (4)	

Tier 2 Attributes (Report only)	% Viable HSPC	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	
	(b) (4)	(b) (4)	
	(b) (4)	Potency	
	(b) (4)	Potency	
	(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)	(b) (4)	

Table adapted from Table 1 in eCTD section 3.2.P.2.3.3 Comparability Assessments [HSPC, Cell Suspension for Infusion]

Table 116. HSPC DP Tier 1 Attributes TOST Results

Attribute	PSD	Normalized Mean Difference (N ^{(b) (4)} 1)	p-value Mean ≤ -PSD	p-value Mean ≥ PSD	Result
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
% Viable HSPC	(b) (4)				
(b) (4)	(b) (4)				
(b) (4)	(b) (4)				
(b) (4)	(b) (4)				
Potency	(b) (4)				
(b) (4)	(b) (4)				
Potency	(b) (4)				
(b) (4)	(b) (4)				
Potency	(b) (4)				

¹ See Major Discrepancy

Table reproduced from Table 5 in eCTD section 3.2.P.2.3.3 Comparability Assessments [HSPC, Cell Suspension for Infusion]

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

(b) (4)

Reviewer Comment: The Applicant's rational for differentiating (b) (4) is reasonable was accepted during the review of the comparability study in the IND. The risk of (b) (4) is based on the risk of (b) (4) causing GVHD. The Applicant was able to establish comparability with the Treg DP and the HSPC-DP using the FDA HDE approved (b) (4) with limited additional process. Considering data collected after this study, (b) (4), there is an overall increase in (b) (4) linked to the (b) (4) step.

Considering the current concerns, it is possible that some of this variability is based on using uncontrolled and not validated contributed to this deviation. It is unlikely that

additional comparability study will be beneficial for HSPC DP given (b) (4) is no longer the product and there would be minimal benefit. HSPC DP is based on CD34+ which the critical quality attributes and relation to engraftment is well understood and the manufacturing process is controlled given the review and widespread use of the CD34+ reagent system.

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

The control strategy is reasonable and the reanalysis of Phase 3 data provide assurances that the data generated can be used to support manufacturing process development. Information provided is acceptable, with no deficiencies identified.

3.2.P.2.4 Container Closure System

HSPC DP Container Closure System is the same as for the Treg DP. See section 3.2.P.2.4 [Treg] of this memo.

3.2.P.2.5 Microbiological Attributes

Microbiological attributes for the HSPC DP are the same as for the Treg DP. See section 3.2.P.2.5 [Treg] of this memo. This includes the release of the HSPC product for administration prior to obtaining the 14 day sterility results.

3.2.P.2.6 Compatibility

See section 3.2.P.8.1 [HSPC] of this memo an assessment of the compatibility of the HSPC DP to the primary container.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

See section 3.2.P.3.1 [Treg].

3.2.P.3.2 Batch Formula

The batch formulation for HSPC DP is $\geq 1.0 \times 10^6$ Viable HSPC Cells per patient kg with 2% (w/v) HSA with up to 100 mL of MEI, Type 1.

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

The manufacturing process of each batch of HSPC DP involves (b) (4), and HSPC

Formulation and Fill. (b) (4)

steps occur in an ISO (b) (4) environment. (b) (4) HSPC Formulation and Fill steps occur in an ISO (b) (4) in an ISO (b) (4) environment.

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

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.3:
Information provided is acceptable, with no deficiencies identified.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The manufacturing of HSPC DP is a continuous process from initiation to formulation with limited hold times. The process control strategy contains the same elements outlined in section 3.2.P.3.4 [Treg] of this memo.

3.2.P.3.4.1 Critical Process Parameters (CPPs)

HSPC DP CPPs were determined using a quality risk ranking and filtering approach (see section 3.2.P.2.3.1.2 [Treg]) and HSPC specific ones are summarized in Table . The CPP for (b) (4) are provided with Treg CPP in Table 43. The methodology and data used to select the PARs for CPPs are provided in section 3.2.P.2.3.1 [Treg] of this memo.

Table 118. CPP in HSPC DP Manufacturing

Unit Operation	CPP (UOM)	PAR	Impacted HSPC CQAs
----------------	-----------	-----	--------------------

HSPC DP Formulation/ Fill	HSPC DP Final Volume (mL)	(b) (4)	- DP Volume
------------------------------	---------------------------	---------	-------------

Table adapted from Table 1 “Summary of Critical Process Parameters in HSPC Manufacture” in eCTD section 3.2.P.3.4 Controls of Critical Steps and Intermediates [Treg] and Table 28 “Critical Process Parameters and Impacted Quality Attributes” and Table 29 “Critical Process Parameters and Proven Acceptable Ranges” in eCTD section 3.2.P.2.3.1 Control Strategy Development [Treg]

3.2.P.3.4.2 In-Process Controls (IPCs)

(b) (4)

(b) (4)

3.2.P.3.4.3 Process Control Points (PCPs)

The Process Control Points (PCPs) for HSPC are (b) (4)

shared with the Treg PCPs and provided in Table 45.

3.2.P.3.4.4 Non-Critical Process Parameters (Non-CPPs)

The non-CPPs for the manufacture of the HSPC DP are provided in Table and Table .

The Non-CPPs for (b) (4)

shared with the Treg PCPs and provided in Table 46

(b) (4)

3.2.P.3.4.5 Key Performance Indicators (KPI)

- (b) (4)

(b) (4)

3.2.P.3.4.6 Control of Intermediates

For information on the control of pre-batch solutions, reagents, and consumables, see section 3.2.P.3.4.6 [Treg].

3.2.P.3.4.4 In-Process Hold Times

The HSPC DP is processed continuously with no formally defined intermediates or process hold points, but in-process material may be (b) (4) as operations are performed or preparations are made for the next step. A historical analysis has been performed to characterize the typical processing times and hold times for the process. See section 3.2.P.2.3.1.4 [HSPC].

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

No deficiencies identified.

3.2.P.3.5 Process Validation and/or Evaluation

The information reviewed within this section were provided in eCTD

3.2.P.3.5 Process Validation and/or Evaluation [Treg, Cell Suspension for Infusion] Orca.

The Applicant process validation approach included all three DP. See section 3.2.P.3.5 [Treg] for a review of the study design. The supporting validation studies include:

- Process performance qualification (PPQ)
- Continued Process Verification (CPV)
- (b) (4) validation
- Solution and consumables hold validations
- Aseptic process simulation (APS)

Reviewer Comment: HSPC specific material is provided here.

3.2.P.3.5.2 Process Performance Qualification

Updated to include reanalysis results reported in eCTD 1.11.1 Quality Information Amendment received in Amendment 52.

The PPQ study included all three DP manufactured for (b) (4) consecutive lots. See section 3.2.P.3.5 [Treg] for a discussion of the PPQ study design. The HSPC specific attributes are provided in Table and the additional PPQ parameters and results in Table and Table .

Table 121. HSPC Drug Product Quality Attributes

Quality Attribute	Method of Testing	Acceptance Criteria
Visual Inspection	(b) (4)	Conforms

(b) (4)

14-Day Sterility	(b) (4)	No growth detected
(b) (4)		No organisms detected
Endotoxin	(b) (4)	
Confirmation of Identity	HSPC (b) (4) Method	HSPC detected
Viability	HSPC (b) (4) Method	(b) (4)
% Viable HSPC	HSPC (b) (4) Method	(b) (4)
(b) (4)		
(b) (4)		
Viable HSPC Cell Dose	Calculation:	(b) (4)
(b) (4)	(b) (4)	

(b) (4)

Table modified from Table 2 in eCTD 3.2.P.3.5 Process Validation and/or Evaluation [Treg, Cell Suspension for Infusion] and table 17 from eCTD 1.11.1 Quality Information Amendment received in Amendment 52.

Reviewer Comment: The reported results are based on the reanalysis of historical data and are acceptable. See deviation section below for discussion of the OOS for total residual T cells.

Table 122. Difference In Reported Results Treg Drug Product Quality Attributes from Legacy Method and Redesigned Method

Attribute
HSPC DP (b) (4) Cell Viability
HSPC DP Viable HSPC Purity %
HSPC DP (b) (4) xE6 Cells/kg
HSPC DP (b) (4) xE6 Cells/kg
HSPC DP Viable HSPC Cell Dose %

(b) (4)

Reviewer Generated Table

Reviewer Comment: See section 3.2.P.5.4 for discussion about the increase in reported residual T cells. This was observed across the reanalysis and represents more accurate

reporting. While (b) (4) number increased, there are not specific safety concerns as reported results are within specifications. The revised results don't raise as specific concerns about the reported PPQ results and the overall assessment.

Table 123. HSPC Critical Process Parameters

Process Step	Process Parameter	Acceptance Criteria	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
HSPC DP Formulation	HSPC DP Final Volume	(b) (4)	(b) (4)

Table adapted from Table 5 in eCTD 3.2.P.3.5 Process Validation and/or Evaluation [Treg, Cell Suspension for Infusion] of the submission

(b) (4)

(b) (4)

(b) (4)

HSPC Drug Product (b) (4) OOS

During batch (b) (4), a critical deviation occurred when the (b) (4) for HSPC DP was determined to be (b) (4) but in specification for (b) (4). The PPQ study uses (b) (4) which is measured by the intended commercial release specification test method. See section 3.2.P.5.1 and 3.2.P.5.6 [HSPC] of this memo regarding the assessment of the change in specifications.

Reviewer Comment: The product is within specification for (b) (4), based on the original analysis (b) (4). The revised Phase 3 records adequately address the risk of under reporting (b) (4). This deviation acceptable based on the reanalysis of the PPQ and Phase 3 batch records.

Validation Assessment of Revisions following PPQ Completion

(b) (4)

(b) (4)

(b) (4)

3.2.P.4 Control of Excipients

This section reviewed by SK.

The HSPC DP uses the same compendial excipients as the Treg DP. There are no noncompendial or novel excipients used in the HSPC DP. See section 3.2.P.4 Treg DP of this memo.

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

The assessment of the information provided to support the excipients for the HSPC DP is acceptable.

3.2.P.5 Control of Drug Product

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

This section is reviewed by EL.

Reviewer comment: This section has been updated using data from eCTD section 3.2.R Regional Information document "RPT-0342- JUSTIFICATION OF COMMERICAL SPECIFICATION FOR ORCA-T" in Amendment 52 (24Apr2026).

3.2.P.5.1 Specifications

The HSPC DP release specifications are provided in Table . The proposed changes to the HSPC DP specifications are provided in Table . The determination of the final acceptance criterion is discussed below with the justification of specifications.

Table 127: HSPC DP Release Specifications

Test Attribute	Analytical Procedure	Commercial Acceptance Criteria	Justification for Specification	Clinical Acceptance Criteria	PPQ Acceptance Criteria
(b) (4)			Manufacturing history, clinical data correlation, and tolerance interval	(b) (4)	
HSPC Phenotype Identity	HSPC (b) (4) method	HSPC detected	Confirm the identity of the active cells of interest	HSPC detected	HSPC detected
Viability	HSPC (b) (4) method	(b) (4)	Manufacturing history, clinical data correlation	(b) (4)	
(b) (4)	HSPC (b) (4) method	(b) (4)	Manufacturing history, clinical data correlation, and tolerance interval	(b) (4)	
(b) (4)	Calculation: (b) (4)	(b) (4)	Clinical outcome correlation data and the review of published literature	(b) (4)	(b) (4)
Viable HSPC Cell Dose	Calculation: (b) (4)	≥ 1E6 cells/kg	Manufacturing history, clinical data correlation, and tolerance interval	≥ 1. (b) (4) E6 cells/kg	≥ 1. (b) (4) E6 cells/kg
Appearance	(b) (4) Visual Inspection of Injection	Clear to opaque liquid Color is off-white, white, yellow, orange, to red No visible foreign particles No defects	Manufacturing history	Conforms	Conforms
Interim Sterility Assurance	(b) (4) Microbial Characterization, Identification, and Strain Typing – (b) (4)	No organisms detected	Safety Limits	No organisms detected	No organisms detected

Sterility ^a	(b) (4) Sterility Tests (14-Day)	No organisms detected (Post administration results)	Safety Limits	No organisms detected (Post administration results)	No organisms detected (Post administration results)
Endotoxin	(b) (4) Bacterial Endotoxins Test (b) (4) Assay	(b) (4)	Based on statistical analysis of manufacturing data	(b) (4)	

Reviewer generated table

^a The product is released based on interim assurances of sterility with final (b) (4) (b) (4)-based sterility results available after administration

Table 128. Changes to Proposed HSPC DP Commercial Specifications

(b) (4)

3.2.P.5.6 Justification of Specifications

See section 3.2.P.5.6 [Treg] for a description of the approaches used to generate and support the proposed acceptance criteria.

□ (b) (4)

(b) (4)

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

(b) (4)

□ **Viability**

The original method tolerance interval is (b) (4) and updated method tolerance interval is (b) (4). The total range of data analyzed for clinical outcome correlations was (b) (4). There was no correlation of Viability to neutrophil or platelet engraftment clinical outcomes. The proposed acceptance criterion is (b) (4) to align with the Phase 3 specifications.

The Applicant also refers to clinical experience with HSCT products with low viability, including post-thaw, to support the (b) (4) viability acceptance criterion. With an acceptance criterion of (b) (4), the calculated highest possible (b) (4) cell dose is (b) (4) cells/kg.

The final commercial acceptance criterion for Viability is (b) (4).

Reviewer comment: The proposed (b) (4) viability specification falls below the range observed during the Phase 3 study; however, the CMC review team agrees that this does not pose a significant safety risk. Dosing is based on viable cell count, and the risk associated with (b) (4) is outweighed by the clinical benefit of the product. Given the lack of alternative treatments and the myeloablative nature of the conditioning regimen, accepting a commercial specification below the Phase 3 range is considered appropriate and is supported by stability data.

(b) (4)

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

(b) (4)

□ **Viable HSPC Cell Dose**

The original tolerance interval is $\geq 1.0 \times 10^6$ cells/kg and the updated methods is $\geq (b) (4) \times 10^6$ cells/kg. The clinical data range examined was $\geq 1.0 \times 10^6$ cells/kg. The clinical data range examined was (b) (4) cells/kg.

Table 132 Phase 3 OOS Batches for HSPC DP Viable HSPC Cell Dose ($\times 10^6$ cells/kg)

Batch Lot	Clinical Acceptance	Revised	Original	Response
(b) (4)				Death, Grade 3 or 4 GVHD
				Alive and free from moderate or severe cGVHD
				Alive and free from moderate or severe cGVHD
				Grade 3 or 4 aGVHD

Reviewer generated table

The final commercial acceptance criterion for Viable HSPC Cell Dose is $\geq 1.0 \times 10^6$ cells/kg.

Reviewer Comment. Due to quality concerns for lots (b) (4) and the clinical outcome, the CMC review team was unable to use those lots to support an acceptance criterion lower than the Phase 3 experience and recommends the lower limit be $1. (b) (4) \times 10^6$ cells/kg. The clinical and clinical pharmacology review team recommended to lower the clinical dose to 1×10^6 cells/kg because engraftment occurred with lot (b) (4), regardless of the Grade 3 or 4 aGVHD outcome. The CMC review team deferred to their assessment of lowest effective dose and established the release acceptance criterion at $\geq 1.0 \times 10^6$ cells/kg.

□ **Visual Inspection**

Reviewed by DBSQC. See DBSQC memo by Salil Ghosh (CBER/OCBQ/DBSQC/LAC).

(b) (4) Visual Inspection of Injection

□ **Sterility**

Reviewed by DBSQC. See DBSQC memo by Claire Wernly (CBER/OCBQ/DBSQC/LMIVTS).

(b) (4) Microbial Characterization, Identification, and Strain Typing

(b) (4) Sterility Test Direct Inoculation

Reviewer comment: See [section 3.2.P.5.6 \[Treg\]](#) for description of the action plan for positive sterility test result.

□ **Endotoxin**

Reviewed by DBSQC. See DBSQC memo by Claire Wernly (CBER/OCBQ/DBSQC/LMIVTS).

(b) (4) Bacterial Endotoxins

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

There are overarching safety concerns regarding Applicant's proposal of widening the acceptance criteria for all three DP at once. The entire MOA of this product is to reduce the GVHD risk of the HSPC DP and Tcon DP. By proposing to change the HSPC and Treg DP outside the ranges assessed in the clinical studies, there is uncertainty about the product's ability to remain effective. Therefore, we could not agree to the Applicant's proposed acceptance criteria and provided alternatives based on the Phase 3 safety and efficacy data. Our concerns were communicated to the Applicant in CMC IR #32 (16Jun2026), in which we asked the applicant to agree to our proposed acceptance criteria. In Amendment 68 (16Jun2026), the Applicant agreed to our proposal. This is acceptable.

Regulatory judgment allowed the HSPC Viability acceptance criterion to be (b) (4) as this is unlikely to result in safety signals.

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

Section reviewed by KK.

The critical findings in this section are related to **Major Deficiency #1 and 2**

(b) (4)

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

Appearance by Visual Inspection

Appearance is performed per (b) (4) Visual Inspection of Injection.

Reviewed by DBSQC. See memo by Salil Ghosh.

Sterility

Sterility is performed per (b) (4) Sterility Test (b) (4) and (b) (4) Microbial Characterization, Identification, and Strain Typing.

Reviewed by DBSQC. See memo by Claire Wernly

Endotoxin

Endotoxin testing is performed per (b) (4) Bacterial Endotoxins Test (b) (4) Assay, using FDA-licensed (b) (4).

Reviewed by DBSQC. See memo by Claire Wernly.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

The release assays are acceptable for commercial use, with PMC.

See individual assessment under each release analytical method.

See DBSQC reviewer memos for assessment of the Appearance, Sterility, and Endotoxin methods and method validations.

3.2.P.5.4 Batch Analyses

Section reviewed by EL.

The critical findings in this section are related to Major Deficiency #3 (communicated on March 26, 2026).

Initial Assessment Leading to Major Deficiency #3

As outlined in section 3.2.P.5.4 [Treg], the Sponsor provides batch records by study for the clinical studies used to support this submission. The Applicant provides tables of the batch records based on the clinical studies, and all lots manufactured at SAC-02, including INDs that cross-reference IND 18873. A summary of the lots, manufacturing location and use is summarized in Table .

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer Comment: The batch records for attributes using (b) (4) based assays (ie HSPC Dose, Viability and % Viable HSPC) cannot be assessed at this time due to deficiencies in the methods.

Initial Assessment of Section 3.2.P.5.4:

There was discussion regarding whether post-marketing monitoring through a PMC/PMR could address this issue. However, after the deficiencies with the (b) (4) analytical methods were identified, it was determined that patient safety would be put at risk because currently there is no ability to distinguish between method variability and process variability. The (b) (4) methods lack critical controls for instrument setup, including compensation controls and viability (b) (4) controls for (b) (4). Without these fundamental controls, the reliability and consistency of release testing results cannot be assured for key product quality attributes including dosing, viability, purity, and identity determinations. This affects not just the HSPC cells but also the (b) (4), where trending data from SAC-02 shows concerning patterns such as (b) (4) HSPC (b) (4) doses. The inability to differentiate whether observed variations are due to flawed measurement from the method or manufacturing process drift means that product released to patients may not meet specifications, potentially resulting in administration of cellular drug product with

inaccurate cell doses, compromised viability, or inadequate purity. These deficiencies must be resolved prior to approval to ensure patient safety, as PMRs are not appropriate for issues that directly impact the ability to demonstrate CGMP compliance and product quality at the time of licensure.

Major amendment declared and Applicant provided final response to Major Deficiencies Outlined in communication sent March 26, 2026 to provide outstanding information required to complete the assessment of the batch records and concerning trends at SAC-02.

MAJOR AMENDMENT: Major Deficiency #3 Assessment:

Data from eCTD 1.11.1.2.4 “Agency Comment 3”, and associated reports received 24Apr2026 in Amendment 52 (and revised in amendment 60) and Appendix 3 in eCTD 1.11.1.2.4 “Sponsor Responses to CMC IR-26 dated 19May2026 received 20May2026 in amendment 60,

To address the Major Deficiency 1, the Applicant reanalysis (b) (4) based methods as closely as possible with the data collected at the time. The revised (b) (4) included improved instructions including for (b) (4) based on the controls. Of the (b) (4) Phase 3 batch records, only (b) (4), which also was not included in Treg reanalysis, could not be reanalyzed.

Reviewer Comment: This reanalysis is critical to provide assurances of what was administered during the Phase 3 study. This reanalysis using a (b) (4) strategy, including using (b) (4) is an improved but not replicate all revised method complete due to limitation over the data collection at the time. The reanalysis to provide updated batch records is acceptable.

The Applicant provided update results for the stability, PPQ, and compatibility of pump based infusion studies, and updated clinical correlation data based on the revised methods and the relevant sections of the memo have been updated.

The Applicant provides trending data to address both the original batch records and the recalculation of the batch records conducted for HSPC viability (Figure), (b) (4) HSPC cells (Figure), HSPC Dose (Figure) and (b) (4) (Figure).

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

he reanalysis of batch records confirmed the identified the concerns with the analytical methods impact the results. The reanalysis, while limited by the data collected at the time, does provide some assurances of the Phase 3 lots for the efficacy study. The revised batch records are sufficient to allow use of Phase 3 batch records and SAC-02 manufacturing.

3.2.P.5.5 Characterization of Impurities

Viable CD34+ cells define the purity of hematopoietic stem and progenitor cell (HSPC) drug product (DP). These key progenitor cells give rise to all hematopoietic lineages (including lymphocytes, monocytes, and granulocytes) for immune reconstitution. Viable HSPCs are identified by their expression of (b) (4) CD34+, and viability (b) (4).

3.2.P.5.5.2.1 Cell Based Impurities

Cell based impurities include (b) (4)

Reviewer comment: The Applicant uses FDA approved device to select CD34+ cells and the process has been historically evaluated with. The impurities listed and the characterization data is supported by the review of the HDE to for output consistency and generally are not expected to require specification limits. There are no concerns at this time, but a complete assessment of batch records is not possible because of deficiencies in the method used to collect the Phase 3 data. Any change in the reported data will impact the analysis.

The (b) (4) pose the greatest safety concern. These impurities have related specifications.

Reviewer comment: Due to deficiencies in the methods, the Applicant cannot assess (b) (4) in the HSPC DP. Even small changes to compensation or method changes can impact the (b) (4) because the target population is small the allowable number of (b) (4) is small making it likely the reported results might impact reported results.

3.2.P.6 Reference Standards or Materials

Analytical method controls including instrument calibration and performance verification standards, microbiological control standards, and quantitative analytical reference standards are used for the analytical methods.

Reviewer Comment: The reference standards used as part of the analytical method is reviewed with the methods, see section [3.2.P.5.1](#) and [3.2.P.5.6 \[HSPC\]](#) of the memo.

3.2.P.7 Container Closure System

This section is from consult review and review summary by Mona Mansouri (CBER/OTP/OCTHT/DCT1/CTTB).

The HSPC DP product is stored fresh for up to 60 hours in the same (b) (4) 150 mL (b) (4) Bag used for Treg DP (described in Section 3.2.P.2.4 [HSPC] above). The filled HSPC DP bag is placed into a secondary sterile resealable (b) (4) bag and co-packaged with the Treg DP bag in a single validated (b) (4) shipper for transport to the clinical site, where both products are stored refrigerated at 2-8°C until administration on Day 0.

Reviewer's Comment: The information provided regarding the HSPC container closure system is adequate. Additional details are provided in the consult reviewer's memo.

3.2.P.8 Stability

Section reviewed by RW.

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

The *in vitro* studies confirming stability of the hematopoietic stem and progenitor (HSPC) drug product (DP) were executed with the same studies for regulatory T cell (Treg) DP. (Please refer to section 3.2.P.8 [Treg] for details.)

Table 142. Primary HSPC DP Stability Batches

Batch Number	Manufacturing Site	Date of Manufacture	Long Term Stability Available Time Points - Hours PAC (Hours post formulation)	In-Use Stability Available Time Points – Hours PAC (Hours at (b) (4))
(b) (4)	SAC-02	(b) (4)	37hr (0hr), 60hr (23hr), 72hr (35hr)	72hr (0hr), (b) (4)
	SAC-02	(b) (4)	26hr (0hr), 48hr (22hr), 60hr (34hr), 72hr (46hr)	72hr (0hr), (b) (4)
	SAC-02	(b) (4)	29hr (1hr), 48hr (20hr), 61hr (33hr), 72hr (44hr)	72hr (0hr), (b) (4)

¹The (b) (4) PAC timepoint was delayed to (b) (4) PAC (b) (4) due to concurrent Treg DP testing Table reproduced from Table 1, eCTD 3.2.P.8.1 Stability Summary and Conclusions [HSPC], and Tables 2 and 3, eCTD 3.2.P.8.3 Stability Data [HSPC, Orca Bio] from original submission (no change in the MA)

3.2.P.8.1.1 Storage Stability Study

The *in vitro* studies confirming stability of the HSPC DP were executed with the same studies for Treg DP. (Please refer to 3.2.P.8.1.1 [Treg] for details.) Testing samples and time points are listed in Table . The container closure system and formulation used for the stability studies were the same as used for the commercial product. Acceptance criteria and summary of storage stability data are list in Table .

Table 143. Summary of HSPC DP Storage Stability Data at 5 ± 3°C

Test Parameter	Acceptance Criteria	Time of Formulation Mean (Range)	60-61hr PAC Mean (Range)	72hr PAC Mean (Range)
Appearance	Conforms	Conforms (b) (4)	Conforms (b) (4)	Conforms (b) (4)
(b) (4)	Report Results	(b) (4)	(b) (4)	(b) (4)
Cell Concentration (×10 ⁶ cells/mL)	Report Results	(b) (4)	(b) (4)	(b) (4)
Sterility (USP (b) (4))	NGD	NGD (b) (4)	Not tested (b) (4)	NGD (b) (4)

HSPC Phenotype	HSPC detected	HSPC detected (b) (4)	HSPC detected (b) (4)	HSPC detected (b) (4)
(b) (4)	Report Results	(b) (4)	(b) (4)	(b) (4)
Viable HSPC Cell Dose ($\times 10^6$ cells/kg)	Report Results	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Viability (%)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	Report Results	N/A (b) (4)	N/A (b) (4)	N/A (b) (4)
(b) (4)	Report Results	(b) (4)	(b) (4)	(b) (4)
(b) (4)	Report Results	(b) (4)	(b) (4)	(b) (4)
Dose ($\times 10^6$ cells/kg)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Viable HSPC (%)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Viable HSPC (b) (4)	Report Results	(b) (4)	(b) (4)	(b) (4)

NGD = No growth detected; PAC = Post-apheresis collection; (b) (4)

¹ (b) (4) had elevated (b) (4) due to (b) (4)

Table reproduced from Table 2, eCTD 3.2.P.8.3 Stability Data [HSPC] from original submission, 48 hour time points not included for simplicity of this table. The revision in the MA only affected % Viability of HSPC DP, % Viable HSPC, and (b) (4). The revised data has been reviewed; it did not affect the conclusion.

Reviewer Comment:

The Applicant assessed stability at formulation, 48-hour, 60-hour, and 72-hour PAC timepoints on HSPC DP stored at $5 \pm 3^\circ\text{C}$ in the commercial container closure system. All critical quality attributes met acceptance criteria through 72 hours PAC, supporting the proposed shelf life. (b) (4) (b) (4) shows a declining trend from a mean of (b) (4) at formulation to (b) (4) at 72 hours PAC, representing a (b) (4) decline over the storage period. However, the 72-hour value remains well above the (b) (4) specification, providing substantial margin for product variability. Viability, % viable HSPC, cell concentration and (b) (4), viable HSPC cell dose, and % viable HSPC (b) (4) remain relatively stable. The elevated (b) (4) for (b) (4) was investigated and attributed to (b) (4) interference in the analytical method. The (b) (4) for this batch was (b) (4), which is acceptable and consistent with the other batches. This finding led to an appropriate method update to exclude (b) (4) from the analysis, as described in Module 3.2.P.5.2.2 (HSPC). The updated method focusing on (b) (4) is more relevant for patient safety, as non-viable cells would not be expected to cause GVHD. Overall, the data support the proposed 72-hour shelf life from end of first apheresis collection when maintained at $5 \pm 3^\circ\text{C}$.

3.2.P.8.1.2 In-Use Stability Study

For HSPC DP in-use stability study, after the drug product was held for 72 hours PAC at $5 \pm 3^{\circ}\text{C}$, the DP was removed from cold storage, sampled, and placed at (b) (4) to simulate (b) (4) conditions during administration. Study samples were collected on time points described in Table . The acceptance criteria and summary of results for HSPC in-use stability are shown in Table .

(b) (4)

Reviewer Comment:

The in-use stability data demonstrate that HSPC DP maintains critical quality attributes when held at ambient temperature (b) (4) for up to (b) (4) following removal from

refrigerated storage. At the (b) (4) PAC timepoint (b) (4), all (b) batches met acceptance criteria for all parameters. Viability and % viable HSPC remained at 100% of the 72-hour PAC values (within analytical variation), demonstrating excellent stability of these critical purity attributes during the initial in-use period.

At (b) (4) PAC (b) (4) batches (b) (4) continued to meet all acceptance criteria. However, batch (b) (4), which was tested at (b) (4) PAC (b) (4) due to the timing delay, failed to pass the (b) (4) acceptance criterion.

This result clearly demonstrates that extended hold times at (b) (4) can compromise the functional activity of HSPC DP, even though viability remains stable. The viable HSPC cell dose was stable. These results support the Applicant's proposed in-use hold time of (b) (4) after removal from 5±3°C storage. The label should specify that HSPC DP should be administered as soon as possible after, and within (b) (4) being taken out of storage into ambient temperature.

3.2.P.8.1.3 In-Use Compatibility Study

The in vitro studies confirming in-use compatibility of the HSPC DP were executed with the same studies for Treg DP. (Please refer to 3.2.P.8.1.3 [Treg] for details.)

Table 145. Summary of In-Use Compatibility Data

Test Parameter	Acceptance Criteria
Appearance	Conforms
(b) (4)	Report Results
Cell Concentration (×10 ⁶ cells/mL)	Report Results
Sterility (b) (4)	NGD
HSPC Phenotype	HSPC detected
(b) (4)	See (b) (4)
(b) (4)	(b) (4) of pre-administration testing
Viable HSPC Cell Dose (×10 ⁶ cells/kg)	Report Results
(b) (4) (b) (4)	(b) (4)
(b) (4)	(b) (4) of pre-administration testing
Viability (%)	See relative viability
Relative Viability (%)	(b) (4) of pre-administration testing
(b) (4)	Report Results
(b) (4)	Report Results
(b) (4)	Report Results

(b) (4)

Viability HSPC (%)	See relative viable HSPC
Relative Viability HSPC (%)	(b) (4) administration testing
Viability HSPC (b) (4)	Report Results

(b) (4)

N/A = Not applicable; NGD = No growth detected; NT = Not tested; (b) (4)

(b) (4) had foreign particle (b) (4) observed in post-administration collection bag initially reported (b) (4) recovery due to (b) (4) error; reanalysis with correct (b) (4) showed (b) (4) recovery

Table reproduced from Tables 5 and 6, eCTD 3.2.P.8.3 Stability Data [HSPC, Orca] from original submission. The revision in the MA only affected % Viability of HSPC DP, % Viable HSPC, and (b) (4). The revised data has been reviewed; it did not affect the conclusion.

Reviewer Comment:

The in-use compatibility study demonstrates that HSPC DP is physically and chemically stable during administration through a standard infusion set with a (b) (4). All (b) (4) batches tested met the primary acceptance criteria, demonstrating that the critical product attributes are maintained during administration.

3.2.P.8.1.4 Clinical Data Analysis

The Applicant analyzed clinical data to provide supportive evidence for the proposed shelf life by correlating clinical outcomes with the vein-to-vein time (elapsed time from end of donor apheresis collection to start of HSPC DP infusion to the patient). The Applicant selected neutrophil engraftment and platelet engraftment for analysis and concluded that there were no correlation exists between the clinical outcomes and the vein-to-vein times.

Reviewer Comment:

The clinical data analysis provides supportive evidence that HSPC DP maintains efficacy throughout the proposed 72-hour shelf life. The lack of correlation between vein-to-vein time and engraftment outcomes (neutrophil and platelet) suggests that product quality and potency are likely maintained within the proposed storage period. The use of engraftment endpoints is appropriate for HSPC DP, as the primary function of these cells is to reconstitute the hematopoietic system following myeloablative conditioning. Successful engraftment is a direct measure of HSPC function and is clinically meaningful for patient outcomes. While the majority of clinical data points are below 60 hours PAC, limiting the direct clinical evidence for the 72-hour timepoint, the two datapoints above 60 hours are informative. Both patients achieved successful engraftment well within the acceptable timeframes. These results suggest that HSPC DP maintains its engraftment potential even at extended storage times approaching the proposed shelf life, which are consistent with results from in vitro stability studies. This clinical evidence complements the analytical stability data and supports the 72-hour shelf life from end of first apheresis collection.

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

The Applicant has committed to annual stability testing for HSPC DP using healthy donor apheresis material using the similar protocol described in eCTD 3.2.P.8.1 Stability Summary. The proposed annual stability schedule will be 72 (b) (4) with one point post expiration at (b) (4), which will allow for the logistics of completing all testing on same day as the 72-hour point. A small-scale stability container for use in Treg DP stability assessments is under development. The full-scale model will be used annually until the small-scale bridging data is completed and submitted.

Reviewer Comment:

The Applicant's post-approval stability commitment for HSPC DP is acceptable and appropriate.

OVERALL REVIEWER'S ASSESSMENT OF SECTION 3.2.P.8 [HSPC]

The information provided is acceptable.

3.2.P DRUG PRODUCT Tcon

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

Section reviewed by EL.

Tcon DP is a single cell suspension of conventional T cells (surface phenotype: (b) (4)CD3+) formulated in 15 ml cryopreservation buffer. Tcon DP is manufactured by formulating a portion of the apheresis material that contains a specific dose of T cells with cryopreservation media and subjecting the material to a (b) (4) freezing process. Other cell types are present in the Tcon DP in approximately the same proportion as their natural abundance in the apheresis starting material. If the Tcon is unable to be manufactured from the apheresis material Tcon DS/DP, the (b) (4) is used to create the Tcon DP.

Tcon DP is provided cryopreserved as a single-dose in an (b) (4) cryopreservation bag containing the cells, multiple electrolyte injection (MEI) (b) (4) mL), human serum albumin (HSA) (3% to 4% [w/v]), dimethyl sulfoxide (7.5% [v/v]) (DMSO), and Hetastarch (1.8% [w/v]) with an approximate volume of 15 mL. At the site of administration, the Tcon DP bag is thawed and diluted with Tcon diluent DP (30 mL of MEI + 2% (w/v) HSA).

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 active ingredient in the conventional T cells (Tcon) drug substance (DS) and drug product (DP) are the same, live cells purified from granulocyte-colony stimulating factor (G-CSF)-mobilized peripheral blood from a human leukocyte antigen (HLA)-matched donor.

3.2.P.2.1.2 Excipients

Table 146: Excipients for Tcon DP

Component	Concentration	Final Concentration	Function
Albumin (Human) Solution, (b) (4)	(b) (4)	3% to 4% (v/v)	Stabilizer
Multiple Electrolytes Injection (MEI) Type 1, (b) (4)	Undiluted	To 15 mL	Isotonic Solution
Hetastarch, (b) (4)	6%	1.8% [w/v]	Stabilizer
DMSO, (b) (4)	(b) (4)	7.5%	Cryopreserve

Table generated from data provided in eCTD 3.2.P.2.1 Components of the Drug Product [Tcon]

□ 2.1 Excipient Selection Rationale

See section 3.2.P.2.1.2.1 [Treg] Treg DP of this memo for rationale for the HSA and MEI as the same rationale is applied to the stabilizing the Tcon DP.

Hetastarch is added as an additional (b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Conventional T cells (Tcon) drug product (DP) is formulated in an (b) (4) cryopreservation bag containing the cells, Multiple Electrolytes Injection (MEI), Type 1, (b) (4), human serum albumin (HSA), dimethyl sulfoxide, and Hetastarch with an approximate volume of 15 mL. At the site of administration, the Tcon DP bag is thawed and diluted with 30 mL of MEI + 2% (w/v) HSA.

Dimethyl sulfoxide (DMSO) is used as an excipient to (b) (4)

□ 2.2 Compatibility of Excipients

The compatibility of the DP to the excipients is reviewed in the stability studies in section 3.2.P.2.2.6 [Tcon] of this memo.

3.2.P.2.2.2 Overages

No overage is provided for Tcon DP.

3.2.P.2.2.3 Physicochemical and Biological Properties

Tcon DS and DP maintain the same physicochemical properties as the active ingredient in both the Tcon DS and DP are the same, live cells purified from granulocyte-colony-stimulating factor (G-CSF)-mobilized peripheral blood from a human leukocyte antigen (HLA)-matched donor.

3.2.P.2.3 Manufacturing Process Development

See section 3.2.P.2.3 [Treg] of this memo for summary of the manufacturing process development history as it applies for all three DP.

Reviewer comment: The only manufacturing process specific to the Tcon DP are included here.

3.2.P.2.3.1 Control Strategy Development

A QTPP was created as described in section 3.2.P.2.3.1.1.1 [Treg].

□ 3.2.P.2.3.1.1 Identification of Critical Quality Attributes

3.2.P.2.3.1.1.1 Tcon DP Quality Target Product Profile (QTPP)

The identified QTPP elements relevant to Tcon DP are provided in Table .

Table 147. Tcon QTPP Elements Relevant to Drug Product Manufacturing

Category	Description
Dosage	<i>For all dosage calculations, “kg” = “kg of ideal adjusted body weight”</i> Tcon: Specified target number (with upper and lower bound) of viable Tcon cells per kg delivered intravenously, once, within a range of specified hours after start of HSPC infusion.
Active Ingredient Composition	Tcon DP: (b) (4) CD3+
Description	The Tcon DP is provided in an (b) (4) freezing bag and is frozen and stored in the vapor phase of liquid nitrogen in an approximate volume of 15 mL.
Formulation	Tcon DP consists of (b) (4) apheresis material formulated in (b) (4) (by volume) MEI (Type 1, (b) (4), 3-4% (w/v) HSA, 1.8% (w/v) hetastarch, and 7.5% (v/v) DMSO.
Cell Viability	Tcon: (b) (4) cells must be substantially viable at the time of administration
Purity	Tcon: Not applicable since neither positive nor negative selection of specific cell phenotypes is required to produce Tcon Drug Product
Potency	Tcon: Within a specified range of viable CD3 ⁺ cells per kg (product of % viable Tcon and (b) (4) limits must consider potential losses in potency during storage, shipment, and administration.
Identity	For cellular Drug Products: Positively identified via appropriate cell phenotyping
Appearance	No obvious visual anomalies and conforms to pre-determined color, opacity, packaging, and labels.
Product related cellular impurities and apheresis residuals	Tcon DP: Tcon DP contains residual (b) (4) from the apheresis process (b) (4) all (b) (4) grade).
Process related impurities and reagent residuals	Tcon DP: Leachables at levels justified or determined to be safe.
Particulates	All DPs: Cellular debris from (b) (4) at levels determined or justified to be safe. Visible and subvisible particles at levels determined to be safe.

Table adapted from Table 1 “QTPP Elements Relevant to Drug Product Manufacturing” in eCTD
3.2.P.2.3.1 Control Strategy Development [Treg]

3.2.P.2.3.1.1.1 Tcon DP Critical Quality Attribute Risk Assessment and Designation

A comprehensive risk ranking and filtering exercise was performed to rank each quality attribute to create a comprehensive list of Tier 1, Tier 2, and Tier 3 quality attributes for the HSPC DP:

- Tier 1: Critical to the QTPP (high criticality, CQA) and must be controlled. Certain attributes related to general composition, appearance, and safety are considered obligatory Tier 1 quality attributes.
- Tier 2: Lower impact to the QTPP and should be assessed to determine the appropriate control and testing strategies.
- Tier 3: Minimal/negligible impact to the QTPP, low criticality and are instead noted as obligatory in the final risk ranking.

To evaluate the list of potential quality attributes and rank them for criticality, a CQA risk assessment was performed using impact scores (potential severity of impact to safety and efficacy) and uncertainty scores (level of information on the attribute at the time of assessment). The impact and uncertainty scores were based on platform/product knowledge, in vitro data, non-clinical in vivo data, and/or clinical experience. The assessment is provided in Table .

Table 148. Tcon Impact Scoring Criteria

Impact Score	Immune Reconstitution (Tcon DP)
16 (High)	- Acute GVHD (Steroid Refractory Grade 3-4) - Severe chronic GVHD
8 (Medium)	- T-cells not reconstituted - Acute GVHD (Steroid Responsive Grade 3-4) - Moderate chronic GVHD
4 (Low)	- T-cells reconstituted however observable impact or delayed reconstitution
2 (Lowest)	- No changes observed - No impact to patient outcome

Adapted from Tables 2 and 3 in eCTD 3.2.P.2.3.1 Control Strategy Development [Treg]

As with the Treg DP (see [section 3.2.P.2.3.1.1.2 \[Treg\]](#) of this memo), overall criticality score classified each quality DP attribute. The HSPC related scoring is in

There was no ranking for safety attributes, including sterility, endotoxin adventitious agents, as they are required to be Tier 1 attributes. Additionally, HSPC phenotype and donor/patient match are required as Tier 1 identity attributes.

Table 149. Tcon Quality Attribute Criticality and Classification

Category	Attribute	Criticality Score (Impact x Uncertainty) / Tier	Classification Rationale
Safety	Sterility	NA / Tier 1	Obligatory safety attribute
	Endotoxin	NA / Tier 1	Obligatory safety attribute
	Adventitious Agents	NA / Tier 1	Obligatory safety attribute
Identity	HSPC phenotype	NA / Tier 1	Obligatory attribute
	Donor/patient match	NA / Tier 1	Obligatory attribute
Appearance	Physical State	NA / Tier 1	Obligatory attribute
	Clarity	NA / Tier 1	Obligatory attribute
	Color	NA / Tier 1	Obligatory attribute

Composition	Cell Aggregates	NA / Tier 1	Obligatory attribute
	Visible Foreign Particles	NA / Tier 1	Obligatory attribute
	Headspace	NA / Tier 1	Obligatory attribute
	Container Integrity	NA / Tier 1	Obligatory attribute
	MEI (Type 1 (b) (4) Concentration	NA / Tier 1	Obligatory attribute
	HSA Concentration	NA / Tier 1	Obligatory attribute
	(b) (4)	NA / Tier 1	Obligatory attribute
	DMSO	NA / Tier 1	Obligatory attribute
	Hetastarch	NA / Tier 1	Obligatory attribute
	Cell Concentration	NA / Tier 1	Obligatory attribute
	Volume	NA / Tier 1	Obligatory attribute
Potency	Viable T cell (CD3+) Cell Dose/kg	48 (16 x 3) / Tier 1	Dosing of Tcon addback based on studies suggest incidence of GVHD in a dose-dependent manner for Tcon addback with a general threshold for GVHD being (b) (4) and in a delayed T cell addback (b) (4) with any T cell dose that could promote immune reconstitution also risked GVHD
	Activation of T cells	48 (16 x 3) / Tier 1	(b) (4) is broadly recognized as an early activation marker of leukocytes, including lymphocytes, granulocytes, macrophages, and DCs
Purity – Target Cells	Purity – Target Cells	64 (16 x 2) / Tier 1	Cell Viability is a generally recognized critical indicator of cell health per Guidance
Purity – Non-Target Apheresis	(b) (4)	64 (8 x 3) / Tier 2	High doses of non-viable cells may theoretically lead to undesired immunogenicity; however, it is unlikely to lead to irreversible safety events; there is no clear risk in dosing non-viable cells from a stem cell transplant or blood product assuming a matched allogeneic donor.
Purity – Process Related	Extractables and Leachables	16 (4 x 4) / Tier 2	Specific compounds identified in worst-case extraction studies of consumables and final product containers are considered Tier 2 attributes if the calculated theoretical worst-case dose is above the PDE. Tier classification is re-assessed once a leachables study (using actual product or representative solutions/conditions) is conducted and assessed against the PDE.

Adapted from Table 5 in eCTD section 3.2.P.2.3.1 Control Strategy Development [Treg]

□ 3.2.P.2.3.1.2 Process Parameter Risk Assessment

A process parameter risk assessment was performed as described in [section 3.2.P.2.3.1.2 \[Treg\]](#), specifically for the process used to generate the Tcon DP. The assessment of the criticality of the process parameters is shown in Table .

Reviewer comment: Table is a list of all pCPP that were further investigated for establishment as CPP or Non-CPP. It is a non-inclusive list of Non-CPP and thus may not recapitulate the Non-CPP listed in [section 3.2.P.3.4.1 \[Tcon\]](#) and [section 3.2.P.3.4.4 \[Tcon\]](#).

Table 150. Summary of Process Parameter Risk Assessment (Rev2.0) for Tcon DP Manufacturing

Unit Operation	Process Parameter	Criticality Score Rev 2.0 (Impact x Control)	PP Criticality
(b) (4)			
Tcon Formulation/Fill	(b) (4) of [Tcon DS] prior to Cryo Media Addition	8 (4 x 2)	Non-CPP
	(b) (4) of Cryo Media prior to Addition to [Tcon DS]	8 (4 x 2)	Non-CPP
	Amount of Cryo Media to Add to [Tcon DS]	16 (16 x 1)	CPP
	Tcon DP Final Volume	16 (16 x 1)	CPP

Cryo Media = Cryopreservation Media

¹ Unit operations noted as they are necessary for generation of Tcon DP from (b) (4) material.

² (b) (4)

Table adapted from Table 27 "Summary of Parameter Classification Changes from Revision 2.0 Assessment" in eCTD section 3.2.P.2.3.1 Control Strategy Development [Treg]

□ **3.2.P.2.3.1.3 Process Development and Characterization by Unit Operation**

Process characterization studies were conducted as described in section 3.2.P.2.3.1.3 [Treg], specifically for the process used to generate the Tcon DP are in Table .

Table 151. Summary of Process Development Studies and Established PAR for Tcon DP Manufacturing Process Parameters

(b) (4)

(b) (4)

Tcon Formulation/ Fill	(b) (4) of [Tcon DS] prior to Cryo Media Addition (b) (4)	(b) (4) (PAR)	NA	Non-CPP	Per characterization testing, no practical differences exist between the preparation of Tcon DP (b) (4).
	(b) (4) of Cryo Media prior to Addition to [Tcon DS]	(b) (4) (PAR)	NA	Non-CPP	Per characterization testing, no practical differences exist between the preparation of Tcon DP at (b) (4).
	Amount of Cryo Media to Add to [Tcon DS] (Cryo Media : Tcon DS Volume, v/v)	(b) (4) (PAR)	(b) (4)	CPP	Based on historical data. No effect on DP quality.
	Tcon DP Final Volume (mL)	(b) (4) (PAR)	13	CPP	Based on historical data. No effect on DP quality.

¹ Unit operations only noted if necessary to generation of Tcon DP from (b) (4) material.

² (b) (4)

Reviewer generated table from information in eCTD sections 3.2.P.2.3.1 Control Strategy Development [Treg] and 3.2.P.3.3 Description of Manufacturing Process and Process Controls [Treg]

□ 3.2.P.2.3.1.4 In-Process Hold Times

In-process hold times were assessed as described in section 3.2.P.2.3.1.4 [Treg] and are provided in Table for the Tcon DP. For more information about the hold time tracking in the planned Continued Process Verification (CPV), including justification, see section 3.2.P.3.5.3 [Tcon].

Table 152. Summary of Hold Time Historical Data for Tcon DP Manufacturing

Unit Operation	In-Process Material ² (Hold Temp °C)	# Batches Analyzed	Mean Hold Time (SD) (b) (4)	Mean (b) (4) *SD Hold Time (b) (4)	Track in CPV?
----------------	--	--------------------	--------------------------------	--	---------------

(b) (4)

(b) (4)

Tcon DP Formulation/ Fill	Tcon DP, Pre-Cryopreservation (b) (4)
Tcon DP Cryopreservation	Tcon DP at (b) (4) (b) (4) Tcon Removal from CRF (b) (4)
Tcon DP Packaging	Tcon Post Cryopreservation Packaging (b) (4)

(b) (4)

¹ Applicant defines the specific hold time start and end steps in Table 13 in eCTD section 3.2.P.2.3.1, which is omitted from this table due to space requirements.

² Unit operations only noted if necessary to generation of Tcon DP from (b) (4) material.

Table adapted from Table 13 “In-Process Hold Time Descriptions and Lots Evaluated” and Table 14 “Historical Data Summary and CPV Inclusion Rationale” in eCTD section 3.2.P.2.3.1 Control Strategy Development [Treg]

□ 3.2.P.2.3.1.5 Process Control Strategy

The Tcon DP process control strategy involves control of:

- Critical process parameters (CPPs) – see [section 3.2.P.3.4.1 \[Tcon\]](#)
- Non-critical process parameters (Non-CPPs) - [section 3.2.P.3.4.4 \[Tcon\]](#)
- In-process controls (IPCs) – see [section 3.2.P.3.4.2 \[Tcon\]](#)
- Key performance indicators (KPIs) – see [section 3.2.P.3.4.3 \[Tcon\]](#)
- DP release testing – see [section 3.2.P.5.1 and 3.2.P.5.2 \[Tcon\]](#)
- Continued process verification (CPV) testing – see [section 3.2.P.5.3 \[Treg\]](#)

The process control strategy was assessed for robustness through the performance of PPQ studies, as described in [section 3.2.P.3.5.3 \[Treg\]](#).

3.2.P.2.3.2 Process History and Process Changes

□ 3.2.P.2.3.2.1 Tcon Drug Product Process Development (b) (4) During Phase 1b and Phase 3 Trials

For summary information on the initial process development, see [section 3.2.P.2.3.2.1 \[Treg\]](#). The changes that apply to the Tcon DP during the Phase 1b and Phase 3 study are outlined in Table .

(b) (4)

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

(b) (4)

(b) (4)

□ **3.2.P.2.3.2.3 Tcon DP Commercial Process Development at SAC-02**

The Tcon drug product manufacturing process has been (b) (4) the commercial manufacturing facility (SAC-02). The Tcon specific changes are in Table .

See section 3.2.P.2.3.2.2 [Treg] and section 3.2.P.2.3.2.3 [Treg] for a summary of commercial process development and post-comparability process development including general process changes applicable to all three cellular DPs, respectively.

Table 156. Summary of Manufacturing Process Changes Between Clinical and

(b) (4)

(b) (4)

Table reproduced from Table 10 “Summary of Manufacturing Process Changes Between Clinical and Comparability/Commercial” in eCTD section 3.2.P.2.3.2 Process History and Process Changes [Tcon.]
Reviewer Comment: This is acceptable.

□ **3.2.P.2.3.2.4 Post-Comparability Manufacturing Changes**

A gap assessment was conducted following the analytical comparability study to document any additional modifications to the SAC-02 CGMP. See section 3.2.P.2.3.2.3 [Treg] for a summary of post-comparability process development including general process changes applicable to all three cellular DPs, respectively.

□ **3.2.P.2.3.2.5 Tcon DP Analytical Development History**

The following changes were made (b) (4) during the Phase 3 study:

- Percent Viable (b) (4) T Cells: % T cells, without accounting for viability, was reported during the Phase 1b study. For the Phase 3 study purity specification, % Viable T cells was calculated by (b) (4).
- Viable (CD3+) T Cell Dose: Tcon T Cell Dose, without accounting for viability, was reported during the Phase 1b study. For the Phase 3 study purity specification, Viable T Cell Dose was calculated by (b) (4).

As part of the Phase 3 filing submitted to IND 18773, the following changes were made to the specification for Tcon DP:

- Visual inspection was included in the lot release.
- T Cell Phenotype was added with a specification of T cells detected.
- Viable T-Cell Dose was added to the specification as (b) (4) x 10⁶ cells/kg, Total T-Cell (CD3+) Dose was removed along with the post thaw counts conducted at the clinical site.

Reviewer Comment: The acceptability of the specification and analytical methods is assessed in section 3.2.P.5.1 [Tcon] and 3.2.P.5.6 [Tcon], respectively, of this memo.

3.2.P.2.3.3 Comparability Assessments

The methodology for the comparability assessment is reviewed in section 3.2.P.2.3.3 [Treg]. The Tcon attributes measured in the comparability assessment were determined based on risk and are summarized in Table . Tier 1 attributes reflect the highest

criticality attributes, followed by Tier 2 as mid-level criticality. As with other DP, the Tcon DP, (b) (4) and Viable T Cell Dose were calculated by assuming a patient weight of 50 kg for material produced at each site.

Table 157. Tcon Quality Attributes Comparability Assessment

Classification	Comparability Attribute	Assay
Safety	14-Day Sterility	(b) (4)
	(b) (4) Stain	
	Endotoxin	
Tier 1 Attributes	(b) (4)	
	(b) (4)	
	Viable T Cell Dose	
Tier 2 Attributes	% Viable T Cells	
	(b) (4)	

Table reproduced from Table 1 in eCTD section 3.2.P.2.3.3 Comparability Assessments [Tcon]

The Applicant used the same approach as with Treg and HSPC DP to conduct a statistical evaluation of the historical experience, described in section 3.2.P.2.3.3 [Treg] of this memo. The analysis is provided in Table .

Table 158: Historical Data Relevant to Deriving Tcon DP PSDs

Attribute	N b	Mean	Min	Max	St Dev	Specification c	PSDs
(b) (4)	(b) (4)						
(b) (4)							
Viable T Cell Dose (x1E6 cells/kg)							

Table reproduced from Table 2 eCTD section 3.2.P.2.3.3 Comparability Assessments [Tcon]

The Tcon manufacturing runs were successful with no discrepancies. The results are reported in Table and Figure .

Table 159. Tcon Drug Product Tier 1 Attributes TOST Results

Attribute	PSD	Normalized Mean Difference (N ^{(b) (4)})	p-value Mean ≤ -PSD	p-value Mean ≥ PSD	Result
(b) (4)	(b) (4)				Equivalent
(b) (4)	(b) (4)				Equivalent
Viable T Cell Dose (x1E6 cells/kg)	(b) (4)				Equivalent

Table reproduced from Table 5 in eCTD 3.2.P.2.3.3 Comparability Assessments [Tcon]

(b) (4)

(b) (4)

Table 160. Tcon Drug Product Tier 2 Attribute Results

Attribute	
% Viable T cells	
(b) (4)	
(b) (4)	

Table reproduced from Table 7 in eCTD 3.2.P.2.3.3 Comparability Assessments [Tcon]

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

This is acceptable

3.2.P.2.4 Container Closure System

This section is from consult review and review summary by Mona Mansouri (CBER/OTP/OCTHT/DCT1/CTTB).

The Tcon DP container closure system is described in Section 3.2.P.2.4 [Treg] of this memo.

Reviewer's Comment: *The information provided regarding the Tcon container closure system is adequate. Additional details are provided in the consult reviewer's memo.*

3.2.P.2.5 Microbiological Attributes

Microbiological attributes for the HSPC DP are the same as for the Treg DP. See section 3.2.P.2.5 [Treg] of this memo.

3.2.P.2.6 Compatibility

See Section 3.2.P.8.1 [Tcon].

3.2.P.3 Manufacture

This section reviewed by EL.

3.2.P.3.1 Manufacturer(s)

See section 3.2.P.3.1 [Treg].

3.2.P.3.2 Batch Formula

The batch formula for the Tcon DP is $1.3 - 6.9 \times 10^6$ viable CD3+ cells per patient kg in up to (b) (4) mL MEI, Type 1 formulated with 3.0% – 4.0% (w/v) HSA, 7.5% (v/v) DMSO, and 1.8% Hetastarch (w/v), and 0.3% (w/v) Sodium Chloride Injection.

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

The BITS-ABC ingredient database provided UNII code 451W47IQ8X for sodium chloride. Information provided is acceptable, with no deficiencies identified.

3.2.P.3.3 Description of Manufacturing Process

The manufacturing process of each batch of Tcon DP involves (b) (4) and Tcon Formulation and Fill. (b) (4) steps occur in an ISO (b) (4) environment. (b) (4) Tcon Formulation and Fill steps occur in an ISO (b) (4) in an ISO (b) (4) environment, see Figure , Tcon DP is preferentially manufactured from the (b) (4) , as outlined in Figure , which is referred to as the “Primary Pathway.” However, there is an “Alternative Pathway” to manufacture the Tcon from the (b) (4) , as outlined in Figure , depending on (b) (4) steps occur in an ISO (b) (4) environment. See section 3.2.P.2.3.2 [Tcon] for comparison of the Tcon using each starting material.

□ 3.2.P.3.3.4.3 (b) (4)

This information is provided in eCTD 3.2.P.3.3.4.3 [Treg] of the submission.

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

□ 3.2.P.3.3.4.6 Tcon Formulation, Fill, and Cryopreservation

This information is provided in eCTD 3.2.P.3.3.4.6 [Tcon] of the submission.

Figure 102: Tcon Formulation, Fill, and Cryopreservation Process Flow

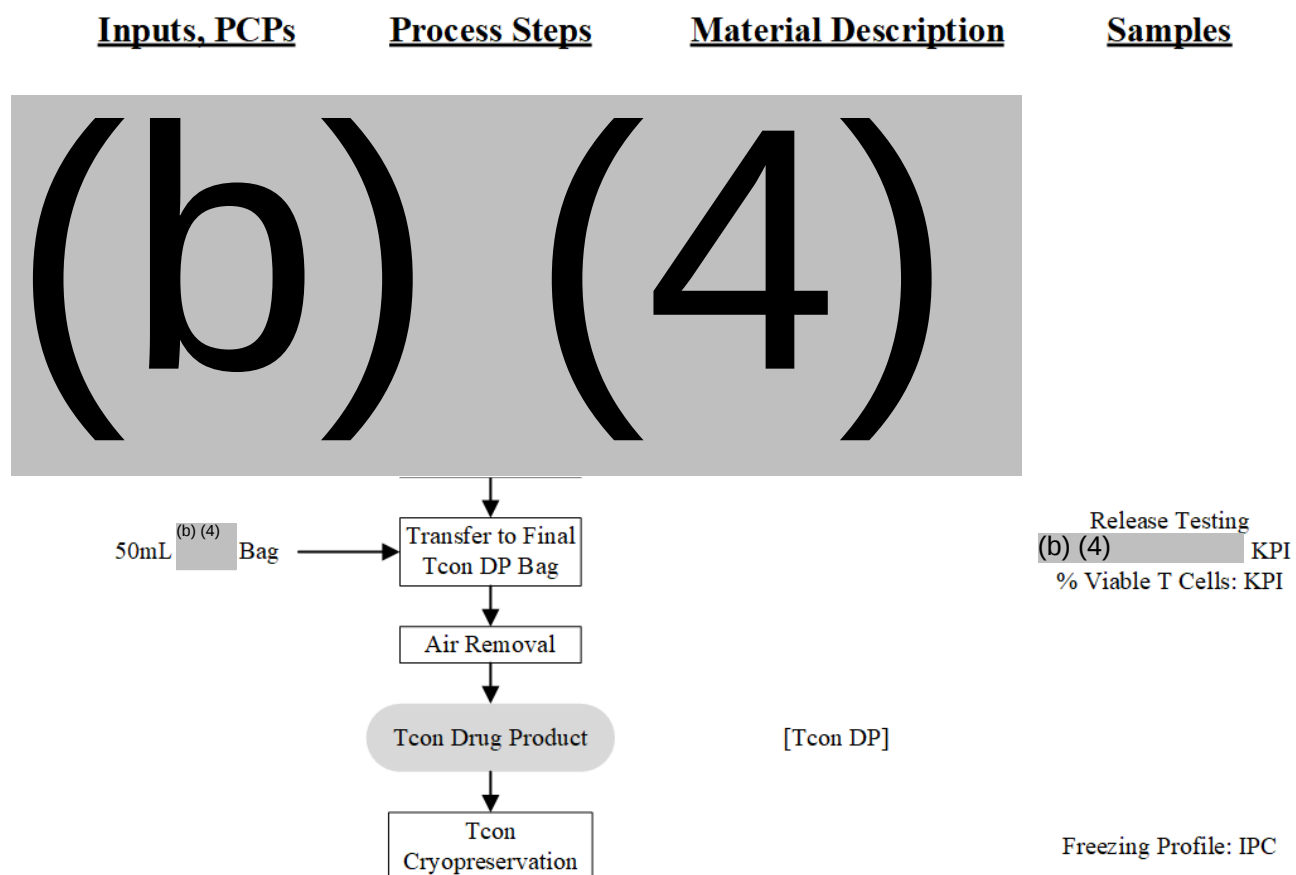


Figure reproduced from Figure 5 in eCTD 3.2.P.3.3 Description of Manufacturing Process and Process Controls [Tcon]

(b) (4)

3. The material is transferred from the (b) (4) into the 50 mL cryopreservation bag using sterile welds (now referred to as [Tcon DP]).
4. Air is removed from the [Tcon DP] container using a syringe, and all samples for testing are removed using a syringe.
5. The tubing of the [Tcon DP] container is (b) (4) closed, label is applied, and a visual inspection is performed.
6. The [Tcon DP] bag (primary container closure) is placed into a secondary sterile resealable (b) (4) bag and transferred with a labeled aluminum cryo-cassette to the freezing room.

7. The [Tcon DP] is immediately placed into a freezing press inside a (b) (4) freezer and, after addition of a temperature probe, is frozen via a pre-defined freezing program.
8. The cryopreserved [Tcon DP] is transferred to the labeled cassette and immediately packaged in a liquid nitrogen dry shipper.

Overall Reviewer's Assessment of Section 3.2.P.3.3:
Information provided is acceptable, with no deficiencies identified.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The manufacturing of Tcon DP is a continuous process from initiation to formulation with limited hold times. The process control strategy contains the same elements outlined in section 3.2.P.3.4 [Treg] of this memo.

3.2.P.3.4.1 Critical Process Parameters (CPPs)

Tcon DP CPPs were determined using a quality risk ranking and filtering approach as described for Treg in section 3.2.P.2.3.1 [Treg] of this memo. CPPs for the Tcon DP are summarized in Table along with the CQAs that may be impacted by the CPP with associated proven acceptable range (PAR). CPPs for (b) (4) Tcon overlap with the CPP for the Treg DP and provided in Table 43. The methodology and data used to select the PARs for CPPs are provided in section 3.2.P.2.3.1 [Treg] of this memo.

(b) (4)

Table generated with data from eCTD 3.2.P.3.3 Description of Manufacturing Process and Process Controls [Tcon] and eCTD 3.2.P.3.4 Controls of Critical Steps and Intermediates [Tcon, Cell Suspension for Infusion]

3.2.P.3.4.2 In-Process Controls (IPCs)

The IPCs for manufacture of the Tcon DP are provided in Table . The IPCs were selected based on the control strategy risk assessment outlined in section of 3.2.P.2.3.1 [Treg] of this memo. There are no IPCs prior to the Tcon Formulation and Fill unit operation that are applicable to the manufacture of the Tcon DP.

Table 162. IPCs in Tcon DP Manufacture

Unit Operation	In-Process Control	Acceptance Criteria	Control Objective
Tcon Formulation, and Fill	Tcon DP Freezing Profile	Comparable to reference (Figure)	Ensure that the Tcon DP underwent freezing at an acceptable rate. If the freezing profile does not conform to the reference, there may be an impact to purity or potency of the Tcon DP administered to the patient.

Table reproduced from Table 2 form eCTD 3.2.P.3.4 Controls of Critical Steps and Intermediates [Tcon, Cell Suspension for Infusion]

(b) (4)

(b) (4)

The Applicant has set criteria for comparing the Tcon DP freezing profile comparable to reference criteria including based on the expected documented stages during the process noted in A-F of Figure . Overall Freezing Program Reference

3.2.P.3.4.3 Process Control Points (PCPs)

he Process Control Points (PCPs) for Tcon are (b) (4) shared with the Treg PCPs and provided in Table 45.

Table 163. PCPs in Tcon DP Manufacturing

Unit Operation	PCP	Controlling Measurement	Decision Tree
----------------	-----	-------------------------	---------------

(b) (4)

3.2.P.3.4.4 Non-Critical Process Parameters (Non-CPPs)

The non-critical process parameters for the Tcon DP manufacturing, are shown in Table . The CPPs for (b) (4) and CPPs the (b) (4) overlap with the CPPs for the Treg DP and are provided in Table 46.

(b) (4)

Reviewer Comment: The CPP for the (b) (4) source material overlap with the CPP already in place for the other DPs. The acceptability of those CPP has been reviewed and are supported for the Tcon for with similar justification as the other DP.

3.2.P.3.4.5 Key Performance Indicators (KPI)

(b) (4)

3.2.P.3.4.6 Control of Intermediates

The cryopreservation media is prepared the day of manufacture in a (b) (4). If cryopreservation media remains at the end of the process, it is discarded.

For information on the control of other pre-batch solutions, reagents, and consumables, see section 3.2.P.3.4.6 [Treg].

3.2.P.3.4.4 In-Process Hold Times

The Tcon DP is processed continuously with no formally defined intermediates or process hold points, but in-process material may be held intermittently as operations are performed or preparations are made for the next step. A historical analysis has been performed to characterize the typical processing times and hold times for the process. See section 3.2.P.2.3.1.4 [Tcon].

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

Information provided is acceptable, with no deficiencies identified.

3.2.P.3.5 Process Validation and/or Evaluation

The information reviewed within this section were provided in eCTD section 3.2.P.3.5 [Treg].

The Applicant process validation approach included all three DP. See section 3.2.P.3.5 [Treg] for a review of the study design. The supporting validation studies include:

- Process performance qualification (PPQ)
- Continued Process Verification (CPV)
- (b) (4) validation
- Solution and consumables hold validations
- Aseptic process simulation (APS)

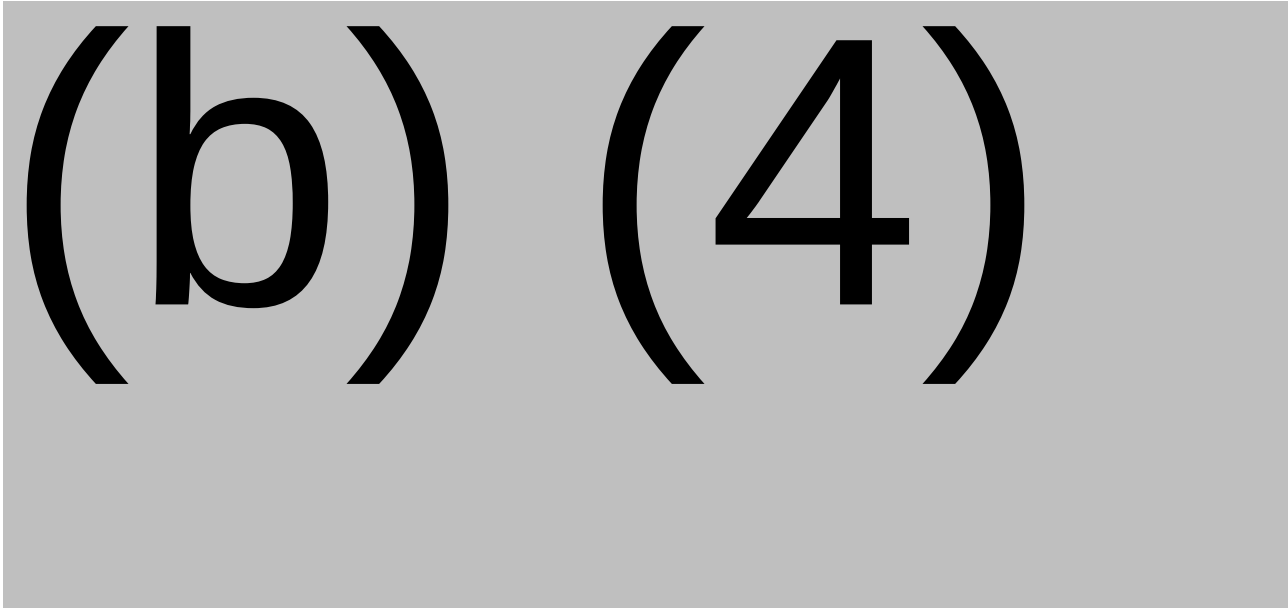
3.2.P.3.5.2 Process Performance Qualification

Updated to include reanalysis results reported in eCTD 1.11.1 Quality Information Amendment received in Amendment 52.

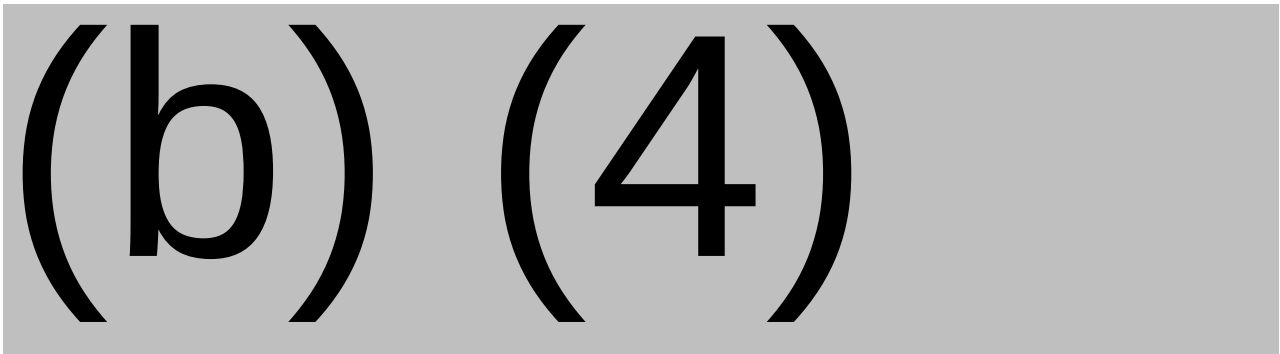
(b) (4)

A large rectangular area of the document is redacted with a solid gray fill.

(b) (4)

A large rectangular area of the document is redacted with a solid gray fill.

(b) (4)

A large rectangular area of the document is redacted with a solid gray fill.

(b) (4)

A large rectangular area of the document is redacted with a solid gray fill.

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

Reviewer Comment: The PPQ study includes both sources of Tcon within the (b) (4) lots rather than (b) (4) lots of each. This is regulatory judgement based on the (b) (4) process overlapping with the Treg DP manufacturing and the Tcon DP composition. This is acceptable for the Tcon DP.

2.4 Validation Assessment of Revisions following PPQ Completion

After PPQ was completed, several lot release quality attributes, IPCs, and CPPs were revised. This was primarily due to finalization of commercial specifications where the PPQ was performed using clinical specifications as shown in Table

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer Comment: The CPV for the Tcon is acceptable.

Overall Reviewer's Assessment of Section 3.2.P.3.5:
Information provided is acceptable, with no deficiencies identified.

3.2.P.4 Control of Excipients

Reviewed by SK.

The excipients in the Tcon DP are outlined in Table , and **Error! Reference source not found..** Tcon DP is formulated using HSA, MEI, 6% Hetastarch in 0.9% Sodium Chloride Injection (HESPAN), and DMSO. Relevant information pertaining to the MEI and HSA is in section 3.2.P.4 [Treg].

Table 171. Compendial Excipients Used in Tcon DP

Excipient	Supplier	Compendial Reference
Albumin (Human) (b) (4) Solution, USP (b) (4)	(b) (4)	(b) (4) Manufactured from human plasma units collected in US plasmapheresis centers licensed by FDA
Dimethyl Sulfoxide (DMSO)	(b) (4)	(b) (4)
Multiple Electrolytes Injection, Type 1, (b) (4) (MEI) (b) (4)	(b) (4)	(b) (4)

Table reproduced from Table 1 in eCTD section 3.2.P.4.1 Specifications [Tcon]

Reviewer Comment: No Tcon DP-specific concerns regarding the (b) (4) excipients. The (b) (4) excipients are acceptable.

Table 172. Non-compendial Excipient Used in Tcon Drug Product

Excipient	Supplier	Approval Reference	Linked Documents
(b) (4)	(b) (4)	Manufacturer's Specification (approved for IV administration under NDA (b) (4))	COA 6% Hetastarch in 0.9% Sodium Chloride Injection

Table adapted from Table 3 in eCTD section 3.2.P.4.1 Specifications [Tcon]

DMSO (b) (4) is a widely used excipient for the cryopreservation of approved cell therapy products.

(b) (4) has been cleared by FDA for use in the manufacture of cord blood products. It is also approved by the FDA for treatment of hypovolemia when plasma volume expansion is desired in settings where adequate alternative treatment is unavailable.

Reviewer Comment: Based on the review of information provided by the Applicant and the associated FDA labeling and COA for excipients used, the compendial and non-compendial (b) (4) excipients used in formulation of Tcon DP are acceptable.

3.2.P.4.1 Specifications

DMSO: Identity testing is performed in-house by label verification and validated external identity testing per (b) (4). DMSO is tested by (b) (4) various attributes shown in Table 2 in eCTD section 3.2.P.4.1 Specifications [Tcon, Cell Suspension for Infusion].

(b) (4) : Identity testing is performed using both (b) (4) identification testing per (b) (4) identification tests) and (b) (4) identification testing via (b) (4)

Reviewer comment: The specifications for the non-compendial excipients are acceptable.

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

All excipients used in the manufacture of Tcon DP are (b) (4) except (b) (4). The (b) (4) excipients conform to the standards outlined in the (b) (4).

(b) (4)

Reviewer Comment: The validation of analytical procedures used for (b) (4) 6% Hetastarch in 0.9% Sodium Chloride Injection is acceptable.

3.2.P.4.4 Justification of Specifications

MEI, HSA and DMSO are (b) (4) excipients. (b) (4) is manufactured under cGMP. It has been allowed for use in cord-blood transfusions.

Reviewer Comment: The justification of specification for excipients is acceptable.

3.2.P.4.5 Excipients of Human or Animal Origin

The HSA is from human origin and is reviewed in section 3.2.P.4.5 [Treg].

3.2.P.4.6 Novel Excipient

There are no novel excipients used in the Tcon DP.

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

The excipients used in the manufacture of Tcon DP are acceptable from quality and safety perspective. No deficiencies 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)

This section is reviewed by EL.

Reviewer comment: This section has been updated using data from eCTD section 3.2.R Regional Information document "RPT-0342- JUSTIFICATION OF COMMERCIAL SPECIFICATION FOR ORCA-T" in Amendment 52 (24Apr2026).

3.2.P.5.1 Specifications

The Tcon DP release specification are provided in Table . The proposed changes to the Tcon DP specifications are provided in Table and Table . The determination of the final acceptance criterion is discussed below with the justification of specifications.

Table 173: Tcon DP Release Specifications

Test Attribute	Analytical Procedure	Commercial Acceptance Criteria	Justification for Specification	Clinical Acceptance Criteria	PPQ Acceptance Criteria
Tcon Phenotype	Tcon (b) (4)	T-Cell detected	Confirm the identity of the active cells of interest	Confirm the identity of the active cells of interest	Confirm the identity of the active cells of interest
Viability	Tcon (b) (4)	(b) (4)	Manufacturing history, clinical data correlation	(b) (4)	(b) (4)
Viable T Cell Dose	Calculation: Product of % Viable T Cells (b) (4)	1.3E6 to 6.9E6 cells/kg	Manufacturing history, clinical data correlation	(b) (4) cells/kg	(b) (4) cells/kg
Appearance	(b) (4) Visual Inspection of Injection	Clear to opaque liquid Color is off-white, white, yellow, orange, to red No visible foreign particles No defects	Manufacturing history	N/A	N/A

Endotoxin	(b) (4) Bacterial Endotoxins Test (b) (4) Assay	(b) (4)	Safety Limits	(b) (4)	
Interim Sterility Assurance	(b) (4) Microbial Characterization, Identification, and Strain Typing – (b) (4)	No organisms detected	Safety Limits	No organisms detected	No organisms detected
Sterility ^a	(b) (4) Sterility Tests (14-Day)	No organisms detected (Post administration results)	Safety Limits	No organisms detected (Post administration results)	No organisms detected (Post administration results)

Reviewer generated table

^a The product is released based on interim assurances of sterility with final (b) (4) -based sterility results available after administration

Table 174. Changes to Proposed Tcon DP Commercial Specifications

Test Attribute	Final Acceptance Criterion	Proposed Commercial Acceptance Criterion	Clinical Acceptance Criterion	Phase 3 Range Responded
Viability	(b) (4)			
Viable T Cell Dose	1.3E6 to 6.9E6 cells/kg	(b) (4) E6 to 6.9E6 cells/kg ¹	(b) (4) cells/kg	1.3E6 to 6.9E6 cells/kg

Reviewer generated table

Reviewer Comment: In Amendment 68 (16Jun2026), the Applicant agreed to the proposed specifications sent in CMC IR #32 (16Jun2026). This is acceptable. See discussion of the final acceptance criteria for each specification below.

3.2.P.5.6 Justification of Specifications

See section 3.2.P.5.6 [Treg] for a description of the approaches used to generate and support the proposed acceptance criteria.

□ Viability

The original method tolerance interval is (b) (4) and the updated methods tolerance interval is (b) (4). The total range of data analyzed for clinical outcome correlations was (b) (4) with only (b) (4) OOS lots. There was no correlation to the clinical outcome of T cell counts at day (b) (4). The calculated highest possible (b) (4).

Figure 104. Phase 3 OOS Batches for Tcon DP Viability

Batch Lot	Clinical Acceptance Criterion	Revised	Original	Response
(b) (4)				Alive and free from moderate or severe cGVHD
				Alive and free from moderate or severe cGVHD

Reviewer generated table

The final commercial acceptance criterion for Viability is (b) (4)

Reviewer Comment: We cannot agree to a viability acceptance criterion lower than (b) (4), as there is no efficacy data at these levels. The Tcon DP is very similar to HSCT from apheresis material, which can be administered even with poor viability. The need to provide regulatory flexibility for this specification is questionable because this attribute consistently meets the acceptance criterion of (b) (4), with only (b) (4) OOS lots generated in both the Phase 1 and Phase 3 studies. In Amendment 68 (16Jun2026), the Applicant agreed to the proposed acceptance criterion for Viability sent in CMC IR #32 (16Jun2026), which is acceptable.

□ **Viable T Cell Dose** The final specification is

The original tolerance interval is $(b) (4) \times 10^6 - 6 \times 10^6$ cells/kg and with the updated methods is $(b) (4) \times 10^6$ cells/kg. The clinical data range examined was $(b) (4) \times 10^6$ cells/kg. With no correlation observed with the clinical outcomes, the proposed specification is based tolerance interval analysis $(b) (4) \times 10^6 - 3.5 \times 10^6$ cells/kg.

Table 175. Phase 3 OOS Batches for Tcon DP Viable T-cell Dose ($\times 10^6$ cells/kg)

Batch Lot	Clinical Acceptance Criterion	Revised	Original	Response
(b) (4)				Alive and free from moderate or severe cGVHD
				Alive and free from moderate or severe cGVHD

Reviewer generated table

The final commercial acceptance criterion for Viable T Cell Dose is $1.3 - (b) (4) \times 10^6$ cells/kg.

Reviewer Comment: We cannot agree to lower Tcon dose as there is no data to support efficacy at the lower range. Lot (b) (4) was not reanalyzed due to lack of additional characterization data collected at time of lot release. However, due to the mixed population in Tcon DP and the overall consistency between the new and old methods for this attribute, it's reasonable to lower the acceptance criterion to 1.3×10^6 cells/kg from $(b) (4) \times 10^6$ cells/kg. In Amendment 68 (16Jun2026), the Applicant agreed to the proposed acceptance criterion for Viable T Cell Dose sent in CMC IR #32 (16Jun2026), which is acceptable.

□ **Visual Inspection**

Reviewed by DBSQC. See DBSQC memo by Salil Ghosh (CBER/OCBQ/DBSQC/LAC).
(b) (4) Visual Inspection of Injection

□ **Sterility**

Reviewed by DBSQC. See DBSQC memo by Claire Wernly (CBER/OCBQ/DBSQC/LMIVTS).

(b) (4) Microbial Characterization, Identification, and Strain Typing

(b) (4) Sterility Test (b) (4)

Reviewer comment: See [section 3.2.P.5.6 \[Treg\]](#) for description of the action plan for positive sterility test result.

□ **Endotoxin**

Reviewed by DBSQC. See DBSQC memo by Claire Wernly (CBER/OCBQ/DBSQC/LMIVTS).

(b) (4) *Bacterial Endotoxins*

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

There are overarching safety concerns regarding Applicant's proposal of widening the acceptance criteria for all three DP at once. The entire MOA of this product is to reduce the GVHD risk of the HSPC DP and Tcon DP. By proposing to change the HSPC and Treg DP outside the ranges assessed in the clinical studies, there is uncertainty about the product's ability to remain effective and safe. Our concerns were communicated to the Applicant in CMC IR #32 (16Jun2026), in which we asked the applicant to agree to our proposed acceptance criteria. In Amendment 68 (16Jun2026), the Applicant agreed to our proposal. This is acceptable.

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

The critical findings in this section are related to **Major Deficiency #1 and 2**

Initial Assessment Leading to Major Deficiency #1 and 2

For a complete assessment of the major deficiencies, please see Appendix 1 and [section 3.2.P.5.2 and 3.2.P.5.3 \[Treg\]](#).

A major amendment was declared on 27Mar2026, after communicating the CMC MAJOR DEFICIENCIES on 26Mar2026, including CMC Major Deficiency #1 and #2 concerning (1) control of the (b) (4) Assay and (2) the need for supplemental validation of the (b) (4)

Assay. The Applicant provided a final response to the CMC MAJOR DEFICIENCIES on 24Apr2026.

MAJOR AMENDMENT: MAJOR DEFICIENCY #1 and #2 Assessment:

(b) (4)

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

(b) (4)



Appearance by Visual Inspection

Appearance is performed per (b) (4) Visual
Inspection of Injection.

Reviewed by DBSQC. See memo by Salil Ghosh.

Sterility

Sterility is performed per (b) (4) Sterility Test (b) (4) and (b) (4)
Microbial Characterization, Identification, and Strain Typing.

Reviewed by DBSQC. See memo by Claire Wernly

Endotoxin

Endotoxin testing is performed per (b) (4) Bacterial Endotoxins Test (b) (4)
(b) (4) Assay, using FDA-licensed (b) (4)

Reviewed by DBSQC. See memo by Claire Wernly.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

The release assays are acceptable for commercial use, with PMC.

See individual assessment under each release analytical method.

See DBSQC reviewer memos for assessment of the Appearance, Sterility, and Endotoxin methods and method validations.

3.2.P.5.4 Batch Analyses

The critical findings in this section are related to Major Deficiencies #3(communicated on March 26, 2026)..

Initial Assessment Leading to Major Deficiency #3

See section 3.2.P.5.4 [Treg] for the Batch record related IRs that are applicable for all three DPs. Only Tcon specific IRs are provide below.

Reviewer comment: As part of the additional information for the batch records requested was to provide the source for the Tcon material. The Applicant is proposing to use ^{(b) (4)} sources for the Tcon and the batch records need to support both routes.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

Reviewer Comment: The increase trending of (b) (4), is similar finding as the Treg DP but less pronounced. The corrective action in complete manufacturing (b) (4) the HSPC manufacturing. This is reasonable. Additionally, impact to patient safety is limited as no OOS Tcon was needed to be administered.

Overall Reviewer's Assessment of Section 3.2.P.5.4

The Applicant has provided data to support the increase in OOS events was not based on the (b) (4) methods and there while there was a cluster of OOS events, additional data supports control of the Tcon DP as SAC-02. The Applicant mitigating the risk of more OOS events by starting formulation of the Tcon DP sooner. There is no direct safety concerns for patients as in specification lots have been release. However, because SAC-02 still has limited experience, increased batch record reporting should be conducted as a PMC to ensure the OOS events remain infrequent going forward. See PMC #12.

3.2.P.5.5 Characterization of Impurities

3.2.P.5.5.2 Product-Related Impurities

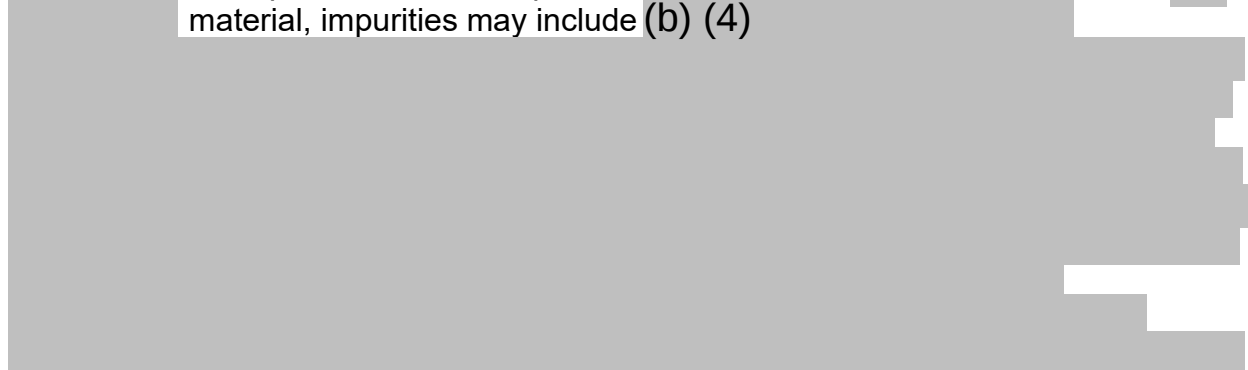
The Tcon DP is intended to comprise conventional T cells and additional donor cells in the apheresis starting material.

(b) (4)

A large rectangular area of the document is redacted with a solid grey box.

3.2.P.5.5.3 Process-Related Impurities

The conventional T cell (Tcon) drug product (DP) process utilizes apheresis starting material yields no process-related impurities. When manufacturing Tcon DP from (b) (4) material, impurities may include (b) (4)

A large rectangular area of the document is redacted with a solid grey box.

(b) (4)

A large rectangular area of the document is redacted with a solid grey box. The text "(b) (4)" is printed in large, bold, black font across the center of the redacted area.

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

Information provided is acceptable, with no deficiencies identified.

3.2.P.6 Reference Standards or Materials

Analytical method controls including instrument calibration and performance verification standards, microbiological control standards, and quantitative analytical reference standards are used for the analytical methods.

Reviewer Comment: The reference standards used as part of the analytical method is reviewed with the methods, see section 3.2.P.5.1 and 3.2.P.5.6 [Tcon].

3.2.P.7 Container Closure System

This section is from consult review and review summary by Mona Mansouri (CBER/OTP/OCTHT/DCT1/CTTB).

The Tcon DP container closure system is described in Section 3.2.P.2.4.

Reviewer's Comment: *The information provided regarding the Tcon container closure system is adequate. Additional details are provided in the consult reviewer's memo*

3.2.P.8 Stability

Section reviewed by RW.

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

The Applicant proposes a shelf life of 7 days post-apheresis collection (PAC) when maintained at $< -125^{\circ}\text{C}$, with an in-use stability of 4 hours at $5 \pm 3^{\circ}\text{C}$ after thawing and dilution with Tcon diluent DP.

The Tcon DP stability study was performed on drug product manufactured at the commercial manufacturing site (SAC-02) using the commercial process from healthy donor apheresis as starting material. This study combines analyses of the stability of the drug product stored at $< -125^{\circ}\text{C}$, in-use hold post-thaw and dilution at $5 \pm 3^{\circ}\text{C}$, and a compatibility assessment with typical administration sets at (b) (4). Tcon DP can be sourced directly from apheresis material as peripheral blood stem cells (PBSCs) or as a (b) (4).

The study included both PBSC and (b) (4) prepared from (b) (4) donors, providing data not only on stability of the Tcon DP but also a comparison of the analytical and stability properties of Tcon DP prepared from both material sources. The Tcon diluent DP used was created using the manufacturing process described in section 3.2.P.3.3 [Tcon Diluent], therefore the study served as a confirmation of the compatibility between Tcon DP and Tcon diluent DP. The information of primary Tcon DP batches used in stability studies are listed in Table .

Table 185. **Primary Tcon DP Stability Batches**

Batch Number	Manufacturing Site	Date of Manufacture	Source Material	Storage Stability Available Time Points (Days PAC)	In-Use Stability Available Time Points
(b) (4)	SAC-02	(b) (4)	PBSC	4, (b) (4)	0hr, 1hr, 2hr, 4hr (b) (4) day PAC)
	SAC-02	(b) (4)	(b) (4)	4, (b) (4)	0hr, 1hr, 2hr, 4hr (b) (4) -day PAC)
	SAC-02	(b) (4)	PBSC	5, 7	0hr, 1hr, 2hr, 4hr (7-day PAC)
	SAC-02	(b) (4)	(b) (4)	5, 7	0hr, 1hr, 2hr, 4hr (7-day PAC)
	SAC-02	(b) (4)	PBSC	5, (b) (4)	0hr, 1hr, 2hr, 4hr (b) (4) day PAC)
	SAC-02	(b) (4)	(b) (4)	5, (b) (4)	0hr, 1hr, 2hr, 4hr (b) (4) -day PAC)

PBSC = Peripheral blood stem cells; (b) (4)

Table reproduced from Table 1, eCTD 3.2.P.8.1 Stability Summary and Conclusions [Tcon, Orca Bio], and Tables 2 and 3, eCTD 3.2.P.8.3 Stability Data [Tcon, Orca Bio] from original submission (no change in the MA)

3.2.P.8.1.1 Storage Stability Study

For the storage stability study, (b) (4) bags of Tcon DP per donor (b) (4) of PBSC source and (b) (4) were used for the study. All bags of Tcon DP were held in liquid nitrogen tanks at < -125°C. (b) (4) from each source/donor was removed for testing at targeted times. Testing samples and time points are listed in Table . The container closure system and formulation used for the stability studies was the same as used for the commercial product. Acceptance criteria and summary of storage stability data are list in Table and Table .

Table 186. Summary of Storage Stability Data at < -125°C Using PBSC Source

Test Parameter	Acceptance Criteria	Pre-cryopreservation from average of bag (b) (4) (Range)	4-5 Day PAC Mean (Range)	7 Day PAC Mean (Range)
Appearance	Conforms	Conforms (b) (4)	Conforms (b) (4)	Conforms (b) (4)
(b) (4)	Report Results	(b) (4)	(b) (4)	(b) (4)
Sterility (b) (4)	NGD	NGD (b) (4)	NGD (b) (4)	NGD (b) (4)
Tcon Phenotype	T cells detected	T cells detected (b) (4)	T cells detected (b) (4)	T cells detected (b) (4)
(b) (4)	Report Results	(b) (4)		
Viable T Cell Dose (×10 ⁶ cells/kg)	(b) (4)			
(b) (4)	(b) (4)			
Viability (%)	(b) (4)			
(b) (4)	Report Results			
Viable T Cells (%)	Report Results			
Viable T Cells (b) (4)	Report Results			

NGD = No growth detected; PAC = Post-apheresis collection; PBSC = peripheral blood stem cells

¹ Cell aggregates observed (AO) in both time points from batch (b) (4)

² (b) (4) had viable T cell dose of (b) (4) at 7-day PAC, slightly above upper limit of (b) (4)

Table reproduced from Tables 2, eCTD 3.2.P.8.3 Stability Data [Tcon, Orca Bio] and Table 3, eCTD 3.2.P.8.3 Stability Summary and Conclusions [Tcon, Orca] from original submission. The revision in the MA only affected % Viability of Tcon DP and % Viable T Cells. The revised data has been reviewed; it did not affect the conclusion.

Table 187. Summary of Storage Stability Data at < -125°C Using (b) (4)

Test Parameter	Acceptance Criteria	Pre-cryopreservation from average of (b) (4) (Range)	4-5 Day PAC Mean (Range)	7 ^{(b) (4)} Day PAC Mean (Range)
Appearance	Conforms	Conforms (b) (4)	Conforms (b) (4)	Conforms (b) (4)
(b) (4)	Report Results	(b) (4)	(b) (4)	(b) (4)
Sterility (b) (4)	NGD	NGD (b) (4)	NGD (b) (4)	NGD (b) (4)
Tcon Phenotype	T cells detected	T cells detected (b) (4)	T cells detected (b) (4)	T cells detected (b) (4)
(b) (4)	Report Results	(b) (4)		
Viable T Cell Dose (×10 ⁶ cells/kg)	(b) (4)			
(b) (4)	(b) (4)			
Viability (%)	(b) (4)			
(b) (4)	Report Results			
Viable T Cells (%)	Report Results			
Viable T Cells (b) (4)	Report Results			

NGD = No growth detected; PAC = post-apheresis collection

¹ Cell aggregates observed (AO) in all samples

Table reproduced from Tables 2, eCTD 3.2.P.8.3 "Stability Data [Tcon, Orca Bio] and Table 3, eCTD 3.2.P.8.3 Stability Summary and Conclusions [Tcon, Orca Bio] from original submission. The revision in the MA only affected % Viability of Tcon DP and % Viable T Cells. The revised data has been reviewed; it did not affect the conclusion.

Reviewer Comment:

The Applicant assessed stability of cryopreserved Tcon DP at 4-5 days PAC and 7^{(b) (4)} days PAC when stored at <-125°C in the commercial container closure system. The study included both PBSC and (b) (4) materials. All critical quality attributes met the Applicant's acceptance criteria through 7^{(b) (4)} days PAC for both source materials.

In CMC IR #3 sent 07Oct2025 (responded 14Oct2025, SN 0009), the Agency questioned the proposed viability specification of (b) (4) for Tcon stability studies, noting it appeared inconsistent with submitted data. The Applicant justified the (b) (4) viability specification based on a characterization study (RPT-0320) with analysis of viability distribution resulting in a 95/95 tolerance interval establishing the lower one-sided limit at (b) (4). A separate stability specification for viable T cell dose ensures adequate target cells after thaw. Although the viability acceptance criterion was set at (b) (4), no testing lots had viability below the release specification of (b) (4). The Applicant assessed the risk of low viability Tcon DP and justified that worst-case (b) (4)

(b) (4) is within the range of typical cord blood transplants. Therefore, the viability specification of (b) (4) had no actual impact on this study.

Cell aggregation had been observed in Tcon DP throughout the entire stability studies. The primary concerns were adverse events caused by cell aggregation during administration and cell loss leading to insufficient dose administered to patients. Those concerns were addressed by two separate CMC IRs.

In CMC IR #4 sent 17Oct2025 (responded 23Oct2025, SN 0013), the Agency noted that cell aggregates were observed in many Tcon DP samples and requested information on visual inspections at clinical sites, observed cell aggregates, and risk assessment. The Applicant reported that 19 of 21 sites confirmed routine visual inspection of Tcon DP. Of 173 Tcon DPs visually inspected, only 1 (0.6%) had cell aggregates. The participant who received this Tcon DP did not experience any adverse events, and vital signs monitored for 4 hours post-infusion showed no abnormalities. The proposed USPI includes instructions to “gently agitate each infusion bag to prevent cell clumping.” The Applicant cited (b) (4) stating that certain inherent particulate matter may be expected in cell therapy products as long as cell clumping is not excessive. An (b) (4) (b) (4) in the administration set is used to remove cell aggregates. Of note, all Tcon DP manufactured from (b) (4) source materials in this stability study had cell aggregates, whereas (b) (4) bags manufactured from PBSC had cell aggregates, indicating that Tcon DP manufactured from (b) (4) source materials may be different from Tcon DP manufactured from PBSC.

In CMC IR #7 sent 31Oct2025 (responded 17Nov2025, SN 0017), the Agency noted that stability study batches lacked representation of lower strength product and requested specification of the minimum target viable Tcon dose and stability data supporting the lowest dose. The Applicant clarified that the minimum target viable Tcon dose is (b) (4) $\times 10^6$ cells/kg with a maximum of 6.9×10^6 cells/kg. The stability study used the tighter phase 3 specification, and all stability samples met specifications even at low viability. The Applicant provided comparative data showing that while overall viability decreases during freeze-thaw, the proportion of viable T cells relative to all (b) (4) almost always increases, and viable T cell dose remains relatively stable. This indicates that viability loss primarily affects (b) (4), leaving viable T cells relatively unaffected. The Applicant stated that across the studied range of viable T cell dose there was no correlation with clinical outcomes. Since there is no evidence that viable T cells in Tcon DP contribute to the mechanism of action of Orca-T, and treatment effects are primarily from HSPC DP, the evaluation of Tcon DP stability is based on safety consideration instead of efficacy. Setting the lower limit even lower will decrease the risk from infusion of non-viable cells. Overall, the stability of Tcon DP may be acceptable due to the lack of clear clinical benefits of Tcon DP. While it is unclear whether Tcon DP plays a role in providing immune support before engraftment, the contributions of Tcon DP as well as Treg DP may be incorporated into overall clinical evaluation for Orca-T product.

3.2.P.8.1.2 In-Use Stability Study

For the Tcon DP in-use stability study, after 7^{(b) (4)} days PAC at < -125°C, (b) bag from each source and batch was thawed and diluted with 30 mL of Tcon diluent DP. The thawed/diluted DP was immediately sampled for the 0-hour time post-thaw timepoint, then held at 5 ± 3°C for additional testing points at 1, 2, and 4 hours. The acceptance criteria and summary of results for Tcon DP in-use stability are shown in Table and Table .

Table 188. Summary of Tcon DP In-Use Stability Data at 5 ± 3°C from PBSC Source

Test Parameter	Acceptance Criteria	0hr Post-Thaw Mean (Range)	1hr Post-Thaw Mean (Range)	2hr Post-Thaw Mean (Range)	4hr Post-Thaw Mean (Range)
Appearance	Conforms	(b) (4)			
Cell aggregates observed (AO)	Reviewer analysis				
(b) (4)	Report Results				
Sterility (b) (4)	NGD				
Tcon Phenotype	Report Results				
(b) (4)	Report Results				
Viable T Cell Dose (×10 ⁶ cells/kg)	(b) (4)				
(b) (4)	(b) (4)				
Viability (%)	(b) (4)				
(b) (4)	Report Results				
Viable T Cells (%)	Report Results				
Viable T Cells (b) (4)	Report Results				
Cell Recovery - Viable T Cell Dose (%)	Reviewer analysis				

PAC = post-apheresis collection; PBSC = peripheral blood stem cells

¹ Cell aggregates observed (AO) in some samples

² Visual inspection not performed for (b) (4) at 1hr timepoint

Table reproduced from Table 3, eCTD 3.2.P.8.3 Stability Data [Tcon, Orca Bio] from original submission. The revision in the MA only affected % Viability of Tcon DP and % Viable T Cells. The revised data has been reviewed; it did not affect the conclusion.

Table 189. Summary of In-Use Stability Data at 5 ± 3°C from (b) (4) Source

Test Parameter	Acceptance Criteria	0hr Post-Thaw Mean (Range)	1hr Post-Thaw Mean (Range)	2hr Post-Thaw Mean (Range)	4hr Post-Thaw Mean (Range)
Appearance	Conforms	Conforms (b) (4)	Conforms (b) (4)	Conforms (b) (4)	Conforms (b) (4)

(b) (4)

¹ Cell aggregates observed (AO) in some samples

³ (b) (4) had (b) (4) (b) (4) of (b) (4) at 2hr, below (b) (4) criterion

Table reproduced from Table 4, eCTD 3.2.P.8.3 Stability Data [Tcon, Orca Bio] from original submission. The revision in the MA only affected % Viability of Tcon DP and % Viable T Cells. The revised data has been reviewed; it did not affect the conclusion.

All batches from both sources met Applicant's acceptance criteria at all time points through 4 hours post-thaw, with two exceptions that were investigated and determined not to impact the overall conclusions.

The in vitro studies confirming in-use compatibility of the Tcon DP were executed with the same studies for Treg DP. (Please refer to section 3.2.P.8.1.3 [Treg] for details.) The Tcon DP from 4-5 days PAC (thawed and diluted) was selected for the compatibility study.

(b) (4)

(b) (4)	Report Results
Sterility (b) (4)	NGD
Tcon Phenotype	Report Results
(b) (4)	Report Results
Viable T Cell Dose ($\times 10^6$ cells/kg)	(b) (4)
(b) (4)	(b) (4)
Viability (%)	(b) (4)
(b) (4)	Report Results
Viable T Cells (%)	Report Results
Viable T Cells (b) (4)	Report Results

(b) (4)

N/A = Not applicable; NT = Not tested; PBSC = peripheral blood stem cells; (b) (4); TD = Tcon detected;

¹ Cell aggregates observed in some samples

² Foreign particle (b) (4) observed in (b) (4) post-administration samples

Table reproduced from Table 5, eCTD 3.2.P.8.3 Stability Data [Treg, Orca Bio] from original submission. The revision in the MA only affected % Viability of Tcon DP and % Viable T Cells. The revised data has been reviewed; it did not affect the conclusion.

Table 191. Summary of In-Use Compatibility Data from (b) (4) Source

Test Parameter	Acceptance Criteria
Appearance	Conforms
Cell aggregates observed (AO)	Reviewer analysis
(b) (4)	Report Results
Sterility (b) (4)	NGD
Tcon Phenotype	Report Results
(b) (4)	Report Results
Viable T Cell Dose ($\times 10^6$ cells/kg)	(b) (4)
(b) (4)	(b) (4)
Viability (%)	(b) (4)
(b) (4)	Report Results
Viable T Cells (%)	Report Results
Viable T Cells (b) (4)	Report Results

(b) (4)

N/A = Not applicable; NT = Not tested; (b) (4); TD = Tcon detected;

¹ Cell aggregates observed in most samples

Table reproduced from Table 6, eCTD 3.2.P.8.3 Stability Data [Treg, Orca Bio] from original submission. The revision in the MA only affected % Viability of Tcon DP and % Viable T Cells. The revised data has been reviewed; it did not affect the conclusion.

Reviewer Comment:

The in-use compatibility study demonstrates that Tcon DP from both PBSC and (b) (4) (b) (4) sources is physically and chemically stable during administration through a standard infusion set with a (b) (4) at (b) (4). All critical quality attributes were maintained following the administration process, except for existing issue with cell aggregation starting from post DP dilution, which likely stems from the inherent product properties of Tcon DP instead of compatibility issues, i.e., (b) (4).

Overall, Tcon DP from both PBSC and (b) (4) sources appear to be compatible with standard administration components including infusion sets and (b) (4).

3.2.P.8.1.4 Clinical Data Analysis

The Applicant analyzed clinical data to provide supportive evidence for the proposed shelf life by correlating clinical outcomes with the vein-to-vein time (elapsed time from end of donor apheresis collection to start of Tcon DP infusion to the patient). The Applicant selected T cell concentration at day 28 post-infusion for analysis and concluded that there were no correlation exists between the clinical outcomes and the vein-to-vein times.

Reviewer Comment:

The use of T cell reconstitution endpoints is reasonable for Tcon DP, as the primary function of these cells is to provide immune reconstitution following the myeloablative conditioning and transplant procedure. It should be noted that T cell reconstitution is a complex biological process influenced by many factors beyond Tcon quality (including conditioning regimen, patient characteristics, GVHD prophylaxis, and infections), which creates inherent variability in the data. Additionally, because a similar amount of fresh Treg DP was administered prior to Tcon DP, and because T cell reconstitution assays (total T cells, (b) (4) T cells, (b) (4) T cells at Day 28) do not distinguish between Tcon and Treg cells or between donor and host T cells, these outcomes can only be interpreted in conjunction with other stability data and serve as supportive evidence rather than definitive proof of Tcon DP efficacy.

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

The Applicant has committed to annual stability testing for Tcon DP using healthy donor apheresis material using the similar protocol described in section 3.2.P.8.1. [Tcon]. The proposed annual stability schedule will be 7 days with one point post expiration at (b) (4) days to confirm characterization of product degradation trends and to confirm the appropriateness of the assigned expiry period.

Reviewer Comment:

The Applicant's post-approval stability commitment for Tcon DP is acceptable and appropriate.

OVERALL REVIEWER'S ASSESSMENT OF SECTION 3.2.P.8

The information provided is acceptable.

3.2.P DRUG PRODUCT [T_{con} Diluent]

The T_{con} Diluent is within its own eCTD DP section, however, the T_{con} diluent not a DP but a dilutant as it does not provide therapeutic benefit.

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

This section reviewed by EL.

The T_{con} Diluent is used to dilute the frozen T_{con} (conventional T cell) drug product immediately before patient infusion on Day +2 post-transplant and comprised of 38 mL of multiple electrolyte injection (MEI) with 2% human serum albumin (HSA), sterile filtered. It is supplied in a 50-mL polyolefin-based (b) (4) bag.

As part of administration of the T_{con} DP, T_{con} Diluent is added to the thawed T_{con} DP either by gravity drain or syringe transfer, then the entire diluted contents are infused into the patient. Approximately 30 mL of T_{con} Diluent is administered.

Table 192. T_{con} Diluent Formulation

Excipient	Purpose	Vendor
Multiple electrolytes injection (MEI)	Provide electrolyte composition approaches that of the principal ions of normal plasma	(b) (4),
Human Serum Albumin (HSA), USP	protect the cells in the drug product (DP) by maintaining their viability, stabilizing the environment, and preventing damage function as carrier protein for essential nutrients, inhibits cell adhesion and aggregation, and (b) (4),	(b) (4)

Table generated with information from eCTD 3.2.P.1 Description and Composition of the Drug Product [T_{con} Diluent]

See section 3.2.P.2.1.2.1[Treg] of this memo to further justification of the MEI and HSA.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

There have been minimal changes to the formulation during the development. The formulation has been consistent. The major changes are based on the (b) (4) the diluent to be manufacturing (b) (4).

3.2.P.2.2.2 Overages

A fill volume optimization study was completed to determine the overage required to deliver 30 ml to each bag. The Applicant determined 8 extra mL is required to compensate for the 8 mL lost in the transfer set.

Reviewer Comment: The study is sufficient.

3.2.P.2.2.3 Physicochemical and Biological Properties

See section 3.2.P.2.1.2.1 Treg DP of this memo to further justification of the MEI and HSA.

3.2.P.2.3 Manufacturing Process Development

(b) (4) engineering runs were executed using the (b) (4) systems and in-house prepared (b) (4) solution of MEI and 2% (w/v) HSA. The (b) (4) engineering runs were executed with a total volume of (b) (4) to characterize varying amounts of (b) (4) solutions. Final Tcon diluent DP bags were collected, and all proposed analytical testing, section 1.5, were completed to confirm that the (b) (4) did not impact the Tcon diluent DP composition.

Reviewer Comment: The formulation of the buffer has not changed. The Applicant has revised the process for (b) (4) to an reduce the manual processing during Tcon manufacturing.

Validate the manifold and (b) (4) systems

The Applicant conducted a study comparing the diluent manufactured using the clinical process and intended commercial process. The 95% confidence intervals were calculated via Student's t-distributions, and the Student's t-test p-values were calculated using unpaired, heteroscedastic, two-tailed distributions. The results are summarized in Table The Applicant concludes the diluents are equivalent.

Table 193. Comparison of Clinical and Commercial Material 3.2.P.2.3 Manufacturing Process Development [Tcon Diluent]

Attribute (Units)	Tcon Thawing Media (Representative of Clinical Study Material)	Tcon Diluent (Representative of Commercial Material)	t-Test p-Value
(b) (4)	Values (b) (4)	(b) (4)	0.16
	Mean (b) (4)	(b) (4)	
	95% CI (b) (4)	(b) (4)	0.49
	Values (b) (4)	(b) (4)	
	Mean (b) (4)	(b) (4)	0.86
	95% CI (b) (4)	(b) (4)	
	Values (b) (4)	(b) (4)	0.86
	Mean (b) (4)	(b) (4)	
	95% CI (b) (4)	(b) (4)	

Table reproduced from Table 4 in eCTD 3.2.P.2.3 Manufacturing Process Development [Tcon Diluent]

Reviewer Comment: The Applicant's assessment of the change in manufacturing the diluent is acceptable given scale (b) (4) manufacturing.

3.2.P.2.4 Container Closure System

This section is copied from consult review and review summary by Mona Mansouri (CBER/OTP/OCTHT/DCT1/CTTB).

The Tcon diluent container closure information is described in Section 3.2.P.7 [Tcon Diluent].

3.2.P.2.5 Microbiological Attributes

Assessment of the microbiological attributes is deferred to DMPQ. Please refer to the review memo by Hector Carrero.

3.2.P.2.6 Compatibility

See section 3.2.P.8.1.3 Compatibility [Tcon].

OVERALL REVIEWER'S ASSESSMENT OF SECTION 3.2.P.2 [Tcon Diluent]

The assessment of the information provide is acceptable.

3.2.P.3 Manufacture

This section reviewed by EL.

3.2.P.3.1 Manufacturer(s)

Table 194. Tcon Diluent Drug Product Manufacturing and Testing Facilities

Name	Address	FEI	DUNS	Responsibility
Orca Biosystems Inc. SAC-02 Facility	7910 Metro Air Parkway Sacramento, CA 95837	3035546696	119463419	DP Manufacturing DP Packaging and labeling DP Release and stability testing

3.2.P.3.2 Batch Formula

The composition of each batch of Tcon diluent DP is summarized in Table .

Table 195. Batch Formula for Tcon Diluent Drug Product

Component	Quality Standard	Amount
HSA	(b) (4)	2% (w/v)
MEI, Type 1	(b) (4)	38 mL

Table adapted from table 1 in 3.2.P.3.2 Batch Formula [Tcon Diluent]

3.2.P.3.3 Description of Manufacturing Process

Tcon Diluent DP is manufactured in a single continuous process (formulation → (b) (4) → fill) without intermediate holds in an ISO^{(b) (4)} functionally closed environment at the SAC-02 facility (Figure).

The target batch size is (b) (4) bags at 38 mL fill volume to yield 30 mL per bag infused. Each bag is labeled with the unique batch number assigned to the patient for final labeling. Both the Tcon diluent batch number and patient specific batch number will be visible on the final Tcon diluent unit shipped.

Figure 111. Tcon Diluent Process Flow Diagram

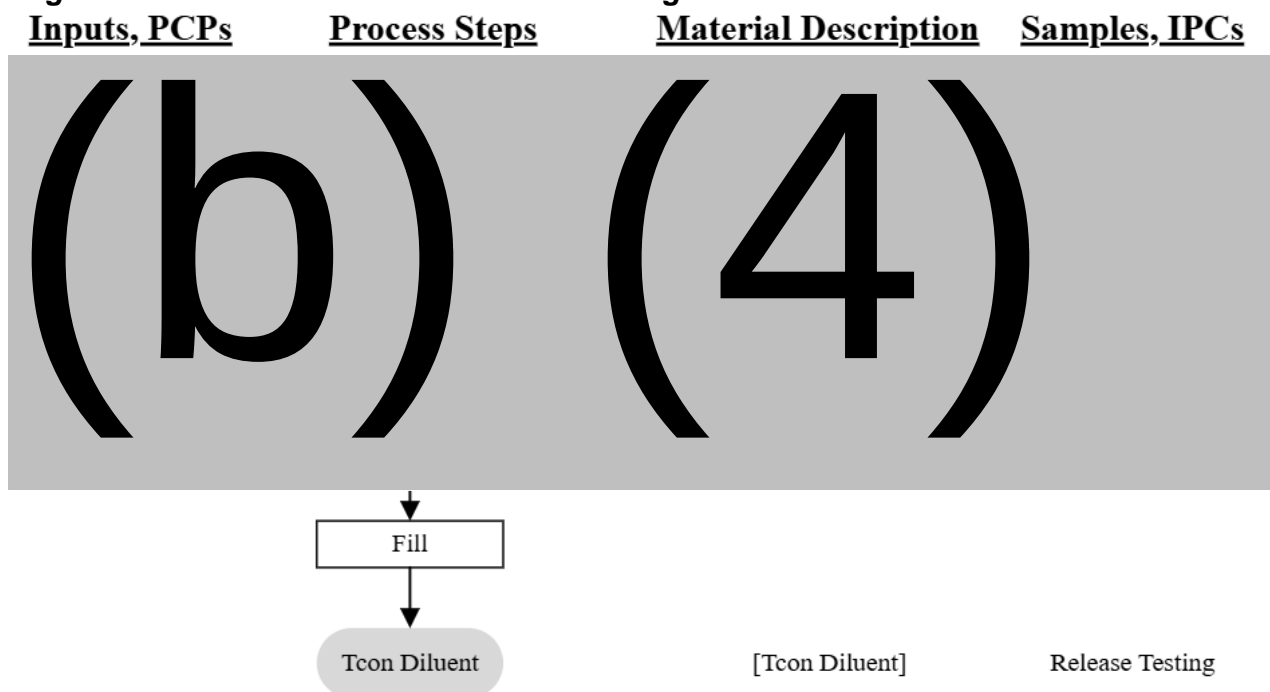


Figure reproduced from Figure 1 in 3.2.P.3.3 Description of Manufacturing Process and Process Controls [Tcon Diluent]

Summary

- (b) (4)
- (b) (4)
- Each bag filled sequentially, (b) (4) from manifold, inspected, labeled, and stored
- Process continues until all (b) (4) solution is used
- (b) (4) test performed to confirm (b) (4) maintained structural integrity

Release Testing

Samples collected for the following tests

- Appearance (visual inspection)
- (b) (4)
- HSA concentration
- (b) (4)
- Sterility (14-day (b) (4))
- Endotoxin
- (b) (4)

Packaging

- Tcon Diluent DP shipped with Tcon DP in separate two-layer cardboard carton

Reprocessing

- **No reprocessing procedures** are established for Tcon Diluent DP

Key Quality Features

- Functionally closed, aseptic process with (b) (4)
- Comprehensive in-process controls and release testing
- Validated sterilization and (b) (4)
- Single-use components to minimize contamination risk
- Process validated through PPQ ((b) (4) runs)

3.2.P.3.4 Controls of Critical Steps and Intermediates

An overview of the CPPs and Non-CPPs for the Tcon diluent DP preparation are provide in Table . Tcon Diluent DP Preparation Process Parameters

Table 196. Tcon Diluent DP Preparation Process Parameters

Process Step	Parameter	Target	UOM	NOR	PAR	Designation
Component Addition	Amount of (b) (4) HSA per L of MEI	(b) (4)				CPP
(b) (4)	Prior to Sample Removal	(b) (4)				Non-CPP
(b) (4)	Prior to (b) (4) /Fill	(b) (4)				CPP
(b) (4)	Pump Speed During (b) (4) /Fill	(b) (4)				Non-CPP
Fill	Final Volume in Container	(b) (4)				CPP

Table reproduced from table 3 in 3.2.P.3.3 Description of Manufacturing Process and Process Controls [Tcon Diluent]

Table 197. Quality Attributes (Average Values Bold in Parentheses)

Quality Attribute	Method of Testing	Acceptance Criteria	Bag pull or Average	Summary results of 4 replicates
Visual Inspection	(b) (4)	Conforms ^a	(b) (4)	All Replicates conform
				All Replicates conform
				All Replicates conform
				All Replicates conform
				All Replicates conform
				All Replicates conform
(b) (4)				(b) (4)
(b) (4)				

HSA Concentration	Protein concentration determination by (b) (4) method	(b) (4)	(b) (4)	
Sterility	(b) (4)	No growth detected	(b) (4)	NGD
			(b) (4)	NGD
			(b) (4)	NGD
			(b) (4)	NGD
			(b) (4)	NGD
			(b) (4)	NGD
Endotoxin	(b) (4)		(b) (4)	(b) (4)
			(b) (4)	
			(b) (4)	
			(b) (4)	
			(b) (4)	
(b) (4)	(b) (4)		(b) (4)	(b) (4)
		container		
			(b) (4)	
			(b) (4)	
			(b) (4)	
	(b) (4)		(b) (4)	(b) (4)
			(b) (4)	
			(b) (4)	

Table adapted from table 2 in eCTD 3.2.P.3.5 Process Validation and/or Evaluation [Tcon Diluent]

3.2.P.3.5 Process Validation and/or Evaluation

(b) (4) lots were included in the process validation and manufactured (b) (4) (b) (4). Initially (b) (4) PPQ runs were planned but a high number of visual inspections failures from (b) (4) in the plastic components were observed. A (b) (4) PPQ run was after updates to the procedures.

Reviewer Comment: The deviation reports and associated investigation and CAPA were also reviewed on inspection. They relate to including additional determination and testing during an inspection following the detection of foreign particles. They are acceptable.

Table 198. Critical Process Parameter

Process Step	Process Parameter	Acceptance Criteria	Summary of all lots

Tcon Diluent Formulation	Amount of (b) (4) HSA per L of MEI	(b) (4)
Tcon Diluent Formulation	(b) (4) Prior to (b) (4) /Fill	
Tcon Diluent (b) (4) /Fill	Final Volume in Container	

Table adapted from table 3 in eCTD 3.2.P.3.5 Process Validation and/or Evaluation [Tcon Diluent]

Table 199. In-Process Controls

Sample	Test Performed	Acceptance Criteria	Use of Results	Summary of all lots
(b) (4)				

Table adapted from table 4 in eCTD 3.2.P.3.5 Process Validation and/or Evaluation [Tcon Diluent]

Discrepancies

A summary of validation discrepancies and major/critical deviations is provided in eCTD 3.2.P.3.5 Process Validation and/or Evaluation [Tcon Diluent].

Reviewer Comment: The deviations were reviewed, and the assessment is acceptable.

Aseptic Process Validation

Reviewed by DMPQ.

OVERALL REVIEWER'S ASSESSMENT OF SECTION 3.2.P.3 [Tcon Diluent]

The assessment of the information provide is acceptable.

3.2.P.4 Control of Excipients

The excipients are same as Treg DP. Please refer to 3.2.P.4 [Treg] of the memo.

3.2.P.5 Control of Drug Product

This section reviewed by EL.

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

The Applicant provides the following justifications for the diluent Table .

Table 200. Specifications for Tcon Diluent Drug Product

Attribute	Test Attribute	Analytical Method	Acceptance Criterion	Purpose
Appearance	Visual Inspection	(b) (4) Visual Inspection of Injection	Physical State: Liquid Clarity: Clear Color: Colorless to yellow Visible Foreign Particles: No visible foreign particles Headspace: Minimal headspace Container Integrity: No defect	Release and Shelf Life

General Composition	HSA Concentration	Protein Concentration Determination by (b) (4)	(b) (4)	Release and Shelf Life
(b) (4)				Release and Shelf Life
(b) (4)				Release and Shelf Life
Safety	Sterility	(b) (4) Sterility Test (b) (4)	No growth detected	Release and Shelf Life
Endotoxin	(b) (4) Bacterial Endotoxins Test (b) (4) Assay	(b) (4) Bacterial Endotoxins Test (b) (4) Assay	(b) (4)	Release
Bioburden (b) (4)	(b) (4) Microbial Enumeration Test (b) (4)	(b) (4) Microbial Enumeration Test (b) (4)	(b) (4)	Release
(b) (4)	(b) (4)	(b) (4)	(b) (4)	Release

Table adapted from table 1 in eCTD 3.2.P.5.1 Specifications [Tcon Diluent]

HSA Concentration (b) (4) Method

The human serum albumin (HSA) concentration in the Tcon diluent DP is determined using a validated protein concentration determination method following the (b) (4) method described in (b) (4) Protein Determination Procedures

(b) (4)

(b) (4)

Reviewer Comment: The reported acceptance criteria are large (b) (4) due to interference from the MEI. See section 3.2.P.5.2 and 3.2.P.5.3 [Tcon Diluent]. To address this, the acceptance criterion also requires linearity at (b) (4) concentrations. This is

acceptable given the test if for Tcon Diluent and the HSA is FDA-cleared with well controlled concentration. Therefore, this approach is acceptable.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.5.2.2 (b) (4) Procedures

Table outlines the (b) (4) methods reviewed by DSQC or DMPQ reviewer's assessment. A brief summary of the methods provided below.

Table 203. Compendial Analytical Method

Quality Attribute	Test Method	Reviewed by
(b) (4)	(b) (4)	DBSQC – Salil Ghosh
(b) (4)	(b) (4)	DBSQC – Salil Ghosh
Endotoxin	(b) (4) Bacterial Endotoxins Test (b) (4) Assay	DBSQC – Claire Wernly
Sterility	(b) (4) Sterility Test (b) (4)	DBSQC – Claire Wernly
Bioburden	(b) (4) Microbial Enumeration Tests	DBSQC – Claire Wernly
(b) (4)		
Appearance	(b) (4) Visual Inspection of Injection	DBSQC – Salil Ghosh
(b) (4)	(b) (4)	DMPQ – Hector Carrero

Reviewer generated table

Visual Inspection (b) (4)

Each Tcon diluent DP in the final container closure is manually examined to confirm physical state, clarity, color, visible particulate as well as any tears, rips or undesired defects in the container (100% visual inspection). Detection of any abnormalities with physical state, clarity, color, packaging defects or visible foreign particles indicates issues with equipment, materials or the manufacturing process.

(b) (4)

(b) (4)

Endotoxin (b) (4)

The endotoxin test is a (b) (4) method performed in compliance with (b) (4) Bacterial Endotoxins Test (b) (4) Assay. The endotoxin acceptance criterion is (b) (4) with the sample points of (b) (4) bags per batch (b) (4) from the Tcon diluent DP final container closure.

Sterility

The sterility test is performed per (b) (4) Sterility Test (b) (4). The sterility acceptance criterion is “no growth detected” with the sample points of (b) (4) bags per batch (b) (4) from the Tcon diluent DP final container closure.

Bioburden (b) (4)

The (b) (4) Microbial Enumeration Test is a (b) (4) assay. The (b) (4) bioburden acceptance criterion is (b) (4) with the sample points of each (b) (4) Tcon diluent DP solution bag

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

Table outlines the compendial methods reviewed by DSQC or DMPQ reviewer’s assessment. A summary of the methods provided below.

(b) (4)

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

(b) (4)

(b) (4)

3.2.P.5.4 Batch Analyses

(b) (4) batches have been manufactured at the Sac-02 facility. Results for the lot release data of all process performance qualification (PPQ) runs are listed in 3.2.P.5.4 (Tcon Diluent).

3.2.P.5.5 Characterization of Impurities

All excipients used in the manufacture of Tcon diluent DP are medicinally approved products and comply with the applicable (b) (4).

A risk assessment was performed to evaluate the potential for materials used in the regulatory T cell (Treg) DP process to introduce (b) (4) agents additionally supports Tcon diluent DP, as the DPs contain the same excipients, MEI Type I, and 2% weight per volume (w/v) HSA. The risk assessment establishes that these impurities are maintained at levels that do not impact patient safety.

Overall Reviewer's Assessment of Section 3.2.P.5:

Information provided is acceptable, with no deficiencies identified.

3.2.P.6 Reference Standards or Materials

This section reviewed by EL.

Analytical method controls including microbiological control standards used for Tcon diluent DP release methods are:

- (b) (4) Sterility Test (b) (4)

- (b) (4) Bacterial Endotoxins Test (b) (4) Assay

3.2.P.7 Container Closure System

This section is summary from consult review and review summary by Mona Mansouri (CBER/OTP/OCTHT/DCT1/CTTB).

The Tcon diluent drug product utilizes a 50-mL end-ported biocontainer made of (b) (4)-based (b) (4) film as its primary container closure system. The Tcon diluent is filled using an (b) (4) (b) (4) Manifold Assembly (b) (4), a pre-sterilized, multi-bag filling system consisting of (b) (4) individual 50 mL (b) (4)-based bags connected to a single inlet tube that branches to each bag, enabling sequential aseptic filling of multiple units from (b) (4). Each bag is filled to 38 mL via (b) (4), then (b) (4) from the manifold and removed for visual inspection and labeling. The functionally closed design of the manifold system minimizes contamination risk during the filling process. (b) (4) testing is performed on the (b) (4) using (b) (4) testing to confirm the (b) (4) maintained structural integrity throughout the filling process. Unlike the Tcon DP, which is maintained at cryogenic temperatures (<-125°C), Tcon diluent is stored refrigerated at (b) (4). The (b) (4) material was selected for its compatibility with the aqueous formulation containing MEI and 2% HSA and its ability to maintain sterility during refrigerated storage. The filled bags are co-packaged with Tcon DP in validated liquid nitrogen dry shippers for transport to clinical sites, where the diluent is stored refrigerated until use for dilution of thawed Tcon DP immediately prior to patient administration on Day +2. Stability studies demonstrated that the container closure system maintains product quality attributes including (b) (4) (b) (4), and HSA concentration (b) (4) throughout the proposed shelf life, with no evidence of container-related degradation or contamination. The extractables and leachables assessment confirmed that any compounds potentially migrating from the (b) (4) container materials remain at levels that do not pose safety concerns for patients.

The container is not regulated as a medical device and is not subject to 510(k) clearance within any classification regulation defined in 21 CFR Parts 862–892.

Reviewer's Comment: The sponsor has not provided the regulatory status of the container used to store Tcon diluent. This information will be requested upon resubmission. In Amendment 53 (received April 28, 2028) in response to CMC IR (not numbered) sent 27Apr2026, the Applicant provides details on the qualification of the container and is acceptable. See *Mona Mansouri memo for a completed assessment*.

Delivery device [Treg, HSPC, and Tcon]

The administration of DP(s) to a recipient is accomplished by connecting the DP bag to an infusion line and a central venous catheter (of at least 18-gauge) via either gravity infusion or pump. The sponsor identifies the (b) (4) administration set used during compatibility testing, which included a (b) (4). The administration accessories

are "not included in the BLA submission" and are "supplied by treatment centers" allowing them to follow their own local procedures and preferences.

Reviewer's Comment:

- Initially, the sponsor did not provide information about the delivery device. Following an IR issued on October 7, 2025, the requested information was provided. From device perspective, the sponsor has provided sufficient information regarding the IV administration set device itself, including types, sizes, and clinical practice considerations.
- In response to our IR sent on December 1st, 2025, the sponsor confirmed that both gravity and pump infusion will be used for all three products (Treg, HSPC, and Tcon). However, since no data regarding pump administration were provided, the sponsor committed to complete both compatibility between the device and drug product(s) as well as comparability between pump and gravity infusion studies submitted in March 30 2026 in Amendment 50. Assessment of the adequacy of both studies is deferred to the CMC review team.

CMC review team deems the study sufficient to support use of both route and included in USPI.

3.2.P.8 Stability

Section reviewed by ELM.

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

The Applicant proposes a shelf life of (b) (4) at intended storage conditions in the warehouse where the temperature range is (b) (4) °C. The stability program is ongoing and will be updated with results of real-time, real-condition testing across multiple storage temperatures, as well as photostability assessment, outlined in Table . In addition, an accelerated stability condition of (b) (4) was executed, and an alternative cold storage condition of 5°C ± 3°C was also included.

Table 206. Stability Conditions and Time Points

Storage Condition	Completed Time Points	Ongoing Time Points
Drug product storage (b) (4) °C stability	(b) (4)	(b) (4)
Accelerated storage temperature of (b) (4)	(b) (4)	(b) (4)
Storage temperature of 5°C ± 3°C, Optional storage condition	(b) (4)	(b) (4)

Table adapted from table 1 in eCTD 3.2.P.8.1 Stability Summary and Conclusion [Tcon Diluent]

Stability Protocol and Analytical Testing

The results of the drug product storage, accelerated storage, and optional 5°C storage studies are in Table , Table , and Table , respectively. (b) (4) bags were tested per stability time point. Appearance testing (for all attributes except (b) (4)) was performed (b) (4) prior to any sample removal. (b) (4) was used completely for (b) (4) testing. The (b) (4) was sampled for (b) (4) sterility at (b) (4) mL per medium and the remaining volume used for the general composition tests.

Table 207. Tcon Diluent Drug Product Stability Study Results

Tcon Diluent Lot	
Attribute	Specification
Appearance, Visual Inspection	C
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
HSA Concentration	(b) (4)
Sterility (b) (4)	NGD

Table reproduced from Table 2, eCTD 3.2.P.8.3 Stability Data [Tcon Diluent]

Reviewer Comment: Due to errors, appearance and sterility testing were not included for all time points. Container closure integrity testing is preferred,

Table 208. Tcon Diluent Drug Product Stability Study Results at Accelerated Conditions (b) (4)

Tcon Diluent Lot	
Attribute	Specification
Appearance, Visual Inspection	C
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
HSA Concentration	(b) (4)
Sterility (b) (4)	NGD

Table reproduced from Table 3, eCTD 3.2.P.8.3 Stability Data [Tcon Diluent]

Table 209. Tcon Diluent Drug Product Stability Study Results at Optional Storage Conditions (5°C ± 3°C)

Tcon Diluent Lot		(b) (4)									
Attribute	Specification										
Appearance, Visual Inspection	C										
(b) (4)		(b) (4)									
HSA Concentration	(b) (4)										
Sterility (b) (4)	NGD	NGD	NGD	NGD	NGD	NGD	NGD	NGD	NGD	NGD	NGD

Table reproduced from Table 4, eCTD 3.2.P.8.3 Stability Data [Tcon Diluent]

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

3.2.P.8.2 Post-Approval Stability Protocol And Stability Commitment [Tcon Diluent]

Testing points for the post-approval studies for shelf-life storage of Tcon diluent DP will be completed at the established stability time point of (b) (4) post-manufacture at intended storage conditions in the warehouse where the temperature range is (b) (4) C. The same methodology will be used

continued process verification (CPV) will be performed to assess trends in release testing data from lots of manufactured using the commercial process. If the CPV

trending indicates any changes to the lifecycle of the Tcon diluent DP, the impact on stability of the Tcon diluent DP will be investigated.

Annually at least one batch of the Tcon diluent DP will be manufactured for a stability study that assesses the storage at (b) (4) °C.

OVERALL REVIEWER'S ASSESSMENT OF SECTION 3.2.P.8 – TCON DILUENT DP

The Applicant proposes to submit additional data from later time point to extend shelf life post approval. is acceptable. The Tcon diluent stability is acceptable.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Assessment of the facilities and equipment is deferred to DMPQ.

3.2.A.2 Adventitious Agents Safety Evaluation

Section reviewed by SK.

Applicants adventitious agent risk management is based on a comprehensive strategy that includes donor screening, materials control, viral safety measures, aseptic procedures, facility design and cleaning programs, and sterility assurance. Viral safety strategies encompass material and supplier controls, closed-system processing, and virus removal/inactivation studies. Sterility assurance includes rapid sterility testing of the final product prior to patient administration using (b) (4) (Microbial Characterization, Identification, and Strain Typing) for (b) (4), and (b) (4) (Sterility Tests) by (b) (4) both before and after administration.

□ Raw materials of human and Animal origin:

- (b) (4) -derived antibody reagents (b) (4) with validated viral clearance steps adopted from (b) (4) reagent.
- Human-derived materials: FDA-approved HSA and (b) (4).
- Animal-derived materials: (b) (4)

Reviewer Comment: The testing and controls for raw materials of animal or human origin are acceptable. These materials include the apheresis starting material, human serum albumin, intravenous immunoglobulin, and (b) (4)

(b) (4) from (b) (4) are used for (b) (4) quality control to verify (b) (4). The (b) (4) are non-product-contacting and are removed from the product flow path. The flow path is

subsequently disinfected using the (b) (4) sample line (b) (4) procedure prior to processing cellular material. This procedure consists of a (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

❑ **Bacterial and Fungal Sterility Testing**

- Release testing: (b) (4) (rapid sterility test) helps to enable timely product release.
- Post-release testing: (b) (4) sterility by (b) (4). Performed for every DP for every batch as well as for the (b) (4). They perform interim sterility reads (b) (4) at the following intervals: (b) (4) to provide a more rapid notification if needed, of positive results.
- Treating physicians will be promptly notified as part of the action plan to ensure patient safety and transparency. Sterility action plan includes a comprehensive root cause analysis process, incorporating microbial identification to understand potential contamination sources.
- Sterility action plan includes interim reads and continuous process verification

Reviewer Comment: Please refer to OCBQ memo for the acceptability of sterility testing method.

❑ **Mycoplasma Risk Mitigation:**

- The drug product (DP) manufacturing process does not require cell expansion or cell culturing steps to produce the individual cellular DPs, however the DP manufacturing process utilizes animal and human-derived materials as well as (b) (4)-based reagents produced by (b) (4) that are relevant for consideration of mycoplasma risk.
- Applicant did not employ routine mycoplasma testing of final DP due to short shelf life. However, risk mitigation includes the following:
 - Facility (b) (4)
 - Donor screening per 21 CFR 1271
 - (b) (4) testing of (b) (4) reagents (negative specification)

- Use of FDA-approved reagents (HSA, (b) (4))
- (b) (4) procedures

Reviewer Comment: Because the manufacturing process does not include cell culture steps, the risk of mycoplasma contamination is extremely low. The controls in place are considered acceptable to mitigate this risk.

□ TSE/Prion Risk Mitigation

- Donors with CJD/vCJD risk factors are excluded.
- Geographic deferrals for vCJD (UK, France, Ireland residence/transfusion) may be accepted if no other ineligibility factors exist.
- All ruminant (cattle, sheep, antelopes, deer, giraffes, and their relatives)-derived materials require BSE/TSE certificates.
- All materials of ruminant origin are sourced from vendors providing certificates confirming minimal risk of BSE/TSE.
- All relevant BSE/TSE certificates are reviewed by quality assurance (QA).

Reviewer Comment: The applicant has submitted a comprehensive donor screening program aligned with 21 CFR 1271 requirements with appropriate exclusion criteria for CJD/vCJD risk factors. This was reviewed by DHT and found to be acceptable.

3.2.A.3 Novel Excipients

3.2.R Regional Information (USA)

Reviewing within relevant BLA sections

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

Reviewer Comment: 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, and no extraordinary circumstances exist. The categorical exclusion claim is accepted.

B. Reference Product Designation Request

Not applicable

C. Labeling Review

The following labels are provided:

- Treg DP Bag Label (Amendment 71 received 29Jun2026)
- HSPC DP Bag Label (Amendment 71 received 29Jun2026)
- Tcon DP Bag Label (Amendment 71 received 29Jun2026)
- Tcon Diluent DP Bag Label FRONT (Amendment 72 received 30Jun2026)
- Tcon Diluent DP Bag Label BACK (Amendment 72 received 30Jun2026)
- Carton for Treg DP and HSPC DP (Amendment 71 received 29Jun2026)
- Carton Label for Treg DP and HSPC DP (Amendment 72 received 30Jun2026)
- Shipment Information Card for Treg DP and HSPC DP (Amendment 71 received 29Jun2026)
- Cassette (Package) Label for Tcon DP (Amendment 71 received 29Jun2026)
- Carton for Tcon Diluent DP (Amendment 72 received 30Jun2026)
- Carton Label for Tcon Diluent DP (Amendment 72 received 30Jun2026)
- Shipment Information Card for Tcon DP and Tcon Diluent (Amendment 71 received 29Jun2026)

The primary container for all three DP, and Tcon Diluent consists of the container closure bags that are directly labeling, referred to as “primary label”. The Tcon DP then placed in a metal cassette which contains the same label.

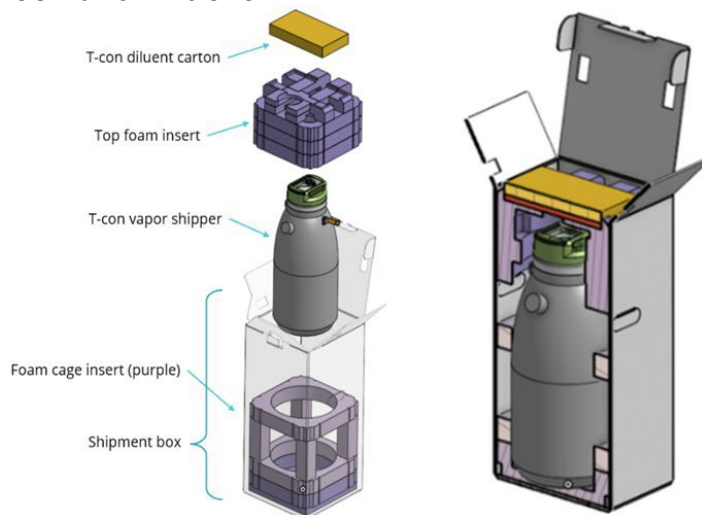
The secondary container has printed information on the carton and lot specific sticker. The HSPC DP and Treg DP share one secondary container together.

Tcon DP and Dilution buffer secondary container label is on the Diluent carton secondary container. The secondary carton is packaged for the Diluent is packaged within the shipment box containing both Tcon diluent and Tcon DP, see Figure .

Figure 113: Packaging Makeup for Tcon and Diluent



Bag Label, primary Label



Treg DP

**allogeneic regulatory T cell immunotherapy
with HSPC and T cells-vldq
TREGZI™**

**Step
2**

NDC 85866-125-01


Step 2 of Administration: Treg Component

Cell suspension for infusion Rx Only
For allogeneic and intravenous use
 Contains 1.3 x 10⁶ to 3.5 x 10⁶ viable cells per kg in 100 mL of multiple electrolytes injection (Type 1) and 2% HSA.

**Store at 2°C to 8°C (36°F to 46°F).
 DO NOT IRRADIATE. DO NOT FREEZE.**
 Infuse prior to the expiry time.

Dosage: Infuse total Treg Component (Step 2) immediately following infusion of HSPC Component (Step 1). See package insert for full dosage and administration instructions.

Recipient: Last Name, First Name
Recipient DOB: YYYY-MM-DD
Orca Patient ID: 00000000
Hospital Patient ID: 0000000000
EXP: YYYY-MM-DD 00:00 UTC
 [+/-] 00:00 PST
LOT: L-0000000000
DIN: W000000000000


 Manufactured by: Orca Biosystems, Inc.
 Menlo Park, CA 94025
 1-877-411-ORCA (6722) U.S. Lic. # 0000
 www.tregziHCP.com 1340



2D code GS1 Data Matrix Info: Expiration Date, Lot Number, Component Name

**allogeneic regulatory T cell immunotherapy
with HSPC and T cells-vldq
TREGZI™**

**Step
2**

NDC 85866-125-01

Step 2 of Administration: Treg Component

Cell suspension for infusion Rx Only
For allogeneic and intravenous use
 Contains 1.3 x 10⁶ to 3.5 x 10⁶ viable cells per kg in 100 mL of multiple electrolytes injection (Type 1) and 2% HSA.

**Store at 2°C to 8°C (36°F to 46°F).
 DO NOT IRRADIATE. DO NOT FREEZE.**
 Infuse prior to the expiry time.

Dosage: Infuse total Treg Component (Step 2) immediately following infusion of HSPC Component (Step 1). See package insert for full dosage and administration instructions.


 Manufactured by: Orca Biosystems, Inc.
 Menlo Park, CA 94025
 1-877-411-ORCA (6722) U.S. Lic. # 0000
 www.tregziHCP.com 1340

	Present/Not Present; notes
(a) The proper name of the product;	Yes (b) (4)
(b) The name, address, and license number of manufacturer; (see notes below)	Yes "Manufactured by: Orca Biosystems, Inc. Menlo Park, CA 94025"
(c) The lot number or other lot identification;	Recipient: Last Name, First Name Recipient DOB: YYYY-MM-DD

	Orca Patient ID: 00000000 Hospital Patient ID: 0000000000 LOT: L-0000000000 DIN: W0000000000000
(d) The expiration date;	EXP: YYYY-MMM-DD 00:00 UTC [+/-] 00:00 PST
(e) The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative";	No <i>Reviewer Comment: need "no preservative" statement</i>
(f) The number of containers, if more than one;	Not applicable (1 bag)
(g) The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;	(b) (4) x 10E6 viable regulatory T-cells in a 100 mL suspension. <i>Reviewer Comment: Need measurement per Kg</i>
(h) The recommended storage temperature;	Refrigerate at 2°C to 8°C (36°F to 48°F).
(i) The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product;	"Infuse at room temperature within the expiry time. Do not irradiate" <i>Reviewer Comment: need "Do not Freeze " statement</i>
(j) The recommended individual dose if the enclosed container(s) is a multiple-dose container;	Not applicable (1 bag)
(k) The route of administration recommended, or reference to such directions in an enclosed circular;	For intravenous use <i>Reviewer Comment: Cell suspension (USPI consistency)</i>
(l) Known sensitizing substances, or reference to an enclosed circular containing appropriate information; (Note – this includes the need to state if there is DMSO)	<i>Reviewer Comment: need to address for murine, dextran</i>
(m) The type and calculated amount of antibiotics added during manufacture;	Not applicable
(n) The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;	<i>Reviewer Comment: should include HSA</i>
(o) The adjuvant, if present;	Not applicable
(p) The source of the product when a factor in safe administration;	For allogeneic use
(q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information;	Not applicable
(r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency."	<i>Reviewer Comment: not addressed</i>
(s) The statement: "Rx only" for prescription biologicals.	included

Reviewer Comment: Due to size, some information can be provided on carton label. The review process of the Treg label is summarized in overall assessment of the labels as multiple labels required similar revisions. The final labels are acceptable.

HPSC DP

allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq TREGZI™		Step 1	NDC 85866-124-01 
Step 1 of Administration: HSPC Component			
Cell suspension for infusion Rx Only For allogeneic and intravenous use Contains $\geq 1.0 \times 10^6$ viable cells per kg in 100 mL of multiple electrolytes injection (Type 1) and 2% HSA. Store at 2°C to 8°C (36°F to 46°F). DO NOT IRRADIATE. DO NOT FREEZE. Infuse prior to the expiry time.	Dosage: Infuse total HSPC Component (Step 1). See package insert for full dosage and administration instructions. Recipient: Last Name, First Name Recipient DOB: YYYY-MMM-DD Orca Patient ID: 00000000 Hospital Patient ID: 0000000000 EXP: YYYY-MMM-DD 00:00 UTC [+/-] 00:00 PST LOT: L-0000000000 DIN: W000000000000		
 Manufactured by: Orca Biosystems, Inc. Menlo Park, CA 94025 1-877-411-ORCA (6722) U.S. Lic. # 0000 1341 www.tregziHCP.com			

2D code GS1 Data Matrix Info: Expiration Date, Lot Number, Component Name

allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq TREGZI™		Step 1	NDC 85866-124-01
Step 1 of Administration: HSPC Component			
Cell suspension for infusion Rx Only For allogeneic and intravenous use Contains $\geq 1.0 \times 10^6$ viable cells per kg in 100 mL of multiple electrolytes injection (Type 1) and 2% HSA. Store at 2°C to 8°C (36°F to 46°F). DO NOT IRRADIATE. DO NOT FREEZE. Infuse prior to the expiry time.	Dosage: Infuse total HSPC Component (Step 1). See package insert for full dosage and administration instructions.		
 Manufactured by: Orca Biosystems, Inc. Menlo Park, CA 94025 1-877-411-ORCA (6722) U.S. Lic. # 0000 1341 www.tregziHCP.com			

c	Present/Not Present; notes
---	----------------------------

(a) The proper name of the product;	Yes (b) (4)
(b) The name, address, and license number of manufacturer; (see notes below)	Yes "Manufactured by: Orca Biosystems, Inc. Menlo Park, CA 94025"
(c) The lot number or other lot identification;	Recipient: Last Name, First Name Recipient DOB: YYYY-MMM-DD Orca Patient ID: 00000000 Hospital Patient ID: 0000000000 LOT: L-0000000000 DIN: W000000000000
(d) The expiration date;	EXP: YYYY-MMM-DD 00:00 UTC [+/-] 00:00 PST
(e) The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative";	No <i>Reviewer Comment: need "no preservative" statement</i>
(f) The number of containers, if more than one;	Not applicable (1 bag)
(g) The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;	(b) (4) x 10 ⁶ viable CD34+ cells in a 100 mL suspension. <i>Reviewer Comment: Need potency and measurement per Kg</i>
(h) The recommended storage temperature;	Refrigerate at 2°C to 8°C (36°F to 48°F).
(i) The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product;	"Infuse at room temperature within the expiry time. Do not irradiate" <i>Reviewer Comment: need "Do not Freeze " statement</i>
(j) The recommended individual dose if the enclosed container(s) is a multiple-dose container;	Not applicable (1 bag)
(k) The route of administration recommended, or reference to such directions in an enclosed circular;	For intravenous use
(l) Known sensitizing substances, or reference to an enclosed circular containing appropriate information; (Note – this includes the need to state if there is DMSO)	<i>Reviewer Comment: need to address for murine, dextran</i>
(m) The type and calculated amount of antibiotics added during manufacture;	Not applicable
(n) The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;	<i>Reviewer Comment: should include HSA</i>
(o) The adjuvant, if present;	Not applicable
(p) The source of the product when a factor in safe administration;	For allogeneic use
(q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information;	Not applicable
(r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a	<i>Reviewer Comment: not addressed</i>

factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency."	
(s) The statement: "'Rx only'" for prescription biologicals.	included

Reviewer Comment: Due to size, some information can be provided on carton label. The review process of the HPSC label is summarized in overall assessment of the labels as multiple labels required similar revisions. The final labels are acceptable.

Tcon DP

□ Bag Label:

allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq TREGZI™		Step 3a	NDC 85866-126-01 
Step 3a of Administration: Tcon Component			
Cell suspension for infusion Rx Only For allogeneic and intravenous use after dilution Contains 1.3 x 10 ⁶ to 6.9 x 10 ⁶ viable cells per kg cryopreserved in 15 mL of multiple electrolytes injection (Type 1), 3-4% HSA, 7.5% DMSO, 1.8% Hetastarch, and Sodium Chloride Injection. Store at ≤ -125°C in vapor phase of liquid nitrogen. DO NOT IRRADIATE. DO NOT REFREEZE. Thaw immediately before use. Dilute with 30 mL Tcon Diluent, for a final volume of 45 mL. Hold at 2°C to 8°C (36°F to 46°F).		Dosage: On Day 2+ to 3+ after infusion of HSPC Component (Step 1) and Treg Component (Step 2), add Tcon Diluent (Step 3b) to Tcon Component (Step 3a). Infuse total diluted Tcon Component. See package insert for full dosage and administration instructions.	
 Manufactured by: Orca Biosystems, Inc. Menlo Park, CA 94025 1-877-411-ORCA (6722) U.S. Lic. # 0000 www.tregziHCP.com 1342		Recipient: Last Name, First Name Recipient DOB: YYYY-MMM-DD Orca Patient ID: 00000000 Hospital Patient ID: 0000000000 EXP: YYYY-MMM-DD 00:00 UTC [+/-] 00:00 PST LOT: L-0000000000 DIN: W0000000000000 	

2D code GS1 Data Matrix Info: Expiration Date, Lot Number, Component Name

Reviewer Comment: Due to size, some information can be provided on carton label. The font is small in some sections, but patient tracking and expiration is in larger font. This is due to limitation of the bag size.

allogeneic regulatory T cell immunotherapy
with HSPC and T cells-vldq
TREGZI™

Step
3a

NDC 85866-126-01

Step 3a of Administration: Tcon Component

Cell suspension for infusion **Rx Only**
For allogeneic and intravenous use after dilution
Contains 1.3×10^6 to 6.9×10^6 viable cells per kg
cryopreserved in 15 mL of multiple electrolytes
injection (Type 1), 3-4% HSA, 7.5% DMSO,
1.8% Hetastarch, and Sodium Chloride Injection.
Store at $\leq -125^\circ\text{C}$ in vapor phase of liquid nitrogen.
DO NOT IRRADIATE. DO NOT REFREEZE.
Thaw immediately before use. Dilute with 30 mL
Tcon Diluent, for a final volume of 45 mL.
Hold at 2°C to 8°C (36°F to 46°F).



Manufactured by: Orca Biosystems, Inc.
Menlo Park, CA 94025
1-877-411-ORCA (6722) U.S. Lic. # 0000
www.tregziHCP.com 1342

Dosage: On Day 2+ to 3+ after infusion of HSPC
Component (Step 1) and Treg Component
(Step 2), add Tcon Diluent (Step 3b) to Tcon
Component (Step 3a). Infuse total diluted Tcon
Component. See package insert for full dosage
and administration instructions.

□ Tcon Cassette label

allogeneic regulatory T cell immunotherapy
with HSPC and T cells-vldq
TREGZI™

Step 3a

NDC 85866-126-02

Step 3a of Administration: Tcon Component

Cell suspension for infusion **Rx Only**
For allogeneic and intravenous use after dilution
Contains 1.3×10^6 to 6.9×10^6 viable cells per kg
cryopreserved in 15 mL of multiple electrolytes
injection (Type 1), 3-4% HSA, 7.5% DMSO,
1.8% Hetastarch, and Sodium Chloride Injection.
No U.S. Standard of Potency
Store at $\leq -125^\circ\text{C}$ in vapor phase of liquid nitrogen.
DO NOT IRRADIATE. DO NOT REFREEZE.
Thaw immediately before use. Dilute with 30 mL
Tcon Diluent, for a final volume of 45 mL.
Hold at 2°C to 8°C (36°F to 46°F).

orcabio
Manufactured by: Orca Biosystems, Inc.
Menlo Park, CA 94025
1-877-411-ORCA (6722) U.S. Lic. # 0000
www.tregziHCP.com 1378

Dosage: On Day 2+ to 3+ after infusion of HSPC
Component (Step 1) and Treg Component
(Step 2), add Tcon Diluent (Step 3b) to Tcon
Component (Step 3a). Infuse total diluted Tcon
Component. See package insert for full dosage
and administration instructions.

VERIFY PATIENT ID

Recipient: Last Name, First Name
Recipient DOB: YYYY-MMM-DD
Orca Patient ID: 00000000
Hospital Patient ID: 0000000000
EXP: YYYY-MMM-DD 00:00 UTC
[+/-] 00:00 PST
LOT: L-0000000000
DIN: W00000000000

1578

*Reviewer Comment: Due to size, some information can be provided on carton label.
The font is small in some sections, but patient tracking and expiration is in larger font.
This is due to limitation of the bag size.*

c	Present/Not Present; notes
(a) The proper name of the product;	Yes (b) (4)
(b) The name, address, and license number of manufacturer; (see notes below)	Yes "Manufactured by: Orca Biosystems, Inc. Menlo Park, CA 94025"

(c) The lot number or other lot identification;	Recipient: Last Name, First Name Recipient DOB: YYYY-MM-DD Orca Patient ID: 00000000 Hospital Patient ID: 0000000000 LOT: L-0000000000 DIN: W0000000000000
(d) The expiration date;	EXP: YYYY-MM-DD 00:00 UTC [+/-] 00:00 PST
(e) The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative";	No <i>Reviewer Comment: need "no preservative" statement</i>
(f) The number of containers, if more than one;	Not applicable (1 bag)
(g) The amount of product in the container expressed as (1) the number of doses, (2) volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;	(b) (4) x 10 ⁶ viable T-cells in a 15 mL suspension <i>Reviewer Comment: Need measurement per Kg</i>
(h) The recommended storage temperature;	Store at ≤ -125°C in vapor phase of liquid nitrogen.
(i) The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product;	Do not irradiate"
(j) The recommended individual dose if the enclosed container(s) is a multiple-dose container;	Not applicable (1 bag)
(k) The route of administration recommended, or reference to such directions in an enclosed circular;	For intravenous use after dilution
(l) Known sensitizing substances, or reference to an enclosed circular containing appropriate information; (Note – this includes the need to state if there is DMSO)	<i>Reviewer Comment: need to address for murine, dextran, DMSO</i>
(m) The type and calculated amount of antibiotics added during manufacture;	Not applicable
(n) The inactive ingredients when a safety factor, or reference to an enclosed circular containing appropriate information;	<i>Reviewer Comment: should include HSA</i>
(o) The adjuvant, if present;	Not applicable

(p) The source of the product when a factor in safe administration;	For allogeneic use
(q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information;	Not applicable
(r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency."	<i>Reviewer Comment: not addressed, need No U.S. standard of potency</i>
(s) The statement: "Rx only" for prescription biologicals.	included

Reviewer Comment: The review process of the Tcon label is summarized in overall assessment of the labels as multiple labels required similar revisions. The final labels are acceptable.

Tcon Diluent

allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq TREGZI™		Step 3b	NDC 85866-127-01 
Step 3b of Administration: Tcon Diluent			
For intravenous use Rx Only Use only for diluting TREGZI™ Tcon Component (Step 3a). Single-use bag Contains 38 mL sterile multiple electrolytes injection (Type 1) and 2% HSA. Store at (b) (4) DO NOT FREEZE. Transfer to 2°C to 8°C (36°F to 46°F) for at least 30 minutes prior to use. Discard unused portion.		Dosage: Add Diluent (Step 3b) to Tcon Component (Step 3a). See package insert for full dosage and administration instructions.	
 Manufactured by: Orca Biosystems, Inc. Menlo Park, CA 94025 1-877-411-ORCA (6722) U.S. Lic. # 0000 1343 www.tregziHCP.com		Recipient: Last Name, First Name Recipient DOB: YYYY-MMM-DD Orca Patient ID: 00000000 Hospital Patient ID: 0000000000 See label on back of bag for lot information and expiration date.	
			

**allogeneic regulatory T cell immunotherapy
with HSPC and T cells-vldq
TREGZI™**

**Step
3b**

NDC 85866-127-01

Step 3b of Administration: Tcon Diluent

For intravenous use Rx Only

Use only for diluting TREGZI™ Tcon Component (Step 3a).

Single-use bag

Contains 38 mL sterile multiple electrolytes injection (Type 1) and 2% HSA.

Store at (b) (4)

DO NOT FREEZE.

Transfer to 2°C to 8°C (36°F to 46°F) for at least 30 minutes prior to use.

Discard unused portion.



Manufactured by: Orca Biosystems, Inc.

Menlo Park, CA 94025

1-877-411-ORCA (6722)

www.tregziHCP.com

U.S. Lic. # 0000

1343

Dosage: Add Diluent (Step 3b) to Tcon Component (Step 3a). See package insert for full dosage and administration instructions.

See label on back of bag for lot information and expiration date.

Back label

Tcon Diluent

allogeneic regulatory T cell immunotherapy
with HSPC and T cells-vldq
TREGZI™



EXP: YYYY-MMM-DD

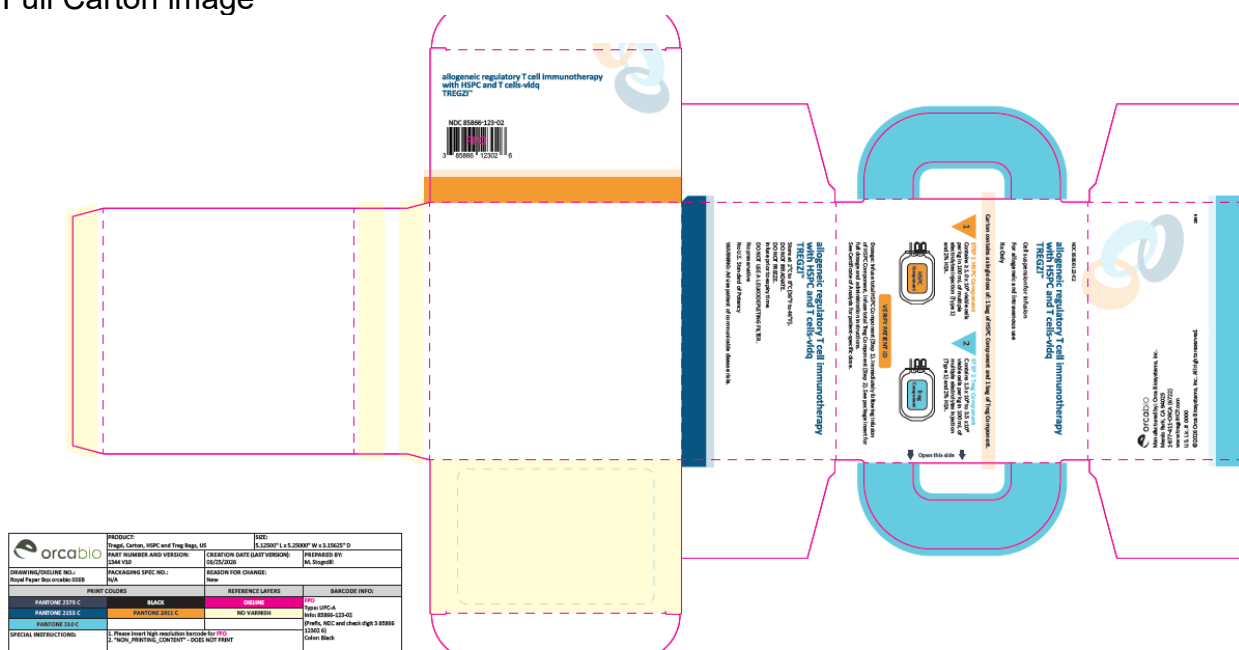
LOT: 00000000

2D Data Matrix Info: lot and expiration date (not including field names) and the product name Tcon Diluent

Reviewer Comment: The review process of the Tcon Diluent label is summarized in overall assessment of the labels as multiple labels required similar revisions. The final labels are acceptable.

Carton Labels

Treg DP/HSPC Carton
Full Carton image



Enlarged section of carton

NDC 85866-123-02

allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq TREGZI™

Cell suspension for infusion

For allogeneic and intravenous use

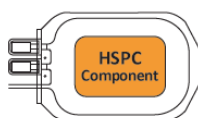
Rx Only

Carton contains a single dose of: 1 bag of HSPC Component and 1 bag of Treg Component.

1

STEP 1 HSPC Component

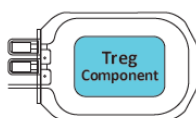
Contains $\geq 1.0 \times 10^6$ viable cells per kg in 100 mL of multiple electrolytes injection (Type 1) and 2% HSA.



2

STEP 2 Treg Component

Contains 1.3×10^6 to 3.5×10^6 viable cells per kg in 100 mL of multiple electrolytes injection (Type 1) and 2% HSA.



Open this side

VERIFY PATIENT ID

Dosage: Infuse total HSPC Component (Step 1). Immediately following infusion of HSPC Component, infuse total Treg Component (Step 2). See package insert for full dosage and administration instructions.
See Certificate of Analysis for patient-specific dose.

allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq TREGZI™

Store at 2°C to 8°C (36°F to 46°F).

DO NOT IRRADIATE.

DO NOT FREEZE.

Infuse prior to expiry time.

DO NOT USE A LEUKODEPLETING FILTER.

No preservative

No U.S. Standard of Potency

WARNING: Advise patient of communicable disease risks.

Patient Carton Label

Recipient: Last Name, First Name
Recipient DOB: YYYY-MM-DD
Orca Patient ID: 00000000
Hospital Patient ID: 0000000000
DIN: W000000000000

HSPC Component
NDC 85866-124-01
EXP: YYYY-MM-DD 00:00 UTC 00:00 PST
LOT: L-0000000000

Treg Component
NDC 85866-125-01
EXP: YYYY-MM-DD 00:00 UTC 00:00 PST
LOT: L-0000000000



2D data matrix Info:
HSPC Component and variable field data of NDC, expiration date and lot number
Treg Component and variable field data of NDC, expiration date and lot number
Reviewer Comment: The review process of the carton is summarized in overall assessment of the labels as multiple labels required similar revisions. The final carton and labels are acceptable.

Tcon DP/Diluent Carton
Full Carton

allogeneic regulatory T cell immunotherapy
with HSPC and T cells-vidq
TREGZI™

ORCA BIO
Manufactured by Orca Biopharm, Inc.
Mesa, AZ 85205
www.orcabio.com
www.tregzi.com
U.S. L.E. # 0000
©2024 Orca Biopharm, Inc.
All rights reserved.

1248

NDC 85866-127-02
3 05068 12702 4

allogeneic regulatory T cell immunotherapy
with HSPC and T cells-vidq
TREGZI™

allogeneic regulatory T cell immunotherapy
with HSPC and T cells-vidq
TREGZI™

For intravenous use
Use only for diluting TREGZI™ Tcon Component (Step 3a). See package insert for full dosage and administration instructions.

Step 3b of Administration: Tcon Diluent
For intravenous use
Use only for diluting TREGZI™ Tcon Component (Step 3a). See package insert for full dosage and administration instructions.

No U.S. Standard of Potency Dosage: Add Diluent (Step 3b) to Tcon Component (Step 3a). See package insert for full dosage and administration instructions.

Store at 2-8°C (36°F to 46°F) for up to 30 days. Discard unused portion. No preservative.

DO NOT FREEZE. If frozen, thaw at room temperature and use within 30 minutes. Discard unused portion.

Rx Only

allogeneic regulatory T cell immunotherapy
with HSPC and T cells-vidq
TREGZI™

	PRODUCT: Tcon, Carton, Diluent, 30 mL, US	SIZE: 120.0000" L x 5.5000" W x 1.5000" D
PART NUMBER AND VERSION: 1248 V11	CREATION DATE (LAST VERSION): 06/29/2024	PREPARED BY: M. Singoff
DRAWING/REVISION NO.: Royal Paper Box orcabio 0128	PACKAGING SPEC NO.: N/A	REASON FOR CHANGE: New
PRINT COLORS: PANTONE 3011 C, PANTONE 2268 C, PANTONE 330 C	REFERENCE COLORS: BLACK, NO VARIATION	BARCODE INFO: 1248, Type UPCA, 1248-00000-127-02, (Profile, NDC and check digit), 3 05068 12702 4, Color Black
SPECIAL INSTRUCTIONS:	1. Please insert high resolution barcode for PFD 2. "NON_PRINTING_CONTENT" - DOES NOT PRINT	

Enlarged section of carton

NDC 85866-127-02

allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq TREGZI™

Step 3b of Administration: Tcon Diluent

For intravenous use

Use only for diluting TREGZI™ Tcon Component (Step 3a).

Single-use bag

Contains 38 mL sterile multiple electrolytes injection (Type 1) and 2% HSA.

Store at (b) (4)

DO NOT FREEZE.

Transfer to 2°C to 8°C (36°F to 46°F) for at least 30 minutes prior to use.

Discard unused portion.

No preservative

No U.S. Standard of Potency

Dosage: Add Diluent (Step 3b) to Tcon Component (Step 3a). See package insert for full dosage and administration instructions.

Rx Only

Step
3b



Carton contains 1 bag of Tcon Diluent.

VERIFY PATIENT ID

Patient label

Recipient: Last Name, First Name

Recipient DOB: YYYY-MMM-DD

Orca Patient ID: 00000000

Hospital Patient ID: 0000000000



EXP: YYYY-MMM-DD

LOT: L-00000000

2D Data Matrix Info: Variable data of Recipient, Recipient DOB, Orca Patient ID, Hospital Patient ID, Lot, and Expiration date fields

Reviewer Comment: The review process of the carton is summarized in overall assessment of the labels as multiple labels required similar revisions. The final carton and labels are acceptable.

Shipment Info Card

Treg/HSPC card

allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq
TREGZI™ consists of four individual products. Refer to the Section 2.2: Preparation and Administration instructions in the Prescribing Information within the HSPC/Treg product carton.

1193

This shipper contains both products to be infused on Day 0.

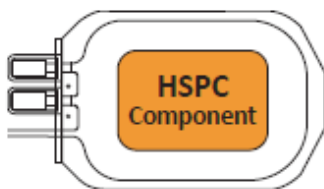
Store both product bags in shipper at 2°C to 8°C (36°F to 46°F) until use. If the bags are removed from the shipper and/or carton due to space constraints or institutional procedures, store at 2°C to 8°C (36°F to 46°F) until use.

In This Shipper

STEP

1

Day 0



In This Shipper

STEP

2

Day 0



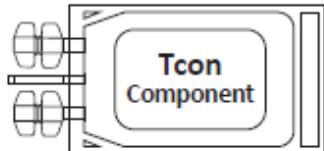
A separate shipper contains the product and diluent to be infused Day +2 to +3.

Packed Separately

STEP

3a

Day + 2
to + 3



Packed Separately

STEP

3b

Day + 2
to + 3



Reviewer Comment: The review process of the shipment card is summarized in overall assessment of the labels as multiple labels required similar revisions. The cards are acceptable.

Tcon/Diluent Card

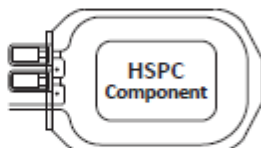
allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq TREGZI™ consists of four individual products. Refer to the Section 2.2: Preparation and Administration instructions in the Prescribing Information within the Tcon diluent carton and shipper.

1349

A separate shipper contains the products to be infused prior, on Day 0.

Packed Separately

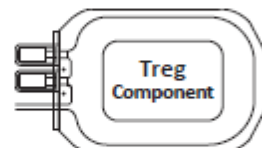
STEP 1
Day 0



HSPC Component

Packed Separately

STEP 2
Day 0



Treg Component

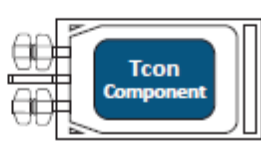
This shipper contains the product and Tcon diluent to be infused on Day +2 to +3.

Store Tcon diluent at (b) (4) in the shipper. If the bag is removed from the shipper and/or carton due to space constraints or institutional procedure, store at (b) (4) until use. Refrigerate at 2°C to 8°C (36°F to 46°F) for at least 30 minutes prior to use.

Store Tcon product at ≤ -125°C.

In This Shipper - LN2 Shipper

STEP 3a
Day + 2 to + 3



Tcon Component

Do not remove from LN2 storage until patient is onsite and awaiting infusion.

In This Shipper - Carton

STEP 3b
Day + 2 to + 3



Tcon Diluent

Reviewer Comment: The review process of the shipment card is summarized in overall assessment of the labels as multiple labels required similar revisions. The cards are acceptable.

Overall Reviewer's Assessment of Bag and Carton Labels:

Final labels were submitted 30Jun2026. Multiple IRs were sent:

- CMC IR#30 sent 5Jun2026; Applicant responses in 66 (received 9June2026)
- CMC IR#31 sent 12Jun2026; Applicant responses in 67 (received 16June2026)
- CMC IR #34 sent 24Jun2026; Applicant responses in Amendment 71 (received 29June2026)
- CMR IR #35 sent 39Jun 2026; Applicant responses in Amendment 71 (received 29June2026)

The following changes were requested in the IRs:

- *Revise names to final Trade Name and Non-Proprietary Name*
- *Update National Drug Code (NDC), revise positioning and use nested approach with package having its own NDC*
- *Adding language to container and/or package labels emphasizing the need to verify patient identity prior to infusion*
- *provide the specific information encoded within each 2D data matrix barcode for all container and package labels.*
- *For the DP bags:*
 - *Remove intervening matter (three-color teal, blue, and orange graphic)*
 - *Reformat administration step related material for clarity, and formatting*
 - *Submit COA*
 - *Use "Cell suspension for infusion."*
 - *Provide dose as per kg vs total cells and full excipient composition*
 - *Use "Store at 2°C–8°C, DO NOT IRRADIATE, DO NOT FREEZE, and infuse within the expiry time." or DO NOT REFREEZE, No U.S. standard of potency.", as applicable*
 - *Remove the statement "For reactive test results reference the COA," as ineligible donors will not be used for commercial product.*
- *For Carton*
 - *Relocate and reduce the size of the three-color graphic, which currently occupies a disproportionate portion of the principal display panel*
 - *Add complete package labeling information for all components*
 - *updating storage/handling instructions (including DO NOT USE A LEUKODEPLETING FILTER), and adding "No preservative" and "No U.S. standard of potency."*
 - *Remove all critical information (currently on the bottom of the box) to the principal display panel.*
 - *Add consistent language and visual elements (e.g., a color band for "Step 3b: Tcon Diluent")*
 - *Include a statement regarding known sensitizing substances (e.g., human serum albumin/HSA) or reference to an enclosed circular.*
- *Shipment Information Cards*
 - *Language on both shipment information cards must be consistent with revised container and package labels.*
 - *Use consistent language as USPI for administration and refer to USPI*
 - *Clarify storage instructions*

Full Prescribing Information (PI):

Reviewed in USPI document. Final USPI is acceptable.

Overall Reviewer's Assessment of Labeling:

Acceptable.