



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 125846/0

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

Through: Natalya Ananyeva, PhD; Branch Chief, CBER/OTP/OPPT/DH/HB2

Applicant: Fondazione Telethon ETS/FTE

Product: Etuvetidigene autotemcel (TL003) [WASKYRA]: Autologous CD34+ cell enriched population that contains haematopoietic stem and progenitor cells (HSPC) transduced *ex vivo* with a lentiviral vector encoding the human Wiskott-Aldrich Syndrome (WAS) gene; IV administration

Indication Treatment of pediatric patients aged 6 months and older and adults with Wiskott-Aldrich Syndrome (WAS) who have a mutation in the WAS gene for whom hematopoietic stem cell transplantation (HSCT) is appropriate and no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available

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

CC: Cecilia Crowley; CBER/OTP/ORMRR/DRMRR2/RRB2
Laura DeMaster, PhD; CBER/OTP/OGT/DGT2/GTB5
David Cantu, PhD; CBER/OTP/OPT/DPT1/PTB3
Zuben Sauna, PhD; CBER/OTP/OPPT/DH
Basil Golding, MD; CBER/OTP/OPPT

Background

The Drug Product (DP) of this original Biologics License Application (BLA) represents autologous CD34+ enriched cells transduced *ex vivo* with a recombinant lentiviral vector for infusion. In product manufacture, the starting cell material is collected by apheresis of peripheral blood. CD34+ cell enrichment is performed by (b) (4) [REDACTED] transduced with the lentivirus, collected, washed, (b) (4) [REDACTED]

In the DP process, (b) (4)

The cell suspension (b) (4)
Dimethyl Sulfoxide (DMSO) concentrations as a formulation with 0.9% NaCl, 7% HSA, and 5% DMSO. The DP (b) (4) is transferred by (b) (4)

Ethylene Vinyl Acetate (EVA) (b) (4) freezing bags (50 mL) by (b) (4). The filled bag (up to 20 mL of cell suspension), which serves as the final Container Closure System, is closed by (b) (4), labeled, and placed in a secondary bag. The package is then frozen and stored at < -130°C in the vapor phase of liquid nitrogen. The manufacturing is a (b) (4) process with a maximum duration of (b) (4) days.

A DP shelf-life of six months is proposed. For clinical use, the cell suspension is thawed and administered to the patient (up to 8 bags without dilution, as a single administration).

Reviewer's comment 1

Based on my assessment, the major high-risk materials for leachables accumulation in the final DP are those contacting the (b) (4)

These materials are the following:

- Excipients: NaCl, HSA and DMSO (used for formulation)
- (b) (4)
- Container Closure System (50 mL (b) (4) freezing bags)

Extractables and Leachables Assessment

This information is summarized in Section 3.2.P.2.6. Initially, a risk assessment of the manufacturing process was conducted to evaluate the potential for leachables. Next, each high-risk material was subjected to an **extractables study**. These materials were: (b) (4)

(b) (4) The study was performed using exaggerated conditions followed by sample analysis for organic compounds using (b) (4)

This study found a broad range of compounds above the reporting limit.

Reviewer's comment 2

1. The Applicant was correct in determining the high-risk step (b) (4) for leachables and related contact components. The list of high-risk materials is close to my assessment. However, the extractables study missed some materials such as those used for the formulation (NaCl, HSA and DMSO).

2. Elemental extractables were omitted from analysis.

Each of the (b) (4) components was further tested in a **leachables study** to target compounds found as extractables. The study used (b) (4) (b) (4). The components were (b) (4), and the samples were analyzed using the above methodology. The Analytical Evaluation Threshold (AET) was set based on the Threshold of Toxicological Concern (TTC) of 120 µg/day for organics for single-use products per ICH M7 and an Uncertainty Factor of (b) (4) (to reflect (b) (4) error). Compounds at levels greater than the TTC required safety evaluation.

Altogether, (b) (4) organic compounds were found above the AET. Three compounds (b) (4) were above their TTCs and evaluated for toxicological risk. This showed that only (b) (4) posed a health risk. However, analytical testing of the (b) (4) prior to the (b) (4) of the DP process showed a safe concentration of (b) (4). Overall, the study concluded that leachables in the DP have acceptable levels.

Reviewer comment 3

The leachables study was performed under accelerated (exaggerated) conditions and indicates DP safety regarding leachables in each component. However, this study may still underestimate the cumulative levels of leachables in final DP because of the incorrect design. Specifically:

- Formulation components NaCl and HSA were not tested. As understood, DMSO was not assessed (b) (4).
- Elemental leachables were not analyzed.
- Leachables were not assessed cumulatively in a single real-time study per (b) (4).

On July 10, 2025, CBER Safety Work Group decided to request addressing the issue via Post-Marketing Requirement (PMR).

Communication for Additional Information

1. On April 23, 2025, FDA sent an information request (IR) to the Applicant. FDA requested to assess leachables, both organic and elemental, cumulatively under actual manufacturing conditions, shelf-life storage, and clinical use, as recommended by USP <1664>. FDA stated that this could be accomplished via a simulated (mock) run from the (b) (4) step through in-use preparation of simulated DP using maximal hold times and temperatures at each operation unit.

2. On April 30, 2025, a teleconference was held with the Applicant to clarify details of the study design. The Applicant confirmed their understanding of the IR and stated they would conduct this study.

3. On May 14, 2025, the Applicant provided additional information that was still insufficient to address the issue (SN0014, Q8, Reports RPT-0248 and RPT-0248, Attachment 3). However, the Applicant agreed to perform additional studies to address the remaining deficiency.

4. On June 26, 2025, during Late-Cycle Meeting with the Applicant, FDA additionally emphasized the request to address the deficiency.

5. On October 7, 2025, the Applicant committed (by email) to perform the study as follows.

An adequate leachables safety assessment for the TLT003 drug product (DP) through its manufacturing process, storage, and in-use conditions. The assessment must include both elemental and organic leachables from the formulation, storage and in-use preparation product-contacting components appearing cumulatively in final DP. The leachables study can be conducted without active ingredient by simulating the DP manufacturing process from the (b) (4) step through in-use preparation steps of the simulated DP. Such study should use maximal hold times and temperatures at respective manufacturing process steps to assess

cumulative leachables in the DP from the (b) (4) through product freezing, shelf-life storage, thawing, and in-use processing. A final study report and toxicological risk assessment should be provided.

- Final Protocol Submission: March 31, 2026
- Study Completion Date: September 30, 2026
- Final Report Submission: December 31, 2026

Review Conclusion and Recommendation

The proposed plan to address the issues in assessment of leachables is acceptable. The available data indicate safety of DP regarding leachables. If supported by toxicologic review of the data (eCTD SN0014, report RPT-0248), the BLA is **approvable** from this perspective, and the issue may be addressed post-marketing. Review of the toxicological assessment of leachables is performed by Dr. David Cantu.