



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 STN 125789/0

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

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

Applicant: Adaptimmune LLC

Product: Afamitresgene autoleucel [TECELRA]

Indication Treatment of adult patients with unresectable or metastatic synovial sarcoma who have received prior systemic therapy

Subject: Extractables and Leachables assessment in final Drug Product

CC: Tigist Assefa, RPM; CBER/OTP/ORMRR/DRMRR1/RMSB1
Elvira Argus, PhD; Chair, CBER/OTP/OGT/DGT2/GTB4
Yves Morillon, PhD; CBER/OTP/OPT/DPT2/PTB4
Kimberly Schultz, PhD; CBER/OTP/OGT/DGT2
Zuben Sauna, PhD; CBER/OTP/OPPT/DH
Mahmood Farshid, PhD; CBER/OTP/OPPT
Basil Golding, MD; CBER/OTP/OPPT

EXECUTIVE SUMMARY

The Drug Product (DP), TECELRA, the subject of this Biologics License Application (BLA), is composed of autologous T cells (CD4+ and CD8+) genetically modified (transduced) with a lentiviral vector (LV) encoding a melanoma-associated antigen 4-specific T-cell receptor. The DP is manufactured as a suspension of cryopreserved cells for treatment of patients with metastatic synovial sarcoma. My review assignment was to review the information on analytical assessment of leachables (process components-related impurities) in final DP. During the review, I requested additional information from the Applicant that was provided. Upon review of all the information, I determined that the data were still incomplete. I deferred the final decision to the toxicology reviewer Dr. Yves Morillon (CBER/OTP/OPT) who reviewed these data and did not identify significant safety concerns. Thus, from my review scope, I recommend **approval of this BLA**. The remaining issues will be addressed post approval, communicated as a post-marketing requirement (PMR) study.

REVIEW SUMMARY

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

The manufacturing process starts with production of transgenic LV, termed Drug Substance (DS)

1. To generate LV, a (b) (4)

DS2 is manufactured from the patient apheresis material (cells), (b) (4)

(section 3.2.S.2. Manufacture [afamitresgene autoleucel, Adaptimmune]).

DP is manufactured upon (b) (4)

(Section 3.2.P.3. Manufacture [afamitresgene autoleucel, Adaptimmune]).

(b) (4)

DP shelf life is 3 months (at $\leq -130^{\circ}\text{C}$). DP bags are thawed and kept for (b) (4) at 20-25°C before administration (Section 3.2.P.8.1). Up to (b) (4) DP bags can be used for a single dose, while in most cases batches are filled into (b) (4) bags (Report VAL 02207).

Review Comment 1

A high-risk for leachables process step starts from Step (b) (4). The respective high-risk contact equipment components are (b) (4)

does not represent a risk for leachables in DP as they are essentially eliminated upon multiple change of (b) (4).

2. Extractables and leachables (E&L) assessment (Section 3.2.P.2.4.5.)

The following assessments were performed.

- Evaluation of risk from the contact materials (Section 4.5.1). Each component was assigned a risk score based on contact (b) (4) from final DP. The highest scores had DP CCS (Step (b) (4) with conclusion that their risks are negligible (Section 3.2.R E and L Risk Assessment_DP).

- b) E/L study for DP CCS, (b) (4) (Sections 4.5.2 and 3.2.R Extractables Assessment_CCS_DP).
- c) E/L study for (b) (4) (Section 3.2.S.6 Container Closure System_ (b) (4)
- d) Studies for impurities in samples representative of DP (Sections 3.2.P.5.5 Characterization of Impurities and 3.2.R Leachables Report_Impurities_DP).

Review Comment 2

Information under b) “E/L study for DP CCS” is most significant for assessment of the risk of leachables (reviewed below). Leachables from other process materials at steps (b) (4) Step (b) (4), are essentially eliminated (as reflected under Comment 1). However, the assessment misses all materials from Step (b) (4) and (b) (4) prior to filling to DP CCS.

The **Extractables Assessment** of DP CCS (performed by the CCS manufacturer using a standard approach with exaggerated conditions) identified (b) (4) compounds of potential concern; among those (b) (4) were at highest levels (Table 9). However, all these compounds were assessed to have negligible risk.

The **Leachables Study** (simulated) was performed on the DP CCS with label. This study was termed “extractables simulation study”, stated as consistent with the recommendations of (b) (4)

. The study was designed to represent the long-term storage, DP thaw, and in-use conditions.

The CCS was filled with (b) (4)

for analysis (Report 3.2.R *Extractables Assessment Arm A-b Testing Report VAL 02207*) and analyzed using the following methods:

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

The AET values were calculated based on (i) the use of (b) (4) CCS bags as worst-case scenario, (ii) one dose per day/lifetime, (b) (4) of a leachable dosage (per Product Quality Research institute (PQRI) recommendations) that produced a value of (b) (4) for organic compounds. The Applicant stated that per ICH M7, such amount is allowed to be 120 µg/day (corresponding to AET of (b) (4)). For tested (b) (4) elemental leachables (most toxic), the AET values were calculated based on specific PDEs per ICH Q3D and (b) (4).

Review Comment 3

The used AET (reporting limit) corresponding to (b) (4) for organic compounds detection is sufficiently low to ensure sensitivity of detection under allowable limit of 120 µg/day per ICH M7.

(b) (4) organic compounds (including (b) (4)) were found above the reporting limit, and one of them (b) (4) was found above the level of toxicological concern of 120 µg/day. The most prominent elemental leachables were (b) (4), found still far below (b) (4) of respective Margins of Safety (MOSs) (Report VAL 02207).

COMMUNICATION FOR ADDITIONAL INFORMATION

I. Based on my Comments 1 and 2, an **Information Request** (IR) was sent on March 01, 2024:

We are in process of reviewing your submission, BLA STN 125789, and need additional information.

1. In 3.2.P.3.3 Description of Manufacturing Process and Process Controls for afami-cel DP, you describe process steps (b) (4) as (b) (4)

(b) (4) These descriptions lack information regarding equipment that comes in contact with the drug substance. Please provide a list of all intermediate-contacting equipment involved in these unit operations and describe the unit operations in detail, including maximal time of each manipulation. This information is necessary for us to determine the adequacy of your extractables and leachables studies.

2. In VAL 02207, *Afamitresgene Autoleucel Drug Product Container Closure Extractables and Leachables Simulation Study Report*, you state that the bags were exposed to (b) (4) (b) (4). Please provide a detailed description of bag thawing and all further holding procedures (including temperature controls, as applicable) up to the point of consequent analytical testing to allow us to determine the adequacy of your extractables and leachables studies.

Response was provided on March 08, 2024 (Amendment 11, eCTD #0012).

1. The operations involving the (b) (4) were described as follows. At the end of Step (b) (4)

2. The operations involving simulated cryobag thawing and further handling in the simulated study are as follows. The bag was thawed/held at (b) (4) for 1 hour considered representative for in-use conditions.

Review Comment 4

The leachables simulation study adequately covers leachables from the DP CCS, whereas assessment of the process from Step (b) (4) (involving the above listed contact materials) was still missing. The study represents “accelerated” study for DP storage and in use-hold.

II. IR2 was sent on March 26, 2024 (Question 4 in cumulative IR):

Considering your clarifications of the leachables simulation study (Arm A, Report VAL 02207) submitted in your Response received on March 08, 2024 (Questions 14 and 15; Amendment 11, eCTD #0012) to our previous information request, we determined that your study, performed under accelerated-like conditions, lacks:

a) Assessment of leachables originating from the (b) (4) high-risk process steps, starting from Step (b) (4)

(b) (4) This segment of your manufacturing process is specified to take up to (b) (4) of contact with the (b) (4) and thus, contributes to the overall leachables profile in final Drug Product (DP). Note, even you assessed these materials as having a lower risk than the Container Closure System (CCS, Cryobag) tested in your study, potential leachables from these materials are additive with other leachables (i. e. cumulative) in DP that may increase the risk.

b) Adequate assessment of leachables accumulated in DP during its storage by: (i) (b) (4)

(b) (4) can be more damaging for the Cryobag material, facilitating release of additional leachables and (ii) for BLA submission we require assessment of the leachables through the product shelf life (and also manufacturing process and in-use conditions) and (iii) accelerated conditions can be used in addition, but not instead of the real-time study (b) (4) pages 3 and 5). Therefore, your study may underestimate total leachables in DP and respective risk; additionally, your simulated in-use conditions may be not representative for the actual in-use conditions.

c) Therefore, while we could still accept your already performed study, please reassess the leachables profile in final DP, considering the contribution of the (b) (4) process. In particular, this can be performed in a simulated process segment starting from Step (b) (4)

(b) (4) cryobag. In analytical testing of samples, please consider the major high-risk materials’ extractables data (likely available from the manufacturers) and ensure covering elemental leachables (b) (4). The identified leachables (above the reporting limit) should be added to the leachables profile already determined in your study with CCS and the resulting leachables profile should be reassessed for toxicological risk.

Response was provided on April 30, 2024 (Amendment 31, eCTD #0032).

1. The Applicant stated that they asked the manufacturers of the (b) (4) components for extractables data. For (b) (4) components (b) (4) the manufacturers

responded they did not do extractables studies, and for the (b) (4) other components (b) (4) the manufacturers did not respond.

2. The Applicant acknowledged that these (b) (4) components are in contact with the (b) (4) solution containing 5% DMSO (aggressive conditions for the leachables) but stated that “potential additional risk of leaching due to DMSO contact is considered low due to known compatibility of DMSO with polypropylene and moderate compatibility with polystyrene”.

Review Comment 5

1. Thus, the leachables assessment is still missing for the listed process components.
2. Chemical compatibility does not ensure that no leaching of material components occurs (considering a relatively high extraction ability of 5% DMSO and the overall contact time of (b) (4)). This explanation and overall response are not acceptable.

III. During the Late-Cycle meeting on May 10, 2024, the Applicant proposed an additional post-approval study with the (b) (4) missing process components to be assessed individually for leachables contribution (in particular, termed “extractables” and using the AET corresponding to 120 µg/day for each compound). I commented on this proposal as follows:

We generally agree with your plan. However, this is not an extractables study where aggressive solutions and conditions are typically used (as guided by respective (b) (4)), but rather, it is a simulated leachables study under conditions similar to the process. Also:

1. Your proposed study design again misses understanding that the leachables in DP are cumulative from all these and (b) (4) components. For correct assessment, you need to sum leachables from each of these (b) (4) components with those from the already performed simulated study with the CCS. If you had the AET in each study of 120 µg/day for organics (and similarly for elements), in the resulting profile, you would have a reporting limit corresponding to 5 times higher value of 600 µg/day (for organics, and similarly for elements) that potentially underestimates a particular leachable up to 5 times. For correct assessment, you will need to decrease the AET in 5 times in each study, meaning that you need to reanalyze results of your already performed study for the CCS with lowered AETs (reporting limit), and use these data for reconstruction the leachables profile.
2. You may consider an alternative design that could be simpler to do. You need to simulate the manufacturing process from Step (b) (4) through Step (b) (4), as we described in the IR sent on 03/26/2024 (Question 4) and analyze leachables from a single sample. In this case, you will need to set up the respective AETs lowering them 2 times in this new and in the already performed studies (meaning reprocessing the data for the CCS), and then sum up the leachables profiles from the two studies to reconstruct their overall profile in the DP. Furthermore, you will likely have a lower and more realistic leachables profile from Steps (b) (4), as solution contact time for each component will be less than in the first study.
3. Considering the low contribution of Steps (b) (4) in the overall leachables profile, you may skip assessments of extractables from the (b) (4) materials in both designs if these data are not available from the manufacturers.

The Applicant agreed with these comments and noted that the alternative study design (2) is favorable. This study protocol would be developed and submitted to FDA for review prior to study initiation, and a new risk assessment would be conducted once the study is completed.

The **PMR text** with proposed study milestones as agreed with Applicant is the following:

“...we have determined that you are required to conduct the following studies:

... 4. An adequate assessment of leachables in the DP including the contribution of (b) (4) major process components utilized in Step (b) (4) of the afami-cel manufacturing process, and an updated toxicological risk assessment once the study is completed with the following milestones:

- Final Protocol Submission: September 30, 2024
- Study Completion: October 1, 2025
- Final Study Report Submission: December 31, 2025.”

REVIEW CONCLUSION AND RECOMMENDATION

From my review scope perspective, the analytical assessment of leachables in the DP is acceptable to recommend **approval** of this BLA. The Applicant committed to address the remaining issues under **PMR**.