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Center for Biologics Evaluation and Research (CBER)
Office of Therapeutic Products (OTP)
Office of Plasma Protein Therapeutics CMC (OPPT)
Division of Hemostasis (DH)
Hemostasis Branch 2 (HB2)

MEMORANDUM

To: Administrative file for BLA STN 125868/0

From: Andrey Sarafanov, PhD; CBER/OTP/OPPT/DH/HB2

Through: Zuben Sauna, PhD; CBER/OTP/OPPT/DH on behalf of Natalya Ananyeva, PhD; CBER/OTP/OPPT/DH/HB2

Applicant: Orca Biosystems Inc.

Product: Allogeneic regulatory T cell immunotherapy with HSPC and T cells-vldq [TREGZI]

Indication For use in matched donor hematopoietic stem cell transplantation with myeloablative preparative regimen, for hematopoietic and immunologic reconstitution and to improve chronic graft vs host disease (cGVHD)-free survival, in the treatment of adults with hematological malignancies

Subject: Review of analytical assessment of leachables in final Drug Product

CC: Linda Le, PhD; CBER/OTP/ORMRR/DRMRR2/RMSB2
Eric Qiao, PhD, CBER/OTP/OPT/DPT2/PTB2
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Background

The Drug Product (DP) is an allogeneic cell therapeutics, comprising three cellular components and one diluent component (also referred to as DP): (i) Regulatory T cells (Treg) DP, (ii) Hematopoietic Stem and Progenitor Cells (HSPC) DP, (iii) Conventional T cells (Tcon) DP, and (iv) Tcon Diluent DP. The cellular components are derived from apheresis starting material, obtained from a human leukocyte antigen-matched donor. HSPC DP and Tcon DP are derived from fractions taken during the Treg DP manufacturing process; therefore, some of the steps described in the Treg DP modules are also relevant to HSPC DP and Tcon DP.

The last manufacturing step (purification) relevant to the accumulation of leachables in cell-based components of DP through further processing, storage, and clinical (in-use) preparation is termed (b) (4)

. Altogether with Diluent, the final composition of the four DP components is as follows:

- HSPC DP and Treg DP are each formulated in a volume of ~100 mL, shipped fresh, and administered intravenously (IV) on Day 0.
- Tcon DP is formulated in a volume of ~15 mL and cryopreserved. On Day +2 to Day +3, the cells are thawed, diluted with Tcon Diluent DP (~30 mL), prepared for infusion at the transplant center, and administered IV.
- Tcon Diluent DP is prepared as a sterile (b) (4) solution of Multiple Electrolytes Injection (MEI) and 2% Human Serum Albumin (HSA). Upon thawing of Tcon DP, its content is diluted with ~30 mL of Tcon Diluent DP.

The primary contact materials contributing appearance of leachables at the (b) (4) and downstream steps include:

- (b) (4) (as well as excipients, such as MEI and HSA)
- Processing materials: (b) (4) (for cell centrifugation) and (b) (4)
- Container Closure Systems (CCSs) for HSPC DP and Treg DP, 150 mL (b) (4) Bag
- Container closure system (CCS) for Tcon DP, 50 mL Cryopreservation Bag ((b) (4))
- Cryopreservation media for Tcon DP (containing Dimethyl Sulfoxide [DMSO] and Hetastarch)
- Tcon Diluent preparation and storage materials: HSA, MEI, MEI bag with syringe, (b) (4), Buffer Transfer System (BTS) custom assembly, (b) (4) Manifold Assembly, and 50 mL Diluent Bag (CCS).

The in-use preparation and administration materials include Infusion/Extension Sets with Tubing, (b) (4), and Saline Solution to rinse the cell bags (with subsequent infusion of this solution). The total volume of infused product exceeds 230 mL.

Analytical Assessment of Leachables in Drug Product

The extractables assessment is summarized in Module 3.2.S.2.3.2 (Treg) and Report RPT-0327, and detailed in Reports RPT-0328, EPR-0025, EPR-0028, EPR-0029, EPR-0031, and MTX-0023. The manufacturing components were initially assessed for risk of sourcing leachables in the final Drug Product (DP) by assigning risk scores. Selected high-risk manufacturing components (b) (4) were subjected to extractables studies using exaggerated conditions following common practice, moderate-risk components were subjected to limited analysis, and low-risk components were excluded from assessment.

The analytical testing of samples used common methods based on: (i) (b) (4) for organic compounds and (ii) (b) (4) for elemental compounds where (iii) identification and quantitation of all compounds used (b) (4). The Analytical Evaluation Thresholds (AETs) for organics were calculated based on a Safety Concern Threshold (SCT) of (b) (4) µg/dose (commonly used for single-use products) and an analytical Uncertainty Factor of (b) (4). Elemental extractables detection was based on respective safety limits. This testing found multiple organic compounds above the AET and did not identify elemental compounds of safety concern. Toxicological assessments of the identified organic compounds identified: (i) (b) (4) extractables with potential safety concerns and (ii) (b) (4) high-risk process components (such as the (b) (4) cell freezing bag, (b) (4)).

(b) (4) Bag, and (b) (4) to be tested in a further leachables study. At the time of BLA submission, no leachables study had been performed.

Review Comments

- The leachables risk assessment was based on in-silico processing of limited extractables data. In the extractables study, some materials assessed as low-risk were omitted from assessment, and moderate-risk components were subjected to only limited analysis. This approach potentially overlooks leachables in the final DP. Additionally, the assessment did not include in-use preparation materials, meaning leachables from those materials were also absent from the assessment.
- The assessment combined multiple datasets, and as a result, the initial AET values were proportionally multiplied in the merged dataset. Consequently, the reporting threshold in the resulting dataset was significantly higher than the target AET values, meaning that some leachables may also have been missed. Furthermore, such an assessment is expected to produce large errors compared to actual leachables levels in the final DP.
- In summary, this assessment lacked a real-time leachables study conducted through the process, storage, and in-use preparation of the DP, as required per (b) (4). As a result, the assessment potentially underestimated leachables in the final DP.

Communications for Additional Information

1. An Informational Request (IR) was sent on September 29, 2025. Deficiencies in the assessment were noted, and a design for a simulated leachables study was suggested (Q10). In the response received on October 7, 2025 (SN0008), the Applicant confirmed plans to conduct a leachables study: (i) for the high-risk components separately, and (ii) via a simulated study for each of the four DP components, though the clinical preparation part was still not addressed.

2. A second IR was sent on October 20, 2025, requesting an update on the study's status and expected completion date. In the response received on October 23, 2025 (SN0013), the Applicant provided their leachables study plan. In this plan, they intended to perform (b) (4) different simulated leachables studies for two parts of the DP and the Diluent, targeting only the (b) (4) compounds identified as potential concerns in the extractables study. The study design was found to be incomplete and incorrect, as no in-use preparation simulation and no cumulative approach were considered.

3. A teleconference meeting with the Applicant was held on October 28, 2025. The above deficiencies were explained to the Applicant, including the following clarifications: (i) if datasets were to be merged, the respective AET values should be lowered proportionally to the number of datasets being merged; and (ii) the simulated study should be performed in (b) (4) for statistical confidence. It was also recommended that simulated samples be (b) (4) in the study design to better mimic the actual DP process while reducing study complexity. The Applicant agreed. These comments were also submitted to the Applicant as a third IR on October 31, 2025. In the response received on November 7, 2025 (SN0017), the Applicant agreed to include in-use preparation materials in the simulated study and informed FDA that they were revising the study protocol to incorporate all comments. The revised study was to be conducted as follows: mock DP components, Treg, HSPC, and Tcon, would be generated using maximum hold times and temperatures and (b) (4) with the T-con Diluent component, constituting the first study segment with a respective leachables dataset upon analytical assessment. Mock administration samples

would be generated using excipient solutions and representative clinical preparation materials, constituting the second study segment and second leachables dataset. The experiment was to be performed in (b) (4).

4. On December 11, 2025, the Applicant submitted updated protocols for sample preparation (PRO-0095) and analytical testing (Protocol 25-1964, draft). They also committed to providing preliminary leachables study results by March 2026 and final results, obtained using validated analytical methods, by October 2026.

5. A fourth IR was sent on December 15, 2025. FDA provided comments regarding the lowering of AETs in each study segment (1 and 2) and the Uncertainty Factors (UF) to be used for AET calculation.

6. On March 31, 2026, the Applicant submitted preliminary leachables study results to fulfill their commitment (SN0051, Documents PRO-0095, 25-1964, RPT-0456, EPR-0037, and EPR-0038). (b) (4) organic leachables were reported at levels above the AET (Document RPT-0456), and (b) (4) of these compounds, (b) (4) ..., were found at levels comparable to the Permitted Daily Exposure (PDE). (b) (4) analyzed elemental leachables (Class (b) (4)) were below respective PDEs (Document RPT-0328).

7. A fifth IR was sent on May 15, 2026, requesting clarifications on analytical details, including control blanks, AETs, and UFs. In the response received on May 29, 2026 (SN0063), the Applicant provided the requested clarifications and confirmed their commitment to provide final leachables study data using validated methods by the end of October 2026. All information was found acceptable. Toxicological review by Dr. Eric Qiao (CBER/OTP/OPT/DPT2/PTB2) also indicated the acceptability of the available data.

Review Conclusion and Recommendation

From both analytical and toxicological perspectives, the available data for leachables assessment in DP are acceptable. The remaining data have been committed by the Applicant to be submitted by October 2026. I recommend **approval** of the BLA from my review scope.

The following PMC text is recommended to the review team if the BLA is approved:

Per the Applicant's commitment given on December 11, 2025 (SN0025) and confirmed on May 29, 2026 (SN0063): Orca Biosystems Inc. commits to providing leachables study results by October 2026. These results will be obtained using validated analytical methods for compounds identified as extractables with high-risk levels (Section 3.2.S.2.3.2, pages 59–74, and Report RPT-0327, pages 19–20).