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CBER BLA Device Review Memorandum

BLA STN 125868

(b) (4) (Orca-T)

Reviewer

Mona Mansouri, PhD, CBER/OTP/OCTHT/DCT1/CTTB

Signature Block

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**Center for Biologics Evaluation and Research
Office of Therapeutic Products
Office of Cellular Therapies and Human Tissue CMC**

1. **BLA 125868**
2. **Submission Subtype:** Original Submission
3. **Applicant Name:** Orca Biosystems Inc.
4. **Product Name/Product Type:** (b) (4) (Orca-T)
5. **General Description of Final Product:** An allogeneic stem cell and T-cell immunotherapy derived from an HLA-matched donor
6. **Proposed Use:** (b) (4) of moderate to severe chronic GVHD (cGVHD) (b) (4)
7. **Route of Administration:** Intravenously (IV)

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I. Executive Summary

Orca-T is an allogeneic stem cell and T-cell immunotherapy for adult patients with hematologic malignancies (acute leukemia and myelodysplastic syndrome) to improve survival free of Graft-Versus-Host Disease (GVHD). The product comprises four drug product components and is delivered intravenously via either pump or gravity infusion. This consultation was requested by DCT1/CTB1 to assess the suitability of delivery device (Standard intravenous (IV) administration set) and infusion bags used for the drug products subject of BLA 125868. Therefore, this memo focuses on the delivery device

and infusion bag's regulatory status, intended use, and any additional concerns related to device use or assembly. The delivery system is not included in the BLA submission but supplied by treatment centers, with the sponsor mandating only minimum specifications of a central venous catheter of at least 18-gauge and an optional in-line filter of at least (b) (4) when cell aggregates are observed.

Additionally, the infusion bags used for three drug products (Treg, HSPC, Tcon) are 510K cleared and being used on label. All intravenous (IV) bags serve as primary container closures and are packaged in secondary packaging consisting of sterile, clear, self-sealing plastic bags.

The Device team issued three Information Requests (IRs) regarding delivery device details and administration procedure used in clinical study. While compatibility between the device and drug product is also covered in the 2nd device IRs, it is not discussed in detail in this memo. Please refer to the Chemistry, Manufacturing, and Controls (CMC) memo for additional details about compatibility studies.

II. Recommendation

From a device perspective, the proposed device used to administer the product to the patient, an infusion line connected to a central venous catheter with a minimum size of 18-gauge, is acceptable for the intended clinical use. The proposed devices are standard FDA-cleared components appropriate for intravenous administration of cellular products, with defined specifications for catheter gauge and filter use.

Regarding the infusion bags, the provided information covers basic assembly procedures and regulatory status. The infusion bags are FDA-cleared and acceptable for their intended use.

However, the submission lacks data on the compatibility of the drug product with pump-assisted infusion. The determination of whether this data gap is acceptable or requires additional information is deferred to the CMC review team.

III. Communication Log

1 st Device IR was sent	October 7, 2025 (CMC IR#3)
Response to the 1 st IR was Received	October 14, 2025
2 nd Device IR was sent	December 1, 2025 (CMC IR#9)
Response to the 2 nd IR was Received	December 15, 2025
3 rd Device IR was sent	May 28,2026 (CMC IR#27)
Response to the 3 rd IR was Received	May 29,2026

IV. Product Description

A. General Overview

Donor	An allogeneic cell therapy
Cell Source	Allogeneic cells from Human leukocyte antigens (HLA)-matched healthy donors
Drug Products (DPs)	Regulatory T cells (Treg) DP

	- Hematopoietic stem and progenitor cells (HSPC) DP - Conventional T cells (Tcon) DP + Tcon diluent DP
Route of administration	Intravenously (IV)
Dosage Form	Suspension for infusion
Administration plan	Day 0: - HSPC DP and Treg DP (ready to infuse) are administered IV in their entirety Day +2 to +3: - Tcon DP is thawed and diluted with Tcon diluent DP at 1:2 ratio (15 mL Tcon + 30 mL diluent = 45 mL final volume)
Container closure system	Treg and HSPC DP: Primary Container: (b) (4) 150 mL (b) (4) Bag (b) (4) Catalog Number (b) (4) 510(k) Number: (b) (4) Classification: Class II medical device per 21 CFR 864.9100 Material: (b) (4) Fill Volume: Approximately 100 mL Storage: 5°C ± 3°C for up to 72 hours post-apheresis collection (PAC) Sterilization: (b) (4) Endotoxin Standard: (b) (4) per bag (b) (4) Secondary Packaging: Sterile clear self-sealing plastic bag (b) (4), 6" x 8" Tcon DP: Primary Container: (b) (4) (b) (4) 510(k) Number: (b) (4) Material: (b) (4) tubular film Fill Volume: Approximately 15 mL Storage: < -125°C (vapor phase of liquid nitrogen) for at least 3 days, up to 7 days PAC Endotoxin Standard: (b) (4) CE-marked in Europe, 510(k) cleared in United States Tcon Diluent: Primary Container: 50-mL end ported bio container made of (b) (4)-based (b) (4) bag 510(k) Number: N/A Fill Volume: Approximately 30 mL (target 38 mL) Storage: 15-30°C, transported at ambient conditions Pre-use: Chill at 5°C ± 3°C for at least 30 minutes
Shipping condition	HSPC DP and Treg DP: - Each formulated in approximately 100 mL volume - Both packaged in separate bags, placed in same two-layer cardboard carton (one on each shelf) - Carton placed in (b) (4) shipping container conditioned to maintain 2°C to 8°C for at least (b) (4)

	Tcon DP: - Formulated in approximately 15 mL volume - Cryopreserved and shipped at < -125°C separately Tcon Diluent: - Approximately 30 mL volume - Stored at 15-30°C, transported at ambient conditions		
In-use stability	(b) (4)	(Treg/HSPC)	
	(b) (4)	(Tcon post-dilution)	
Details of Delivery Methods	Parameter	Gravity (b) (4)	(b) (4) peristaltic pump (b) (4)
	Length	79 in (201 cm)	117 in (297 cm) - worst case
	Tubing	(b) (4)	(b) (4)
	Drop Factor	10 drops/mL	20 drops/mL
		(b) (4)	
	Flow Control	Roller clamp	(b) (4)
	Flow rate	≤ 5 mL/min for all three drug products for both the gravity and pump	

V. Container Closure System: Infusion Bags

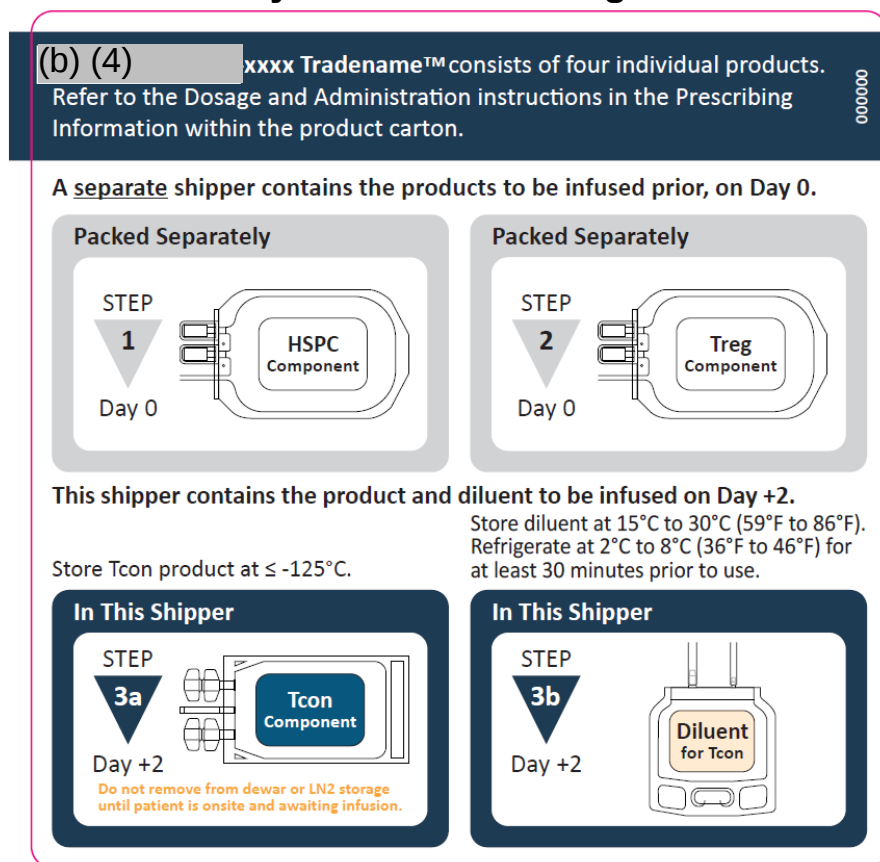


Figure 1: Four shipment information card for each DP(s), outlining the administration and storage requirements. The figure is taken from Module 1.14.1.1 (labeling)

1. Treg infusion bag

The Treg DP product is stored fresh for up to 72 hours post-apheresis collection (PAC) in the (b) (4) 150 mL (b) (4) Bag (b) (4) a Class II medical device manufactured by (b) (4) that received FDA 510(k) clearance in (b) (4) as a container for collection and processing of blood and blood components.

The container is constructed of (b) (4) and holds approximately 100 mL of product that appears off-white, white, yellow, orange, to red in color with a (b) (4). Other features of the bag are detailed in Table 1.

Storage stability has been demonstrated at $5\pm 3^{\circ}\text{C}$ across multiple time points from 53 to 72 hours PAC, with comprehensive monitoring of 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 PAC, with an established in-use stability of (b) (4) at (b) (4) after removal from cold storage.

2. HSPC infusion bag

The HSPC DP product is stored fresh for up to 60 hours in the same primary container as the Treg DP: the (b) (4) 150 mL (b) (4) Bag (b) (4), a Class II medical device manufactured by (b) (4). The (b) (4) bag design includes

features that enhance mixing and reduce the risk of kinking during use, thereby improving overall handling and performance.

A drawing of the bag with inner dimensions and tubing size after sterilization is shown in Figure 2 below:

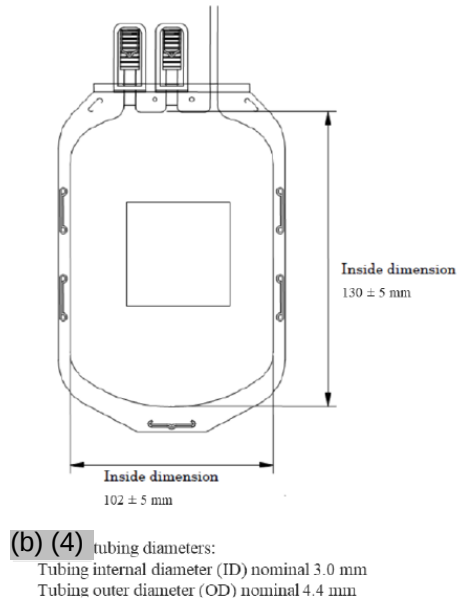


Figure 2: (b) (4) Bag with 150 mL Capacity, detailing its inside dimensions of 130 ± 5 mm in height and 102 ± 5 mm in width, and specifies the associated (b) (4) tubing diameters as a nominal 3.0 mm for the internal diameter (ID) and 4.4 mm for the outer diameter (OD).. The image is taken from 3.2.P.7 Container Closure System [Treg, Cell Suspension for Infusion], Page 3

Table 1: Specification of Treg and HSPC IV bags. The table is taken from 3.2.P.7 Container Closure System [Treg, Cell Suspension for Infusion], page 3.

Test Attribute	Analytical Procedure	Acceptance Criteria
Chemical Test for PV Material	Verified from COA	Pass
Chemical Test for Other Plastic Material	Verified from COA	Pass
Function test for (b) (4) Container	Verified from COA	Pass
Biological Test (Bacterial Endotoxin)	(b) (4)	Pass
Microbiological Test (Biological Indicator Test)	(b) (4)	Pass
Identification	Label Verification	150 mL (b) (4) Bag
Visual Inspection	In-house	Pass

(b) (4) bags conform to (b) (4) (Figure 3).

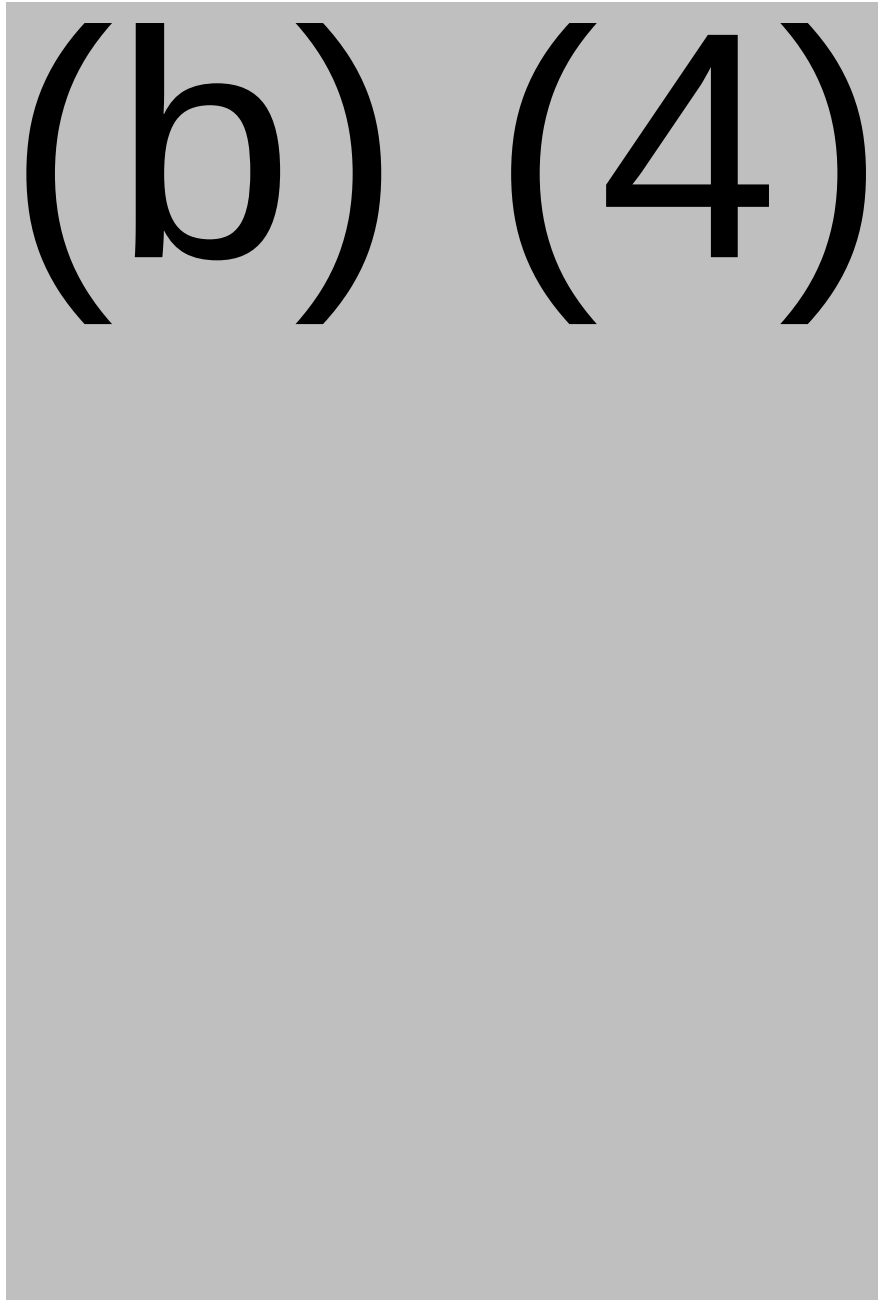


Figure 3: Certificate of analysis for the (b) (4) 150 mL (b) (4) Bag. This image is taken from 3.2.P.7 Container Closure System [Treg, Cell Suspension for Infusion]. Page 2.

Terumo (b) (4) 150 mL (b) (4) Bag has been (b) (4) tested by the vendor following (b) (4) standards (b) (4), meeting the requirements outlined in the U.S. Department of Transportation's (DOT) Hazardous Materials Regulations (HMR) (49 CFR Parts 171–180). Extractable/leachable data for the (b) (4)

(b) (4) mL (b) (4) Bag and container closure integrity testing for the (b) (4)
(b) (4) 150 mL (b) (4) Bag is discussed in Module 3.2.P.2.4 (Treg).

3. Secondary container closure for Treg and HSPC

The primary bag is enclosed inside a sterile ziplock bag. These bags are 6" x 8" and manufactured from (b) (4). This bag is used to protect the primary container from environmental contaminants. Specifications for the sterile ziplock bags are provided in table 2.

Table 2: Specification of secondary container closure detailing that the visual inspection and that the sterility test is done. The table is taken from 3.2.P.7 Container Closure System [Treg, Cell Suspension for Infusion], page 4.

Vendor/Catalog Number	Test Attribute	Analytical Procedure	Acceptance Criteria
(b) (4)	Visual Inspection	In-house	Pass
	Sterility	(b) (4)	(b) (4)

4. Tertiary Container Closure for Treg and HSPC

Both regulatory T cell (Treg) drug product (DP) and hematopoietic stem and progenitor cell (HSPC) DP are shipped in the same two-layer cardboard carton (b) (4), one in each section of the carton. The carton is made of 24-point white clay coated solid bleached sulfate (CCSBS), coated one side (C1S). The carton is 5 1/8" long x 5 1/4" wide x 3 7/32" deep and contains handles for ease of extraction from the (b) (4) shipper. The carton is placed into the (b) (4)

. An illustration of the cardboard box for the Treg DP and HSPC DP including orientation within the outbox is shown in Figure 4.



On left is an empty box, and on right is the box with Treg DP and HSPC DP within the carton
Abbreviations: Treg, regulatory T cell; HSPC, hematopoietic stem and progenitor cell; DP, drug product.

Figure 4: Tertiary container closure for Treg and HSPC, displaying an empty white shipping carton and the same carton holding the Treg and HSPC drug products. The image is taken from 3.2.P.7 Container Closure System [Treg, Cell Suspension for Infusion], page 5.

5. Shipping box for Treg and HSPC

The (b) (4) is a durable, reusable passive shipping container engineered to safely transport temperature-sensitive medical materials by maintaining a consistent 2°C to 8°C environment (Table 3 and Figure 5).

Table 3: Key Features & Components of (b) (4) shipping container which helps to maintain 2°C to 8°C environment. The table is taken from 3.2.P.7 Container Closure System [Treg, Cell Suspension for Infusion]

Feature	Description
Temperature Stability	Maintains a controlled 2°C to 8°C environment for (b) (4) hours.
Construction	Built with advanced (b) (4) for superior thermal protection.
Durability & Reusability	Designed for repeated use with robust materials, reducing single-use packaging waste.
Ease of Use	Modular (b) (4) walls simplify assembly and minimize human error.
Tracking & Monitoring	Features a bottom-mounted sensor for real-time temperature and location tracking, viewable remotely via (b) (4) software.
Compliance	Includes an (b) (4) sheet required by (b) (4) for transporting biohazardous human materials.

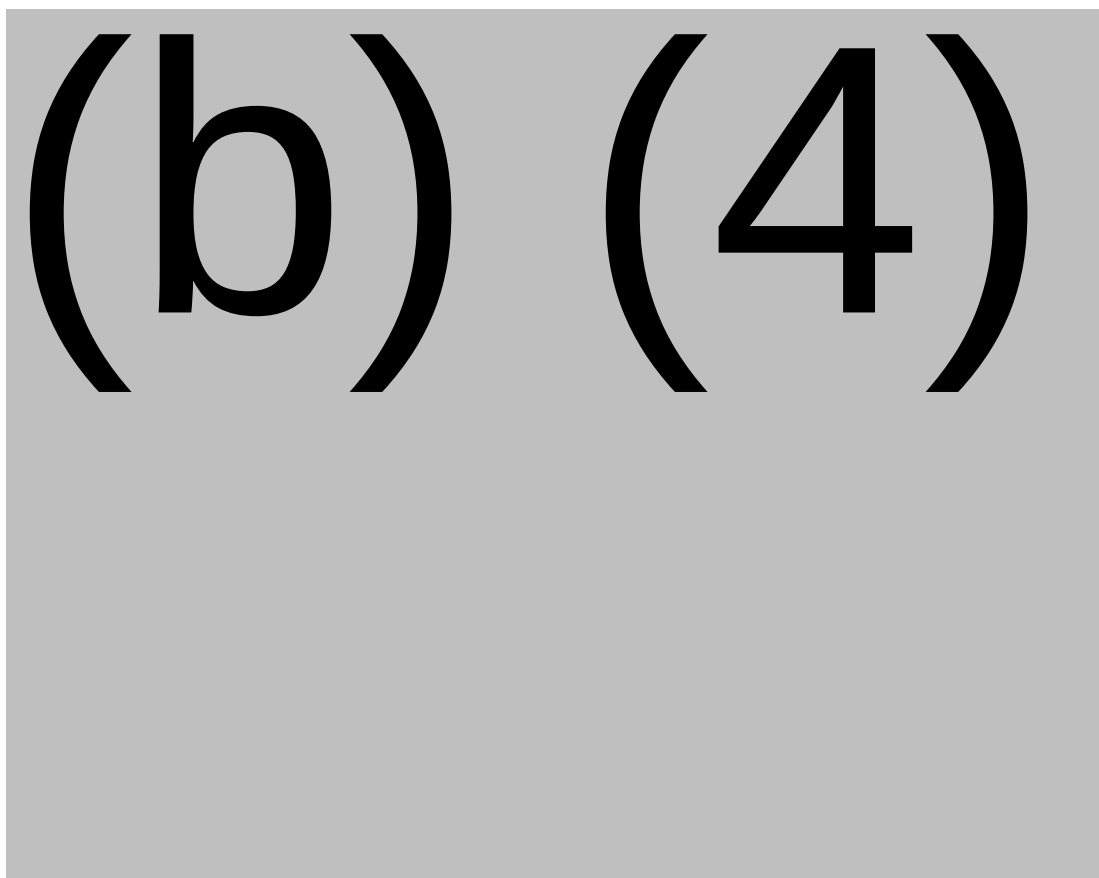


Figure 5: Illustration of the (b) (4) Assembly. On left is the (b) (4) Assembly, on top right is the monitoring device, middle right is the (b) (4) material on top of the monitoring device and bottom right is the carton containing the two DPs within the cold chamber. The final (b) (4) goes on top of the DP containing carton then the (b) (4) lid. The two layer cardboard carton containing the Treg and HSPC DP sit on top of the monitoring device and (b) (4) material. The (b) (4) contains (b) (4) panels. Abbreviations: (b) (4); Treg, regulatory T cell; HSPC, hematopoietic stem and progenitor cell; DP, drug product. The image is taken from 3.2.P.7 Container Closure System [Treg, Cell Suspension for Infusion], page 6.

Reviewer's Comment: The information provided regarding the container closure system of Treg and HSPC drug products is adequate. Both products are administered intravenously via either pump or gravity infusion (flow rates (b) (4) mL/min) with an infusion duration of (b) (4), as stated in the sponsor's response to our first information request received on October 14, 2025. Additional details about administration are provided below.

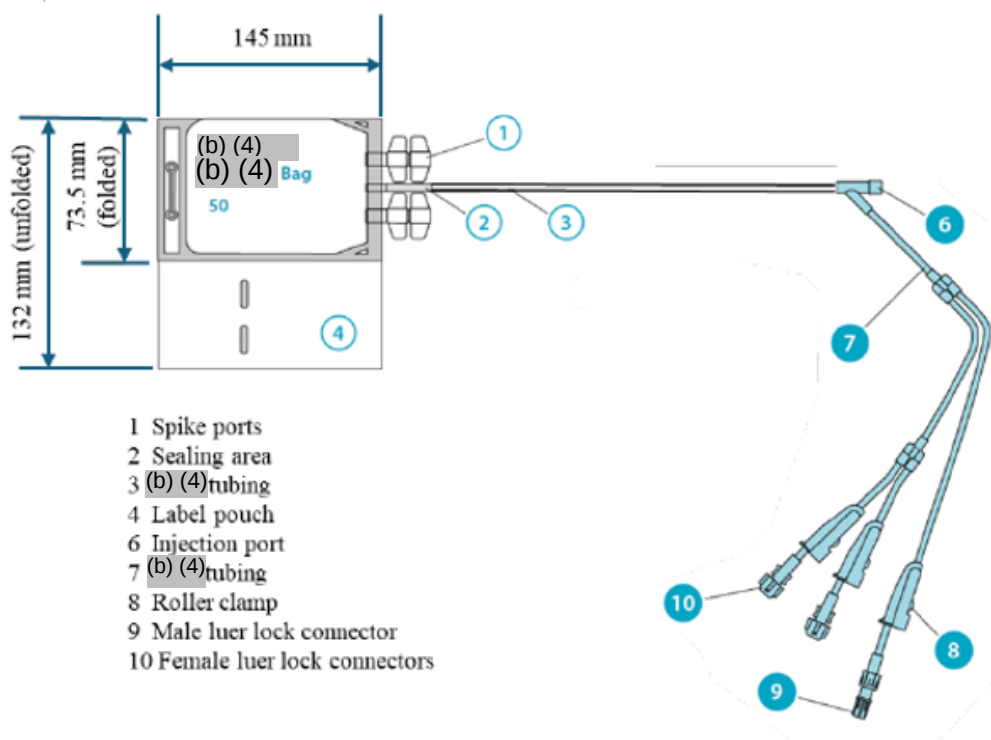
6. Tcon DP

The conventional T cell (Tcon) drug product utilizes a (b) (4) Bag 50 manufactured by (b) (4) as its primary container closure system, constructed from (b) (4) material specifically designed to withstand cryogenic temperatures as low as -196°C for storage at < -125°C.

The bag is a Class II medical device (per 21 CFR 864.9100). This CE-marked and 510(k)-cleared (b) (4) infusion bag is (b) (4) for sterility per (b) (4) standards, contains (b) (4) endotoxin units per device, and features robust heat seals

validated for freezing and thawing cycles with secure port systems compatible with sterile welders and cryogenic tubing (Figure 6).

The Tcon diluent DP, consisting of MEI with 2% HSA in a 30 mL volume, is packaged separately in a two-layer cardboard carton that is shipped alongside the Tcon DP in the top section of the vapor dry shipper box, with both products demonstrating compatibility during the validated in-use stability studies.



Abbreviations: (b) (4)

Figure 6: (b) (4) Bag 50, which measures 145 mm wide and 132 mm high when unfolded. The diagram shows the bag connected to a tubing system that includes spike ports, an injection port, a roller clamp, and various connectors, with the tubing made from both (b) (4) ., This image is taken from module 3.2.P.7 Container Closure System [Tcon, Cell Suspension for Infusion], page 3.

Reviewer's comment: During the initial review, it was noted that the 510(k) number for the Tcon freezing bag was omitted. This information was requested in the first IR (CMC IR#3), issued on October 7, 2025. The sponsor subsequently provided 510(k) number (b) (4) , which is considered acceptable.

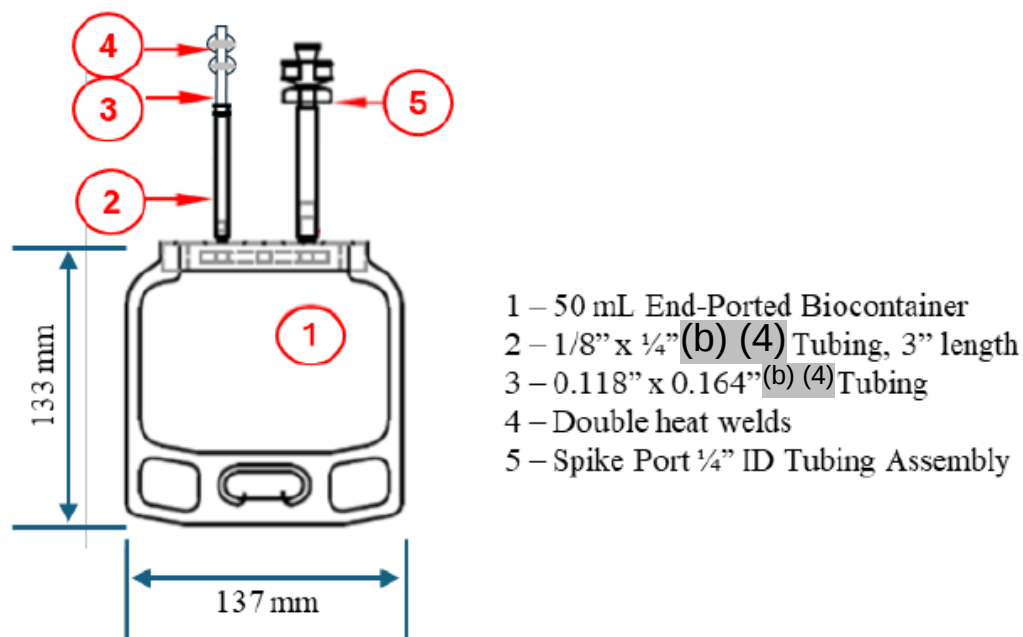
7. Tcon Diluent

The Tcon diluent drug product utilizes a 50-mL end-ported biocontainer made of (b) (4) -based (b) (4) as its primary container closure system, which is received as part of an (b) (4) 50 mL (b) (4) manufactured by (b) (4) .(Figure 7)

The (b) (4) features a (b) (4) construction with a total thickness of 320 µm (12.7 mil), consisting of a (b) (4)

(b) (4); notably, the film is manufactured without slip agents to provide better clarity, seal integrity, and a low extractables/leachables profile. Comprehensive E&L testing has been conducted as part of the overall drug product development and is documented in Module 3.2.P.2.4 (Tcon Diluent).

Unlike the Tcon DP, which is maintained at cryogenic temperatures ($< -125^{\circ}\text{C}$) within the vapor dry shipper's temperature-controlled chamber, the Tcon diluent DP carton is positioned outside both the temperature-controlled chamber and the shipper itself, where it is stored at ambient temperature throughout transit. This packaging configuration allows both products to be shipped together as a complete system while maintaining the distinct storage temperature requirements for each component—cryogenic for the Tcon DP and ambient for the Tcon diluent DP—until the point of use when the thawed Tcon DP is diluted with the refrigerated Tcon diluent prior to administration.



Abbreviations: ID, identification: (b) (4)

Figure 7: Tcon Diluent Primary Container Closure, measuring 133 mm in height and 137 mm in width, and identifies its key components, including (b) (4) (b) (4) tubing, double heat welds, and a spike port tubing assembly. The picture is taken from 3.2.P.7 Container Closure System [Tcon Diluent], Page 4

Reviewer's Comment: The 510(k) number for the Tcon Diluent container was unknown within the current submission; consequently, we sent an IR to the sponsor on April 27, 2026 to get additional information about this bag. The sponsor responded on April 28, 2026, stating the bag is neither regulated as a medical device nor subject to 510(k) clearance. Their response is acceptable from a device perspective because the sponsor provided sufficient information within the BLA to independently demonstrate the bag's safety, performance, and suitability for its proposed use.

According to the sponsor's response the bag is manufactured by (b) (4) for storage of diluent, and the qualification package covers multiple aspects of container performance (Table 5). On the safety side, container closure integrity was demonstrated through (b) (4) testing per (b) (4) and (b) (4) testing per (b) (4) both conducted at (b) (4), with all containers passing. Sterilization was validated through (b) (4) at (b) (4) per (b) (4) achieving a (b) (4), with documentation maintained in (b) (4) DMF (b) (4). Biocompatibility was established through a full suite of (b) (4) tests performed by the supplier, including (b) (4)

Extractables and leachables testing demonstrated that elemental impurities fall below parenteral permissible daily exposure limits and that observed leachable levels do not pose a significant safety risk. Animal-derived material risk was assessed and found to be compliant with EMA guidance on TSE risk minimization. Upon receipt, the product Certificate of Analysis (COA) (Figure 8), and sterilization documentation are reviewed by the sponsor to confirm the following prior to release for commercial use, along with visual inspection and label verification:

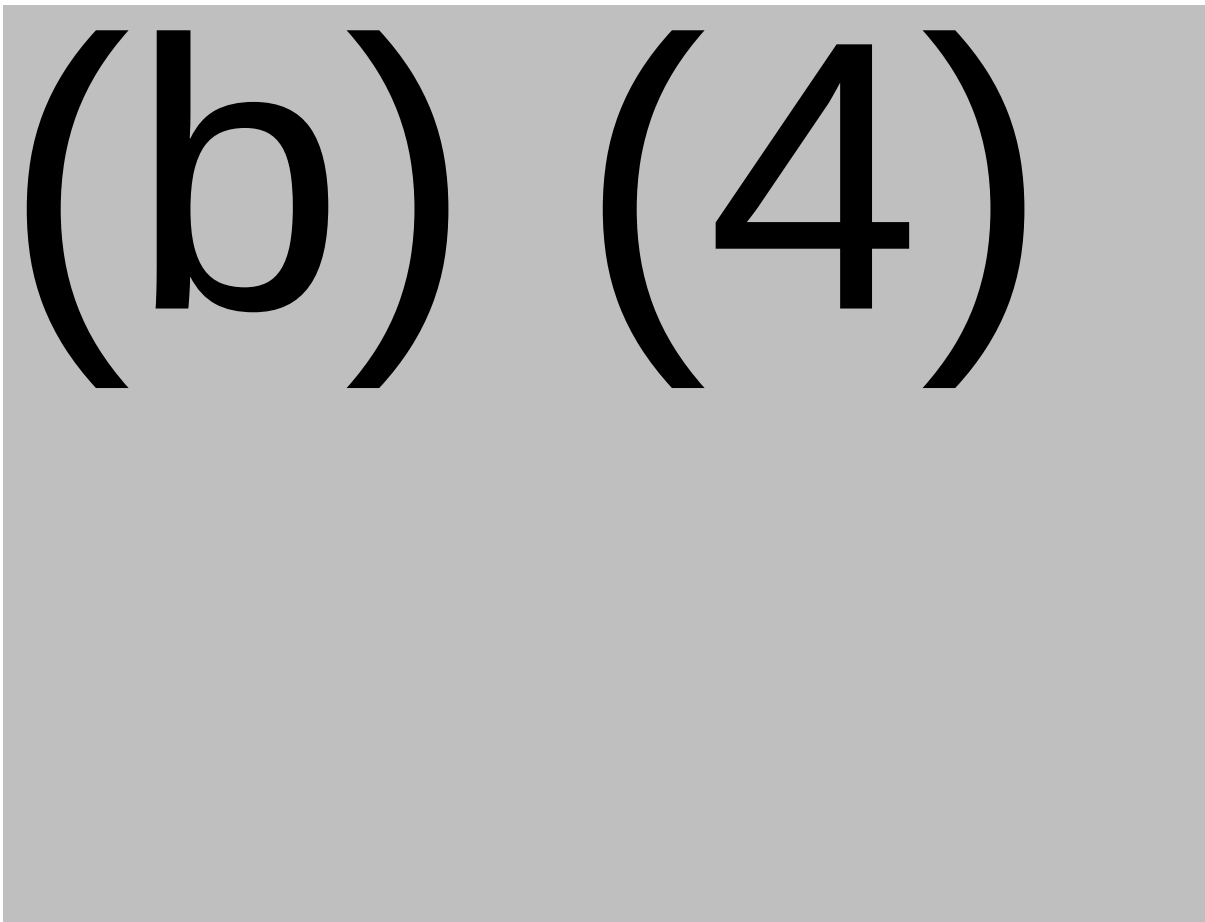


Figure 8: Certificate of Quality for (b) (4). This document certifies that the product, (b) (4), meets specific quality criteria. The certificate confirms it has passed tests for Product Quality, Materials of Construction, (b) (4), Pyrogenicity, and Particulate matter. (This image is taken from sponsor's response to our IR sent on April 27, 2026)

Table 4: Qualification Summary of Tcon Diluent Primary Container. This table contains a table that outline the testing plan for the product. The table is organized into three columns: the characteristic being evaluated; relevant industry standards or specific study conducted; and the person responsible for doing the test. (Response to IR received on April 28, 2026)

Item	Applicable Standards/Study	Study information
Materials and Composition	See Table 3	See Table 3
Extractables & Leachables	(b) (4)	Performed by Supplier
	Drug Product Leachables Screening Study	Applicant responsibility Refer to section 2.1.1.2.5
Biocompatibility	(b) (4)	Performed by Supplier
		Performed by Supplier
		Performed by Supplier
		Performed by Supplier
Container Closure Integrity	(b) (4)	Performed by Supplier: (b) (4) verified across multiple lots of (b) (4)
		Performed by Supplier: (b) (4) verified across multiple lots of (b) (4)
		(b) (4)
		Performed by Supplier on representative (b) (4) bags to characterize leak rates and locations of leaks
		Performed by Supplier: (b) (4) testing to qualify barb-to-tube integrity for all combination of connections
		Applicant Responsibility
		Refer to section 2.1.1.2.1
Functionality	Container Closure	Applicant Responsibility Refer to section 2.1.1.2.1 and section 2.1.1.2.2 .
	Shipping Validation of Tcon Diluent DP	Applicant Responsibility Refer to Module 3.2.P.3.5 (Tcon)
	Particulate Matter	Particular matter assurance per Supplier COA, (b) (4)
Product Compatibility and Stability	Comparability and stability studies	Applicant Responsibility Module 3.2.P.8.1 (Tcon)
Sterility	(b) (4)	Supplier certificate, (b) (4) Refer to DMI (b) (4) (Module 1.4.2)
	Tcon Diluent DP Release Testing Sterility Test (b) (4)	Applicant Responsibility Refer to Module 3.2.P.5.1 (Tcon Diluent)
Endotoxin	Testing Bacterial Endotoxins Test (b) (4)	Supplier certificate, (b) (4)
	Tcon Diluent DP Release Testing Bacterial Endotoxins Test (b) (4)	Applicant Responsibility Refer to Module 3.2.P.5.1 (Tcon Diluent)
Supplier Qualification	Audit	Applicant Responsibility Audit performed on 18 NOV 2025
	Qualification summary	Meissner is a qualified vendor
	Quality Agreement	Quality agreement in place with LOA for DMF for Sterilization services.

Abbreviations: (b) (4) COA, certificate of analysis; DMF, drug master file; (b) (4)
(b) (4) LOA, letter of authorization; (b) (4)

The Tcon Diluent container is positioned by Orca Bio as a manufacturing and storage container. The sponsor argues that the diluent is transferred out of the bag and into the Tcon DP bag at the clinical site via a spike port connection and there is no contact between patient and the bag. Thus, they state the 510K number is not required for this bag.

Because the diluent bag is a passive drug storage container, from device perspective the provided information is adequate. The assessment of extractable and leachable and DP compatibility is deferred to CMC team.

8. Secondary Packaging for Tcon

The Tcon drug product and Tcon diluent drug product each utilize individual sterile secondary containers, with the Tcon DP placed in a sterile, clear, self-sealing ziplock bag (b) (4) and the Tcon diluent DP placed in a sterile resealable bag (b) (4) both sterilized per (b) (4) standards with a (b) (4)

9. Tertiary Container Closure for Tcon

For shipping, the Tcon diluent DP (in its sterile resealable bag) is placed in one half of a two-layer cardboard carton manufactured by (b) (4) made of 24-point (b) (4) measuring 10 1/16" × 5 9/16" × 1 9/16", while the other half contains an information card and patient information leaflet (PIL) as shown in Figure 8. This cardboard carton is housed in a foam insert in the top section of the Tcon DP vapor dry shipper box, positioned outside the temperature-controlled chamber where it remains at ambient temperature, while the Tcon DP itself (in its sterile ziplock bag within the (b) (4) Bag 50) is stored inside the vapor dry shipper at < -125°C. Both the vapor dry shipper box and the cardboard carton are secured together using an outer shipper soft case that allows the complete package to be attached to a two-wheel hand truck or secured with (b) (4) transport to the administering site.

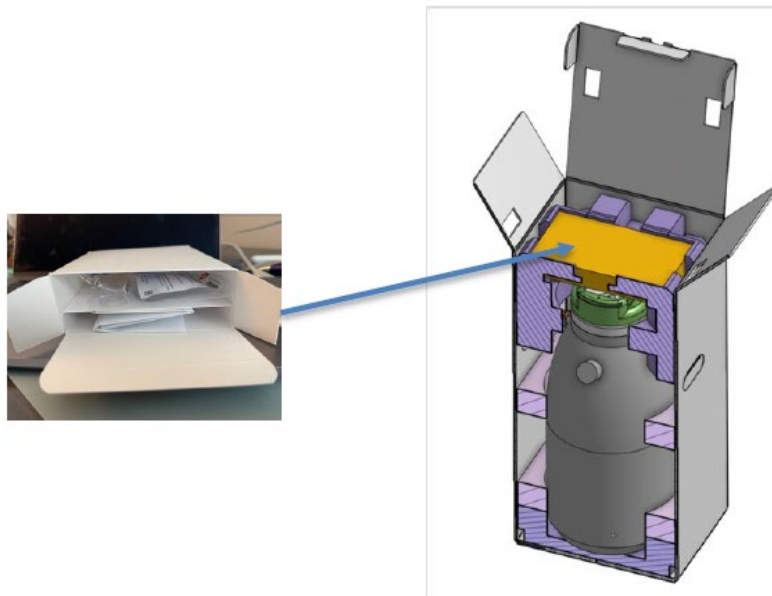


Figure 9: The packing configuration for a shipping container, showing a photo of a small carton on the left and a diagram on the right where an arrow indicates that this carton is placed in a designated slot at the top of the main shipper, above a cylindrical canister secured by protective inserts. . The picture is taken from 3.2.P.7 Container Closure System [Tcon Diluent], page 6.

Reviewer's comment: Tcon is mixed with Treg and administered to the patient via either gravity or pump infusion at a flow rate of ≤ 5 mL/min. The information about Tcon DP and Tcon Diluent bags are adequate.

CMC reached out to the Extractables and Leachables (E&L) reviewer (Dr. Andrey Sarafanov) to confirm whether E&L data had been provided and reviewed for the three infusion bags used in the manufacturing process: the 150 mL (b) (4) Bag (b) (4) for Treg and HSPC, the 50 mL (b) (4) Bag (b) (4) for Tcon, and the 50 mL (b) (4) (b) (4) bag for Tcon diluent.

The E&L reviewer responded that the applicant initially provided only an in-silico assessment that combined extractables data from selected components, which was deemed insufficient. Following multiple information requests and a teleconference, the applicant committed to conduct a proper simulated leachables study with preliminary results by March 13 2026 and final validated results by October 2026, meaning comprehensive E&L safety data for the three infusion bags will not be available until after the current review cycle.

VI. Delivery device

Reviewer's Comment: Information provided for the proposed delivery device lacked critical details, prompting the issuance of an Information Request (IR) to the sponsor requesting additional information on administration details.

In the first IR (CMC IR#3) which was sent on October 7, 2025, we asked the sponsor to provide a detailed description of the delivery device components (infusion set, tubing, catheter), including manufacturer details, materials of construction, and regulatory status

(e.g., 510(k)). The sponsor clarified that administration components are not included in the drug product configuration but are instead supplied by treatment centers using standard, commercially available medical-grade equipment cleared for blood product transfusion.

An inquiry was also made to the clinical reviewer (Dr. Xiong) regarding IV administration sets used in clinical studies. Dr. Xiong confirmed this information was not available in clinical documents and directed the inquiry to the CMC team. The CMC reviewer (Dr. Lessey-Morillon) identified that Phase 3 study site instructions (Section 3.2.3) indicate:

- Drug products are shipped ready-to-infuse
- Sites are instructed to follow institutional SOPs/guidelines for drug product transfer and infusion
- No specific IV administration set is specified by the sponsor

Thus, the sponsor allows clinical sites to use any IV administration set consistent with their standard of care procedures for stem cell transplants.

Furthermore, the agency requested a scientific justification for the minimum requirements of the administration devices. The sponsor explained that tubing is supplied according to individual site protocols for cellular therapy. For the 18-gauge minimum catheter requirement, the sponsor provided a rationale based on a survey of 10 clinical sites and supporting literature demonstrating that cellular products can safely pass through needles as small as 25-gauge. Regarding the (b) (4), the sponsor justified its use as the most restrictive clinical standard (worst-case scenario); they noted that (b) (4)

The response was acceptable, as the sponsor allows sites to follow local procedures while mandating key specifications.

VII. Administration

In Module 1.14.1.2 and 1.14.1.3 (Draft labeling) the sponsor has described the administration method.

1. Administration of HSPC and Treg

- Prior to infusion, gently agitate each infusion bag to prevent cell clumping.
- To begin, infuse the entire contents of HSPCs on day 0 by either gravity or a peristaltic pump at a rate of up to (b) (4) mL/min.
- After infusion of the entire content of the HSPC infusion bag, add approximately 10 mL of normal saline to the empty infusion bag and administer to the patient at the same infusion rate to ensure all product is delivered. Repeat this process to achieve a total of two rinses.
- Infuse the entire contents of the Tregs on day 0 as soon as the HSPC component has been infused. Infuse the Tregs by either gravity or a peristaltic pump at a rate of up to (b) (4) mL/min.
- After infusion of the entire contents of the Treg infusion bag, add approximately 10 mL of normal saline to the empty infusion bag and administer to the patient at the

same infusion rate to ensure all product is delivered. Repeat this process to achieve a total of two rinses.

2. Administration of Tcon

- To begin, on day +2 to +3 (after the start of HSPC infusion on day 0) remove Tcons in cryobag from liquid nitrogen storage no more than (b) (4) prior to infusion and verify product information.
- Thaw Tcons in cryobag in a water bath at 37°C in a sterile plastic bag. Seal the bag tightly. Gently massage the Tcons in the cryobag until the cell suspension is slushy in texture, approximately 1 to 1.5 minutes. Discard plastic bag. Wipe down the Tcon cryobag with 70% isopropanol.
- Refrigerate the Tcon diluent for at least 30 minutes at 2 to 8°C oC prior to use.
- Add the entire contents of the diluent into the Tcon cryobag either using a sterile dispensing pin and syringe or a transfer set using a gravity transfer. Over a period of approximately 3 minutes, slowly rock the Tcon infusion bag while adding chilled Tcon diluent into the Tcon infusion bag.
- Once thawed, Tcons should be administered as soon as possible but are stable for up to 4 hours at 2 to 8°C.

Reviewer's Comment: A discrepancy was identified in the initial submission: Module 3 described only gravity infusion, while other modules referenced both gravity and peristaltic pump methods. The first Information Request (CMC IR#3), issued on October 7, 2025, noted the absence of data comparing the two administration methods. The sponsor acknowledged the discrepancy, offering theoretical calculations and literature references to argue that mechanical stress from a pump would be negligible and would not impact cell integrity.

This response was deemed not acceptable. The provided justification was insufficient to demonstrate equivalency. Because both methods are intended for interchangeable clinical use, a direct comparability study was required, prompting a second IR.

The second IR (CMC IR#9), issued on December 1, 2025, requested a formal comparability study demonstrating that pump-assisted delivery is non-inferior to gravity infusion for all three drug products. The sponsor confirmed the clinical use of both methods and formally committed to completing the required comparability studies. They provided the associated protocols (PRO-0096, PRO-0097, and PRO-0098) outlining split-sample, paired non-inferiority trials designed to assess cell viability, recovery, purity, and potency. The full study reports were subsequently submitted on March 31, 2026. The final assessment of the comparability data is deferred to the CMC review team. The specific administration method information utilized in these protocols is documented below.

In three reports (PRO-0096, 0097 and 0098) provided in Module 3.2.R regional information, the sponsor conducted comparability study between gravity and pump

infusion delivery methods. Each of these reports focuses on a different drug product with distinct storage requirements. Table 4 is a summary of the main differences:

Table 5: Summary of the specific storage conditions for three different drug products as documented in their corresponding "Pump vs Gravity" reports. This table is made by the reviewer based on sponsor's response to our IR sent on April 27, 2026.

Report	Pump vs Gravity.pdf (RPT-0457)	Pump vs Gravity-2.pdf (RPT-0458)	Pump vs Gravity-3.pdf (RPT-0459)
Drug Product Tested	Treg (Orca-T regulatory T cell)	HSPC (Orca-T hematopoietic stem and progenitor cells)	Tcon (Orca-T conventional T cells)
Storage Conditions	Stored at 5°C ± 3°C for up to 72 hours.	Stored at 5°C ± 3°C for up to 72 hours.	Cryopreserved at < -125°C for at least 3 days, then thawed and diluted.

In all these three reports the sponsor has specified information on infusion devices:

Gravity Infusion Device

- Manufacturer: (b) (4)
- Device: (b) (4)
- Catalog Number: (b) (4)
- Materials of Construction:
 - Tubing: (b) (4)
 - Drip Chamber: (b) (4)
 - Spike: (b) (4)

Pump Infusion Device (Peristaltic Pump)

- Manufacturer: (b) (4)
- Device: Administration Set
- Catalog Number: (b) (4)
- Regulatory Information: The documents note that this pump infusion set is cleared by the FDA under 510(k) (b) (4) .
- Materials of Construction:
 - Tubing: (b) (4)
 - Drip Chamber: (b) (4)
 - Pump Segment: (b) (4)

3. Comparability study between Gravity and Pump assisted infusion

The core of the experiment was a (b) (4) , paired design. Each drug product (DP) batch was (b) (4)

. This design removed donor-to-donor variability, ensuring a direct comparison of the infusion methods.

Key Components Used:

The sponsor clarified the sequence of events leading to the discrepancy and provided a rationale.

Specifically, the sponsor confirmed that the Phase 3 Precision-T Study and Administration Manual had instructed all clinical sites to use a flow rate of ≤ 5 mL/min for all three drug products.

A post-study site survey corroborated that ≤ 5 mL/min was the rate actually used in clinical practice. The comparability studies were subsequently designed based on these real-world findings. The higher rate of (b) (4) mL/min had been proposed only as part of a theoretical evaluation intended to support flexibility in the USPI, and the sponsor has since committed to revising the proposed USPI to align with the empirical data, specifying ≤ 5 mL/min for all three drug products.

A second issue was also raised in CMC IR #27 regarding the (b) (4) administration procedure described in the comparability protocols, which involved (b) (4) . The FDA requested confirmation of whether this procedure was used in clinical study. The sponsor clarified that the (b) (4) administration procedure was never used clinically and was not outlined in the Phase 3 Administration Manual. Rather, it was incorporated into the comparability study design as a robustness exercise to simulate worst-case contact time between the drug product and infusion lines, given that the final drug product had to be (b) (4) for the study. The sponsor confirmed that clinical sites used a constant flow rate of ≤ 5 mL/min once infusion was initiated. The specific administration method parameters utilized in the comparability protocols are documented below.

These responses are acceptable from a device perspective.