



Our STN: BL 125706/0

**COMPLETE RESPONSE**

August 1, 2023

Mesoblast, Inc.  
Attention: Susan T. Sukovich  
505 Fifth Avenue 3<sup>rd</sup> Floor  
New York, NY 10017

Dear Ms. Sukovich:

Please refer to your Biologics License Application (BLA) received January 31, 2023, for remestemcel-L manufactured at your Singapore location and submitted under section 351(a) of the Public Health Service Act.

We have completed our review of all the submissions you have made relating to this BLA. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

As stated in the Formal Dispute Resolution Request (FDRR) letter dated May 28, 2021, the Center for Biologics Evaluation and Research (CBER) was unable to determine that the product you used in Study MSB-GVHD001 was “standardized as to identity, strength, quality, purity, and dosage form” according to 21 CFR 314.126(d). Therefore, CBER was unable to confirm that the clinical data in the BLA provided substantial evidence of effectiveness of remestemcel-L for the treatment of SR-aGVHD in pediatric patients. This conclusion was based on insufficient information on the potency assay matrix as described in Comment #3 in the complete response letter (CRL) dated September 30, 2020.

In your BLA resubmission, you propose to implement a potency bioassay for lot release testing of remestemcel-L to address the deficiencies described in Comment #3 in the CRL. For the reasons explained in the comments below, we have determined that the data provided in your resubmission are not sufficient to demonstrate that your proposed potency bioassay and its acceptance criterion will ensure the continued potency of your product (21 CFR 601.2(d)). As a result, you have not resolved the deficiencies described in Comment #3 in the CRL, and therefore you have not demonstrated that the product used in Study MSB-GVHD001 was adequately standardized per 21 CFR 314.126(d) as requested in our FDRR response. The outstanding deficiencies are described in detail below.

Chemistry, Manufacturing, and Controls

1. In your resubmission (SN0065, dated January 30, 2023), you propose to control the potency of the remestemcel-L drug product (DP) using a bioassay measuring the inhibitory activity of your product toward T cells (referred to as the inhibition of IL-2R $\alpha$  assay). The bioassay you propose is a modified version of a similar bioassay that was reviewed during the original BLA review cycle and previously determined to not be suitable for release testing due to poor performance characteristics. The new version of this assay (C50826) incorporates several changes from the previous version (21371) intended to improve the assay's performance characteristics.

While we acknowledge that the changes implemented appear to improve assay performance, the data provided are not sufficient to demonstrate that the C50826 assay and proposed acceptance criterion provide meaningful control of the potency of remestemcel-L. For all DP lots used in the clinical study intended to provide the primary evidence of effectiveness (MSB-GVHD001), you tested for potency with the 21371 assay only with an acceptance criterion of (b) (4) inhibition. You use this same acceptance criterion for the C50826 assay. You have previously acknowledged, however, that the 21371 assay "is currently not suitable as a quantitative assay" (SN0032, Module 1.11.4, dated June 13, 2020), and we agree that the 21371 assay cannot be considered a reliable measure of product potency. Additionally, in our analysis of results for (b) (4) commercial DP lots you provided during the review period (SN0074, dated April 26, 2023; and SN0083, dated June 8, 2023), we find no statistical relationship between the 21371 and C50826 assays by linear regression ( $R^2$ (b) (4)). You provided results from your own analysis of these data in which you (b) (4) [REDACTED], but we do not agree that such an approach is justified. In the absence of an established statistical relationship between these assays, there is no justification for setting the acceptance criterion for the C50826 assay based on results from the 21371 assay. The C50826 assay and proposed acceptance criterion are therefore not sufficient to ensure the continued potency of the commercial product (21 CFR 601.2(d)) and therefore, you have not adequately addressed Comment #3 in the CRL dated September 30, 2020. To demonstrate that your potency assay(s) are appropriate for a licensed biologic, please provide data demonstrating that your potency assay(s) accurately and reliably measure a product attribute that is relevant to the intended therapeutic effect and have acceptance criteria that ensure that the potency of the commercial product is consistent with the potency of the product administered in the clinical trials submitted as evidence of effectiveness.

2. Establishing an assay that reliably measures product potency is necessary to establish a meaningful shelf life for your product. In Module 3.2.P.8.1 (SN0081, dated May 22, 2023), you provide a summary of completed and ongoing stability studies for the remestemcel-L DP. In Table 1, you indicate that Studies SP-011 and SP-013 are the primary long-term stability studies supporting your proposed

48-month shelf life for the cryopreserved remestemcel-L DP. You measured potency in SP-011 using the 21371 version of the inhibition of IL-2R $\alpha$  assay at all timepoints. SP-013 is ongoing, but the 21371 assay was used for all timepoints through 24 months, while the C50826 assay was used only for the most recent timepoint (36 months). As noted above in Comment #1, the 21371 assay is not suitable for use as a quantitative measure of potency and you have not adequately demonstrated a meaningful statistical relationship between the 21371 and C50826 assays. Studies SP-011 and SP-013 are therefore not sufficient to support your proposed shelf life. Expiration dates for approved DPs must be “determined by appropriate stability testing” that includes “reliable, meaningful, and specific test methods” (21 CFR 211.137(a) and 21 CFR 211.166(a)(3)).

Please provide data from stability studies that include at least one quantitative test for potency that measures a product attribute that is relevant to the intended therapeutic effect to support your proposed shelf life.

#### Clinical

3. You have not provided substantial evidence of effectiveness from an adequate and well-controlled trial of remestemcel-L for treatment of steroid-refractory acute graft-versus-host disease (SR-aGVHD) in pediatric patients.
  - a) As noted in 21 CFR 314.126 (d), ‘for an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.’ With the lack of a suitable potency assay for the product used during the MSB-GVHD001 study, the study cannot be considered an adequate study for the purpose of demonstration of substantial evidence of effectiveness required for a marketing approval.
  - b) You submitted a retrospective ad hoc analysis of Study MSB-GVHD001 results compared to an external control from the Mount Sinai Acute GVHD International Consortium (MAGIC) and a long-term Center for International Blood and Marrow Transplant Research (CIBMTR) survival analysis of subjects treated in Study MSB-GVHD001. Note that these retrospective analyses are not considered adequate and well-controlled trials, and as such, the results do not provide substantial evidence of effectiveness.

To address this deficiency, in addition to addressing the Chemistry, Manufacturing, and Controls (CMC) deficiencies, please submit the results of an adequate and well-controlled randomized trial of remestemcel-L for treatment of aGVHD in adult and/or pediatric subjects using an adequately characterized product, identical or comparable to the to-be-marketed form.

## Labeling

4. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

## Following Comments

In addition to the deficiencies that were the basis for not granting approval, we have identified the following comments:

## Chemistry, Manufacturing, and Controls

1. We completed a pre-license inspection of the Lonza Bioscience Singapore manufacturing facility in May 2023 and found no objectionable conditions. The second comment in our CRL (dated September 30, 2020) has therefore been resolved.
2. In Section 6.5 of your BLA resubmission (Module 1.11.4, SN0065), you address additional CMC comments from our CRL (dated September 30, 2020). After reviewing your responses to these comments, we have determined that additional CMC comments #1, 2, and 4-8 from the CRL have been adequately resolved or are no longer relevant due to new information provided in your resubmission and subsequent amendments.
3. In Section 6.5.3 of your BLA resubmission (Module 1.11.4, SN0065), you describe accelerated stability studies conducted to demonstrate that the inhibition of IL-2R $\alpha$  assay is stability indicating for (b) (4) (Study SP-019) and DP (Study SP-018) to address additional CMC comment #3 from the CRL (dated September 30, 2020). It is not clear, however, which version of the inhibition of IL-2R $\alpha$  assay was used in these studies. If you used the 21371 assay in the accelerated study for DP, we recommend that you repeat this study using an assay that reliably measures product potency and will be used for lot release testing of the commercial product.
4. In Section 6.5.7 of your BLA resubmission (Module 1.11.4, SN0065), you describe a simulated-use extraction study you conducted for the DP container closure and a toxicological risk assessment of the compounds identified in this study. While this study is sufficient to support the use of the proposed DP container closure, leachable compounds from materials upstream in the manufacturing process also accumulate in the DP and may pose risk to those receiving your product. In general, for a BLA approval, we require assessment of total leachables presented in DP that accumulate throughout the manufacturing process, storage over the shelf-life and in-use hold. Such assessment should be performed in a real-time study using maximal hold times and temperatures at respective steps. In addition, this assessment (i) may use simulated intermediate

solution(s) [without active ingredient and other complex compounds (e.g., cells, proteins) that may interfere with analytical detection of leachables], and (ii) may be started from a process step when no removal of potential leachables is performed (e.g., change of the buffer).

Therefore, please assess cumulative leachables from the upstream manufacturing steps. The study should evaluate leachables that accumulate after the (b) (4) to the final DP (e.g., from (b) (4) through final filling of the DP). In addition, we recommend that you include the assessment of leachables from upstream manufacturing steps in the design of the proposed protocol for the ongoing DP stability studies (PR-111), if feasible.

5. In Report RD-006 (Module 3.2.S.3.1, SN0065), you provided results from analyses purporting to show a relationship between product potency and clinical outcomes in MSB-GVHD001. After we notified you of apparent discrepancies between the analysis methods described in this report and the clinical datasets used to conduct these analyses, you acknowledged that the analysis methods were "inaccurately described" in Report RD-006 and provided corrected results in SN0070 (dated April 5, 2023). Additionally, you provided further justification for analyzing potency data by grouping subjects and results from reverse cumulative distribution analyses in SN0074 (dated April 26, 2023).

We do not agree that the results reported in Report RD-006 and additional information provided in SN0070 and SN0074 establish an association between product potency and clinical outcomes because of limitations in the product potency dataset and analysis methods. The most significant of these limitations is that the analyses rely on potency data collected with the 21371 version of the inhibition of IL-2R $\alpha$  assay, and as noted above in Complete Response Comment #1, this assay has poor performance characteristics and no statistical relationship to the C50826 assay you proposed to use for lot release testing. Additionally, the moderate significance of the associations reported must be interpreted conservatively because of the large number of statistical tests performed and the post-hoc selection of analysis methods. Most subjects in MSB-GVHD001 received product from two or more DP lots and integrating potency from multiple lots into a single value for each subject limits the statistical power to detect a true relationship between product potency and clinical outcomes.

Establishing a relationship between product attributes and the product's clinical effect is not generally required for licensure. However, it will be very challenging for you to complete a convincing comparability exercise to support new DCB manufacturing without at least one product attribute with established relevance to the product's clinical efficacy. We therefore recommend that in future clinical studies you consider taking steps to avoid the limitations described above (e.g., pre-specify your analysis methods and ensure each subject receives product from only one DP lot) and thoroughly characterize the product used.

6. In SN0083 (dated June 8, 2023), you indicate that you can potentially treat (b) (4) patients with DP lots currently in inventory, and another (b) (4) patients with material from future DP lots made from your remaining DCB materials. In Section 6.3.5.1 of your BLA resubmission (Module 1.11.4, SN0065), you acknowledge that you will need to conduct a comparability exercise for new DCBs when the current stock is depleted. Additionally, you suggest that you will be able to demonstrate analytical comparability to support new DCBs using the inhibition of IL-2R $\alpha$  assay because the attribute this assay measures is associated with clinical outcomes.

As stated above in Additional Comment #5, however, we do not agree that you have demonstrated that the attribute measured by the inhibition of IL-2R $\alpha$  assay is associated with clinical outcomes, and therefore it is not clear that your current Critical Quality Attributes (CQAs) will be sufficient to demonstrate analytical comparability. Even if meaningful CQAs can be established, there is a reasonable likelihood that DP made from these new DCBs may not be comparable to DP made from the current DCB stock because your new DCB manufacturing process was developed more than 10 years after your current DCBs were manufactured and new DCBs will be manufactured at a different facility (SN0085). As demonstrating analytical comparability to support new DCBs will therefore be very challenging, we recommend that you establish new DCB manufacturing and use DP made from these new DCBs in any new clinical studies.

7. A critical challenge for potency assays developed after completion of a clinical study is that the potency of DP lots used in the clinical study cannot be directly measured at the time of release, and data obtained by testing retained samples of these DP lots are difficult to interpret because the potency of the retained product may have degraded since release. As we have done previously (Preliminary Meeting Responses dated November 23, 2021), we again recommend that you qualify any new potency assays before initiating a new clinical study. This approach allows you to test product potency at the time of release and provides additional data to characterize the relationship between product attributes and clinical outcomes.

#### Clinical

8. We recommend that you request a meeting with the FDA to discuss the trial design and statistical analysis plan (SAP) before conducting a new study with a registrational intent.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c).

You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

Please submit your meeting request as described in the guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547.pdf>, and CBER's SOPP 8101.1 *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Adriane Fisher, at (301) 796-9691 or by email at [adriane.fisher@fda.hhs.gov](mailto:adriane.fisher@fda.hhs.gov).

Sincerely,

Celia M. Witten, PhD, MD  
Acting Director  
Office of Clinical Evaluation  
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