

**Addendum to  
CBER CMC BLA Review Memorandum**

**BLA STN 125706**

**Ex Vivo Cultured Adult Human Mesenchymal Stem Cells**

**Ekaterina Allen, PhD, RAC / Consumer Safety Officer / CBER/OCBQ/DMPQ/MRB2**

1. **BLA#:** STN 125706/0

2. **APPLICANT NAME AND LICENSE NUMBER**

Mesoblast, Lic.# 2140

3. **PRODUCT NAME/PRODUCT TYPE**

Non-Proprietary/Proper/USAN: Ex Vivo Cultured Adult Human Mesenchymal Stem Cells

Proprietary Name: RYONCIL

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

Ex Vivo Cultured Adult Human Mesenchymal Stem Cells [remestemcel-L; ce-MSD] is an allogeneic culture-expanded cell product isolated from human bone marrow of adult donors. The product is supplied as a frozen cell suspension in 6 mL cryogenic vials for intravenous infusion. RYONCIL is available in a concentration of  $6.68 \times 10^6$  cells/mL in 3.8 mL. The product is intended for treatment of acute steroid-resistant graft versus host disease (SR-aGVHD) in pediatric patients.

5. **MAJOR MILESTONES**

6/4/2019 Module 4 submitted

12/31/2019 Module 5 submitted

1/31/2020 Modules 3 and 1 submitted. Start of PDUFA clock

3/31/2020 Filing Action

6/1/2020 Mid-Cycle Meeting

7/16/2020 Late-Cycle Meeting

9/30/2020 First Action Due

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Ekaterina Allen, OCBQ/DMPQ/MRB2	CMC/Facilities

7. **INTER-CENTER CONSULTS REQUESTED**

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No )
NA		

**8. SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
01/31/2020	125706/0.3	See primary memo. Module 3 of rolling submission
03/17/2020	125706/0.13	IR (Information Request) #1. See primary memo. Cold chain and sterility assurance of Donor Cell Bank (DCB) manufacture
6/4/2020	125706/0.28	IR#2. Follow-up on facility issues from filing review and issues identifies during review of eCTD Modules 3.2.S and 3.2.P
6/24/2020	125706/0.35	Visual inspection, equipment, and facilities
6/29/2020	125706/0.36	Aseptic Process Validation
7/1//2020	125706/0.38	Updated floor plans and Lonza Bioscience Singapore Pte. Ltd. (LBSS) facility section
7/14/2020	125706/0.42	Shipping and release sterility testing
7/27/2020	125706/0.46	Follow-up on equipment qualification
7/6/2020	MF(b) (4)	Pre-inspection document request (see respective memo) and Master File (MF) update (see this addendum memo)
7/22/2020	MF(b) (4)	Clarification of the scope of the MF update

**9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)**

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF(b) (4)	Lonza Bioscience Singapore Pte. Ltd.	3.2.A.1 Facilities and Equipment	Yes	MF was reviewed and review was documented in the primary memo except the amendments listed above (see item 8).

**10. REVIEWER SUMMARY AND RECOMMENDATION****A. EXECUTIVE SUMMARY**

The information provided in the original BLA submission was brief, and lacked details about the qualification of the facility, equipment and utilities, and on-site media production for remestemcel. In addition, the BLA did not provide sufficient information to address the

DP CCIT method, aseptic process validation, cell factory (b) (4) qualification, segregation, clearance and changeover procedures. Finally, primary review identified several potential issues related to sterility assurance and cold chain maintenance of Donor Cell Bank (DCB), shipping validation of DCBs, and Drug Product (DP) manufacture (material controls and final visual inspection).

Additional information regarding all of the issues listed above was requested on March 5, 2020 (by email), May 4, 2020 (by email), June 2, 2020 (by email), June 18, 2020 (email follow-up to a telecon on the same date), and June 30, 2020. Response to the information request of March 5, 2020 was provided on March 17, 2020 in the amendment 125706/0.13; this amendment was reviewed in the primary memo. The responses submitted in the other amendments listed above (see Section 8. *Submissions Reviewed* above) are reviewed in this addendum memo.

This memo also documents the review of the unsolicited amendment MF(b) (4) (Module 3.2.A submitted together with the response to the pre-inspection document request) and Lonza Bioscience Singapore Pte. Ltd. (LBSS) response to a follow-up information request in the amendment MF(b) (4).

## B. RECOMMENDATION

### II. COMPLETE RESPONSE (CR)

1. Due to the inadequacy of the data submitted to support approval, the agency did not conduct a pre-license inspection of your manufacturing facility. This inspection will need to be performed after the agency receives a complete response with adequate data to address the deficiencies identified in this letter (21 CFR 601.3(a)(2)).

*Please note that the CR item 1 above refers to inadequate clinical and product CMC data. DMPQ has no further CR comments.*

### II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Ekaterina Allen, Reviewer, OCBQ/DMPQ/MRB2	Concur	Ekaterina N. Allen -S <small>Digitally signed by Ekaterina N. Allen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=200116898 /, cn=Ekaterina N. Allen -S Date: 2020.09.16 15:28:50 -0400</small>
Anthony Lorenzo, Acting Branch Chief OCBQ/DMPQ/MRB2	Concur	Anthony Lorenzo -S <small>Approved 2020.09.21 09:41:58 -04'00'</small>
Jay Eltermann, Director, OCBQ/DMPQ	Concur	John A. Eltermann -S <small>Digitally signed by John A. Eltermann -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300049305, cn=John A. Eltermann -S Date: 2020.09.21 10:20:58 -0400</small>

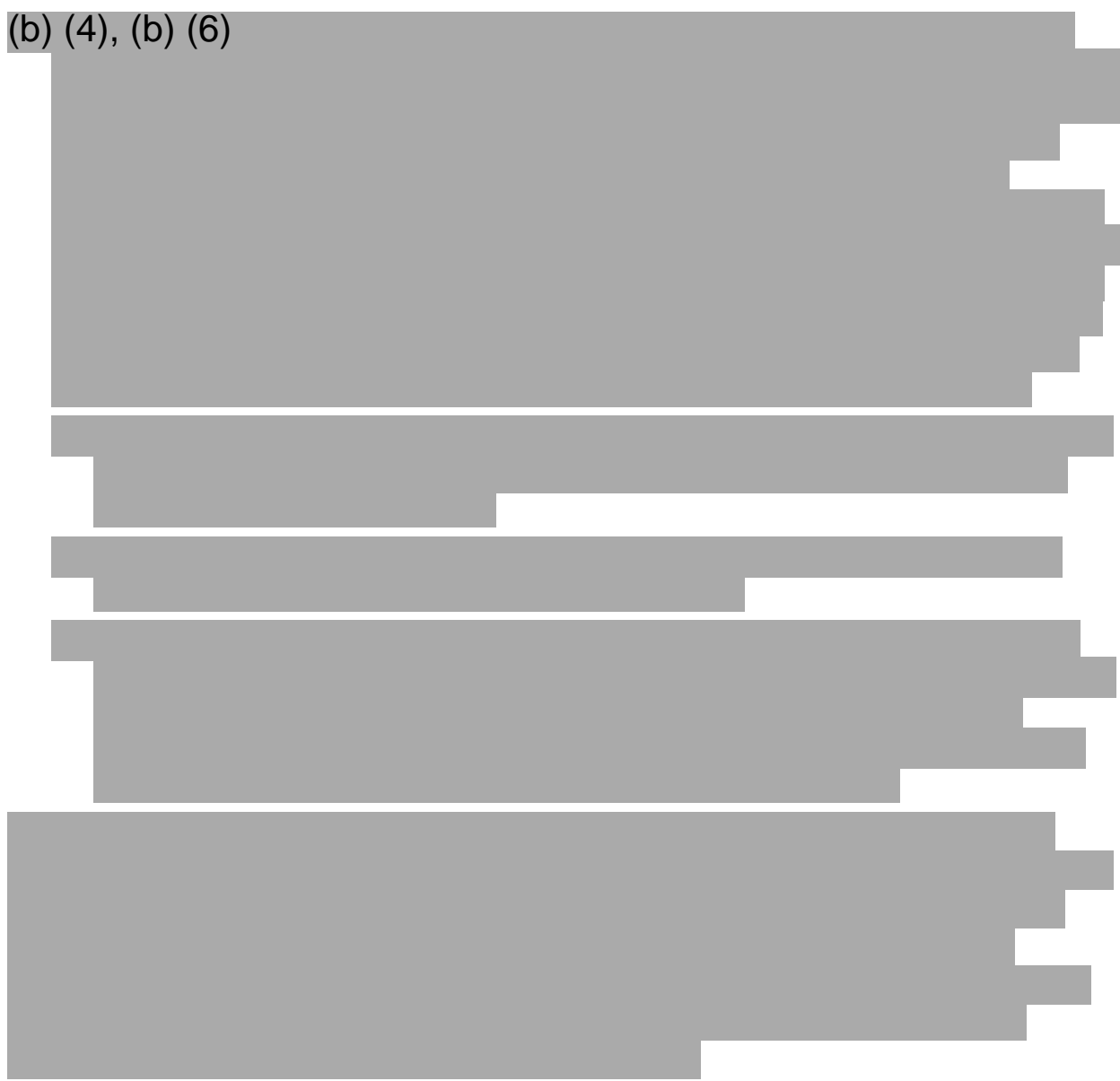
**REVIEW OF AMENDMENTS TO THE BIOLOGIC LICENCE APPLICATION**

In this addendum memo, I review Mesoblast responses to the CBER Information Requests submitted in amendments 125706/0.28, 125706/0.35, 125706/0.36, 125706/0.38, 125706/0.42, and 125706/0.46. LBSS unsolicited amendment to MF(b) (4) and the amendment containing a related response to CBER information request are reviewed further below (see Review of Amendments to the Master File).

CBER comments are in bold, followed by the sponsor's response in plain lettering.







**INFORMATION REQUEST #2.** See the primary review memo for the Information Request (IR) #1. The IR#2 was sent to Mesoblast on 5/1/2020 and the response was received in the amendment STN125706/0.28 (eCTD seq 0028) on 6/4/2020.

(b) (4), (b) (6)




2 pages determined to be not releasable: (b)(4),(b)(6)

(b) (4), (b) (5), (b) (7)(E)



(b) (4), (b) (7)(E)



4. You stated that of 608 DP lots released since 2003, all tested negative for sterility and met release endotoxin specification. Please provide a list of all drug product batches initiated, but not released. For each batch please include production dates and facility, indicate disposition of each batch, rationale for aborting/rejecting, and indicate all batches with confirmed or

**suspected sterility failures and batches that did not meet endotoxin specification.**

Mesoblast clarified that 608 DP lots released since 2003 were based on the number of lots used in clinical studies during development. All lots that were aborted or rejected and not released from the manufacturing sites are summarized below, by the facility:

- Osiris Therapeutics, 2001 Aliceanna Street, Baltimore, MD 21231 (2004-2006)  
No such data is available for 2004. Of (b) (4) lots initiated, but not released in 2005-2006, 42 lots were rejected/aborted due to sterility failures, one lot due to endotoxin OOS, one lot was aborted at final harvest (no root cause provided) and three more lots for other reasons.
- (b) (4)
- Lonza Walkersville, 8830 Biggs Ford Road, Walkersville, MD 21793 (2003-2009)  
All lots manufactured at this facility met endotoxin specification. In 2003-2006 15 lots were rejected for various reasons unrelated to sterility failures. In 2007 38 lots were rejected/aborted, including eight lots due to sterility failures or contaminations and six due to product exposure to Class (b) (4) environment (leaks). In 2008 35 lots were rejected/aborted, including one due to sterility failure. Investigation PR31037 of 2007-2008 sterility failures and related CAPAs were previously reviewed (see the primary review memo Section 3.2.S.2.5 for more detail). Of 15 lots rejected/aborted in 2009, four were due to sterility failures or contaminations. The root cause is attributed to cell factory defects, as these CFs lots were manufactured prior to implementation of new packaging material by the supplier.
- Lonza Bioscience Singapore Pte Ltd, 35 Tuas South Ave 6, 637377 Singapore  
Out of 17 lots rejected between 2015 and February 2020, none were to sterility failure or contamination and two were due to leaks during (b) (4).

**Reviewer Comment:** See IR#1, Q.1. It is not clear why the applicant stated in in the original submission (Table 3, p. 4 of mr-097-supp-report-dcb-process-osiris-lwi-v2) that remaining DCB (b) (4) manufactured using BMA (b) (4), (b) (6) were later also rejected due to multiple sterility failures in downstream manufacture, though no such failed lots are included in the list of rejected/aborted lots at LBSS. See IR#5, Q.1 for clarification.

5. You performed post-long-term storage CCIT for final DP container on (b) (4) vials. Please justify the number of samples used in the study.



Mesoblast explained that the study was performed to supplement long term storage stability studies that included sterility testing at 12, 24, 36, and 48 months, but not CCIT (SP-008 and SP-011, previously reviewed; see primary memo section 3.2.P.8 for more details). Sample quantity was selected based on the typical batch size ((b) (4)) vials of which ((b) (4)) vials are used for release testing and retains). Due to limited inventory and small batch size, CCIT at 48 months was performed on ((b) (4)) per lot.

CCIT at 12, 24, 36, 48, and 60 months is included in currently ongoing long-term stability study SP-013 and post-approval stability commitment study SP-016 ((b) (4)) /will be tested per time point per lot).

**Reviewer Comment: This response is acceptable.**

**6. Regarding DP manufacturers listed on your Form 356h and in eCTD 3.2.P.3.1:**

- a. Please clarify which facilities will perform commercial manufacture and lot release (vs. historical)
- b. We were unable to find ((b) (4)) using the FEI or DUNS numbers provided in 356h form. Please verify the FEI and DUNS numbers associated with the facility.

The following facilities were used in manufacture of PPQ lots and are proposed for commercial manufacture:

- Lonza Bioscience Singapore Pte. Ltd. DP manufacture, primary packaging, QC in-process and batch release testing, DP storage
- ((b) (4)). QC batch release and stability testing.
- ((b) (4)). QC batch release testing.
- ((b) (4)). QC stability testing.
- ((b) (4)). (subcontracted by Lonza Bioscience Singapore) QC in-process and batch release testing.
- ((b) (4)). QC stability testing.
- Mesoblast International Sarl. QA review and bulk batch release.
- ICS Amerisource Bergen (not used during PPQ). Secondary packaging, DP storage and distribution.
- Mesoblast Inc. Final packaged product batch release.

Correct DUNS and FEI numbers of ((b) (4)) respectively. Form 356h and DP manufacturer section of the BLA were updated accordingly.

**Reviewer Comment: This response is acceptable.**

**7. Please clarify the following regarding your DP manufacturing process:**

- a. Whether (b) (4) processing during (b) (4) is sequential (i.e. (b) (4) or concurrent (e.g. multiple (b) (4) are (b) (4) at the same time); how many (b) (4) are (b) (4) at a time.

(b) (4)

**Reviewer Comment: This is acceptable.**

- b. You stated that all filled final product vials (including rejected vials) are (b) (4) labelled and sorted and rejected vials have their labels defaced. Please explain how you address the high potential for mix-ups that such practice creates.

Mesoblast provided a summary of vial handling throughout filling, visual inspection, and labeling process. Sequential order of the vials is tracked using (b) (4) and accompanying paperwork.

(b) (4)

**Reviewer Comment: This is acceptable.**

- c. Please provide the maximum number of batches that will be produced/processed simultaneously in the same manufacturing suite from the same or different DCB lots and explain your procedures for segregation and prevention of cross contaminations and mix-ups.

(b) (4)

Additionally, segregation is achieved by

- (b) (4)

**Reviewer Comment:** This is acceptable. (b) (4) use for different lots (b) (4) step) was challenged during APV.

- d. You stated that growth media maximum use time is (b) (4) days. Please clarify how the media is used and stored after (b) (4) (e.g. use on multiple days,



for different lots, etc.). Please provide data supporting that sterility of the media is maintained under conditions of use.

Mesoblast explained that all media that is stored (b) (4)

**Reviewer Comment:** This is acceptable. Qualification of the (b) (4) room (b) (4) in room (b) (4) should be provided. This information was requested in IR#5, Q.16.

8. (b) (4), (b) (6)

(b) (4)



**9. Regarding your material controls (related to DP manufacture):**


- a. Please explain what controls are in place for Plasma-Lyte A, Human Serum Albumin, and Dimethyl Sulfoxide (e.g. supplier qualification, incoming lots testing, testing performed by supplier and included in Certificate of Analysis [CofA], etc.), particularly as they apply to bioburden limits or sterility and endotoxin levels of these supplies. Please include the specification, where applicable.**

Plasma-Lyte, HSA, and DMSO are accompanied by a CofAs (each includes endotoxin and sterility results). All manufacturers and suppliers of these reagents are qualified. Upon receipt, CofA is verified and physical inspection is performed. Testing at LBSS includes identity testing and additional (b) (4), sterility, and endotoxin testing of DMSO. Plasma-Lyte is tested for endotoxin (b) (4) lots and (b) (4) thereafter). For additional detail see primary review memo section 3.2.P.4.

**Reviewer Comment: This response is acceptable.**

- b. Please provide a tabular list of all product contact materials (e.g. cell culture implements) used during DP manufacture. For each material please specify what it is used for, whether it is reusable or single use, and what controls are in place to assure that each material is sterile and free of endotoxin prior to its use in manufacture (e.g. incoming lots testing, testing performed by supplier and included in CofA). Please include the specification, where applicable.**

Mesoblast stated that all product-contact materials are single use and all suppliers have been qualified. The only product contact material where incoming lots are tested for endotoxin and sterility is the final container. All other materials are released based on their CofAs and physical inspection. The following product contact materials are not tested for endotoxin by the supplier:

- (b) (4)
- 

- (b) (4) [REDACTED]

**Reviewer Comment:** *There is no sufficient assurance that incoming lots of product contact materials are sterile and free of endotoxin. A number of product-contact materials are not tested for endotoxin by either the supplier or by LBSS upon receipt. During the late cycle meeting the applicant committed to implementation of endotoxin testing of product contact materials.*

(b)  
(4)  
(b)  
(4)  
(E)

**10. Regarding your aseptic process validation (DP process):**

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

(b) (4) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

**Reviewer Comment: This response is acceptable.**

11. Regarding your cell factory (b) (4) qualification:

(b) (4) [Redacted]

[Redacted]

(b) (4)

[REDACTED]

[REDACTED]

- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]

[REDACTED]

[REDACTED]

**Reviewer Comment:** Overall this response is acceptable. Mesoblast should specify the number of different (b) (4) lots used for each of the facilities/products. This information was requested in IR#5, Q.3.

12. Regarding your PPQ:



7 pages determined to be not releasable: (b)(4);(b)(5);(b)(7e)

**13. Regarding your DP visual inspection of PPQ lots:**

(b) (4)

(b) (4)

\_\_\_\_\_

\_\_\_\_\_

[REDACTED]

\_\_\_\_\_

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(b) (4), (b) (5), (b) (7)(E)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

**14. Regarding your product shipping validations:**

(b) (4)



(b) (4)

**Reviewer Comment:** *This is acceptable. However, it is not clear what qualification activities besides the initial ones (liquid nitrogen (b) (4) were done to the rest of the shippers. Is dynamic hold time done under actual shipping conditions? None of the shipper IDs in Tables 32-33 of the response (equipment used in product shipping validations) matched the shippers S/Ns in the qualification reports. Additional information was requested in IR#5, Q.4.*

*The rest of the response is acceptable.*

**15. Please provide the following information for LBSS facility:**

- a. HVAC qualification report(s), including but not limited to the description of testing procedures, sampling locations, acceptance criteria, results, and summary of any deviations.

Qualification of the following AHUs was provided: (b) (4)



(b) (4)

***Reviewer Comment:*** OQ air change rates data was not provided. Description of sampling locations and procedures (duration/volume, where applicable, air changes, etc.) was not provided for OQ/PQ. It appears that there were modifications to HVAC system in 2017 and 2019 [(b) (4)], though no details were included. No PQ supporting manufacture of PPQ lots was provided for modified AHUs. This information was requested in IR#4, Q.5a.

***Rationale/risk assessment for selection of testing location during PQ was requested in IR#4, Q.5b.***

***It appears that no manufacturing activities were performed during PQ. Customer training runs were performed during PQ of (b) (4) though no explanation what manufacturing operations it involved was included. (b) (4) was performed during PQ of (b) (4). It is not clear whether the worst case challenge was performed (maximum number of operations/equipment running simultaneously). Additional information was requested in IR#4, Q.5c.***

***Temperature and humidity mapping of clean rooms was not performed, recovery time and air velocity for (b) (4) Grade (b) (4) area were not determined. (b) (5), (b) (7)(E).***

***There were numerous excursions air viable and/or surface viable excursions for (b) (4) and pressure differential alarms, sometimes with reversal of air flow, during PQ of all AHUs except (b) (4). The deviations were resolved and CAPAs implemented. The firm performed post-PQ monitoring with acceptable results. The details are limited (no information about sampling locations or operations performed, inconsistent***

*frequency/duration of sampling). Additional information was requested in IR#4. Q.5d.*

- b. Description of routine EM program, including sampling frequency (static and dynamic), a diagram showing sampling locations, rationale for location selection (i.e. risk assessment), and acceptance criteria.

Sampling locations and frequency of routine EM were established based on worst-case locations established during PQ. Sampling types include non-viable air (by (b) (4) ), viable air (b) (4) and viable surface (b) (4) . Routine static sampling is performed (b) (4) in Grade (b) (4) and (b) (4) areas and includes non-viable air sampling only. Routine dynamic (b) (4) is performed (b) (4) (Grade (b) (4) in production suites). It includes all types of sampling in rooms (except settle plates) and viable surface and air sampling of the equipment. Batch-specific monitoring is performed during manufacturing operations, (b) (4) of production batch activity. It includes all types of sampling above and personnel sampling.

Acceptance criteria for action levels are based on (b) (4) . Alert levels are based on statistical analysis of (b) (4) historical data per suite and are reevaluated every (b) (4) . Action limits for dynamic monitoring were included and reviewed in EM section (see primary memo section 3.2.A.1 LBSS). The static action limits are below:

(b) (4)

Provided risk assessment for EM SGTS-20315 employed Failure Modes and Effects Analysis to determine risk level associated with existing sampling plan. Severity (corresponds with air classification, with Grade (b) (4) being ranked the highest), occurrence probability, and detection/EM frequency were evaluated (each ranked from (b) (4) and risk priority number was calculated by multiplying all numerical values. Historical EM data (b) (4) was used for the analysis), but individual EM sampling locations were not evaluated. RPN score of (b) (4) was deemed high risk, (b) (4) medium risk, and NMT (b) (4) – low risk. RPN did not exceed (b) (4) for any of the areas and equipment (where data for occurrence probability was available).

Mesoblast stated that sampling locations selected for routine monitoring are based on (b) (4)

Non-viable and viable air sampling location selection was based on:



- (b) (4)

Surface viable location selection was based on:

- (b) (4)

Specific sampling locations (description and floor plans) provided for Remestemcel-L and media production areas, kitting room, and clean corridor. I noted that overall, the number of sampling locations increased with the area of the room, criticality of the process, and equipment quantity. Pass throughs and critical equipment (BSCs, incubators) are sampled as well. It appears that unlike in Mesoblast statements included above, (b) (4) of the room is not always surface sampled (e.g. Media Prep, Kitting room, Staging (b) (4) Inspection suite), (b) (4) are not sampled (e.g. Production suite, Media Fill, Kitting room).

Separate details were batch-specific monitoring, which is reduced to the most critical areas and equipment (b) (4) comparing to the routine static/dynamic sampling. Surface viable sampling is performed (b) (4) production, non-viable air and settle plate sampling are performed (b) (4), viable air – (b) (4). Both Grade (b) (4) and supporting Grade (b) (4) (surface and air viable, air non-viable) areas are sampled.

An additional acceptance criterion was set on contamination recovery rate for (b) (4) areas supported by each AHU.

**Reviewer Comment: Overall acceptable, though rational for certain sampling locations (or lack thereof) is not clear. (b) (5), (b) (7)(E)**

**c. Regarding disinfectant effectiveness study, please provide:**

- A list of surfaces tested vs. present in the facility and rationale for test surface selection.
- A rationale for selection of test organisms and for limiting the study to in-house isolates only

- A summary of the study procedures (i.e. how coupons were prepared, treated, and results obtained)

Mesoblast stated that all surfaces, except (b) (4), were assessed using (b) (4)

Mesoblast stated that (b) (4) reference organisms (Gram positive cocci, Gram negative bacilli, Gram positive bacilli spore former, mold, and yeast) were successfully challenged in 2009 Disinfectant Effectiveness Study. The subsequent studies were limited to predominant in-house isolates of different Gram type and morphology, mold, and yeast selected from clean room qualification and routine monitoring; they represent actual flora of the area where disinfectants are applied. The following in-house microorganisms were tested:

- (b) (4)

- (b) (4)

[REDACTED]

Per Mesoblast, all acceptance criteria were met.

**Reviewer Comment:** *This is acceptable. Mesoblast should provide a report for 2009 study where (b) (4) microorganisms were used. It was requested in IR#4, Q.6.*

- d. Please clarify how WFI supplied by LBSS water system is used in DP manufacture, facility or equipment cleaning, incubator/facility air humidification, etc.

(b) (4)

**Reviewer Comment:** *The response is acceptable.*

- e. Please clarify how clean steam, clean compressed air, and (b) (4) are used in DP manufacture. For (b) (4), please specify whether it is direct product contact (i.e. used for (b) (4) or similar) and describe any filtration of (b) (4) performed prior to use (i.e. in-line sterile filters or similar)

Mesoblast explained that (b) (4)

**Reviewer Comment:** *The response is acceptable.*

- f. Water system distribution and storage system diagram and qualification report, including but not limited to the description of testing procedures,

sampling locations, duration of sampling, acceptance criteria, results, and summary of deviations, if any, and requalification criteria.

WFI at LBSS originates at (b) (4)

[REDACTED]

. The system was qualified in

2012.

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

**Reviewer Comment:** *This response is acceptable. It appears that the WFI heater and cooler are swapped on the provided diagram.* (b) (5), (b) (7)(E)

**g. A description of routine monitoring programs for water and process gases, including frequency and type of testing performed.**

WFI. Storage tank (b) (4) and LBSS distribution and POU's are tested (b) (4) for (b) (4) and (b) (4) for (b) (4). WFI distribution (b) (4) are tested (b) (4) for (b) (4). WFI returns distribution (b) (4) point is tested for (b) (4) and for (b) (4). There is continuous (b) (4).

Clean steam is monitored (b) (4) for (b) (4).

Process gases (clean air and (b) (4) are tested for air viables (b) (4) the microbial impaction air/gas sampler with the (b) (4) for total particulates using (b) (4) is also release tested upon receipt, including (b) (4).

**Reviewer Comment:** *Acceptance criteria for WFI were included in the original submission. WFI and clean steam monitoring is acceptable. Acceptance criteria for (b) (4) release testing and routine monitoring were requested, as well as clarification of "assay" performed for release in IR#4, Q.7.*

**h. A tabulated list of all equipment used in DP manufacture, release testing, and storage at LBSS, with inventory numbers, description of its use, location (room number). Please indicate which equipment is considered critical and which is dedicated or shared (between different products or lots of the same product).**

At LBSS equipment is classified as either "direct impact" (i.e. expected to have impact on product quality) if any of the following applies:

- Direct product contact equipment
- Equipment has direct contact with an ingredient or material used directly in the process
- Cleaning/sterilization equipment
- Equipment preserves product status
- Equipment can affect product strength, identity, safety, purity, or quality

A system with indirect impact has no direct product contact but can cause variation to critical parameters used to produce the product. Lists of equipment used in DP

manufacture, media manufacture, release testing (at LBSS only), and storage were provided.

All equipment used for DP manufacture is shared between different products and lots except for the (b) (4) that is shared between different lots only.

The following equipment is classified as direct impact:

- (b) (4)

Indirect impact:

- (b) (4)

No impact:

- (b) (4)

**Reviewer Comment:** All requested information was provided. Response is acceptable. It was noted that although the (b) (4) hold (time from (b) (4) is (b) (4), there is no equipment listed that would provide temperature-controlled environment during fill/finish and visual inspection. PO was notified; any follow-up is deferred to PO.

i. For all critical equipment please provide

- Qualification reports, complete with description of testing performed, acceptance criteria, results, and summary of deviations, if any.
- Cleaning validation reports, where applicable

Mesoblast provided qualification reports for all direct impact equipment except scales, which are calibration only. Unless stated otherwise, the equipment was qualified in 2012.

Biologic Safety Cabinets. BSCs (b) (4) are installed in the (b) (4) are installed in (b) (4). For each BSC IQ included (b) (4)

. OQ included (b) (4)

**Reviewer Comment:** No data or test method description was provided for HEPA filter integrity, airflow velocity, or smoke tests. For static non-viable particulate test sampling location and sample volume were not provided. No PQ results were included. A description of dynamic conditions (number of personnel in BSC, equipment running, manipulations performed, etc.) was not included. See IR#4, Q.8a for the follow up.





**Reviewer Comment:** *The response appears acceptable. Mesoblast should provide results obtained in clean and dirty hold time validation, summary of cleaning procedure and storage conditions. Additional information was requested in IR#4, Q.11.*

16. Please provide the following information for ISP facility:

- a. SOPs covering bulk DP vial receipt, storage, packaging, and shipping to the final user

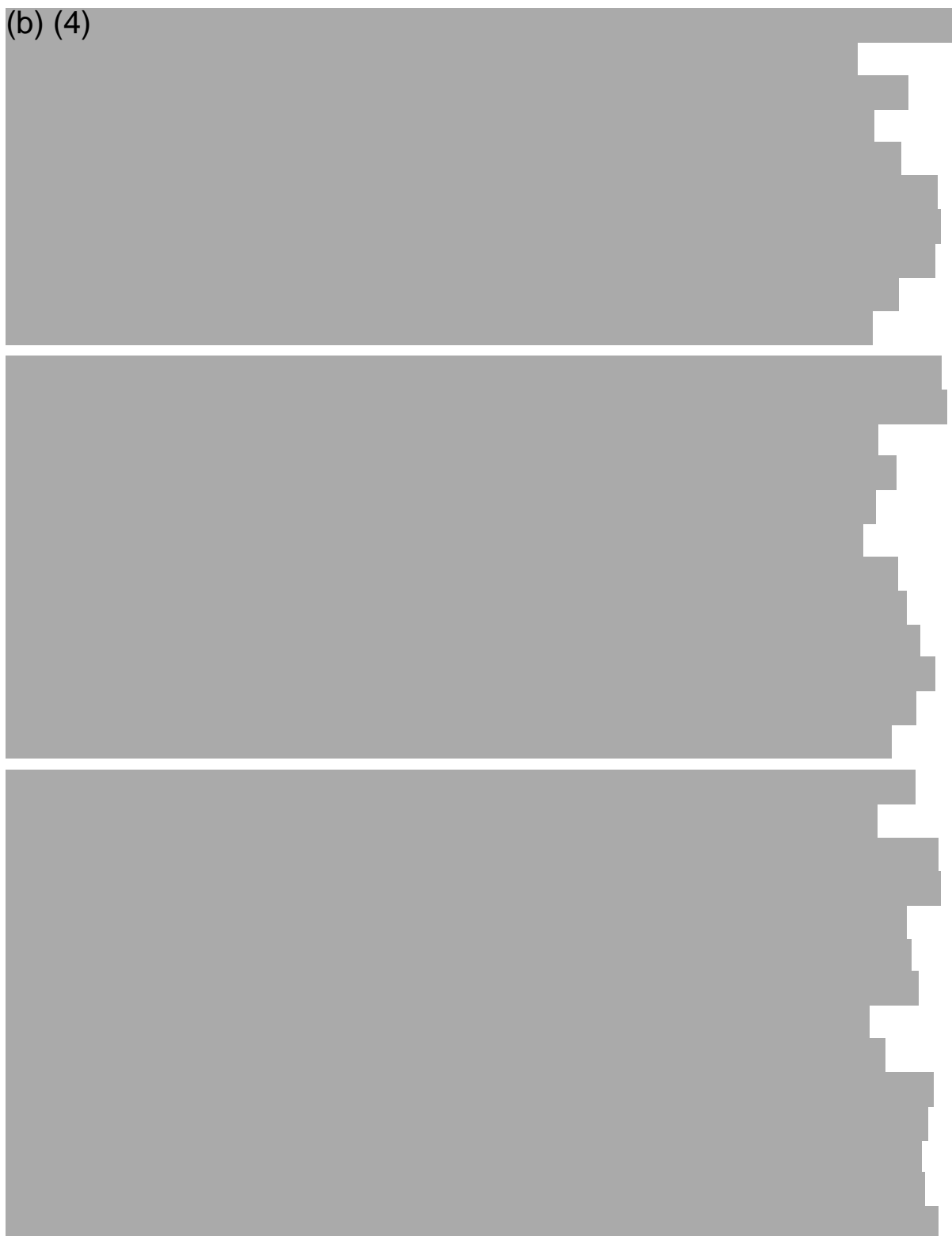
(b) (4)







(b) (4)



**Reviewer Comment:** *Not clear if all cryoboxes are removed from cryoshipper prior to visual inspection or boxes are removed and inspected individually (i.e. the first box is removed, inspected, and cryostored, then the second box is*

*removed, inspected, cryostored, etc). If unload in parts, how do they ensure storage conditions during the shipper unloading (closing the lid, running templates, etc). Additional information was requested in IR#4, Q.12.*

*SOP does not instruct to record (b) (4) information (temperature, time of loading/unloading). (b) (5), (b) (7)(E)*

- b. A list of all associated equipment, with inventory numbers, description of its use, location (room number). Please indicate which equipment is considered critical and which is dedicated or shared.

All equipment listed is critical, shared, located under (b) (4)

**Reviewer Comment:** *This response is acceptable.*

- c. For all critical equipment please provide qualification reports, complete with description of testing performed, acceptance criteria, results, and summary of deviations, if any.


(b) (4)

**Reviewer Comment:** *According to the SOPs included in response to Q.16a above, (b) (4) are used for holding and visual inspection of DP vials/cartons during receipt/packaging/packing, which would be performed with an (b) (4) were qualified based on a simulated use test performed on an (b) (4)*  
*Additional information was requested in IR#4, Q.13.*

(b) (4)



(b) (4)



**Reviewer Comment:** *The use of equipment cannot be approved unless qualification package is provided. A comment was sent to Mesoblast in IR#4, Q.15.*

**INFORMATION REQUEST #3.** The IR was sent to Mesoblast on 6/2/2020 and the response was received in the amendment STN125706/0.35 (eCTD seq 0035) on 6/24/2020. Response to Q.8 was submitted in the amendment STN125706/0.38 (eCTD seq 0038).

1. Please clarify the following regarding your final container closure integrity testing (CCIT) and CCIT method validation:

- a. (b) (4) Method results could be impacted by (b) (4) variation. Please clarify how many different lots of vials were used during method validation.

Mesoblast stated that (b) (4) DP lots filled into (b) (4) vial lots ((b) (4) were used for method validation. Rejection limit was statistically established using positive and negative controls (b) (4) vials each) from (b) (4) lots of vials and (b) (4) lots of drug product.

**Reviewer Comment: This response is acceptable.**

- b. Please describe how negative and positive control vials were prepared (filled, capped, etc.) and whether the fill volume range of control vials used to establish rejection limit is representative of the DP filled on (b) (4) filling line according to the established procedures. Alternatively, please provide supporting data demonstrating that variation in fill volume has no impact on test results.

Mesoblast stated that negative controls were filled using (b) (4) equipment, using the proposed commercial process for Remestemcel and same acceptance criteria/process parameters (target fill (b) (4)). Positive controls were prepared (b) (4) closed with the stopper, vial ring, and yellow cap. Mesoblast explained that the product fill volume recommendation for (b) (4)

**Reviewer Comment: The response is acceptable.**

- c. Please clarify the location of defects in positive control vials and whether defects were in direct contact with liquid inside the vials.

Mesoblast explained that vial defects are on the (b) (4) All (b) (4) defects were (b) (4)

**Reviewer Comment: This response is acceptable.**

- d. For type defects used in range determination studies, (b) (4) Please demonstrate that the method is capable of detecting (b) (4)

Based on the information provided in response to Q. 1c above, the nature of the method is such that any defect comes in contact (b) (4).

**Reviewer Comment: This is acceptable.**

- e. Your acceptance criterion in range studies was “the system must either abort the test or the (b) (4) should exceed (b) (4) rejection limit”. Please explain how aborting of the test by the system due to CCI failure can be distinguished from such outcome due to unrelated reasons. Please summarize your procedures for DP vial retesting and disposition if a test is aborted.

Mesoblast explained that if the test is aborted due to (b) (4) exceeding (b) (4) (maximum readout), the reason for test failure could be established based on (b) (4) showing on the printout. All failed vials are retested after performing a system check (testing of a negative control vial). An OOS investigation will be initiated and will include comparison of sample (b) (4) to those of master negative controls to determine any shifts of baseline that could be indicative of a false positive result.

**Reviewer Comment: This is acceptable.**

- f. Your method validation was performed with (b) (4) used as a surrogate of DP. Please provide supporting data demonstrating that presence of the cells does not impact the results.

Mesoblast explained that negative control vials used for establishing the cutoff (b) (4) level were filled with DP and hence contained cells; only positive controls were filled with a (b) (4). Though this was not tested directly, Mesoblast stated that cells in the final product (b) (4) are unlikely to affect the outcome of (b) (4) test due to the following:

- (b) (4)

**Reviewer Comment: This response is acceptable.**

- g. Please submit a list of deviation summaries, with investigations, CAPAs and outcomes associated with CCIT validation

Mesoblast stated that the only issue encountered during the method validation was one (b) (4) positive control vial and one negative control vial each having (b) (4). This was not considered a deviation, but rather not meeting system suitability requirements. The results were invalidated and replaced with a (b) (4) of respective vials, both of which met the system suitability requirements.

**Reviewer Comment: This is acceptable.**

- h. Your CCIT method is considered non-destructive and allows for 100% testing. Please clarify what samples will be tested by this method. Please

note that if the product tested by this method is intended for patient treatment (now or in the future) you will be required to demonstrate absence of negative impact of (b) (4) on product quality.

Mesoblast stated that samples tested by (b) (4) will not be distributed for human use or used for any other testing.

**Reviewer Comment: This is acceptable.**

- i. Please provide the equipment qualification report for (b) (4) or justify why those are not necessary.

Mesoblast explained that the (b) (4) is a model recommended by the vendor of (b) (4)

**Reviewer Comment: This is acceptable. Any potential (b) (4) buildup would increase (b) (4) reading and, therefore, creates a risk of a false positive (CCIT fail) result.**

- j. During DP filling (b) (4). Please demonstrate that your CCIT method is capable of detecting this CCI defect in the event that it is not properly sealed by the (b) (4).

Mesoblast stated that due to (b) (4)

which is a limitation of the method.

Mesoblast believes that this is acceptable due to the following reasons:

(b) (4)



**Reviewer Comment:** Given that every stopper (b) (4) during the filling process, Mesoblast should have validated (b) (4) using an alternative method capable of detecting potential stopper defects. Validation of (b) (4) sealing by the equipment vendor was not performed on the actual equipment used for filling of Remestemcel-L and therefore does not provide an assurance that DP vials can be adequately sealed by LBSS operators under the actual conditions of use.

During review of summary qualification reports of (b) (4) filling/sealing equipment, it was noted that (b) (4) lines were qualified using (b) (4) method, however, insufficient detail was included for evaluation. Additional information was requested in IR#4, Q.9e.

- k. You stated that “the approximate expected frequency of sample vials having (b) (4) results greater than (b) (4). Therefore, the estimated rejection limit was set at (b) (4). According to the provided results average (b) (4) value of negative control measurements was (b) (4). Please explain. Mesoblast stated that (b) (4) value was generated during the method development, whereas (b) (4) was based on the validation data. The validation was designed to confirm the rejection limit established during development; indeed, all negative controls were below, and all positive controls were above (b) (4).

**Reviewer Comment:** This is acceptable.

**2. Regarding your operator qualification for visual inspection:**

- a. Please confirm that the challenge set is filled in the container closure system identical to that used for Remestemcel-L.

Mesoblast confirmed that the challenge set was filled in 6.0 mL ready-to-fill closed vials (b) (4).

- b. Please provide your SOP for creation and maintenance of the defect kit used for training visual inspectors.

Qualification and management of visual inspection reference standards is covered by SOPs SGTS-16659 and SGTS-13937 (operator qualification; previously provided and reviewed in 3.2.P.5.2).

Reference standards are generated by a third party/client to contain (b) (4). Standards are stored at (b) (4). Qualification of standards prior to use in challenge sets is proceduralized (see review of section 3.2.P.5.2).

- c. You provided the following description of critical visual inspection defects: “container closure system defects or unusual type or increased frequency of visible particles, suggesting a system failure”. Please clarify if the

operators performing visual inspection are trained on rare defect types and how determination of an increased frequency is made.

The vials in the training and challenge set have a variety of defects (container/closure and particulate) that have been observed during DP visual inspection. The defect library is designed to provide (b) (4)

. If a new defect type is observed during the visual inspection, (b) (4)

Visual defects (defects and particle types) are trended (b) (4)

Any increases in frequency will be noted and could be used to modify the inspection training kit.

**Reviewer Comment Q.2a-c:** *The response is acceptable. However, creation of new standards based on defects observed in manufacture or replacement of standards (periodic or due to deterioration) are not proceduralized. Also, given that increase in defect frequency suggestive of system failure is based on (b) (4) trending data, it is not clear how the firm can respond in a timely manner if such failure does occur [i.e. if a frequency of a specific particle defect increases from (b) (4) the batch will still be released (provided acceptable AQL) as the limit for all particulate defects is set at (b) (4) (b) (5) (b) (7) (E)]*

3. You stated that each lot of final container vials and caps is visually inspected and identified by (b) (4). Please clarify the following:

a. The scope of the visual inspection (defects, dimensions, particulate etc.)

Mesoblast explained that 100% of vial packages are inspected upon receipt at LBSS (packaging and vials are (b) (4) QC

testing of the vials (see review of 3.2.P.7) also includes testing for (b) (4)

. Prior to use, vials are evaluated and are rejected if (b) (4)

b. Whether the (b) (4) of the vial body or the stopper or both is performed

Mesoblast explained that (b) (4)

c. What in house testing of caps is performed

Mesoblast stated that 100% of cap packages are visually inspected upon receipt

(b) (4) CofA is verified (b) (4)

but no in-house testing is conducted.

**Reviewer Comment Q.3a-c:** *The response is acceptable except for the lack of periodic in-house sterility testing of caps.* (b) (5), (b) (7)(E)

**4. Please clarify the following acronyms in your Facilities and Equipment Section:**

- a. (b) (4) room (floor plans)  
(b) (4) room
- b. (b) (4) wall panel system  
(b) (4) is the name of the company that provides the clean room modular wall panel systems.
- c. (b) (4) (AHU zoning diagram)  
(b) (4)

**Reviewer Comment Q.4a-c:** *The response is acceptable.*

**5. Please describe how the following areas of the LBSS facility are used:**

- a. (b) (4) room  
(b) (4) is an electrical power distribution room for LBSS facility.
- b. (b) (4)  
(b) (4) are used for non-GMP activities only (investigational, feasibility, pilot runs and technical training).
- c. (b) (4)  
(b) (4) room is used for access to (b) (4) only; no activities take place there. (b) (4) is used for thawing of materials at (b) (4) prior to use.

**Reviewer Comment Q.5a-c:** *The response is acceptable. Room (b) (4) qualification was provided in response to IR#4, Q.16.*

**6. Regarding your facility pass throughs, please provide the following:**

- a. A list of all facility pass throughs (with location, ID, classification and description of use, dedication, if any).

Mesoblast provided a list of (b) (4)

(b) (4)

**b. A clarification whether the pass throughs are active or passive.**

See response to Q.6a above.

**c. A representative qualification report, including description of testing performed, acceptance criteria and results. Please specify differences in qualifications of different passthroughs, if any.**

Mesoblast explained that based on the product quality impact risk assessment, all pass throughs at LBSS were classified as either “no impact” or “indirect impact” (systems that have no direct product contact but could cause variation of critical parameters used to produce the product).

For “no impact” pass throughs operational verification is performed (b) (4)

For “indirect impact” passthroughs IOQ included verification (b) (4)

A qualification summary report was included for (b) (4) (active pass through with (b) (4) for transfer of final product/QC samples from (b) (4) suite). OQ total particulate test consisted of (b) (4)

Results met the acceptance criteria.

**d. Qualification completion dates and summary of deviations/ investigations/ CAPAs associated with qualification of all pass throughs.**

Pass throughs were qualified in 2012 (date of PQ completion), except (b) (4) that were qualified in 2017. I reviewed the summarized deviations, and with the exception described below there were no deviations with potential impact on qualification validity.

During PQ of pass through (b) (4) were noted (August 10-17, 2012); they were attributed to (b) (4)

No further excursions were noted for this location after sampling resumed from Media Prep side (August 18-September 8, 2012). Additional excursion for surface viables of the same pass through on September 7, 2012 was attributed to daily movement of carts to Media Fill. CAPA (b) (4) 216712 was implemented for EM tracking and to (b) (4) to specific clean areas. No further excursions were noted during PQ or post-EMPQ sampling.

I cross-referenced the information about the pass throughs provided in response to this question to the routine sampling locations (EMPQ sampling locations with descriptions were not provided) in the response to Q.15b, STN 125706/0.28.

Sampling of pass throughs to unclassified areas is limited (b) (4)

**Reviewer Comment Q.6a-d: This is acceptable. Pass throughs were sampled during EMPQ (see response to IR#3, Q.7 below). There was an additional pass through (b) (4) for transfer of product (b) (4) included in the response to IR#2, Q.15b and IR#3, Q.7 below but not listed with the rest of the facility pass throughs. (b) (5), (b) (7)(E)**

7. Unless already provided in response to our IR of 5/1/2020, please provide EMPQ report, including but not limited to the following: duration, sampling location diagrams, descriptions of sampling type, duration, and volume (where applicable). For dynamic sampling please specify type of operations performed and number of personnel present.

Mesoblast explained that EMPQ at LBSS was included in PQ of AHUs and included (b) (4) of dynamic monitoring for air viable and non-viable, and surface viable. PQ summary reports were provided in STN 125706/0.28 (in response to IR of 5/1/2020). The following additional information was provided:

*Identification of sampling location for HVAC qualification activities* was based on HVAC validation plan. The minimum number of air samples was determined per (b) (4)

(b) (4)

**Reviewer Comment:** Given that the Clean Corridor is a (b) (4) shaped Class (b) (4) it appears acceptable to not define maximum occupancy for this area, provided the typical use was challenged during EMPQ. However, maximum occupancy should have been determined for all other classified areas. (b) (5), (b) (7)(E)

Remaining EMPQ issues, including manufacturing activities during EMPQ were followed up in IR#5, Q.5.

8. Please explain the following regarding your floor plans and provide the updated diagrams, if applicable:

a. Flow of Donor Cell Banks into the facility was not shown

DCBs arrive via the (b) (4)

b. Please clarify if your storage areas room classification are CNC or not-controlled



3 pages determined to be not releasable: (b)(4),(b)(5),(b)(7)(E)



(b) (4)

(b) (4)

10. It was stated in the LBSS MF that (b) (4) is used as a (b) (4). Please confirm that this is not applicable to Remestemcel-L process. (b) (4) is used for a different Lonza customer's process in the facility, not for Remestemcel-L.

**Reviewer Comment: This is acceptable.**

11. Personnel exits and enters the facility through the same sequential rooms:

(b) (4)

(b) (4). Please describe engineering and procedural controls to ensure the personnel entering and exiting paths do not cross. Mesoblast explained that the (b) (4)

(b) (4)

**Reviewer Comment:** Controls appear acceptable from the cross-contamination perspective given the products in the facility (allogeneic cell therapies) as long as no products are processed at risk, prior to donor material testing results are available. (b) (5), (b) (7)(E)

12. Waste room is also called Waste Autoclave room in LBSS MF. Please clarify if any waste is autoclaved and also specify differences in liquid vs. solid biohazardous waste handling, if any.



Mesoblast clarified that waste is (b) (4)

**Reviewer Comment:** This response is acceptable.


13. Please provide the description of your HVAC system including a diagram showing the equipment, duct work, and instrumentation of your HVAC system for our review to understand the use of the systems air flows, recirculation, and exhaust in your contamination and cross contamination controls. Please make sure you include the following information:
- Air pre-treatment (pre-filtration, etc) for each of the AHUs in the facility
  - Exhaust location relative to intake and exhaust treatment, if any
  - For AHUs providing recirculated air, please specify whether the source of recirculated air is limited to each respective AHU's serving area

Mesoblast explained that the HVAC system consists of (b) (4)

(b) (4)




**Reviewer Comment:** *This is acceptable. Given that the diagram of exhaust and intake locations is not to scale, (b) (5), (b) (7)(E)*



14. Unless included in your response to our IR of May 1, 2020 please provide a description of routine monitoring program for source and pre-treated water, including sampling frequency, procedure, and acceptance criteria.

Mesoblast explained that routine monitoring program for the source and pre-treated water includes microbial and chemical tests per (b) (4)



Specifically, (b) (4)





Results are trended and results exceeding alert levels are investigated.

**Reviewer Comment:** *This response is acceptable.*

15. Qualification of clean steam generator and distribution system, including but not limited to the description of testing procedures, sampling locations, duration of sampling, acceptance criteria, results, and summary of deviations, if any, and requalification criteria.

Mesoblast explained that clean steam (CS) is generated by (b) (4)



**Reviewer Comment:** *This response is acceptable.*

16. Please clarify whether Instrument Air (IA) is the same utility as Clean Compressed Air (CCA) and if they have the same distribution system, routine monitoring, and acceptance criteria.

Mesoblast explained that the source of CCA and IA (b) (4)



(b) (4)

**Reviewer Comment: This is acceptable.**

17. We notice that you included (b) (4) different types of sealers (b) (4) and (b) (4) different tube welders (b) (4) in your equipment list. Please provide the following information:

a. Qualification reports for welders and sealers, complete with procedure descriptions, acceptance criteria, results, and deviation summaries (unless included in the response to our May 1, 2020 information request)

There are (b) (4)

IOQ summary reports were provided for all equipment. Qualification of all equipment was completed by September 2018.

The following tubing types are used in the Remestemcel process:

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**Reviewer Comment: Qualification of sealers and welders is incomplete. For example, (b) (4) was qualified using (b) (4)**

***None of (b) (4) sealers or welders were qualified to seal (b) (4) tubing. Due to the limited information provided, it is not clear whether all welders/sealers were qualified for use with all required tubing sizes/types and types of seals (b) (4) or whether pressure test was included in all qualifications. (b) (5), (b) (7)(E)***

- b. An explanation when each type of the sealer/welder is used

Mesoblast stated that (b) (4)

**Reviewer Comment:** *It is not entirely clear, how this relates to the list of tubing above, reproduced from (b) (4) sealer qualification reports, particularly which tubing types are being welded by each type of welder (see also comment to IR#3, Q.17a above). (b) (5), (b) (7)(E)*

- c. What types of welders were used during (b) (4) Please provide inventory numbers, if you use more than one of each type for Remestemcel-L

All except (b) (4) welders were used in at least (b) (4) runs. (b) (4)

(b) (4) was used in the first (b) (4) run only. (b) (4)

(b) (4) were not used during (b) (4).

**Reviewer Comment:** *This is acceptable. Most welders were challenged during successful (b) (4). Remaining ones were qualified identically to those used in (b) (4)*

- d. Please explain if you allow tubing reuse for welding

During welding, (b) (4)

**Reviewer Comment:** *This is acceptable.*

- e. A list of any tubing weld/seal deviations and associated CAPAs

A list of 8 deviations (08/06/2014-03/21/2020) due to bad welds or leaks was provided. Deviations were associated with (b) (4) welders (4) or radio frequency (b) (4) sealers (4). Bad welds were largely due to misaligned clamps; CAPAs included equipment repair/maintenance, updating SOP and operator retraining. Where a leak size was too small to be detected by the (b) (4) was (b) (4) and not used in the downstream process, without any additional preventive actions.

CAPAs for leaks due to poor seals included SOP updates and operator retraining, and, on one occasion, equipment repair.

**Reviewer Comment:** *This response is acceptable.* (b) (5), (b) (7)(E)

18. Unless already included in your response to our May 1, 2020 information request, please provide qualification reports (complete with procedure descriptions, acceptance criteria, results, and deviation summaries) for the following equipment:

- a. (b) (4)
- b. Product pumps and any other pumps used during (b) (4)
- c. Freezers and refrigerators (including walk-ins, if applicable) used for storage of (b) (4)

Qualification summary reports for the following equipment were provided in response to 5/1/2020 IR (STN 125706/0.28): (b) (4)

See respective review for any follow-up.

Qualification of the additional equipment is summarized below.

(b) (4)



(b) (4)

**Reviewer Comment: Insufficient data was provided for the evaluation. Specifically, for (b) (4) no PQ results were provided. For temperature-controlled equipment, diagrams/descriptions of thermocouple locations during temperature mapping (OQ or PQ) were not included, as well as (in most cases) the results of such mapping. (b) (5), (b) (7)(E)**

**19. Regarding your computerized systems:**

- a. It appears that your LIMS and (b) (4) systems are redundant please clarify the use of each system.

LIMS system is used for sample workflow, including raw material, in-process, DS/DP samples. Authorized sample result report from LIMS is used for CofA generation.

(b) (4) consists of (b) (4) modules, (b) (4)

- b. Please provide a brief description of your change control and back-up procedures (including back-up storage location) for all computerized systems

All computerized systems have automated and validated (b) (4) database backup with backup locations in either (b) (4)

Change control is managed via either Change Management for Corporate IT Computer Systems (global systems) or via local Computerized System Change Control Procedure (Singapore systems). Both procedures are aligned with industry GAMP practices and Lonza global change control standards and have the following workflow: change proposal, change impact assessment, pre-execution approval by system/process owner and QA, implementation, post-change verification of change, documentation, executed test scripts, protocols, task completion; post-change approval by system owner and QA; release for GMP use.

**Reviewer Comment: This response is acceptable.**

**20. We noted that several additional pieces of equipment were listed for Remestemcel-L in DMF (b) (4) but not in the BLA. This includes media production equipment, (b) (4) etc.**

- Please provide a separate list of all equipment used for media production only, including IDs, locations, and description of use.
- Please verify and confirm that the equipment list submitted in response to our IR dated May 1, 2020 is complete

Mesoblast provided a list of equipment used for Remestemsel media manufacture (not previously provided), where major equipment includes (b) (4)

(b) (4) (qualification of this equipment was included in STN125706/0.28).

Additionally, an updated list of equipment used in DP manufacture was provided. Equipment not used for Remestemcel was removed and (b) (4) cryoshipper was renamed to Cryoshipper (b) (4)

**Reviewer Comment: This is acceptable.**

**21. Please clarify the following regarding your segregation, clearance and changeover procedures:**

- a. You stated that (b) (4) can be processed in the same room at the same time. Please explain if you allow different lots of the same product processed in the same room at the same time and summarize associated segregation/lot clearance/changeover procedures, if applicable. This information was provided and reviewed under Q.7c response in STN125706/0.28.

- b. You allow (b) (4) in the same room at the same time. Please explain associated spatial segregation procedures, if any (e.g. use of different (b) (4), etc.)

This information was provided and reviewed under Q.7c response in STN125706/0.28. Mesoblast further clarified that (b) (4)

- c. You stated that (b) (4)

Please define “open workstation” and “production line”. Provide photographs if needed for clarity.

An open workstation is (b) (4)

A production line is (b) (4)

. Further information was provided and reviewed under Q.7c response in STN125706/0.28.

- d. Please provide a comparison of your lot clearance and changeover (product clearance) procedures. Please clarify which procedure is performed for the Filling room between different lots of the same product and between different products.

This information was provided and reviewed under Q.7c response in STN125706/0.28. Lot clearance and product clearance procedures apply to both Suite (b) (4) and Final Fill.

**Reviewer Comment: This response is acceptable.**

- 22. Please clarify differences between different aseptic qualification requirements (Basic Operator Aseptic Process Simulation, Advanced Cell Therapy Operator Aseptic Process Simulation, and Aseptic Technique in the Cell Therapy Manufacturing Areas) and explain your requalification procedures for your operators.**

Mesoblast provided a summary of various aseptic qualifications, with description and requalification requirements. It includes:

- (b) (4)

(b) (4)

**Reviewer Comment: This response is acceptable.**

**23. Regarding the gowning:**

- a. Per MF(b) (4), gowning requirements for entry into the facility include (in chronological order): (b) (4)

**Given that scrubs are not mentioned please explain if you allow street clothes in the facility.**

Mesoblast stated that street clothes are not allowed in the facility. They are removed in Male Lockers (Room (b) (4)), Female Lockers (Room (b) (4)) or Visitor Gowning (Room (b) (4)).

Personnel are gowned in (b) (4)


**Reviewer Comment: This is acceptable.**

- b. Please provide a brief description of your degowning procedures, with locations.

Per Mesoblast, degowning procedures for Production suite (b) (4) are as follows:

- (b) (4)

(b) (4)




**Reviewer Comment: This is acceptable.**

24. Please provide your (b) (4) distribution system qualification report, complete with the diagram of the system, sampling/testing descriptions, acceptance criteria, results, and deviation summaries.

According to the information provided by Mesoblast, (b) (4) at LBSS is supplied from a

(b) (4)



(b) (4)

**Reviewer Comment:** Distribution system was not qualified for (b) (4). This is acceptable as the product is cultured in (b) (4) system cell factories with validated (b) (4). Mesoblast stated that distribution system delivers (b) (4) but no supporting data was provided. (b) (5), (b) (7)(E)

**INFORMATION REQUEST #4.** This information request was sent as a follow-up to the teleconference on June 18, 2020. The response to Q.1 was received on 6/29/2020 (STN 125706/0.36, Q.1). The rest of the response was received on 7/14/2020 in STN 125706/0.42.

1. In your response to the IR received on June 4 (eCTD seq 028, Q.10a) you included a table with a side by side comparison of your manufacturing process steps and how they were simulated during APV. The table was limited to the steps where the simulation differed from the production process. Please expand this table to include all process steps and resubmit for our review. Please include all interventions performed (e.g. personnel crossing over to another side of the production suite during capacity limits simulation). Additionally, please confirm the following:
  - That all product/media contact surfaces (e.g. media (b) (4)) used in your process were challenged during APV
  - That all in-process solutions were replaced with (b) (4) (i.e. (b) (4) rather than “trypsin” mentioned in the side-by-side comparison table was used)

Mesoblast provided a side by side comparison of APS to manufacturing process for all process steps and interventions. A summary of non-routine (corrective) interventions was also included. APS simulated personnel cross over from

1 page determined to be not releasable: (b)(4)

- (b) (4)

**Reviewer Comment:** APS design is acceptable. Results have been reviewed in the primary memo for this BLA and were found acceptable. There was no maximum personnel limit established for Grade (b) (4) areas during EMPQ and therefore the worst-case limit was not challenged during APS. (b) (5), (b) (7)(E)

2. Please provide studies to demonstrate that your shipping and storage of the sterility samples from your Singapore manufacturing site to the (b) (4) testing sites does not alter the accuracy of your sterility test results.

Mesoblast stated that the following samples are shipped from Singapore to (b) (4) for sterility testing:

- (b) (4)

The firm referred to the previously reviewed shipping study SGTS-16366 (2015) to support shipping temperature of these samples at (b) (4) for the duration of transit. They stated that samples are currently packed and shipped using the same procedure.

Mesoblast will perform a study to address the Q.2 and will provide the final report by 9/18/2020. Per the provided protocol, a sample of each (b) (4)

Additional protocol was provided for a study to address Q.2 for DP sterility samples. (b) (4)



(b) (4)

**Reviewer Comment:** *Shipping study SGTS-16366 (2015) did not validate temperature conditions in transit (no worst temperature challenge, a single temp recorder, load is not representative – see more in Q.9 below).*

*The proposed study design appears acceptable. However, the study report has not been yet received at the time of this memo.* (b) (5), (b) (7)(E)

3. During our teleconference on June 18, 2020 you stated that shipping of DP release samples from LBSS to (b) (4) was validated because it is covered by the shipping validation of such samples from LBSS to (b) (4)

Please provide data demonstrating that shipping duration to (b) (4) does not exceed that to (b) (4)

Mesoblast stated that shipping studies MR-084 (Singapore to (b) (4) and MR-109 (Singapore to (b) (4) with maximum shipping duration of (b) (4) will cover shipping of samples from Singapore to (b) (4) because packing and shipping process are the same and shipping duration is similar.

Shipping data was provided for March-May 2019 (b) (4) shipments to (b) (4). All shipments were (b) (4).

**Reviewer Comment:** *The response is acceptable.*

4. During our teleconference on June 18, 2020 you stated that some DP release samples are cryoshipped from LBSS to (b) (4) where they can be stored until they are shipped on (b) (4) for testing. You only provided a shipping validation for LBSS to (b) (4)

Please provide a validation for shipping of DP release samples to the final testing destination and a summary of sample handling procedures (e.g. receipt, storage, packaging, shipping, etc) of your release samples at (b) (4)

Shipping validation on (b) (4) from (b) (4) to other (b) (4) sites, including one in (b) (4) was provided (2014-2015). Shipments were performed using (b) (4) container (b) (4)



5. For all in-process and DP release sterility samples shipped from Singapore to (b) (4) for testing, please specify the maximum allowed sample storage time and storage conditions prior to shipping from LBSS, at the final site prior to testing, and at any intermediate transit sites, such as (b) (4)

Mesoblast explained that maximum allowed storage time is not specified. Based on the shipping data from (b) (4)

**Reviewer Comment:** *The response is acceptable. Storage and shipping/handling conditions will be tested in microbial recovery study proposed in response to IR#4, Q.2 (see above).*

6. Please confirm that you will continue monitoring in-transit temperature for all of your future DP and in-process/DP release samples and specify the temperature monitor location for all loads/temperature conditions.

LBSS confirmed that all future shipments of DP, in-process and DP release samples from LBSS will be monitored, per their SOP. (b) (4)

**Reviewer Comment:** *This response is acceptable.*

7. You indicated during our teleconference on June 18, 2020 that in-process solutions used in DP manufacture are shipped from Singapore to (b) (4) for release sterility testing. Please provide a list of all raw materials, including any compounded media, that are subject to such shipping/testing. For each reagent please specify what it is used for and their respective storage and shipping conditions (duration and temperature). Please include maximum allowed storage time prior to shipping.

Mesoblast explained that maximum allowed storage time was not specified for any compounded media or raw materials.

(b) (4)

- (b) (4)

**Reviewer Comment:** *The response is acceptable. Storage and shipping/handling conditions of the media/reagents will be tested in microbial recovery study proposed in response to IR#4, Q.2 (see above).*

8. Regarding your sample shipping validation from LBSS to (b) (4) Note 2 at the bottom of Tables 3-5 stated that information regarding data/time the temperature monitor was stopped, documented in SGTS-20647 was incorrect. In all cases a longer shipping time was used instead. Please explain.

Mesoblast explained that the footnote refers to the adjustment of the incorrect calculation of shipping duration accounting for the time difference of (b) (4) between Singapore (b) (4) used by temperature monitors, which should have been added, but was subtracted instead.

**Reviewer Comment:** *This response is acceptable.*

9. Regarding your sample shipping validation from LBSS to (b) (4) /LWI (b) (4) please provide the following:

- A description of your typical load and its packaging
- A photograph of the shipping container used
- A description of any differences in the amounts of insulation and cold packs/blue ice used for different load and container size combinations.

Per Mesoblast a typical load from LBSS to (b) (4) /LWI consists of in-process and reagents samples or media.

In-process and reagent samples below are packed into a (b) (4)

- (b) (4)

- (b) (4)

**Reviewer Comment:** *Loads used in the shipping validation (see IR#2, Q.12b) to (b) (4) are representative of media samples only: (b) (4) in-process samples. Based on packaging details described above, I agree that (b) (4) shipper is the worst case. Additional issues regarding this shipping validation remain (no temperature loggers on the outside of the maximum load, (b) (4) shipping conditions not challenged). Shipping should be revalidated. I recommend this made a CR item.*

**INFORMATION REQUEST #5.** The IR was sent to Mesoblast on 6/30/2020 and the response was received in the amendment STN125706/0.46 (eCTD seq 0046) on 7/27/2020.

1. You stated in the original submission (Table 3, p. 4 of mr-097-supp-report-dcb-process-osiris-lwi-v2) that (b) (4), (b) (6) were rejected due to turbidity (sterility failures) observed at DP (b) (4) stage. In your response to our IR (STN 125706/0.28, Q.1c) you stated that no DP lots were initiated using the DCB lots mentioned above. Please explain.

Mesoblast stated that (b) (4), (b) (6)

\_\_\_\_\_ were rejected and not used in DP manufacture or to support process characterization and limit evaluation.

**Reviewer Comment:** *The response is acceptable. Concern about (b) (4), (b) (6) is due to their similarity to lots (b) (4), (b) (6) planned for use in commercial manufacture:*

- *All DCB lots above were manufactured as part of PPQ VAL-094 that had numerous sterility failures attributed to (b) (4)*
- *Both sets of DCBs had a sister lot that failed sterility release testing.*
- *(b) (4) manufactured on-site lot (b) (4) was shared between all DCB lots above; lot (b) (4), (b) (6) was shared between DCB (b) (4) made from BMA lot (b) (4), (b) (6)*
- *Same (b) (4) were used in manufacture of all (b) (4) lots.*

*The following information supports use of (b) (4), (b) (6) :*

- *Individual media (b) (4) were never shared between (b) (4)*
  - *Of the (b) (4) DP lots initiated using (b) (4), (b) (6) sterility specifications and were released. One lot was rejected prior to sterility testing.*
  - *(b) (4), (b) (6) was used for manufacture of (b) (4) DP lots at LWI and LBSS in 2009-2020. Two lots were rejected for reasons unrelated to sterility testing. All others were released.*
- It is acceptable to use lots (b) (4), (b) (6) lots in commercial manufacture.*

2. In your response to Q.3a (STN 125706/0.28) you intended to provide original Osiris specification for the DCB container and (b) (4). Please note that both submitted files were for the (b) (4) specification. Please provide the missing specification for DCB container, including dimensions of the container.

Mesoblast stated that DCB container has dimensions of (b) (4). A copy of the original Osiris specification was also provided.

(b) (4) Container, (b) (4), w/ Label Pocket, (b) (4), nonpyrogenic, was manufactured (b) (4) and distributed by (b) (4)

Supplier specification (per CofA) included (b) (4), and endotoxin (NMT (b) (4)) were visually inspected upon receipt for damage to (b) (4) and for appearance ((b) (4))

Container expiration date was set to (b) (4) years from receipt or per CofA, whichever comes first".

**Reviewer Comment: This response is acceptable.**

3. In response to our Q. 11 (STN 125706/0.28) you stated that based on you manufacturing experience (use of (b) (4) for different products and at different facilities), different lots of (b) (4) demonstrated similar performance. Please provide a list of cell factory (b) (4) lots used for each of the products/facilities.

Mesoblast provided a table with lot numbers of (b) (4) used in manufacture of DCBs ((b) (4)), product number (b) (4) lots), DP at LWI ((b) (4)), product number (b) (4) lots, including (b) (4) not used in DCB manufacture), and DP at LBSS (b) (4), product number (b) (4) additional lots).

**Reviewer Comment:** *This response is acceptable. Mesoblast has previously addressed the part number discrepancy (see IR#2, Q.11).*

4. Based on the information provided in response to Q.14 (STN 125706/0.28) it appears that (b) (4) will supply qualified cryoshippers of a specific model at random for DP shipment.
- a. Given that particular shippers used for future DP transport might not be covered by the provided qualification report, please provide a brief description (and acceptance criteria) of qualification activities performed by (b) (4) on all shippers prior to use in addition to liquid nitrogen capacity, evaporation rate, and dynamic hold time, if any. Please clarify the conditions that the dynamic hold time is determined under.

Mesoblast explained that in addition to the initial shipper qualification upon receipt (Q.14c, STN 125706/0.28), (b) (4) shipper inspected, serviced (inspected and cleaned), and released prior to each shipment. Units are inspected for (b) (4)

Dynamic hold time is calculated based (b) (4)

**Reviewer Comment:** *This response is acceptable.*

- b. Please clarify if any cleaning procedures are performed between uses of the (b) (4) cryoshippers.

Per Mesoblast, (b) (4) uses its proprietary and validated cleaning process, (b) (4)

(b) (4)

**Reviewer Comment:** *Provided cleaning description is high level. However, this is acceptable as risk of cross-contamination is low due to the following:*

- *Remestecel-L DP transported in the dewars is filled into integral vials packaged into secondary containers (either cryobox or DP carton). Dewars are not direct product-contact equipment.*
- *Low risk of spills of other products as they would be solid during transport at cryo temperatures.*

**5. Regarding your HVAC qualification:**






- a. It appears that there were modifications of (b) (4) as you provided respective EMPQs dated 2019. Please provide a description of the changes, date when they were implemented and EMPQ to support manufacture/filling of PPQ lots.

Mesoblast explained that the following modifications were performed to (b) (4)


- (b) (4)



(b) (4)




**Reviewer Comment:** *The following information was not included in the qualification reports: description of testing and results of room air change and HEPA integrity tests, diagrams of sampling locations (see response to IR#5, Q.5b below regarding sampling locations). It is not clear whether activities during PQ were representative of the worst case.* (b) (5), (b) (7)(E)




- b. Please provide diagrams showing EMPQ sampling locations and a rationale (e.g. risk assessment) for selection of testing locations for PQ.

Mesoblast provided information regarding identification of sampling locations for qualification activities for (b) (4) only.


(b) (4)



(b) (4)



**Reviewer Comment:** *The response is acceptable. However, sampling diagrams in support of Production suite <sup>(b) (4)</sup> and other shared areas (i.e. Kitting room) were not provided. (b) (5), (b) (7)(E)*



- c. It appears that no manufacturing activities were performed during PQ of (b) (4). Customer training runs were performed during PQ of (b) (4)
- 





- Please explain what manufacturing operations/equipment were included in customer training runs/engineering runs and specify any differences from PPQ and routine media manufacture.
- Please clarify how you ensure the AHUs can maintain room classification under the worst-case challenge (maximum number of operations/equipment running simultaneously).

Mesoblast stated that (b) (4)




(b) (4)

(b) (4)








**Reviewer Comment:** *The response is acceptable. It appears that sampling was reduced for routine EM, at least for (b) (4), for which EMPQ sampling diagram was provided. (b) (5), (b) (7)(E)*



6. Please provide 2009 disinfectant effectiveness study where (b) (4) reference organisms were used.

(b) (4)



(b) (4)

**Reviewer Comment:** *The response is acceptable. All disinfectants are used with contact time of (b) (4). However, (b) (4) surface (walls) was not included in the provided study. Evaluation of this surface in SGTS-19905 study (see primary review memo) was limited to (b) (4)*

*In all cases only in-house isolates were used*

(b)  
(5)  
(b)  
(7)  
(E)

(b) (4)

**Reviewer Comment:** *The response is acceptable.*



1 page determined to be not releasable: (b)(4)

- (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

**Reviewer Comment: The response is acceptable.**

- e. (b) (4) controlled rate freezers: Empty chamber mapping design was not clear as it involved use of (b) (4) vials. Thermocouple placement in the load and chamber was not provided for both OQ and PQ. Actual results were not included. No details (description of the study or results) were provided regarding the additional performance verification run.

(b) (4)

[REDACTED]

[REDACTED]





(b) (4), (b) (5), (b) (7)(E)

9. The following additional issues were identified during review of the equipment qualification reports submitted to STN125706/0.28:

(b) (4)



(b) (4), (b) (5), (b) (7)(E)

10. Please describe the use of items sterilized by (b) (4) (production load items and the (b) (4) ).

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

**Reviewer Comment: This response is acceptable.**

**11. Please provide the following regarding the manual cleaning validation of miscellaneous parts:**

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

- (b) (4), (b) (5), (b) (7)(E)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**Reviewer Comment: This response is acceptable.**

12. Regarding the receiving work instruction at ICS facility, please clarify whether all cryoboxes are removed from cryoshipper prior to visual inspection or boxes are removed and inspected individually (i.e. the first box is removed, inspected, and cryostored, then the second box is removed, inspected, cryostored, etc). If boxes are unloaded, inspected, and stored one by one, please clarify how you ensure storage conditions for the boxes remaining in the shipper during the unloading.

See response to Q.13 below.

13. According to the SOPs included in response to Q.16a (STN125706/0.28), (b) (4) are used for holding and visual inspection of DP vials/cartons during receipt/packaging/packing, which would be performed with an (b) (4) [REDACTED] Please justify qualifying (b) (4) based on a simulated use test performed on an empty chamber with the (b) (4) [REDACTED]

Mesoblast explained that (b) (4) [REDACTED]

[REDACTED]

**Reviewer Comment:** *The response appears acceptable. However, provided work instructions are in draft. They do not specify the limit on number of cryoboxes that can be held in the (b) (4) at any given time or instruct to monitor temperature during use.* (b) (5), (b) (7)(E)

14. The empty chamber mapping of (b) (4) ) was limited to (b) (4) other. (b) (4) temperature mapping was limited to (b) (4) . Please provide the following:

- a. A narrative and an overall diagram of the equipment showing how cryoracks/boxes are retrieved from the tank and “delivered” to the operator.

Mesoblast explained that the (b) (4)

1 page determined to be not releasable: (b)(4)



(b) (4)

- b. Please explain temperature controls in place, if any, to ensure the temperature of the product in the cryobox remains acceptable during retrieval until “delivery” to the operator or to the (b) (4).

Mesoblast explained The (b) (4)

- c. Please provide data showing how long it takes for the (b) (4)

Mesoblast explained that retrieval consists of the following steps: (b) (4)

(b) (4)

- d. A diagram of the (b) (4) showing the (b) (4) and the placement of the (b) (4)

Per the diagram provided by Mesoblast, (b) (4)

(b) (4)

**Reviewer Comment:** *The response is acceptable.*

15. (b) (4) and serialization equipment at ICS facility are not qualified for its intended use. Please note that all equipment submitted for use in licensed manufacturing should be fully qualified and equipment not qualified for use may prevent approval.

Mesoblast stated that execution of OQ/PQ specific to Mesoblast cartons and serialization process was planned for August 3, 2020 and the final report would be provided by August 31, 2020.

(b) (4) qualification reports were included. IOQ included verification of documentation, installation, and calibration. (b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]

**Reviewer Comment:** *Given that the storage temperature of the product was not exceeded during PQ, the results are acceptable. Proposed additional controls are inadequate. Specifically, hot spot determined during PQ is in the (b) (4), therefore operators cannot rely on (b) (4) thermometer measurements during packaging operations as its sensor is placed on the side of the cart. (b) (5), (b) (7)(E).*

16. You stated that media for use in Remestemcel-L process is (b) (4)

[REDACTED] Please provide qualification of the equipment/room.

Mesoblast provided executed IOPQ protocols for both rooms.

(b) (4)

[REDACTED]

(b) (4) [Redacted]

[Redacted]

I [Redacted]

I [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

acceptance criteria.

**Reviewer Comment: This response is acceptable.**

**REVIEW OF AMENDMENTS TO THE MASTER FILE**

LBSS unsolicited amendment to the cross-referenced MF (b) (4) (amendment 4) and the amendment MF (b) (4) containing a related response to CBER information request are reviewed further below.

CBER comments are in bold, followed by the sponsor's response in plain lettering.

I reviewed Module 3.2.A.1 of the amendment MF (b) (4) received by CBER on 07/06/2020. According to the associated cover letter, the document contained updates of the MF, such as additional details, amended descriptions and narratives, tables, floor plans, SOP list, and new validation summary reports related to a broad spectrum of facility, equipment, and utility related issues. Pages 13 to 60 were updated.

***Reviewer Comment: It was noted during the review, that the MF was updated with the information already submitted to the LA 125706 in response to CBER information requests. Also, the total number of pages increased from 742 (most recent MF update received on 1/14/2020 in the amendment MF (b) (4) to 1401 pages. A clarification was requested in IR#1, Q.1.***

This information request was sent to LBSS on 7/21/2020. The response was received on 7/22/2020 in MF (b) (4)

- 1. We noticed that you updated the facility information Section 3.2.A.1 in your most recent MF (b) (4) amendment (eCTD 0005) received on 7/6/2020. The updates to the section listed in the cover letter are for pages 13-60. However, the total number of pages in the document increased from 742 (eCTD 0004) to 1401. Please submit a complete summary of updates. Please indicate for each update, whether it is relevant to Remestemcel and if the information has already been submitted to the BLA 125706/0 for this product.**

LBSS confirmed that the update was performed as a part of periodic MF review and to provide additional documents which were also submitted in response to FDA information requests for BLA 125706, though the updates are not necessarily specific to Remestemcel. The pages after page 60 consist of attachments that have, which were summarized in a table. References to IRs were provided.

**Reviewer Comment: The response is acceptable. All new information has been reviewed in the amendments to BLA 125706.**