



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

MEMORANDUM

To: Administrative file for BLA STN 125758/0

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

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

Applicant: Orchard Therapeutics (Europe) Limited

Product: Atidarsagene autotemcel [LENMELDY]

Indication Treatment of pediatric patients with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD)

Subject: Extractables and Leachables assessment in Drug Product

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EXECUTIVE SUMMARY

The Drug Product (DP) LENMELDY represents a cell-based therapeutic agent to treat patients with metachromatic leukodystrophy. My assignment was to review information on analytical assessment of manufacturing equipment-related impurities (leachables) in DP. To identify a process step from which leachables accumulate in DP, I also reviewed the process description. During my review, I requested additional information from the Applicant that was provided. Upon review of all information, I found that the data indicated safety of the leachables in DP, and I recommended **approval**. However, I also found that the assessment of leachables in DP is incomplete. The remaining issues will be addressed in a post-marketing study, communicated as post-marketing requirement (**PMR**). Review of toxicological assessment of the analytical data

was performed by Dr. Rukmini Bhardwaj (OTP/OPT/DPT2/PTB2) who concluded that the leachables in DP do not pose a safety risk.

REVIEW SUMMARY

1. Identification of process step from which leachables accumulate in drug product

The manufacturing process starts from cells derived from a patient, and involves multiple steps of cell culturing, including transduction with a lentiviral vector produced in (b) (4), resulting in obtaining Drug Substance (DS) (Section 3.2.S.2). Then, the cells are subjected to (b) (4), formulation (into (b) (4) and 5% dimethyl sulfoxide (DMSO)), transferring (using a (b) (4)) into Container Closure System (CCS; (b) (4) cryobags), cryopreservation and storage (in liquid nitrogen vapor phase) at Steps (b) (4) (Section 3.2.P.3).

Reviewers Comment (1). I assessed DP Step (b) (4) and downstream processing, storage and in-use hold as the high-risk processes for leachables appearance in DP. The respective contact materials and excipients represent the source of the potential leachables.

2. Extractables and leachables (E&L) assessment (Section 3.2.P.3.5.5.)

Upon assessment of respective intermediate contact materials, (b) (4) components were assessed as high risk: DP CCS, (b) (4).

Extractables study

This study was performed using (b) (4). (b) (4) organic compounds, (b) (4) were identified, while elemental extractables were not assessed. Upon post-toxicology assessment, (b) (4) were deemed as having low risk, while (b) (4) was assessed as a high-risk compound. Further testing was performed to quantify the actual levels of (b) (4) present in samples from Process Performance Qualification (PPQ) lots (as leachable).

Leachables study

1) A simulated leachables study was performed to mimic the DP formulation. Each high-risk component part (b) (4) and Bag) was individually subjected to extraction using (b) (4) % DMSO (worst-case condition), but (b) (4), at volumes reflective of typical volumes used for DP manufacturing. Analytical Evaluation Threshold (AET) calculation was based on the limit of (b) (4) for the compounds, 60-mL dose of DP (further updated to 160-mL, see below), and Analytical Uncertainty Factor (AUF) of (b) (4) % by Product Quality Research Institution (PQRI) recommendation, that resulted in AET (reporting limit) of (b) (4). However, this limit was provided only for (b) (4) assay (b) (4).

- a) From (b) (4), the Applicant identified (b) (4) at estimated patient exposure (b) (4), concluded to be safe, and (b) (4) at estimated patient exposure of (b) (4), further testing of which was performed in the PPQ lots' samples.
- b) From (b) (4) and Tubing of the bag, the Applicant identified (b) (4) at levels of (b) (4) and (b) (4), respectively (b) (4) cumulatively) that was concluded to be significantly lower the safety concern.

Risk assessment of the remaining simulated leachables is provided in Report *RPT-0053 E&L Risk Assessment OTL-200 VP and DP, Attachment 5*.

2) Further testing was performed to quantify levels of (b) (4) in samples from (b) (4) PPQ DP lots. The samples ((b) (4)) were taken as (b) (4) procedure. In these samples, (b) (4) was below the limit of detection (LOD; (b) (4)) in (b) (4) DP lots, and (b) (4) in (b) (4). The Applicant concluded minimal risk to reaching the threshold of toxicological concern (TTC, 120 µg/day per ICH M7). Similar to Extractables study, elemental leachables were not tested in both leachables studies.

Reviewers Comment (2). Not performing cumulative leachables assessment and omission of elemental leachables assessment is not acceptable. The levels of (b) (4) in DP should be assessed in real-time conditions. To address these concerns, the Applicant should perform a simulated study starting from the (b) (4) step and throughout the in-use storage of DP.

COMMUNICATION FOR ADDITIONAL INFORMATION

I. An Information Request (IR) was sent to the Applicant on January 04, 2024.

In Section 3.2.P.3.5 you provided information, including RPT-0053, on your extractables and leachables assessment of the OTL-200 manufacturing process. We need additional information to assess the adequacy of your extractables and leachables assessment for OTL-200. Please address the following:

- a) Please provide the limits of quantitation (LODs) and describe how the LODs were validated for the methods used for analysis of non-volatile, semi-volatile, and volatile extractables and leachables described in Section 3 of Report GSK2696274: Extractables and Simulated Leachables Studies (Attachment 2 of RPT-0053).
- b) In Section 4.1.1 of Report GSK2696274, you describe how a reporting threshold of (b) (4) was set for the non-volatile extractables analysis. However, Section 4.2.1 states that the semi-volatile and volatile leachables detected at levels close to or above the level of the internal standard were reported. Please provide the numerical reporting analytical threshold (µg/mL) for the semi-volatile and volatile leachables assessment and explain how it relates to the Analytical Evaluation Threshold (AET) action limit.
- c) Your simulated leachables studies do not include the assessment of (b) (4), which is a potential source of leachables as present in the final OTL-200 drug product (DP) formulation. Please provide an evaluation of the potential of (b) (4) to contribute leachables to the final DP.
- d) The calculations for reporting thresholds and action limits in Report GSK2696274 assume a worst-case dosing of 3 DP bags with a total 60 mL dose (e.g., the calculations described in Table 6). Please confirm the maximum volume and number of bags of OTL-200 that can be used for a single patient.

- e) We note that the extractables and leachables studies did not test elemental leachables. Please clarify why elemental leachables were not included and provide justification for the exclusion of elemental leachables assessment. Alternatively, please provide the results for elemental leachables.
- f) The semi-volatiles and volatiles testing identified (b) (4) as a leachable compound from the (b) (4) with an estimated exposure of (b) (4) (Table 21 of Report GSK2696274). Table 5 of RPT-0053 describes the analytical results for (b) (4) in (b) (4) DP batches tested from the DP PPQ. You used this data to claim that the concentration of (b) (4) in the DP is likely to be significantly lower than the (b) (4) calculated from the simulated leachables study. In response to questions regarding this analysis in our CMC IR #3, you confirmed that the samples for this analysis were taken from (b) (4) to the final formulation in (b) (4), 5% DMSO, (b) (4). This (b) (4) was collected (b) (4) in the final formulation solution, and use of the (b) (4) the DP to the final container closure. We do not agree that this data can be used to justify that the concentration of (b) (4) is likely to be lower than the (b) (4) calculated from the simulated leachables study, as this study did not address cumulative leachables through the entire manufacturing segment from the (b) (4) step until the (b) (4) drug product thawing before administration.
- i. To address all the concerns described above, you should perform a leachables study that simulates the DP manufacturing process steps with high-risk potential for leachables appearance in DP, beginning from the (b) (4) step and continuing through freezing, storage, thawing and in-use time hold of DP, before its analysis. This simulation study should include (b) (4) (or its simulated production) as part of the manufacturing process, as well as all other relevant operations, and also the assessment of elemental leachables (they should be also preliminarily assessed as extractables from the high-risk process components). Such a study will adequately address the overall (cumulative) leachables through the DP manufacturing process and storage conditions, as required for BLA submissions.
- ii. Please provide a detailed description of how the (b) (4) estimated exposure for (b) (4) was calculated.
- iii. In RPT-0053 and its appendices, you claim that the (b) (4) estimated exposure is likely to be an over-estimate of the concentration of (b) (4) in the DP. Please provide a new estimate of the concentration of (b) (4) in the DP along with justification of the adjustments to the calculations.
- g) To address all the concerns described above, you should perform a leachables study that simulates the DP manufacturing process steps with high-risk potential for leachables appearance in DP, beginning from the (b) (4) step and continuing through freezing, storage, thawing and in-use time hold of DP, before its analysis. This simulation study should include (b) (4) (or a simulation of its contribution to cumulative leachables) as part of the manufacturing process, as well as all other relevant operations, and also the assessment of elemental leachables. In addition, elemental leachables should be preliminarily assessed as extractables from the high-risk process components. Such a study will adequately address the overall (cumulative) leachables through the DP manufacturing process and storage conditions, as required for BLA submissions.

The **Response** was provided on January 18, 2024 (eCTD Sequence #0031).

1a) The Applicant explained that for the used methods, LOQs were established based on (i) the ability to recover a respective internal standard (listed), specific to each of the (b) (4) methods used and spiked at the AET, and (ii) a signal to noise ratio of (b) (4) for the respective internal standard and provided details of samples preparation.

Review Comment (3). The actual values for assay-specific LOQs were not provided, and thus it is unclear how these values were related to the AET. The response is not sufficient and not acceptable.

1b) The Applicant provided the LOQs in µg/test, but not in µg/mL.

Review Comment (4). It is still unclear how these values were related to the AET. The response is not sufficient and not acceptable.

1c) The Applicant explained that (b) (4) interferes with measurements of leachables in DP, that is why it was omitted from the studies. In response (1g), the Applicant agreed to perform a leachables study that simulates both the DP manufacturing process and the product formulation (including (b) (4)), freezing and storage.

Review Comment (5). Omission of (b) (4) from the real-time leachables study is not acceptable. However, considering the Applicant's commitment to perform the simulated leachables study, the overall response is acceptable.

1d) The Applicant clarified that the maximum volume and number of bags of DP to be used for a patient are 8 bags with 20 mL fill volume each. The respective calculations and conclusions were updated from the original 60 mL DP volume to 160 mL. For safety assessment, they used the $TTC > 120\mu\text{g/day}$. Overall, it was concluded that there is no safety concern arising from the leachables identified. The updated information was added to Section 3.2.P.3.5.

Review Comment (6). The revised AET should be (b) (4). If the requested LOQs (not provided) are still below or comparable to this value, the data would be acceptable from the analytical perspective.

1e) The Applicant provided a justification of not measuring elements, stating that they are (i) not typically used as catalysts or reagents in the manufacturing of biotech products and (ii) purified in the steps upstream the filling.

Review Comment (7). I disagreed with this justification. From FDA review experience, elemental leachables are added as catalysts in some polymeric process components, *etc.* and may appear in DP from all contacting materials. The response is not acceptable. However, the PMR (response 1g and section *Further Communications*) would address this deficiency.

1f) The Applicant acknowledged that the data provided for (b) (4) do not demonstrate the cumulative effect of leachables in DP and provided a revised estimate of that, concluding its safety. Furthermore, as discussed in the response (1g), Applicant agreed to evaluate the cumulative effect from process Step (b) (4) to final fill at Step (b) (4), as part of a leachables study to which they committed including the testing of (b) (4) in samples.

1g) The Applicant agreed to perform a leachable study simulating the DP manufacturing process steps and evaluate the presence of high-risk potential leachables as well as assessing the potential elemental leachables.

Review Comment (8). The responses (f) and (g) are acceptable. Dr. Bhardwaj, who performed toxicological assessment, confirmed adequacy of the analytical data to DP safety and concluded that the leachables in DP do not pose a safety risk. This provides the basis for BLA approval.

II. Further communications: (i) FDA proposal of the PMR text (sent on February 05, 2024), (ii) Applicant's response with proposal of the study milestones (received on February 09, 2024, Amendment 40, eCTD #0041), and (iii) Applicant's confirmation of the final version of the PMR (received on February 22, 2024, Amendment 45, eCTD #0045). The language of the mutually agreed PMR is as follows.

FDA Postmarketing Requirements Under 505(o):

[The Applicant commits to perform] An adequate leachables safety assessment for the OTL-200 drug product (DP) through its manufacturing process, storage, and in-use conditions. This assessment must include the following:

- a. Assessment of elemental extractables from relevant DP manufacturing/storage components, and both elemental and organic leachables (i.e., cumulative) in the final DP.
- b. The leachables study can be conducted by simulating the DP manufacturing process from the step with high-risk for leachables components ((b) (4)), may include simulation of respective (b) (4) , should be conducted with all operations performed using maximal hold times and temperatures at respective steps, and continue through the product freezing, shelf-life storage, thawing, and in-use processing.
- c. This evaluation will also include a full toxicological risk assessment for the identified leachables.

Study milestone dates:

- Final Protocol Submission: August 31, 2024.
- Study Completion Date: July 31, 2025.
- Final Study Report Submission: September 30, 2025.

REVIEW CONCLUSION AND RECOMMENDATION

The analytical and toxicological assessments of leachables in DP indicate its safety, and the remaining issues will be addressed under the PMR. I recommend **approval** of this BLA from the scope of my review subject.