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CBER CMC BLA Review Memorandum

BLA STN 125868

TREGZI [allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq]

Hector Carrero, Consumer Safety Officer, CBER/OCBQ/DMPQ

1. **BLA#:** STN 125868/0

2. **APPLICANT NAME AND LICENSE NUMBER**

Orca Biosystems, Inc. License # 2404

3. **PRODUCT NAME/PRODUCT TYPE**

Non-Proprietary/Proper/USAN: allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq

Proprietary Name: TREGZI

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

- a. Description: Allogeneic stem cell and T-cell immunotherapy
- b. Dosage Form: Cell Suspension for Infusion
- c. Strength/Potency: 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
HSPC Drug Product (DP): $\geq 1.0 \times 10^6$ cells per patient kg in 100 mL Multiple Electrolytes Injection and 2% HAS
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)
- d. Route of Administration: Intravenous infusion
- e. Indication: Treatment of adult patients with hematologic malignancies to improve survival free of Graft-Versus-Host disease (GVHD) in conjunction with an appropriate preparative regimen.

5. **MAJOR MILESTONES**

Original BLA Received	August 6, 2025
Application Filed	October 1, 2025
Mid-Cycle Meeting	December 3, 2025
Late-Cycle Meeting	January 23, 2026
Pre-License Inspections	January 8-9, 12-15, 2026
Major Amendment Determination	March 27, 2026
PDUFA Action Date:	April 6, 2026 (after MA July 6, 2026)

6. **DMPQ CMC/FACILITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Hector Carrero, OCBQ/DMPQ/MRBII	3.2.S Drug Substance (as per CBER *SOPP 8401.4) 3.2.P Drug Product (as per CBER *SOPP 8401.4) 3.2.A.1. Facilities and Equipment (as per CBER *SOPP 8401.4)

7. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
August 6, 2025	STN 125868/0	Original submission
November 25, 2025	Amendment STN 125868/0.19 (Response to DMPQ IR #1)	Orca's response regarding (b) (4) validation

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF [REDACTED]	(b) (4) [REDACTED]	[REDACTED] Drug Product container	Yes	No DMF review required, information pertinent to container closure is provided in the BLA

9. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

CBER received this electronic submission on August 6, 2025. Orca Biosystems Inc. (Orca) submitted this BLA to provide information to support US market authorization of allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq. Allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq is indicated for the treatment of adult patients with hematologic malignancies to improve survival free of Graft-Versus-Host disease (GVHD) in conjunction with an appropriate preparative regimen. Allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq is supplied as a cell suspension for intravenous infusion. The product is formulated in multiple electrolytes injection (MEI) + 2% human serum albumin (HSA) medium suitable for infusion and filled into bags. The manufacturing of allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq drug substance (cellular components) and manufacturing of drug product (formulation, fill, cryopreservation, packaging) is performed at Orca Biosystems in Sacramento, California, USA. To support this BLA, the firm provided facility information and containment strategies, equipment description and qualifications, cleaning validations, and computer systems, container closure and container closure integrity, manufacturing process description and process validation to include aseptic process simulations and conformance lots, stability studies and shipping validations.

The reviewed and evaluated information under DMPQ purview (as per CBER SOPP 8404.1) appears acceptable. All the identified deficiencies were addressed with the amendments in response to information requests.

CBER conducted a pre-license inspection (PLI) in support of this BLA at Orca Biosystems FEI # 3035546696, 7910 Metro Air Parkway, Sacramento, CA 95837. The inspection was classified as Voluntary Action Indicated (VAI).

B. RECOMMENDATION

I. APPROVAL

Based on the information reviewed in the BLA submission and amendments approval is recommended.

The following facility is used for the manufacture and testing of allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq drug substance (DS) and drug product (DP):

- Orca Biosystems Inc. SAC-02 Facility, 7910 Metro Air Parkway, Sacramento, CA 95837

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Hector Carrero, CSO OCBQ/DMPQ/MRBII	Concur	
Anthony Lorenzo, Branch Chief OCBQ/DMPQ/MRBII	Concur	
Nicole Li, Acting Division Director, OCBQ/DMPQ/MRBII	Concur	

Review of CTD

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Module 3

3.2.S DRUG SUBSTANCE

TREGZI drug substances (DS) are cell suspensions for infusion comprised of Hematopoietic stem and progenitor cell (HSPC) DS, Regulator T cell (Treg) DS, and Conventional T cell (Tcon) DS. All cells are naturally occurring and isolated from the granulocyte-colony stimulating factor (G-CSF)-mobilized apheresis starting material from a human leukocyte antigen HLA-matched donor.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

See section 3.2.A.1 for a complete list of drug substance manufacturers.

3.2.S.2.2 Description of Manufacturing Process

Manufacturing is a continuous process, with no distinct DS and DP. Refer to 3.2.P.3.3 Description of Manufacturing Process of this memo.

3.2.S.2.3 Control of Materials

The materials used in the allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq manufacturing process include donor apheresis material, required for the stem cell and T-cell immunotherapy, and ancillary raw materials.

An evaluation of the critical components used in the allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq manufacturing process is deferred to OTP.

3.2.S.2.4 Controls of Critical Steps and Intermediates

DP is produced using a continuous manufacturing process. There is no hold, release, or storage of DS prior to filling of the DP. Refer to Module 3.2.P.3.4 for DS and DP controls of critical steps and intermediates.

3.2.S.2.5 Process Validation and/or Evaluation

The manufacture of TREGZI is a continuous process. Information on validation for the entire manufacturing process is evaluated under section 3.2.P.3.5 Process Validation and/or Evaluation.

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s)

TREGZI is manufactured as part of a continuous manufacturing process and there is no formal drug substance release testing. Please refer to Section 3.2.P.5.1 Specification and 3.2.P.5.6 Specification for justification of specifications.

3.2.S.4.4 Batch Analyses

Refer to Section 3.2.P.5.4 for batch analysis.

3.2.S.6 Container Closure System

There is no packaging of drug substance. Please refer to Section 3.2.P.7 Container Closure System for drug product packaging details.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data

Refer to Section 3.2.P.8 for the drug product stability data.

3.2.P DRUG PRODUCT

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

The TREGZI product is an allogeneic stem cell and T-cell immunotherapy. The final product consists of four individual drug products (DPs): HSPC DP, Treg DP, Tcon DP, and Tcon diluent DP.

HSPC DP and Treg DP are each formulated in a volume of approximately 100 mL and are shipped fresh, to be administered intravenously (IV) in their entirety on day 0. Tcon DP is formulated in a volume of approximately 15 mL and is cryopreserved as single dose for shipment. On day 2 to 3, Tcon DP is thawed, diluted with Tcon diluent DP, and prepared for infusion at the transplant center. The entire infusion bag of Tcon DP is administered IV.

Route of Administration and Dosing Regimen

Orca-T Drug Product	Dose Regimen	Target Viable Cell Dose Range
HSPC	Intravenous, once, on day 0	$\geq 1.0 \times 10^6$ Cells per Patient kg
Treg	Intravenous, once, on day 0	(b) (4) $\times 10^6$ to 3.5×10^6 Cells per Patient kg
Tcon	Intravenous, once, on day +2 (48 to 72 hours after the start of HSPC infusion) Infusion bag may be (b) (4)	(b) (4) $\times 10^6$ to $6^{(b) (4)} \times 10^6$ Cells per Patient kg
Tcon Diluent	Intravenous, once, administered with Tcon drug product	30 mL

3.2.P.2.4 Container Closure System

Refer to section 3.2.P.7 Container Closure System for information and assessment including CCIT.

3.2.P.2.5 Microbiological Attributes

For details of the microbial attributes, refer to section 3.2.P.5 Control of Drug Product.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Refer to section 3.2.A.1 for a complete list of all manufacturing facilities.

3.2.P.3.3 Description of Manufacturing Process

TREGZI is manufactured in a continuous process that begins with receipt of donor apheresis starting material, through to formulation and final fill of the drug product (DP). No modification of the cells is involved. There is no hold, release, or storage of DS prior to filling of the DP. A brief overview of the process is provided below.

The manufacturing process of each batch of Treg DP involves (b) (4)

and Formulation and Fill. The final volume is brought up to a target volume of 100 mL with multiple electrolytes injection (MEI) + 2% human serum albumin (HSA).

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

and HSPC Formulation and Fill. The final volume is brought up to a target volume of 100 mL with MEI + 2% HSA. The Treg and HSPC DPs are shipped together. Reprocessing may be initiated if the (b) (4) cannot meet the HSPC dose specification.

The primary manufacturing process of each batch of Tcon DP involves (b) (4)

and Tcon Formulation, Fill, and Cryopreservation unit operations. During Tcon Formulation, Fill, and Cryopreservation, cryopreservation media is added, and the material is transferred into the final container closure. Tcon DS is formulated in MEI + HSA and immediately formulated into DP with the addition of cryopreservation media to a final volume of 15 mL. The cryoprotectant contains dimethyl sulfoxide (DMSO), Hetastarch and sodium chloride. (b) (4)

Conventional T cell (Tcon) diluent drug product (DP) is used to dilute thawed Tcon DP prior to infusion. The Tcon diluent DP consists of multiple electrolytes injection, Type 1 (MEI) solution and human serum albumin (HSA) to a final concentration of 2% (w/v). The target batch size for Tcon diluent DP is (b) (4) bags (including bags used for release testing) at a target fill volume of 38 mL. The (b) (4) solution is (b) (4) Tcon diluent DP is shipped together with Tcon DP.

All processing steps are performed using closed systems in an International Organization for Standardization (ISO) (b) (4) or via aseptic techniques in an ISO (b) (4) within an ISO (b) (4) environment. Each donor apheresis is used to make one Treg/HSPC/Tcon drug product (DP). Batch number assignment is auto generated via a validated electronic system. One unique batch number is assigned to each patient batch.

Chain of custody controls ensure that donor apheresis material and the manufactured DPs intended for a patient always remain in the custody of authorized personnel during transport and production, and that each transfer of custody is documented. Chain of Identity (COI) controls ensure that unique identifying information used to trace a batch to a unique patient are defined, standardized, documented and tracked throughout the transport and manufacturing activities, and that any changes to the identifying information used during the process are clearly linked, thus preventing mix-ups.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The final critical process parameters (CPPs) and quality attributes were established using a risk-based approach. The in-process controls (IPC) were selected based on the control strategy. The IPCs include (b) (4)

The Tcon diluent manufacture IPCs include (b) (4)

Reviewer's Assessment of Section 3.2.P.3.4: Suitability of the in process testing to demonstrate that the manufacturing process for TREGZI is well controlled and capable of consistent production of a quality product is deferred to the OTP.

3.2.P.3.5 Process Validation and/or Evaluation

Process Performance Qualification (PPQ)

Treg, HSPC, Tcon PPQ

The study required (b) (4) consecutive successful batches based on statistical analysis of historical data from DP manufacturing. Each PPQ run covers all three cellular drug products: Treg, HSPC and Tcon. Data were evaluated against critical process parameters, in-process controls and final lot release criteria. All quality attributes, CPPs, and IPCs under DMPQ purview were within their acceptance criteria for all (b) (4) runs. These are summarized in the tables below.

Summary of PPQ Batches

Replicate Number	Graft ID	Date of Production
(b) (4)	(b) (4)	(b) (4)

Treg and HPSC Drug Product Quality Attributes

Quality Attribute	Method of Testing	Acceptance Criteria
Visual Inspection	(b) (4)	Conforms
Sterility	(b) (4)	No growth detected
(b) (4)	(b) (4)	No organisms detected
Endotoxin	(b) (4)	(b) (4)

Tcon Drug Product Quality Attributes

Quality Attribute	Method of Testing	Acceptance Criteria
Visual Inspection	(b) (4)	Conforms
Sterility	(b) (4)	No growth detected
(b) (4)	(b) (4)	No organisms detected
Endotoxin	(b) (4)	(b) (4)

Critical Process Parameters

Unit Operation	Process Step	Process Parameter	Acceptance Criteria
Treg DP Formulation and Fill	Treg DP Formulation	Treg DP Final Volume	(b) (4)
HSPC DP Formulation and Fill	HSPC DP Formulation	HSPC DP Final Volume	(b) (4)
Tcon Formulation, Fill, and Cryopreservation	Tcon DP Formulation	Tcon DP Final Volume	(b) (4)

Deviations

The deviations during the PPQ runs were due to human error, instrument/system errors, parameter error, documentation errors, and environmental monitoring (EM) excursions. All deviations and EM excursions were investigated and closed. The deviations were appropriately addressed and determined by the firm to have no impact on the process, product, or performance qualification.

Tcon Diluent PPQ

(b) (4) consecutive PPQ runs were performed in the Sacramento manufacturing facility ((b) (4)). All quality attributes, CPPs, and IPCs under DMPQ purview met the acceptance criteria for all four runs. These are summarized in the tables below.

Summary of Batches

Replicate Number	Batch ID	Date of Production
(b) (4)	(b) (4)	(b) (4)

Tcon Diluent Drug Product Quality Attributes

Quality Attribute	Method of Testing	Acceptance Criteria
Visual Inspection	(b) (4)	Conforms
Sterility	(b) (4)	No growth detected
Endotoxin	(b) (4)	(b) (4)

Critical Process Parameters

Process Step	Process Parameter	Acceptance Criteria
Tcon Diluent Filtration/Fill	Final Volume in Container	(b) (4)

In-Process Controls

Sample	Test Performed	Acceptance Criteria
Tcon Diluent, (b) (4)	Bioburden per (b) (4)	(b) (4)
(b) (4)	(b) (4) testing	Pass

Deviations

The deviations during the Tcon diluent PPQ runs were due to embedded particles in bags, incorrect recipe criteria, missing release data for one unit, and documentation error. All deviations were investigated and closed. The deviations were addressed and determined to have no impact on the process, product, or performance qualification.

Reviewer's Comments: *The PPQ appears to have been appropriately performed and is adequate to support the manufacture of TREGZI DP at the Orca Sacramento facility. The PPQ lots met all the required DMPQ in-scope acceptance criteria for process control and release testing. Evaluation of the acceptability of the other testing and manufacturing parameters for these lots is deferred to the assigned product reviewer. In general, the deviations do not appear to have had any adverse effect on the PPQ or the manufactured lots, but final review of the deviation is deferred to the assigned product reviewer.*

(b) (4)



(b) (4)

Aseptic Process Simulation (APS)

Treg, Tcon and HSPC APS

An initial performance qualification (PQ) of the APS was executed consisting of (b) (4) consecutive runs per suite. The PQ simulated all process steps that occur in the Grade (b) (4)/ISO (b) (4) and Grade (b) (4) ISO (b) (4) production suites. The APS covers all three cellular DPs (Treg, Tcon and HSPC) simultaneously. The APS runs include (b) (4)

Environmental monitoring is conducted during APS runs. The aseptic process is re-qualified every (b) (4) months (b) (4) yearly). Routine re-qualification APS is performed on alternating workstations in each production suite.

The manipulations, equipment used, and the environmental conditions during the APS were representative of the routine manufacturing process. Qualification activities are conducted in Grade (b) (4) suite and in a Grade (b) (4) within each Grade (b) (4) suite. All open manufacturing steps are performed in Class (b) (4)

The aseptic process simulation uses (b) (4). All cell suspension, media and reagents used throughout the process are (b) (4). (b) (4) The process simulation follows the routine manufacturing process as per batch record and focuses on operations carried out by operators involving all manufacturing steps. All samples are tested for sterility and growth promotion.

Samples were (b) (4). The acceptance criteria states that all samples must be free of microbial growth and units must pass positive control testing. APS results passed all acceptance criteria. All final product bags no growth after (b) (4). The test results are summarized in the following table:

Summary of APS Results

(b) (4)

T con diluent APS

The APS qualification program of Tcon diluent DP formulation, (b) (4), and aliquoting occurred in the same environment as production, Grade (b) (4) ISO (b) (4) production suite. The process was conducted using (b) (4) and included all manufacturing operations performed during the routine production. The qualification includes non-routine interventions challenge. The Tcon diluent aseptic process is requalified on a (b) (4) basis. The initial PQ included (b) (4) runs, and all results met the criteria (no contaminated units and passing growth promotion testing).

Summary of APS Results

(b) (4)

Reviewer's Comments: *The Aseptic Process Validation appears appropriate. The Aseptic Process Simulation program was also reviewed as part of the PLI performed at Orca on January 8-15, 2026, and the studies were found acceptable.*

Shipping Validation

Treg/HSPC DP

The living cells drug product must be kept in a 2-8°C controlled environment. Both Treg and HSPC DPs are shipped in the same type of bag and within the same shipper (b) (4) therefore the shipping operational qualification (OQ) covered both DPs. The study was conducted following (b) (4) to replicate physical hazards such as (b) (4), and (b) (4) testing with (b) (4) thermal profiles to evaluate temperature extremes. (b) (4) container closure integrity testing with surrogate bag contents material was conducted after shipping simulation.

A dynamic shipping performance qualification (PQ) was conducted with Treg and HSPC DP containers within the graft (b) (4). The study assessed shipping to various representative destinations covering (b) (4) using (b) (4) transport methods with intentional interventions to mimic (b) (4). Treg/HSPC DP packed in the (b) (4) shipper maintained internal temperature of 2-8°C for a minimum of 62 hours. (b) (4) container closure integrity testing was conducted after the dynamic shipments were completed. All tests' results met the criteria: primary package is damage free/intact including no (b) (4), and primary containers remain within temperature range for duration of allowed time.

Tcon/Tcon Diluent DP

The Tcon cells DP are cryopreserved and must be shipped at < -125°C, this is done inside of a dry shipper which is packed inside of a cardboard box. The Tcon diluent is shipped together with the dry shipper. An operational qualification of both the storage temperature of Tcon and durability of the Tcon DP and Tcon diluent DP primary container were performed. The study was conducted following (b) (4) to replicate physical hazards and (b) (4) testing with (b) (4) profiles to evaluate temperature extremes. (b) (4) container closure integrity testing with surrogate materials was conducted on each bag type after shipping simulation.

A dynamic shipping performance qualification (PQ) was conducted with Tcon DP within a dry shipper and Tcon diluent DP in its shipping box. The study assessed shipping to various representative destinations covering (b) (4) using (b) (4) transport methods with intentional interventions to mimic (b) (4). The Tcon DP packed in the dry shipper maintained internal temperature of < -125°C range for (b) (4) container closure integrity testing was conducted for each DP bag after the dynamic shipments were completed.

All tests' results met the criteria: primary package is damage free/intact including no (b) (4), and primary containers remain within temperature range for duration of allowed time.

Reviewer's Comments: The transportation studies performed to support the shipping of allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq from the manufacturing site to the clinics appears appropriate. There were only minor protocol discrepancies determined to have no impact to validation.

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)

The final product release tests and acceptance criteria for microbial attributes under DMPQ purview are summarized in the tables below.

Treg/HSPC DP Specifications

Test Attribute	Analytical Method	Acceptance Criterion
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
Sterility	(b) (4) Microbial Characterization, Identification, and Strain Typing – (b) (4)	No organisms detected
Endotoxin	(b) (4) Bacterial Endotoxins Test (b) (4) Assay	(b) (4)

Tcon DP Specifications

Test Attribute	Analytical Method	Acceptance Criterion
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
Sterility	(b) (4) Microbial Characterization, Identification, and Strain Typing – (b) (4)	No organisms detected
Endotoxin	(b) (4) Bacterial Endotoxins Test (b) (4) Assay	(b) (4)

Sterility testing under (b) (4) is not used to release the cellular DPs but it is still performed for every batch. There are interim sterility reads after the start of (b) (4) at the following intervals: (b) (4)

Tcon Diluent DP Specifications

Test Attribute	Analytical Method	Acceptance Criterion
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
Sterility	(b) (4) Sterility Test (b) (4)	No growth detected
Endotoxin	(b) (4) Bacterial Endotoxins Test (b) (4) Assay	(b) (4)
Bioburden (b) (4)	(b) (4) Microbial Enumeration Test (b) (4)	(b) (4)
(b) (4) Test	(b) (4) Test	Pass (b) (4)

Reviewer's Comment: The final product release tests and acceptance criteria for microbial attributes under DMPQ purview are acceptable. The release of finished product using (b) (4) and interim sterility results is acceptable due to the shelf-life of the cells and the short time to deliver the product to patient before the final sterility test result is available. The evaluation of the rest of quality attributes and acceptance criteria is deferred to the product office.

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

Refer to section 3.2.P.2.4 Microbiological Attributes for assessment of CCIT.

3.2.P.5.4 Batch Analyses

The batch analysis data presented for the PPQ lots manufactured at Orca using the commercial manufacturing process appear acceptable. Sterility (b) (4) and endotoxin results for all PPQ lots met the acceptance criteria. The Tcon diluent DP batches also met (b) (4) bioburden and (b) (4) tests.

Reviewer's Comments: The Batch Analysis results are acceptable. Review and evaluation of all other parameters for the lots manufactured to support the BLA are deferred to the PO reviewer.

3.2.P.7 Container Closure System

The primary container closure system (CCS) for the Treg and HSPC DPs is a sterile single-use 150 mL (b) (4) Class II medical device transfer bag by (b) (4), 150 mL). The (b) (4) was cleared under FDA 510(k) number (b) (4). The bag has undergone seal integrity testing using both (b) (4). The bags are sterilized by (b) (4) per (b) (4). The bag is also tested for integrity by a (b) (4) test. The primary container closures are manually labeled with a patient specific drug product label. The primary bag is enclosed inside a sterile ziplock bag used to protect the primary container from environmental contaminants. HSPC and Treg DPs are placed into a (b) (4). The cardboard carton is placed into a (b) (4) shipping container. Transport occurs in pre-conditioned (b) (4) validated to maintain a temperature of 2-8°C during shipping.

Tcon DP is provided cryopreserved as a single-dose in an (b) (4) cryostorage infusion bag by (b) (4); 510k cleared Class II medical device) containing the cells, MEI, HSA, DMSO, and Hetastarch with an approximate volume of 15 mL. The bag is tested for (b) (4). The firm performed seal integrity testing using both (b) (4). The bags are sterilized via (b) (4) per (b) (4) standard. The Tcon DP bags are manually labeled with a patient specific drug product label. Following cryopreservation, the bag is protected within an aluminum cassette. Transport occurs in a dry shipper validated to maintain an internal temperature of < -125°C during shipping.

The primary CCS used for the conventional T cell (Tcon) diluent DP is a 50-mL end ported biocontainer bag which is received as part of the (b) (4) by (b) (4).

The bags have been integrity tested using both (b) (4). The (b) (4) Tcon diluent bag is sterilized by (b) (4) according to (b) (4). The bags are used routinely for storing and mixing of liquids in the biopharmaceutical industry. After filling, the bag is heat sealed, inspected and labeled. The Tcon diluent DP is shipped with the Tcon DP in a (b) (4) cardboard carton. The Tcon diluent DP is shipped at ambient temperature.

Incoming packaging components are inspected for visual appearance, and the certificate of analysis (CoA) is verified.

Reviewer Comment: *The three primary container closure systems for the DPs are acceptable. The containers are widely used in blood banks and biopharmaceutical industry.*

Container Closure Integrity (CCI)

Orca conducted validation studies to confirm appropriate CCI. (b) (4)

(b) (4) test were used to evaluate the integrity of all the DP bags.

Treg/HSPC DP CCS

The (b) (4) test of the (b) (4) was performed using (b) (4)

(b) (4)

The following (b) (4) testing results were obtained:

(b) (4)

For the (b) (4) testing, the bags were (b) (4)

(b) (4)

The following (b) (4) testing results were obtained:

(b) (4)

(b) (4)

Tcon DP CCS

The (b) (4) test of the (b) (4) Bag was performed using a (b) (4)

(b) (4)

The following (b) (4) testing results were obtained:

(b) (4)

For the Tcon DP bag (b) (4) testing, the bags were (b) (4)

(b) (4)

The following (b) (4) testing results were obtained:

(b) (4)

Tcon Diluent CCS

The Tcon diluent (b) (4) DP bags were integrity tested using a (b) (4)

(b) (4)

(b) (4)

The following (b) (4) testing results were obtained:

(b) (4)

For the (b) (4) testing, the (b) (4) DP bags were (b) (4)

The following (b) (4) testing results were obtained:

(b) (4)

The (b) (4) challenge units, negative controls, positive controls, and (b) (4) test units showed acceptable results.

Reviewer's Comments: *The container closure information is acceptable as submitted. The firm did perform (b) (4) CCIT of the container closure system for the packaging and storage of all the DPs and the results appear acceptable. Evaluation of the acceptability of compatibility, extractables and leachables, and stability studies is deferred to the OTP reviewer.*

3.2.P.8 Stability

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

Evaluation of the acceptability of the stability data and the overall testing plan is deferred to the assigned OTP reviewer. The lot available data for DMPQ to review was sterility for Treg/HSPC DP shelf-life of 72 hours post apheresis collection (PAC), Tcon DP 7-day shelf-life PAC, and Tcon diluent sterility at time 0 (release), (b) (4); all lots met the criteria of no growth. Orca commits to submit stability data (b) (4) for (b) (4) batch to support a drug product shelf life.

Reviewer's Comments: The proposed shelf-life and storage conditions with respect to microbial quality and/or sterility assurance appear appropriate. I defer to the OTP reviewer for a full assessment of the stability testing plan and results.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	CMO	Comments
Facility: Orca Biosystems Inc 7910 Metro Air Parkway, Sacramento CA 95837 FEI#: 3035546696 Manufacturing of drug substance and drug product DP Release Testing, Stability	Inspection	Yes	Yes	No	CBER/DMPQ VAI January 2026

The Orca Biosystems site located at 7910 Metro Air Parkway, Sacramento, CA is used for the manufacture of TREGZI. The total facility is approximately (b) (4) square feet designed for allogeneic cell therapy phase III clinical and commercial manufacturing of DP. The facility includes support areas and utilities including offices, production areas, QC laboratories, and warehousing for commercial manufacturing of TREGZI. The current construction of the facility space in use containing the (b) (4) production suites (b) (4) and supporting areas is approximately (b) (4) square feet. The facility core consists of Grade (b) (4) areas that are supplied with (b) (4) HEPA

filtered air and controlled not classified (CNC) spaces. The scope of this submission includes (b) (4) only; (b) (4)

. There is restricted entry for authorized personnel via an access control system. This is a manufacturing site for the following: TREGZI, cell suspension for infusion (the scope of this submission). No other commercial products are manufactured at the site. Clinical products may be manufactured in the commercial production suites.

Facility Flows

Orca provided the facility flow diagrams and narratives in the BLA submission and stated that the flows are defined in approved SOPs. The suites are designed to provide unidirectional flow for personnel, material, product, and waste to or from the workstation. All employees with access to classified spaces are trained on the approved flow procedures and must demonstrate proficiency in cleanroom gowning. The information is reviewed below:

Material Flow

The facility is designed to provide adequate flow for material. The materials used for the manufacture of TREGZI are transferred to the manufacturing rooms via the corridor and subsequent (b) (4). Materials are disinfected prior to entry into the classified area.

Product Flow

The manufacturing process takes place in the Grade (b) (4) and Grade (b) (4) workstations. All manufacturing process steps are performed in Class (b) (4). From the receipt of the apheresis to formulation/fill/cryopreservation, the product is handled in classified areas using closed systems, any open manipulations are performed in a (b) (4).

After receiving, the blood product is taken to a Grade (b) (4) production suite (PS) using the (b) (4). After processing in a Grade (b) (4) PS, the product is transferred to a Grade (b) (4) PS for further processing using the (b) (4) between the suites. The final drug product travels through the (b) (4) between the PS (b) (4). The Treg, HSPC, and Tcon diluent DPs are taken to product staging. The Tcon DP undergoes cryopreservation, and then the cryopreserved Tcon DP is taken to product staging/shipping. The product is transferred between Grade (b) (4) areas in closed/sealed containers as needed throughout the process.

Waste Flow

All waste from the manufacturing areas is collected and brought to the exit air locks and return corridor for disposal. There are procedures in place for the removal and disposal of waste.

Personnel flow

Before entering classified areas, personnel don gowning appropriate for the area as defined in approved SOPs. Employees change into cleanroom clothing in the personnel lock rooms (PAL). Employees are trained for proper gowning and flows in the production area. Each manufacturing suite has separate (b) (4) for entry/exiting of personnel and material from the room to the corridor.

Reviewer's Comments: *Overall, the facility flows described and illustrated in diagrams appear to be appropriate to support the manufacturing process. The facility flows were also reviewed during the PLI conducted January 8-15, 2026. No objectionable issues were noted.*

Prevention of Contamination/Cross-Contamination

Orca stated that facility design, gowning requirements and flow patterns within the facility have been designed to maintain cleanliness, minimize contamination/cross-contamination, and reduce handling errors. The contamination control strategy includes:

- Risk assessments
- Gowning procedures and qualification
- Cleaning and disinfection validation
- Materials control
- Aseptic Process Qualification
- Environmental Monitoring
- Changeover procedures

Control measures are employed to simultaneously process drug product batches for (b) (4) in the cleanrooms, handle materials, and prevent mix-ups and cross-contamination. Multi-batch control procedures implemented include (b) (4)

a single-batch is processed in workstation at a time. Procedural controls include use of barcodes, color coding, batch-dedicated operators, and mandatory exit and re-entry for scenarios when personnel transition to another batch. Human verification is performed at high-risk points in the process.

The manufacturing process utilizes single-use disposables for most product contact manipulations. The open aseptic processing steps are performed within an ISO (b) (4) and the cabinet is sanitized between each lot. Changeover/Line clearance between batches in the classified area is performed per written procedures and includes:

- Removal of batch-specific materials
- Cleaning of work surfaces
- Documentation of line clearance procedures

Reviewer's Comments: *The Orca facility is currently manufacturing one single product and seems to have appropriate controls and procedures to prevent contamination and*

cross contamination. The prevention of contamination procedures was verified during the PLI. No issues were identified.

Gowning

Orca provided a description of gowning requirements. Personnel are trained in gowning procedures and required to follow instructions outlined in approved Standard Operating Procedures (SOPs) prior to entering the manufacturing suites. Gowning for the cleanroom areas is performed in the designated gowning areas. The garments required for the Grade (b) (4) ISO (b) (4) rooms include (b) (4)

(b) (4). The gowning to enter Grade (b) (4) manufacturing rooms includes (b) (4)

In addition, (b) (4) covers are required for the aseptic operations in the Grade (b) (4) ISO (b) (4)

Reviewer's Comments: The gowning procedures appear to be appropriate. The Orca Sacramento site gowning procedures were also reviewed during the PLI and found acceptable.

HVAC

The heating, ventilation, and air conditioning (HVAC) system supplies air to all the cleanroom and CNC spaces located at the 7910 Metro Air Parkway Sacramento facility. The system is made up of air handling units (AHU) and exhaust fans. A supply fan brings air to the high efficiency particulate air (HEPA) filters mounted on the ceiling area. This unit filters, conditions, and dehumidifies the outdoor air before it is supplied to each recirculation air handling unit. There is a minimum of (b) (4) air exchanges per hour in the grade (b) (4) ISO (b) (4) areas, a minimum number of (b) (4) air exchanges in the grade (b) (4) (ISO (b) (4) areas and a minimum number of (b) (4) exchanges in the grade (b) (4) (ISO (b) (4) areas. Enough airflow is provided to generate a positive pressure cascade from the cleaner area to less clean areas with a minimum pressure differential of (b) (4). The GMP production area has a dedicated HVAC system. The system operates 24 hours a day, 7 days a week. The room air change rate differential pressures are continuously monitored. Air visualization studies are performed for all grade (b) (4) (ISO (b) (4) areas.

The facility core includes (b) (4) Grade (b) (4) and (b) (4) Grade (b) (4) manufacturing suites. The scope of this submission includes Grade (b) (4). A single suite is composed of (b) (4) workstations. (b) (4) is restricted to processing a single batch of product at one time. Open manipulation of product is performed in a (b) (4)

Each of the suites is accessed through a Grade ^{(b) (4)} corridor with (b) (4)

Production Suite Descriptions and Classifications

Production Suite	Cleanroom Description	Manufacturing System	ISO Classification
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(b) (4)

Reviewer's Comments: The HVAC System in the 7910 Metro Air Parkway Sacramento site used for TREGZI appears to be acceptable. A pressurization plan with room differential pressures provided by the firm was deemed acceptable. The qualification and maintenance of the HVAC system including HEPA filters was reviewed during the PLI. No objectionable issues were noted.

Environmental Monitoring

The Orca Sacramento site has implemented an Environmental monitoring (EM) program. The facility is routinely monitored for microbial and particulate levels as required per area classification according to the established standard operating procedures. The EM program uses a risk-based approach to focus sampling on critical areas and times within manufacturing. EM sample locations are based on the size of cleanroom or clean zone area and the consideration of high risk or high use areas, personnel, and/or material flow patterns. The data generated through the EM program is tracked within the quality management system and trended (b) (4)

EM consists of microbial (viable) and particle (non-viable) monitoring during each production event at representative sampling locations. The sampling locations include air samples (viable and non-viable), surfaces, and personnel in ISO ^{(b) (4)} during aseptic processing operation. Passive air sampling is performed using (b) (4); a (b) (4) is installed in the ^{(b) (4)} to provide continuous (b) (4) particle count. The work surface is sampled by (b) (4) at the conclusion of aseptic processing for each step before cleaning the ^{(b) (4)}. (b) (4) are sampled at the conclusion of aseptic manipulations within the ^{(b) (4)} using (b) (4).

Routine EM is performed (b) (4) and includes active viable air sampling, (b) (4), surface sampling and non-viable airborne particles. EM viable air monitoring includes both, (b) (4) and active air in ISO (b) (4) during processing and (b) (4) in Grade (b) (4). All EM samples are collected, incubated, and evaluated per SOP.

Action limits excursions during routine EM are handled per standard procedures. Microbial Identification is performed for any organisms recovered from the ISO (b) (4) environment; organisms from ISO (b) (4) environment are identified when action levels are exceeded. Any mold growth is considered an action level excursion. The routine EM acceptance criteria are summarized in tables below.

Acceptance criteria for viable sampling

(b) (4)	
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Acceptance criteria for routine non-viable environmental samples at rest

Area Classification	Action Limit (b) (4)	Action Limit (b) (4)
Grade (b) (4)	(b) (4)	
Grade (b) (4)		
Grade (b) (4)		
Grade (b) (4)		

Acceptance criteria for routine non-viable environmental samples in operation

Area Classification	Action Limit (b) (4)	Action Limit (b) (4)
Grade (b) (4)	(b) (4)	
Grade (b) (4)		
Grade (b) (4)		
Grade (b) (4)		

EMPQ

The environmental monitoring performance qualification (EMPQ) was performed under (b) (4) conditions in July 2024, the studies included (b) (4) days of (b) (4) sampling and (b) (4) days of simulated (b) (4) (in

operation) sampling. Orca provided a summary report for static and (b) (4) EMPQ. The PQ included Grade (b) (4) rooms, and the (b) (4) (Grade (b) (4) ISO (b) (4) used in manufacturing operations.

All specified sample types (viable air, (b) (4), surface) for each room and location were collected according to approved protocol. The samples were collected in (b) (4) days of testing). Aseptic process simulations (APS) were performed concurrently during (b) (4) studies at room maximum capacity. The qualification testing also included (b) (4)

There were two exceptions due to alarms, program system error, locations with insufficient number of samples, EM excursions, and documentation error; these were investigated and closed. The samples were recollected where necessary, all areas passed acceptance criteria. Orca stated that the predefined acceptance criteria (see tables above) were met, and all areas were qualified.

Reviewer's comments: *The EMPQ appears to have been appropriately performed. I reviewed the data and list of discrepancies, and they do not appear to have had any adverse effect on the PQ. Additionally, the EMPQ and EM program including trend analysis for the Orca facility were evaluated as part of the PLI and no issues were identified.*

Facility Cleaning

The facility is designed with smooth non-porous cleanable floors, walls and ceilings surfaces. The facility is cleaned and sanitized at regular intervals per approved procedures using conventional cleanroom techniques. Cleaning agents and disinfectants are qualified by (b) (4) representative of critical work surfaces per (b) (4)

The facility sanitization process is monitored routinely via an environmental monitoring program.

Reviewer's Comments: *The facility cleaning and disinfectant effectiveness studies were reviewed as part of the PLI and were deemed acceptable. Refer to Establishment Inspection Report (EIR) for further details.*

Equipment

Orca stated that all equipment has been qualified for use during production. The equipment is maintained under a calibration and maintenance program. Major equipment includes Class (b) (4)

heat sealer/welder, refrigerators, (b) (4)

. Class (b) (4) are used to maintain aseptic conditions during open processing. (b) (4)

. The heat sealer is used to seal the tubing and packaging during manufacturing process steps including final product container closure. The (b) (4) freezers are used to cryopreserve the Tcon drug product. The equipment has been validated and qualified for cGMP use and undergoes periodic reviews and requalification per procedures.

Most direct product contact materials are sterile, single use disposables. The major critical equipment includes the (b) (4)

(b) (4)

(b) (4)



Reviewer's Comments: *A list of all major equipment was provided in the original submission. The equipment qualification studies were also reviewed during the PLI and found acceptable.*

Equipment Cleaning

(b) (4)



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

(b) (4)

Utilities

Clean Dry Air (CDA)

CDA is used for the (b) (4). To create (b) (4) for production use, air is (b) (4). The CDA system consists of an air supply and distribution system. CDA is (b) (4) and then distributed to the facility with additional (b) (4). The CDA meets the international standards requirements for non-viable particle counts, Water and Oil, and viable particles. The CDA is controlled and routinely monitored per approved procedures. This is the only critical product contact utility used at the site.

Reviewer's Comments: *The CDA appears appropriate to support manufacturing of TREGZI. The systems' qualification, monitoring and specifications were further reviewed during the PLI. Refer to Establishment Inspection Report (EIR) for details.*

Computer Systems

According to Orca, all computer systems involved with the manufacture of TREGZI have been validated per 21 CFR Part 11. The computer systems used at Orca include:

- Building Management System (BMS) – visualization and control of the HVAC system and the plant utilities
- Facility Monitoring System (FMS) – real-time monitoring, alarms, reporting, and data collection system (temperature, pressure and relative humidity)
- MasterControl Electronic Quality Management System – used to create, store, and manage electronic records and documents, approval routing information, document training, electronic signatures, and capture data in electronic forms
- (b) (4) Manufacturing Execution System – used for material management and asset/equipment management

- (b) (4) – used to manage manufacturing scheduling, apheresis and graft shipment planning, and the generation and collection of key patient parameters

Reviewer's Comments: *The computer systems at the Orca Sacramento facility used for TREGZI appear acceptable. The computerized automation validation including laboratory systems was reviewed on the PLI and found acceptable.*