

To facilitate the conversation, Mesoblast has prepared brief responses to the issues identified in the Late Cycle Meeting materials, provided on 15th July 2020.

Discussion of Substantive Issues

1. **Critical Quality Attributes and Product Efficacy:** FDA notes that “we identified several issues with your new analyses that make the results difficult to interpret”, and “you indicate that no significant association was observed when only data from the pivotal study MSB-GVHD001 is considered”

Mesoblast Response:

We acknowledge your concerns and the limitations of the statistical methodology used, but also feel the analyses provide important information regarding the (b) (4) of the TNF-R1 receptor on the cells and the relationship to survival. As we continue to build our knowledge of these cells and the biomarker development in this and other indications with inflammatory states, we welcome the ability to collaborate with the Agency.

2. *We note that a potency assay/critical quality attribute (CQA) with a demonstrated relationship to clinical efficacy may not be required for licensure, however a lack of CQAs relevant to clinical efficacy will likely limit the interpretability of any future comparability exercises you may conduct after implementing changes to the manufacturing process.*

Mesoblast Response:

We acknowledge your concerns and understand that TNF-R1 as a CQA may not alone demonstrate comparability. The nature of a cell-based product is very complex, and Mesoblast continues to work to create a broader panel of measures, including extended characterization measures to demonstrate comparability of cells manufactured before and after certain changes. We also acknowledge that it will not always be possible to demonstrate comparability with in-vitro analysis alone. We welcome the ability to collaborate closely on a comparability approach with the Agency to ensure appropriate comprehensiveness of any approach that will be commensurate with the nature of any proposed changes.

3. **Inhibition of IL-2Ra Assay and Product Quality:** FDA notes at the bottom of Page 3: “while we acknowledge that increased variability due to differences in the (b) (4) could potentially explain this observation, a reduction in the quality of commercial lots due to changes in the manufacturing process or (b) (4) cannot be ruled out with the data provided in your response. Additionally, as several changes have been made to the manufacturing process, this apparent reduction in potency may also indicate that commercial lots made using the revised process are not sufficiently similar to those using the previous process.”

Mesoblast Response:

The manufacturing changes made between the time of manufacture of product at LBSS facility for GVHD001 and the PPQ and commercial batches made in 2019-2020 have all been listed in section **3.2.P.2.3.1.3.3. PPQ DP Process**. These changes include the following:

- (b) (4) [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Mesoblast evaluated each change and determined that none of these changes have the potential to substantially impact the potency of the cells. In addition, the results for the inhibition of IL-2R α have not been routinely lower, rather there is an increase in the variability of results – which our investigations point to an analytical issue. As previously described in the response to RFI#24 (SN0032), we are investigating the method and will continue to apply increased controls in relation to the qualification of the (b) (4) used for the analysis.

In regard to the impact of DCB age, Mesoblast have committed to retest all DCBs prior to any further manufacturing and they will only be utilized if they meet Quality Control criteria. In addition, the final product must meet the quality controls for release of the product. The stability program for both DCB and DP support the long-term storage. This program continues through the post approval/on-market phase. In summary we don't consider that the age of the DCB has impact on the variability of the IL-2R α results seen in the batches manufactured from 2019 onward.

4. **Product Specifications:** FDA note “your specifications should be revised further to include both a minimum and a maximum value that together ensure that lots released for commercial use are consistent with observed values of DP lots used in study MSB-GVHD001”.

In regard to IL-2R α assay you state “we therefore request that you revise the minimum specification for this assay to (b) (4) inhibition so that the commercial DP lots will have a level of bioactivity more consistent with DP lots used in the MSB-GVHD001 study.”

Mesoblast Response:

In response to your proposal Mesoblast agrees to tighten the specifications for TNF-R1 and inhibition of IL-2R α to align with the batches included in the MSB-GVHD001 study. The proposed specifications have been provided below.

Attribute	Acceptance Criteria	Rationale
TNF-R1	(b) (4)	MSB propose a threshold (minimum specification) only. As there are minimal safety issues related to the treatment with the cells a maximum specification does not appear to be justified.
Inhibition of IL-2R α	(b) (4) inhibition	As proposed by FDA

DMPQ Items

GMP Compliance Status of Manufacturing facilities

5. *Your DP release testing facility (b) (4) is in Official Action Indicated status based on the outcome of the last US FDA Inspection (b) (4)*

Mesoblast Response:

Mesoblast seeks clarification if this status will impact the anticipated BLA action date.

In regard to the DP release testing, (b) (4) conduct the residual Trypsin release testing. This testing was conducted in the Chemistry GMP laboratory, which in (b) (4) was under an independent FEI#(b) (4), and not in scope of the inspection in question. The previous status given to FEI#(b) (4) was No Action Indicated (NAI).

Mesoblast has requested (b) (4) to also confirm from the FDA Compliance Division the impact to the Mesoblast BLA review and approval status.

6. *Compliance status of your DP manufacturing facility Lonza Bioscience Singapore Pte. Ltd. (35 Tuas South Ave 6, Singapore, 637377; FEI#3009725845) cannot be verified at this time.*

Mesoblast Response:

Mesoblast seeks clarity from the FDA on their plan to verify the compliance status of the LBSS site, and if the current pandemic may impact the anticipated action date for the BLA.

Mesoblast acknowledges that the pandemic has created restrictions in travel that have limited FDA's ability to assess the LBSS facility.

Request for Information #28, which is due to be provided to FDA on Friday 24th July contains a significant number of pre-inspection documentation requested from Lonza. In addition, Lonza provided a substantial package of documents via their master file on 6th of July 2020. Is the review of the documentation provided expected to impact the action date for the BLA?

In addition, LBSS have confirmed their willingness to participate in a virtual inspection. Is this a suitable alternative avenue for FDA to consider? In relation to such a proposal the following considerations points are requested:

- The audit be hosted during Singapore working hours
- Only one audit stream of audit could be facilitated by the LBSS team due to technical and logistical constraints of a remote set-up
- Documents can be shared through secure document management tools
- Interviews can be conducted through online tools such as Microsoft Teams or software of the FDA's choice
- A pre-recorded walk down of the facility can be provided.

Sterility Assurance of the Final Product

7. *You indicated during our teleconference on June 18th, 2020 that you have no data to support microorganism recovery in release and in process sterility samples shipped under various conditions to the (b) (4) for testing. This issue also applies to in-process solutions/media that are shipped for sterility assurance testing from LBSS (Singapore) to (b) (4)*

Mesoblast Response:

As committed in RFI#26, protocols were provided in the RFI response to assess the recovery of microorganisms and Mesoblast has committed to providing the final study reports by 18 September 2020. Does FDA concur this acceptable?

8. *No periodic testing of incoming lots of product contact materials for sterility and endotoxin. Many product contact materials are not tested for endotoxin by the supplier.*

Mesoblast Response:

Lonza is assessing all contact materials and will request all suppliers to implement endotoxin testing. Lonza will also establish an internal program to routinely test for endotoxin levels on product contact materials. A written plan will be provided to the FDA prior to implementation.

9. CCIT of final container by (b) (4) [REDACTED] Test is not capable for detecting holes in the stopper. Stopper (b) (4) [REDACTED]
[REDACTED] Effectiveness of (b) (4) [REDACTED] was not validated by an alternative method.

Mesoblast Response:

Mesoblast acknowledges that the current test method for CCIT may not be capable of detecting a hole in the stopper. Therefore, Mesoblast will undertake a further validation study using alternative testing; the data for which will be available and provided to FDA by 31st August 2020.

A protocol for the study and the validated test method is currently available and will be can be provided upon request. The testing will be implemented into the long-term stability protocol at the next testing cycle.

Clinical

To be discussed in the meeting as time permits

Minor review issues

Item	Current status
Robustness of IL-2R α	As noted in the response to RFI#24, the investigation is ongoing. The protocol for the robustness assessment can be provided on request.
Leachables study	Mesoblast has provided their response and proposed study plan in the response to RFI#32 submitted to FDA July 21, 2020.
Stability data to be re-evaluated	Acknowledged. Updated stability data assessment will be provided.
Qualification of (b) (4) for packaging	(b) (4) qualification is complete. Information is included in the response to RFI#28, which will be submitted to FDA on Friday 24 th July 2020
Qualification of serialization equipment	The validation master plan and qualification protocol are included in the response to RFI#28 which will be submitted to FDA on Friday 24 th July 2020. The plan covers the qualification of the serialization equipment. Mesoblast will commit to providing the final report by August 31, 2020, as noted in RFI#28.

Advisory Committee

Mesoblast seek any further clarification of the expectations for the Advisory Committee.

Applicant Questions

Mesoblast submitted the application for the biologics suffix during the BLA review period in Q1 2020. No feedback has been received. It is critical for Mesoblast to have confirmation of the brand name, including the suffix, to support labelling, serialization and subsequent launch activities. When can we expect the decision?