



DHT CONSULT REVIEW MEMO

REVIEW DATE: June 9, 2026

REVIEWERS: Safa Karandish, BS, MT
Consumer Safety Officer, OTP/OCTHT/DHT/HTRS

Simone Porter, MD, MPH
Medical Officer, OTP/OCTHT/DHT/HTRS

CONCURRENCE: Ping He, MD
Staff Chief, OTP/OCTHT/DHT/HTRS

Irma Sison, MD, MBA
Division Director, OTP/OCTHT/DHT

TO: Elizabeth Lessey-Morillon, PhD
CMC, OTP/OCTHT/DCT1/CTB1

Linda Le
RPM, OTP/ORMRR/DRMRR2/RMSB2

STN: 125868/0

SUBMISSION TYPE: Biological License Application (BLA)

PRODUCT: (b) (4) Orca-T (non-proprietary name), TREGZI
(proprietary name)

HCT/P SOURCE: Hematopoietic stem/progenitor cell apheresis (HPC, Apheresis)

APPLICANT: Orca Biosystems Inc (Orca Bio)

SUBJECT: Consult review of donor eligibility (DE) and tracking information

ASSESSMENT: DE and tracking information are acceptable and the Applicant has confirmed that only apheresis products from eligible donors will be used to manufacture the licensed commercial product.

DISCIPLINES

REVIEWED: DE and tracking Information

INDICATIONS

FOR USE: An allogeneic stem cell and T-cell immunotherapy derived from an HLA-matched donor indicated for use in adult patients with hematologic malignancies to improve survival free of graft-versus-host disease (GVHD) in conjunction with an appropriate preparative regimen.

DOCUMENTS REVIEWED / Informal Teleconference:

Date Received	Submission	eCTD module/ Description
August 6, 2025*	STN 125868/0/0	- 2.3.S Drug Substance [TREG, ORCA BIO]: 1 General Information, 2.3.1 Apheresis Starting Material [Information in Treg module also applies to HSPC and Tcon] - 3.2.S.2.3.1 Apheresis Starting Material [TREG, ORCA BIO]: 1 Control of Apheresis Starting Material, 2 Apheresis Centers (includes donor eligibility information in 2.1), and 4 Traceability, Chain of custody and Chain of Identity (HSPC and Tcon information section cross reference to 3.2.S.2.3.1 [Treg]) - 3.2.A.2 Adventitious Agents Safety Evaluation: 1 Introduction and Overview, 2 Donor Screening and Testing, 7 Transmissible Spongiform Encephalopathy (Prion/TSE) Risk
October 7, 2025	STN 125868/0/7	Response to CMC IR #2, dated September 29, 2025- Responses to Comments 1-9
November 7, 2025	STN 125868/0/16	Response to CMC IR #7, dated October 31, 2025- Responses to Comments 5.a-i
December 31, 2025	STN 125868/0/31	Response to CMC IR #13, dated December 19, 2025- Responses to Comments 1-4 (response to Comment 4 regarding U.S. Apheresis Collection Centers includes a cross reference to the (b) (4) Master File (b) (4))
April 16, 2026	STN 125868/0/51	Response to CMC IR, dated March 26, 2026, regarding DE, Comment #6

Date Received	Submission	eCTD module/ Description
May 11, 2026	STN 125868/0/57	Response to CMC IR #22, dated May 5, 2026, regarding DE and revised SOP-0355 v6

* Major amendment received on March 13, 2026. Action due date changed to July 6, 2026.

Informal Teleconference

Date	Summary
12/10/2025	The Applicant continued to propose use of apheresis products from ineligible donors for manufacturing licensed products. The Agency indicated that under section 351(a)(1) of the Public Health Service Act, 42 U.S.C. 262(a)(1) only apheresis products from eligible donors may be used for manufacture of licensed drug products.

Standard Operating Procedures (SOPs)/Other Documents Reviewed

Submission	SOP/Document
STN 125868/0/7	QAA-0083 (b) (4) Biological Quality Agreement
STN 125868/0/16	Template-004 Orca Bio ATC Registry Quality Agreement
STN 125868/0/31	- SOP-0355 Control of Apheresis Starting Material (Rev. 05) - SOP-0460 Authorized Treatment Center/Apheresis Center Supplier Management (Rev. 02)
STN 125868/0/51	- SOP-0355 Control of Apheresis Starting Material (Rev. 06)
STN 125868/0/57	- SOP-0355 Control of Apheresis Starting Material (Rev. 07)

SUMMARY:

TREGZI is manufactured using HLA-matched apheresis products collected from donors after mobilization with granulocyte colony-stimulating factor (G-CSF). The Applicant works with donor registries and individual hospitals or medical centers for collection of the HPC, Apheresis products from both unrelated and related donors. The apheresis products are shipped to the Orca Bio manufacturing facility. The Applicant reviews the donor screening, donor testing, DE determination information provided by the collection

centers to determine whether the starting apheresis product is acceptable for manufacture of TREGZI.

The original BLA did not include adequate information on the Applicant's procedure for verifying that apheresis collection centers perform donor screening, donor testing, and make the DE determination in accordance with the regulations in 21 CFR part 1271. In response to IRs, the Applicant submitted updated quality agreements with the apheresis collection centers, SOPs for review of the DE information provided by the collection centers, and the acceptance criteria for the starting apheresis product.

Based on the information submitted in the original BLA and the responses to two IRs, the Applicant initially proposed using apheresis products from ineligible donors for the manufacture of TREGZI. The Applicant indicated that this was consistent with the limited uses of HCT/Ps from ineligible donors that are permitted under 21 CFR 1271.65(b)(1)(ii) and (iii). Through two IRs and an informal teleconference, the Applicant was informed that only apheresis products from eligible donors may be used for manufacture of licensed drug products (DP). We explained that licensed biological products must be safe, pure, and potent to meet the statutory standards. A product manufactured using apheresis products from ineligible donors may not be safe and thus, would not comply with these statutory standards.

CMC-related deficiencies, including the issue related to the use of ineligible donors, were communicated to the Applicant in an email dated March 26, 2026. In their response dated April 16, 2026 (Amendment 51), the Applicant confirmed that they will only accept apheresis products from eligible donors for manufacture of licensed TREGZI and submitted the revised SOP-0355 v6. The Applicant also addressed the remaining DE related issues in the revised SOP-0355 v7 submitted in Amendment 57.

BACKGROUND:

Manufacturing summary:

The HLA-matched apheresis product from a single unrelated or related donor undergoes depletion, enrichment, and sorting steps to manufacture the DP, TREGZI, which consists of the following 3 cellular components and a diluent DP:

- 1) Hematopoietic stem and progenitor cells (HSPCs) DP- fresh CD34 positive fraction administered intravenously (IV) on day 0 for immune reconstitution.
- 2) Regulatory T cells (Treg) DP - fresh CD4+/CD25+/CD127 fraction (b) (4), administered IV on day 0 to reduce the risk of graft versus host disease
- 3) Conventional T cells (Tcon) DP- cryopreserved unmanipulated apheresis product administered IV on day 2^{(b) (4)} to induce graft-versus-leukemia or graft-versus-infection immune response.
- 4) Tcon diluent DP

REVIEW:

Starting Apheresis Products

The starting apheresis products are collected from HLA-matched unrelated or related allogeneic donors after granulocyte colony-stimulating factor (G-CSF) mobilization. Each donor is selected by the healthcare providers according to institutional practice for a specific recipient. [REDACTED] apheresis products may be collected from a single donor.

Apheresis products from unrelated donors are collected at apheresis centers under contract with donor registries and transported to the manufacturing site by the registry's designated couriers. Apheresis products from related donors are collected at hospitals or medical centers and transported to the manufacturing site by the Applicant. The Applicant has established quality agreements with the donor registries and the hospitals or medical centers that provide the starting apheresis products. The quality agreements address requirements, including but not limited to, collection, donor screening, labeling, documentation and records, audits, and complaint handling.

Reviewer comment: The original BLA did not provide sufficient information about the donor registries, hospitals, or medical centers that collect the starting apheresis products, or the scope of DE information covered in the quality agreements. The Applicant provided a list of collection centers and donor registries, including the (b) (4)

[REDACTED] in Amendment 7. In response to CMC IR #7 (Amendment 16), the Applicant clarified that to date, they have only received starting material from U.S.-based apheresis centers but plan to include international collection centers in the future. In response to CMC IR #13 (Amendment 31), the Applicant submitted the list of U.S. collection centers, including a cross-reference authorization letter to (b) (4) Master File (b) (4). The Applicant also acknowledged and agreed to submit a supplement before adding international collection centers in the future.

In Amendment 31, the Applicant submitted the updated procedure (SOP-0460 Authorized Treatment Center/Apheresis Center Supplier Management), which includes a detailed checklist for review of apheresis collection centers' donor screening and testing procedures (additional information provided in the section below).

Donor Screening, Donor Testing and DE Determination

The Applicant describes that donor screening, donor testing, and making the DE determination are performed in accordance with 21 CFR part 1271.

All donors are screened for relevant communicable disease agents or diseases (RCDADs), including review of the donor's medical history and physical examination. Donors are screened for risk factors for HIV, HBV, HCV, *Treponema pallidum* (syphilis), HTLV, human transmissible spongiform encephalopathy (TSE), including Creutzfeldt-

Jakob disease (CJD) and variant CJD (vCJD), vaccinia, sepsis, WNV, and communicable disease risks associated with xenotransplantation.

Donor testing is performed by CLIA-certified laboratories using FDA-licensed, approved, or cleared donor screening tests. Donors are tested for anti-HIV types 1 and 2, HIV-1 nucleic acid test (NAT), HBsAg, Anti-HBc, HBV NAT, anti-HCV, HCV NAT, *Treponema pallidum*, anti-HTLV I and II, WNV NAT, and anti-CMV (total IgG and IgM).

The apheresis collection facilities are responsible for donor screening, donor testing, and making the DE determination. Under established quality agreements (SOP-0460 Authorized Treatment Center/Apheresis Center Supplier Management), the Applicant evaluates the collection facilities' DE procedures to verify compliance with the regulations in 21 CFR part 1271.

The Applicant reviews the DE information provided by the donor registry or the hospital/medical center apheresis collection centers to determine whether the starting apheresis product is acceptable for manufacture of TREGZI (SOP-0355 Control of Apheresis Starting Material- Rev. 05, Amendment 31). The Applicant submitted examples of documents and a summary of records that accompany the apheresis starting material and the final drug product. (Amendments 7 and 16: documents titled "Example Intake Packet_URD", "Example Intake Packet_MRD", and "Example Outgoing Product Packet").

Reviewer comments:

- The quality agreement procedure (SOP-0460 Authorized Treatment Center/Apheresis Center Supplier Management, Amendment 16) was inadequate because it did not include details about the Applicant's procedure for review of collection facilities' DE procedures, including the donor medical history questionnaires (DMHQ). The Applicant submitted the revised procedure (SOP-0460 Authorized Treatment Center/Apheresis Center Supplier Management, Rev 02, Amendment 31) that includes a detailed checklist for review of collection facilities' DMHQ and other DE-related information and documenting whether they comply with the applicable regulations. The revised procedure appears to be adequate.
- In the original BLA, the Applicant described that apheresis products from an ineligible donor or from a donor with incomplete DE are accepted for manufacture of TREGZI. In response to CMC IR #2 (Amendment 16), the Applicant clarified that they would not use apheresis products from donors for whom DE determination has not been completed. However, they continued to propose use of apheresis products from ineligible donors because they believed their proposed approach was consistent with the limited use of ineligible donors provided under 21 CFR 1271.65(b)(1). Specifically, according to SOP-0355 Control of Apheresis Starting Material, the Applicant accepted ineligible donors with any risk factor for RCDADs identified during donor screening (except for items in section 6.5.5.7 related to active or suspected CJD or vCJD), if donor testing results are negative. For example, the Applicant proposed to accept an ineligible donor who has identified risk factors for

HIV or HBV due to high-risk sexual behavior, injection of drugs for non-medical reasons or other risk factors for RCDADs (e.g., vCJD travel-associated risk factors, vaccinia, or communicable disease risk for xenotransplantation) for which there is no appropriate testing. Products from ineligible donors identified through screening pose RCDAD transmission risks even with negative test results, as donor screening addresses the critical "window period" between infection and detectable antigen/antibody levels for diseases such as HIV. Furthermore, the Applicant proposed to accept an ineligible donor who was "seropositive" for HBV (i.e., positive result for HBsAg and/or total anti-HBc) if the HBV NAT result was negative (SOP-0355 Control of Apheresis Starting Material, Amendment 31).

In CMC IR #7, the Applicant was informed that we did not agree with their proposal regarding use of ineligible donors for manufacture of licensed DP, and explained that apheresis products from these ineligible donors may be used under the IND. In response to CMC IR #7 (Amendment 16), the Applicant restated their position and explained that if apheresis products from ineligible donors could not be used for manufacture of the licensed DP, the patients would receive a standard "allo-HCT" with cells from the same ineligible donor.

During an informal teleconference on December 10, 2025, we reiterated our disagreement with the Applicant's proposal. We explained that licensed biological products must be safe, pure, and potent to meet the statutory standards. A DP manufactured using apheresis products from ineligible donors would not comply with these statutory standards. This issue and other remaining CMC-related deficiencies were communicated to the Applicant in an email, dated March 26, 2026 (FDA Comment #6 below). Specifically, we reiterated our disagreement with the Applicant's proposed use of HPC, Apheresis products from ineligible donors for manufacture of licensed products and requested that the Applicant revise SOP-0355 and associated documents.

We further explained that while the regulations in 21 CFR part 1271 (FDA's current good tissue practice (CGTP) requirements) provide for limited uses of certain HCT/Ps from ineligible donors (e.g., 21 CFR 1271.65), the Applicant's product is not subject solely to CGTP requirements. The Applicant is seeking to license TREGZI under section 351(a)(1) of the Public Health Service Act, 42 U.S.C. 262(a)(1). Such licenses are issued only after showing that the biological product is safe, pure, and potent. An HPC, Apheresis product from an ineligible donor may not be safe in the commercial marketing context for the reasons summarized above. Therefore, the use of apheresis products from ineligible donors may mean that the product would not comply with this statutory standard that must be met for FDA to license a biological product.

In their response dated April 16, 2026 (Amendment 51), the Applicant confirmed that they will only accept apheresis products from eligible donors for manufacture of licensed TREGZI and submitted the revised SOP-0355 v6. The Applicant submitted revised SOP-0355 v7 (Amendment 57) that addressed additional comments related to DE.

TRACKING

The Applicant's tracking system, including procedures for chain of identity (COI) and chain of custody (COC) is designed for tracking products from the donor to the recipient and vice versa. The tracking system utilizes multiple unique identifiers including:

- Applicant-assigned donor and recipient IDs
- Donor Global Registration ID (GRID) and Recipient ID (RID) (for apheresis products supplied by donor registries)
- ISBT 128 Donation Identification Number (DIN)
- Batch Identification (batch ID)

The donor and recipient identification numbers and batch number are included in the COC documentation and batch records. The patient and batch ID, which are unique alphanumeric codes, are used for COI to link the donor and recipient information from the collection site and/or hospital (eCTD section 3.2.S.2.3.1). The DP label includes the lot number, DIN, recipient information, and Orca Patient ID.

Reviewer comment: In response to CMC IR #7 (Amendment 16), the Applicant clarified that "Batch ID" and "Lot ID" (also referred to as "Batch number" and "Lot number") all refer to the same unique ID code related to a specific batch. The tracking system appears to be adequate.