

**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	Module 3 of rolling submission
03/17/2020	125706/0.13	IR: Cold chain and sterility assurance of DCB manufacture

**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 Walkersville, Inc	3.2.A.1 Facilities and Equipment	Yes	No MF review is required. The facility was deemed to be cell bank manufacturer.
DMF(b) (4)	Lonza Bioscience Singapore Pte. Ltd.	3.2.A.1 Facilities and Equipment	Yes	MF was reviewed and review was documented in Facilities and Equipment section below
DMF(b) (4)	Mesoblast	None	No	No IND review is required. All pertinent information was included in the BLA
IND7939	Mesoblast	None	No	No IND review is required. All pertinent information was included in the BLA

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

The product was originally developed by Osiris Therapeutics under IND7939. In 2013 Mesoblast acquired MSC business of Osiris Therapeutics, including the sponsorship of the IND and the ownership of the donor cell bank (from bone marrow aspirate) lots manufactured for Osiris by Lonza Walkersville, Inc (LWI) in 2008-2009. Since acquisition Mesoblast implemented a range of manufacturing changes including Drug Product (DP) process transfer from LWI to Lonza Bioscience Singapore (LBSS) in 2014.

Mesoblast intends to use Osiris donor cell banks (DCBs) for commercial manufacture. DCBs have not been manufactured since 2009 and Mesoblast intends to resume manufacture post-approval (b) (4). Per OCBQ management decision DCB manufacture was deemed manufacture of cell banks. As such, facility information for DCB manufacturer, LWI, was not reviewed. The scope of the DCB review was limited to sterility assurance and cold chain records (DCBs are cryopreserved), which were requested, and which review is documented in this memo.

Facility and equipment information provided in the original submission was limited to a high-level overview and facility floor plans, i.e. no HVAC, manufacturing equipment, or

utility qualification reports, and no information about routine monitoring programs (environmental monitoring or utilities) was provided. For DP manufacturing facility, LBSS, some information required for assessment was available in cross-referenced DMF (b) (4). Its review is documented under 3.2.A.1 section below.

Major issues followed up via interactive review are listed below:

**DCB manufacture:**

- Unmitigated gaps in cold chain records of up to 22 days;
- Inadequate sterility assurance for lots manufactured prior to 2009 (lack of sterility testing of several in-process solutions, (b) (4))
- DCB shipping to LBSS is not validated (no prospective validation and no runs were performed at worst case conditions)

**DP manufacture:**

- Insufficient controls to ensure product-contact materials are sterile and free from endotoxin (no periodic testing of incoming lots)
- Final DP visual inspection defects and acceptance criteria are not well-defined (no limit established for any defects except for particulate for (b) (4) visual inspection; categorization of defects for AQL inspection is vague, with no limit set for minor/overall rejects).

Information was also requested where further details were needed for an assessment, including but not limited to

- Facilities, equipment, utilities information for LBSS and for AmerisourceBergen ICS, DP packaging and distribution facility;
- DP CCIT method
- Aseptic process validation
- Cell factory (b) (4) qualification
- On-site media production process, controls and equipment
- Segregation, clearance and changeover procedures.

All additional information provided by the applicant in response to the information requests is documented in the addendum review memo, unless stated otherwise. During its review several additional issues were identified

**Inspection**

The Pre License Inspection (PLI) of the DP manufacturing facility, LBSS, is pending due to the travel restrictions from the COVID-19 pandemic.

**B. RECOMMENDATION**

Recommendation is pending until all responses to Information Requests (IRs) are received and reviewed, and the outcome of the PLI is determined. See Addendum memo for the recommendation.

**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 7, cn=Ekaterina N. Allen -S Date: 2020.09.09 07:03:32 -04'00'</small>
Anthony Lorenzo, Acting Branch Chief OCBQ/DMPQ/MRB2	Concur	Anthony Lorenzo -S <small>Approved 2020.09.14 14:30:10 -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: 2020.09.19 21:25:16 -04'00'</small>

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**Module 3**

**3.2.S DRUG SUBSTANCE**

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

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

[REDACTED]

[REDACTED]

32 pages determined to be not releasable: (b)(4)

(b) (4)

### 3.2.P DRUG PRODUCT

#### 3.2.P.1 Description and Composition of the Drug Product

The DP is a liquid cell suspension of ex vivo cultured adult human mesenchymal stromal cells. DP is (b) (4)

DP is supplied in 6 mL closed ready-to-fill cycloolefin copolymer (b) (4) Closed Vials with thermo plastic elastomer stoppers (b) (4) It is stored at NMT -135°C in the liquid nitrogen vapor phase until thawed and diluted in Plasma-Lyte A prior to administration.

Each vial is filled with (b) (4) (target fill volume) for a nominal amount of  $25 \times 10^6$  viable cells in 3.8 mL dose of the following composition:

Component	Amount per vial (3.8 mL)	Function	Quality standard
Ce-MSCs	(b) (4) viable cells, includes (b) (4) cell concentration overage	Active substance	In-house release testing (see 3.2.P.5 below)



Component	Amount per vial (3.8 mL)	Function	Quality standard
25% HSA solution	20% or (b) (4) (b) (4) Human Albumin and (b) (4) buffer)	Cell stabilization and protection from shearing forces	(b) (4); FDA approved product manufactured by (b) (4)
DMSO	10% or (b) (4)	Cryopreservative	(b) (4)
Plasma-Lyte A	70% or (b) (4)	Diluent providing osmolality and pH	USP; FDA approved product manufactured by Baxter Healthcare Corp

Composition of 25% HSA solution is as follows (per (b) (4) ):

- (b) (4)

Proposed excess volume is in line with (b) (4) recommendation for viscous liquids: (b) (4) overage for (b) (4) labeled volume, (b) (4).

Dosing of DP is based on patient body weight ( $2 \times 10^6$  cells/kg). The appropriate number of DP doses is thawed and added to 40 mL of Plasma-Lyte A (diluent) per dosage.

### 3.2.P.2 Pharmaceutical Development

#### 3.2.P.2.1 Components of the Drug Product

##### 3.2.P.2.1.1 Drug Substance

The active agent in the DP is ex vivo cultured adult human mesenchymal stromal cells (ce-MSCs), remestemcel-L. The mesenchymal stem cells are derived from the bone marrow of unrelated and human leukocyte antigen (HLA) unmatched healthy adult donors. In the manufacturing process, the MSCs are isolated and expanded through a series of 5 cell culture expansions. Intermediate produced after the first two expansions (DCB) is filled into (b) (4) bags and stored in liquid nitrogen vapor phase until thawed and used for further cell culture expansions. The ce-MSCs are harvested following Passage 5 and formulated into final drug product (DP) at a concentration of  $6.68 \times 10^6$  viable cells/mL.

DP CQAs were determined to be cell viability, concentration, phenotype (CD166, CD105, and CD45) and potency (expression of TNF R1 and inhibition of IL-2R $\alpha$ )

### 3.2.P.2.1.2 Excipients

Excipients used in DP formulation are used to maintain stable, viable cells through the cryopreservation freezing process, long-term cryostorage and preparation for clinical administration. All excipients are of pharmaceutical grade, sterile and comply with compendial requirements:

- Plasma-Lyte A is used as both excipient and diluent. It is an electrolyte solution for injection approved by FDA (Baxter, NDC#0338-0221-04) and indicated as a source of water and electrolytes or as an alkalinizing agent, compatible with blood and blood components. It makes up 70% v/v of the final DP formulation and is intended to provide physiological osmolality and pH.
- Human Serum Albumin (HSA) functions as a cellular stabilizer for maintenance of cell stability of cryopreserved cells. HSA solution (25%) makes up 20% v/v of the final DP formulation. It is an FDA approved product (b) (4) indicated for restoration and maintenance of circulating blood volume.
- DMSO (b) (4) is a cryopreservative agent composed of not less than (b) (4) DMSO with a maximum water content of (b) (4). It makes up 10% v/v of final formulation and is intended to ensure cell survival and maintenance of cell structural integrity during cryofreezing and cryostorage.

Mesoblast stated that the suitability of excipients by evaluation of DP CQAs during formulation, cryopreservation, long term cryostorage, thaw and DP dilution for clinical administration and is supported by the studies that evaluated formulation hold time, cryopreservation freezing profile, long term stability in cryostorage, post-thaw formulation stability.

### 3.2.P.2.2 Drug Product

#### 3.2.P.2.2.1 Formulation Development

The nominal concentration of cells/mL ( $6.68 \times 10^6$  viable cells/mL) and proportion of excipients used in the DP formulation has remained the same over clinical development. Container closure system changes from (b) (4) container (b) (4) to a closed vial (b) (4) in 2015. There were also changes of (b) (4) as follows:

- (b) (4)

- (b) (4)

Primary efficacy trials in support of the current BLA (MSB-GVDH001 and MSB-GVDH) used 2015 formulation.

### 3.2.P.2.2.2 Overages

Mesoblast indicated two types of overages are used:

1. Cell concentration overage of (b) (4) to ensure a minimum viable cell concentration of  $6.68 \times 10^6$  cells/mL after cryostorage and thawing.
2. Volume overage of (b) (4) (3.8 mL nominal fill vs. (b) (4) target fill) to ensure nominal extraction volume.

### 3.2.P.2.2.3 Physicochemical and Biological Properties

Ce-MCS cells are adherent in culture and display a spindle shaped, fibroblastic morphology. Cells are typically 20 to 30 microns in size.


The general biological properties of ce-MSc include:

- Plastic-adherent in culture and proliferative ex vivo
- Express positive cell surface markers for MSC, CD166 and CD105, and lack of expression of CD45. Phenotype is tested as part of DCB and DP batch release specification.
- Low level expression of MHC Class I and an absence of HLA-DR and the co-stimulatory molecules, CD40, CD80 and CD86. Do not elicit proliferation of alloreactive T cells in vitro and do not stimulate clinically significant immune responses following allogeneic transplantation in vivo.
- Suppress alloantigen- and mitogen-driven T cell proliferation and stimulate an increase in the proportion of CD4+CD25+ T cells, including regulatory T cells. Decrease expression of pro-inflammatory cytokines [e.g. interferon gamma IFN $\gamma$ , tumor necrosis factor  $\alpha$  (TNF $\alpha$ )] and increase secretion of anti-inflammatory cytokines [e.g. interleukin-4 (IL-4), interleukin-10 (IL-10)] by dendritic cells, naïve and effector T cells and natural killer (NK) cells. These effects are mediated by expression of tumor necrosis factor receptor type 1 (TNF R1) and secretion of soluble factors such as prostaglandin E2 (PGE2).
- Functional activity of ce-MSc is tested as part of the DCB and DP batch release specification, including expression of TNF R1 and inhibition of IL-2R $\alpha$  expression on activated peripheral blood mononuclear cells

**3.2.P.2.3 Manufacturing Process Development**

DP production starts with DCB thaw and seeding, followed by three more cell expansions (P3-5), and harvest. Cells are filled into final containers and cryopreserved. Changes in manufacturing sites and DP process during development are described in 3.2.S.2.6 Manufacturing Process Development above.

(b) (4)





(b) (4)

### 3.2.P.2.4 Container Closure System

The final DP container is a 6.0 mL ready-to-fill (b) (4) Closed Vials (b) (4). Container closure system consists of cyclo-olefin copolymer (COC) vial body, stopper made of the proprietary thermo plastic elastomer to allow for (b) (4) after filling, top ring to ensure closure integrity between the vial and the stopper and flip away snap fit cap to ensure sterility assurance level of the (b) (4) area.

Vials and stoppers meet (b) (4) requirements (biological reactivity tests). Additionally, vials meet (b) (4) (containers) and (b) (4) (polyolefins). Stoppers meet (b) (4) (elastomeric closures for injection).

Closed vials (vial body with stopper and a top ring) and caps are (b) (4) at a validated (b) (4) and supplied sterile and ready to use.

Final DP is filled into closed vials by (b) (4), a cap is attached, vials are labeled, (b) (4), and stored in liquid nitrogen vapor phase at LBSS.

Cryopreserved DP vials are transported to the secondary packaging site, Integrated Commercialization Solutions (ISC) in (b) (4). At ISC either 1 or 4 DP vials are packaged into labelled cartons (b) (4) 55x52x48 mm). For the single vial presentation, the vial is held in place within the box by an insert. Vials are maintained at NMT -135°C until thawed immediately prior to administration.

Container Closure Integrity Testing (CCIT). Container closure integrity of 6 mL (b) (4) Closed Cryovials (b) (4) containing (b) (4) of DP was evaluated using validated (b) (4) method. The test method utilizes a (b) (4) (same equipment piece as was used for validation). The test samples are (b) (4)

This method is intended to detect defective vials through a (b) (4) result (b) (4) that is greater than the rejection limit. The (b) (4) results of the test samples must be less than or equal to the rejection limit in order for the test samples to pass the test. The limit of detection for this method was determined to be a defect size of (b) (4).


Container closure suitability was assessed as follows:

1. *Post-shipping.* Shipping validation followed by CCIT was used to support transport of cryopreserved DP vials from LBSS to ICS (distribution center).

Per MR-084 Shipping Validation and CCIT Report, DP was filled in 6 mL (b) (4)


(b) (4)

(b) (4)




(b) (4)

(b) (4)

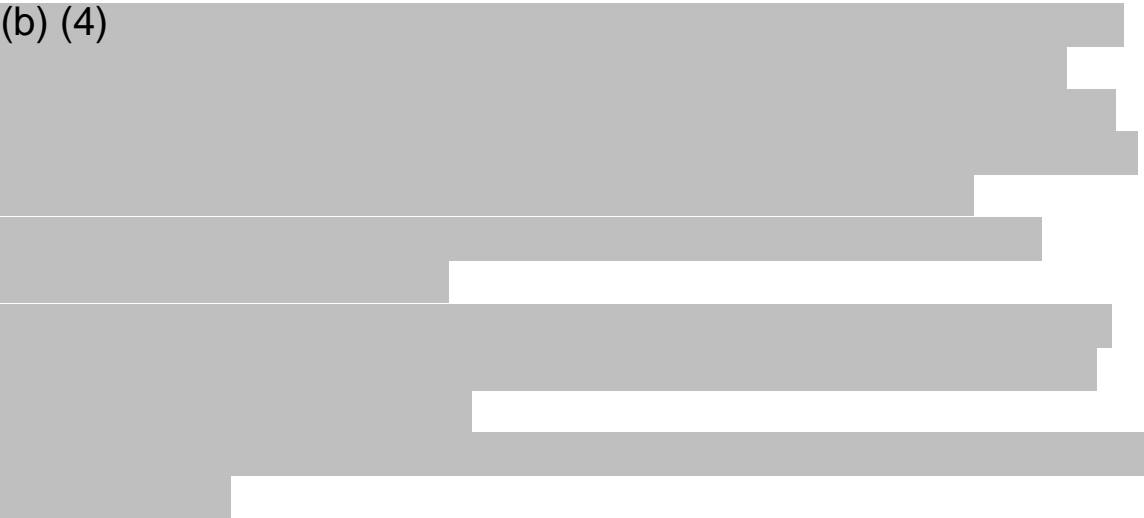


### 3.2.P.2.5 Microbiological Attributes

The DP is a sterile cell suspension. Microbial contamination of the Donor Cell Banks (DCB) and DP are controlled through in-process and batch release testing at assigned stages during the manufacture for mycoplasma and sterility. DCBs are requalified (including sterility testing) prior to use for downstream manufacture. Potential microbial contamination is minimized via the following:

- (b) (4)
- 



- (b) (4)
- 

### 3.2.P.2.6 Compatibility

Preparation of DP for clinical administration involves thawing required number of DP units (dose is calculated based on body weight) and adding the appropriate volume of DP to 40 mL of Plasma-Lyte A (both an excipient and a diluent) per dosage and administration instructions. Based on post-thaw formulation stability studies, the administration instructions recommend storage of diluted product at room temperature and administration of the product within 5 hours of resuspension.

### **Overall Reviewer's Assessment of Section 3.2.P.2:**

Several issues were noted during the review of this section. For issues related to release sample shipping to the (b) (4) for testing please see review of section 3.2.P.3.5 IR of 5/4/2020 Q.12b,c below. Clarification and supporting information regarding other review issues pertaining to this section were requested in the IR sent to the applicant on 5/4/2020. The responses to the IR will be reviewed in the addendum memo. The initial request is shown in bold below.

**Q.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.**

**Q.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.**

### 3.2.P.3 Manufacture

#### 3.2.P.3.1 Manufacturer(s)

1. Lonza Bioscience Singapore Pte. Ltd. (LBSS)  
35 Tuas South Ave 6, 637377, Singapore  
FE# 3009725845  
DP manufacture, primary packaging, in-process and release testing, DP storage
2. (b) (4)  
[REDACTED]  
DP release testing, stability testing
3. (b) (4)  
[REDACTED]  
DP release testing, stability testing
4. (b) (4)  
[REDACTED]  
DP release testing
5. (b) (4)  
[REDACTED]  
DP stability testing
6. (b) (4)  
[REDACTED]  
DP in-process and release testing
7. ISC Amerisource Bergen  
(b) (4)  
[REDACTED]  
DP secondary packaging, storage, and distribution

Mesoblast International Sarl [21 Biopolis Road, #01-22 Nucleos (South Tower), 138567 Singapore] is responsible for QA review and DP bulk batch release. Mesoblast Inc (505 5<sup>th</sup> Avenue, New York, NY 10017) is responsible for final package product batch release.

#### 3.2.P.3.2 Batch Formula

Batch size depends on the cell yield during (b) (4), washed ce-MSCs are concentrated to (b) (4) viable cells/mL (b) (4) formulation) and diluted (b) (4) with cryoprotectant solution to make final bulk DP with a target concentration of (b) (4)

viable cells/mL. Vials are filled with (b) (4) cell concentration overage to account for cell loss during cryopreservation and (b) (4) mL overfill to ensure extractable volume of 3.8 mL and  $6.68 \times 10^6$  cells/mL available after thaw. A typical batch size is (b) (4) vials. Nominal amounts (excluding overages) per batch are:

- Ce-MSD, (b) (4) cells
- HSA solution (25%), (b) (4)
- DMSO, (b) (4)
- Plasma-Lyte A, (b) (4)

Quality standard used for all components except ce-MSD is (b) (4). Ce-MSDs are per batch release testing.

**Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:**

Overall the information provided is acceptable. However, a clarification related to the provided list of manufacturers is required. It was requested on 5/4/2020. The response to the IR will be reviewed in the addendum memo. The IR is shown in bold below.

**Q.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.**

**3.2.P.3.3 Description of Manufacturing Process**

(b) (4)



(b) (4)

Upon completion of the receipt and inspection process in ICS, the verified product is released by QA for secondary packaging.

The final packaging configuration consists of either a single vial or four vials enclosed in a carton, with each configuration having a separate product code and batch record.

(b) (4)

DP remains in quarantine status until released by QA.

When an order is placed for the packaged vials, a pick ticket is generated in the (b) (4) system. After confirming the product code, lot number, expiration date of the physical product against the pick ticket, the requested quantity of the packaged product is placed into the (b) (4)

. The product is then placed into the fully charged, certified Dewar for shipping to the end user. During transit the temperature within the dewar is monitored and must remain NMT -135°C.

Batch numbering system. Each DP lot is manufactured from (b) (4). DP lots are not (b) (4), and each can be tracked back to the original BMA donor.

Lot numbers are autogenerated by Lonza's (b) (4) system. Each number is unique, but may not be in running sequence. Lot numbers are printed on batch records and DP vial labels. Lonza-generated lot number (bulk vials) is entered and tracked in (b) (4) system at ISC. For the packaged product, the lot number is the Lonza generated lot number with a letter suffix assigned to represent the number vials in the packaged carton as 1 or 4. This lot number is assigned by ICS and tracked in (b) (4).

Control of materials used in DP manufacture. Control of materials by Mesoblast is limited to the following:

- (b) (4)

LBSS maintains material documentation from the vendors (CofA, TSE/BSE statement, etc.) and performs the majority of material controls on behalf of Mesoblast, including purchasing materials from approved suppliers, qualifying materials per established SOP (acceptability and suitability assessment and setting up raw material specifications), material disposition, transfer for use or storage, and segregation of rejected materials.

The following material controls within DMPQ purview are in place for materials and reagents used in DP manufacture:

*Fetal Bovine Serum* (FBS; (b) (4)

(b) (4) in the final container to achieve (b) (4) and the validation is included by the manufacturer (supplier qualification). CofA includes endotoxin (NMT (b) (4) depending on supplier) and sterility testing results and is reviewed upon receipt. (b) (4) of incoming material is tested for sterility (b) (4) and endotoxin (NMT (b) (4)

(b) (4)

*Recombinant trypsin* (b) (4)). CofA includes (b) (4) testing results (NMT (b) (4) and is reviewed upon receipt. No additional endotoxin or sterility testing is performed upon receipt.

*Plasma-Lyte A* (Baxter Healthcare)

*Human Serum Albumin, 25%* (HSA; (b) (4)

*Dimethyl sulfoxide*, (b) (4)

All DP in-process solutions are manufactured at LBSS facility and are subject to the following controls:

(b) (4)



(b) (4)

All *auxiliary materials* used in DP manufacture are single use and supplied sterile. Mesoblast stated that manufacturers and suppliers of the auxiliary materials, as well as incoming materials themselves were qualified per SOP. Such qualification included assessment of material acceptability, suitability, and setting up raw material specifications. Quality standard applied to all critical product-contact materials is “CofA: sterile”. The following materials (not all) are also non-pyrogenic (per CofA):

- (b) (4)

The endotoxin specification of final DP container (per CofA) is NMT (b) (4).

**Overall Reviewer’s Assessment of Section 3.2.P.3.3:**

Several issues related to DP manufacturing process and related material controls were noted during the review of this section. Clarification and supporting information were requested on 5/4/2020. The response to the IR will be reviewed in the addendum memo. The IR is shown in bold below.

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

- 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. 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.
- 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.
- 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.

**Q.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.
- 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.

**3.2.P.3.4 Controls of Critical Steps and Intermediates**

Process control strategy development started with defining the Quality Target Product Profile (QTPP). The QTPP was then used to evaluate potential CQAs and decide which were critical and which were non-critical. A risk assessment was done to evaluate the risk of each process parameter to impact CQAs. Criticality of process parameters was based on overall risk to product CQA, potential impact to product quality, likelihood of occurrence and detectability. The process parameter limits have been derived through studies conducted during manufacturing development and small and full scale process limit evaluation (PLE) studies. Critical process parameters have been verified through Process Performance Qualification (PPQ) studies (see 3.2.P.3.5 below).

Critical Performance Parameters (CPeP) were defined as an output that cannot be directly controlled but is a critical indicator that the process is operating as expected. Additionally, some non-critical process parameters (NCPPs) have batch record limits,

similarly to CPPs. Such NCPPs, CPPs and CPePs during DP manufacture, as well as in-process testing are summarized below:

(b) (4)

**Overall Reviewer's Assessment of Section 3.2.P.3.4:**

Though this section is primarily outside of DMPQ purview and is deferred to PO, process step criticality does have an impact on which equipment is deemed critical and was reviewed with that in mind.

Control strategy for critical steps and intermediates is not entirely clear. Though manufacturing ranges/specifications appear to be set for most, if not all, process parameters, only a few process parameters are considered critical by Mesoblast [e.g. (b) (4) have set points and are monitored/alarmed but are listed as NCPP]. Additionally, some (but not all) NCPPs have batch record limits, similarly to CPPs, where others appear to just be recorded in batch record (no limit).

In-process controls within DMPQ purview are (b) (4)

Otherwise (b) (4)

Issues regarding DCB post-thaw viability specifications were discussed in 3.2.S.2.2 IR of 5/4/2020 Q.8b. Issues regarding growth media use and sterility assurance were discussed in 3.2.P.3.3. IR of 5/4/2020 Q.7d.

**3.2.P.3.5 Process Validation and/or Evaluation**

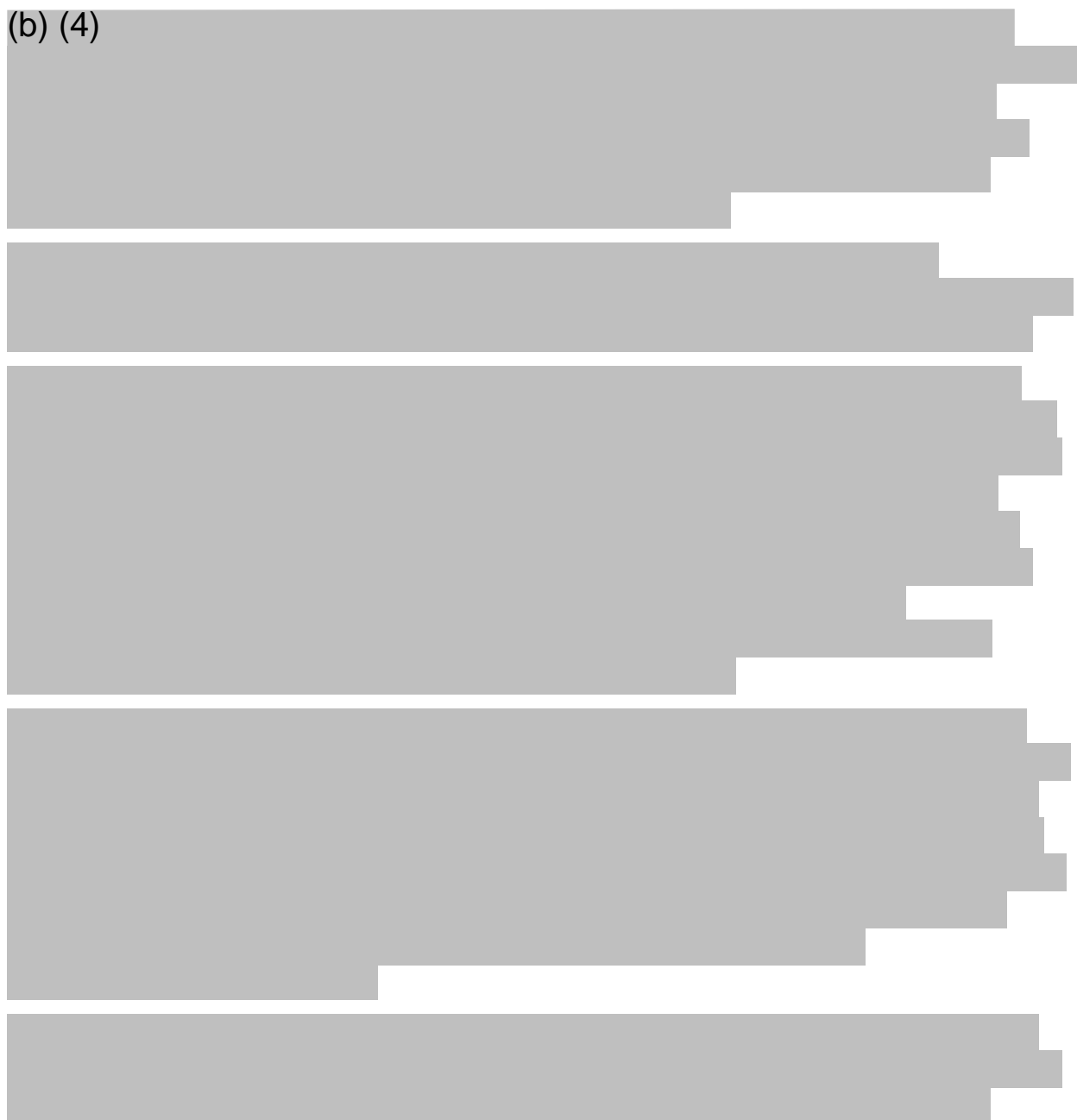
Process validation of the current commercial process consisted of the following components:

- Aseptic Process Validation, including media challenge studies, evaluation of the (b) (4)
- PPQ of the DP manufacturing process to ensure consistent manufacture
- Shipping validation (DP vials from LBSS to secondary packaging and distribution site, ICS; final packaged DP from ICS to customer)
- Continuous process verification

Aseptic Process Validation. (b) (4)

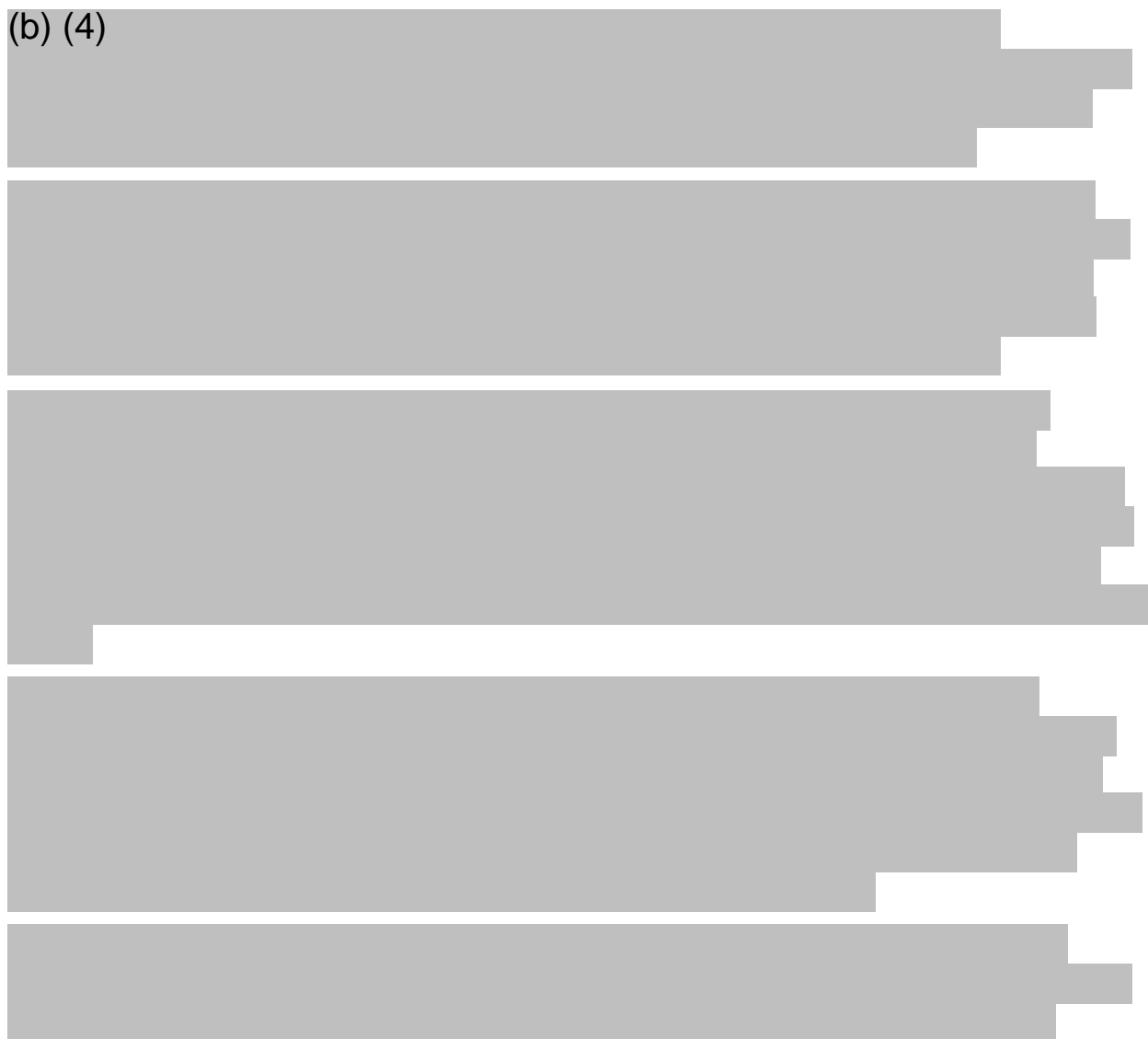


(b) (4)



Shipping of final packaged product. The provided validation report (mr-099) covers the shipping process for final packaged frozen DP vials (filled with (b) (4) ) transported from AmerisourceBergen ICS, (b) (4) to the end user within the US inside a (b) (4) standard shipper (aluminum dewar with a holding well surrounded with material (b) (4) with liquid nitrogen, with a lockable vapor plug cap). Temperature inside the dewar is monitored during transit with a (b) (4) data logger (b) (4) and a calibrated thermocouple (all thermocouples were with their respective calibration dates).

(b) (4)




Continued process verification program. The CPV program collects and evaluates product and process data, including critical materials, process parameters, in-process attributes, and product quality attributes periodically. The data will be statistically trended and reviewed to ensure process consistency and robustness and appropriate control of quality attributes.

**Overall Reviewer's Assessment of Section 3.2.P.3.5:**

APV description was not clear or detailed enough for evaluation. Additionally, several issues were noted regarding APV, cell factory (b) (4) qualification, process validation (and visual inspection of PPQ lots in particular), and product shipping validation. Clarification and additional supporting information was requested on 5/4/2020. The response to the IR will be reviewed in the addendum memo. The IR is shown in bold below.


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

(b) (4)



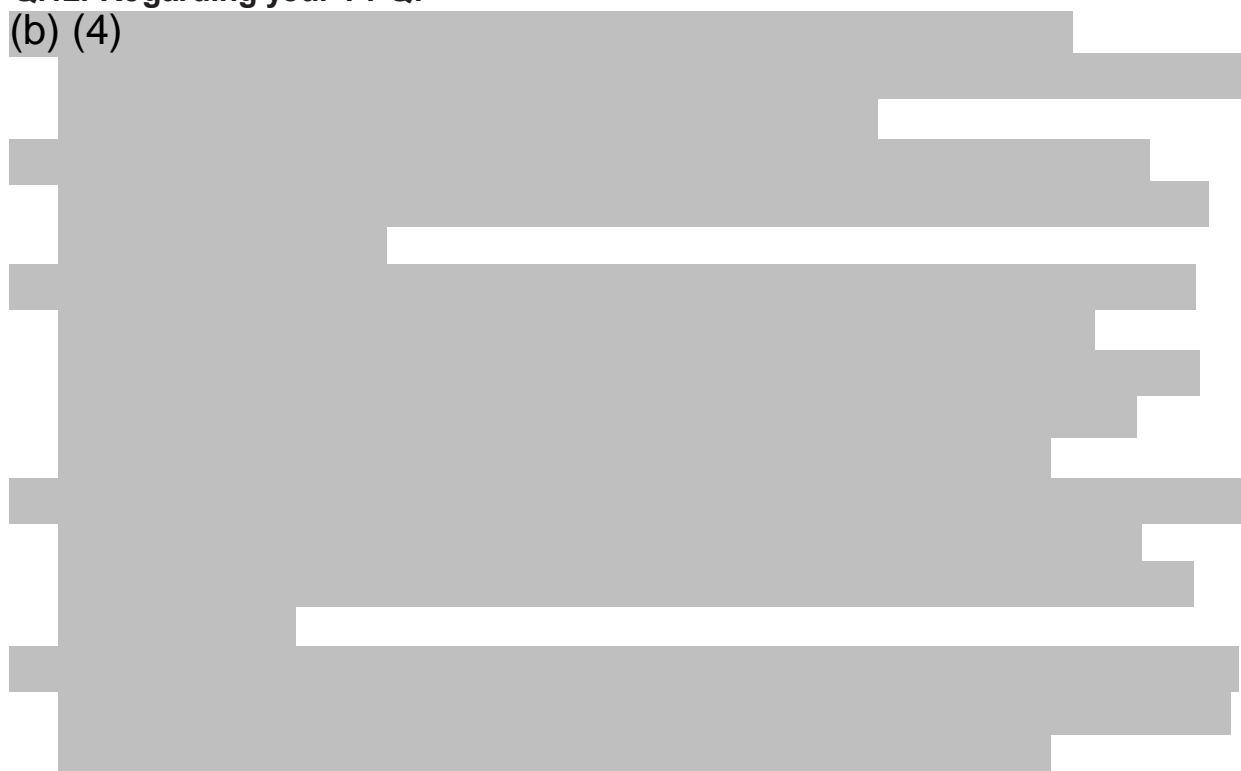
**Q.11. Regarding your cell factory (b) (4) qualification:**

(b) (4)




**Q.12. Regarding your PPQ:**

(b) (4)






(b) (4)

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

(b) (4)

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

(b) (4)

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(b) (4)

### 3.2.P.4 Control of Excipients

#### 3.2.P.4.1 Specifications

There are three excipients present in DP: Human Serum Albumin solution (HSA), DMSO, and Plasma-Lyte A. All excipients are pharmaceutical grade, supplied sterile and comply with compendial requirements (monographs for Human Albumin Solution, Dimethyl Sulfoxide, and Multiple electrolytes injection Type I, respectively). Plasma-Lyte and HSA are FDA-approved products (NDC# 0338-0221-04 and (b) (4) respectively).

A CofA for each excipient is provided by the supplier. It includes storage conditions and expiration dates. The following testing (with acceptance criteria) in DMPQ purview is performed by the supplier:

- Plasma Lyte-A (Baxter): endotoxin (b) (4) sterility (b) (4) release)
- DMSO (b) (4) closure test by (b) (4) Sterility (b) (4) test (sterile), endotoxin (b) (4)
- Human Albumin, 25% (b) (4) sterility (sterile), endotoxin (NMT (b) (4) CBER lot release action (released)

Upon receipt, CofA is verified and 100% physical inspection of containers is performed for all excipient lots. Incoming lots are tested at LBSS as follows:

- Plasma Lyte-A (Baxter): (b) (4) lots and (b) (4) thereafter are tested for endotoxin (b) (4)
- DMSO (b) (4) is tested for sterility and endotoxin (NMT (b) (4)

#### 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

Defer to DBSQC. Sterility testing is per (b) (4) endotoxin is per (b) (4) for multiple electrolytes injection type I (Plasma-Lyte A only). Methods were verified at LBSS.

**3.2.P.4.4 Justification of Specifications**

Defer to PO.

**3.2.P.4.5 Excipients of Human or Animal Origin**

HSA solution is the only excipient of human or animal origin. The excipient is sourced from a manufacturer that certifies each lot is obtained from normal healthy donors who fulfill current donor requirements in the US and Europe and provided by FDA approved blood establishments. All HSA solution lots are received from the manufacturer (b) (4) with a CoA certifying that each lot has been tested and meets the requirements of (b) (4) for Human Albumin Solution. Review deferred to PO.

**3.2.P.4.6 Novel Excipient**

NA

**Overall Reviewer's Assessment of Section 3.2.P.4:**

It is not clear whether identity testing of the excipients is performed upon receipt. This will be verified during prelicensing inspection (PLI) at LBSS.

**3.2.P.5 Control of Drug Product****3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)**

The following ce-MSD DP tests within DMPQ purview are conducted for DP lot release on samples of final DP (b) (4) unless indicated otherwise:

<b>Test Parameter (Attribute)</b>	<b>Analytical Procedure</b>	<b>Final Acceptance Criteria</b>	<b>Justification for Specification</b>	<b>Proposed acceptance criteria (process validation)</b>
Safety (In-process sterility)	(b) (4)	Negative	(b) (4), 1993 FDA's "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals"	Negative

Test Parameter (Attribute)	Analytical Procedure	Final Acceptance Criteria	Justification for Specification	Proposed acceptance criteria (process validation)
Safety (In-process sterility)	(b) (4)	Negative	(b) (4) 1993 FDA's "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals"	Negative
Safety (Endotoxin)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Appearance (b) (4) sampling)	AQL sampling and manual visual inspection at LBSS	(b) (4)	(b) (4)	(b) (4)

Clinical specifications for DP lots used in pivotal study are identical to those used in PPQ, except (b) (4) sampling (visual inspection) post (b) (4) visual inspection, which was introduced during PPQ. Additionally, sterility and endotoxin testing of clinical lots (post-thaw final container DP) was performed elsewhere (see 3.2.P.2.3 Manufacturing Process Development above).

**Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:**

Specifications within DMPQ purview are acceptable.

**3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures**

Deferred to DBSQC except Container Closure Integrity Validation (CCIT) and visual inspection qualification included in this section and reviewed below.

**Container Closure Integrity Testing Method Validation.** Mesoblast provided method validation report (effective 2/9/2019) for CCIT by (b) (4)

Validation was performed per

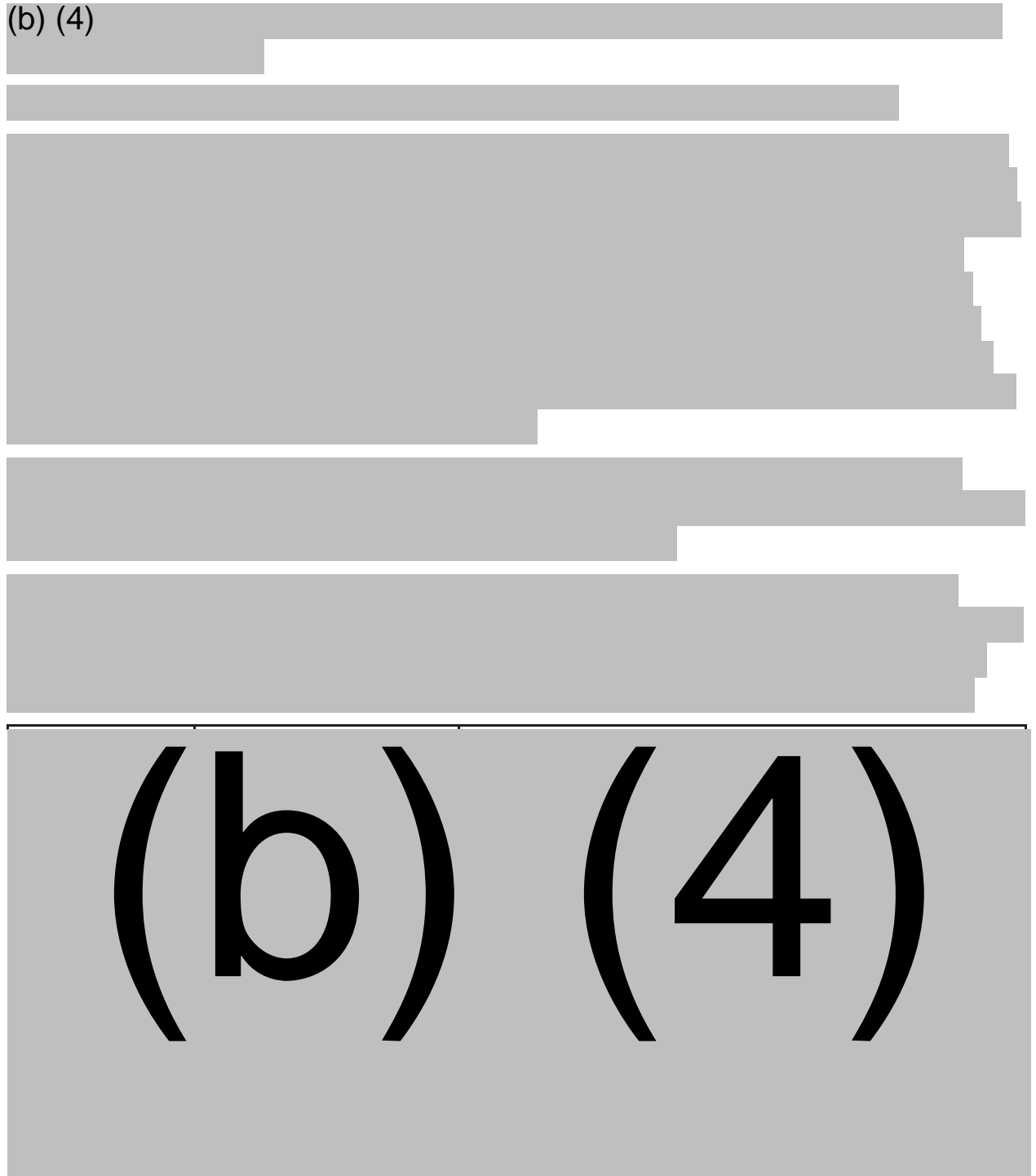


(b) (4)

I

**Visual Inspection for Operator Qualification.** An SOP SGTS-13937 effective December 23,2019 was provided. Qualification is performed using the (b) (4)

(b) (4)



**Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:**

Several issues were noted regarding CCIT and operator qualification for visual inspection. Clarification and additional supporting information were requested on 6/2/2020. The response to the IR will be reviewed in the addendum memo. The IR is shown in bold below.

**Q.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.
- 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.
- c. Please clarify the location of defects in positive control vials and whether defects were in direct contact with liquid inside the vials.
- d. For type defects used in range determination studies, (b) (4) . Please demonstrate that the method is capable of detecting (b) (4)
- 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.
- 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.
- g. Please submit a list of deviation summaries, with investigations, CAPAs and outcomes associated with CCIT validation
- 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.
- i. Please provide the equipment qualification report for (b) (4) or justify why those are not necessary.
- 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).
- 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.

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

**3.2.P.5.4 Batch Analyses**

Release data for the following lots manufactured at LBSS was provided:

- Lots manufactured at LBSS and released by full scale GMP commercial process during 2015 to 2016 (b) (4):
  - 31 DP lots were used in the Phase 3 primary efficacy study in pediatrics SR-aGVHD, MSB-GVHD001
  - (b) (4) DP lots were used in a long-term stability study conducted over the proposed shelf-life of 48 months at storage conditions of  $\leq -135^{\circ}\text{C}$  in liquid nitrogen (LN2) vapor phase
  - (b) (4) of the DP lots were used in a container closure integrity study stored in LN2 freezer over 48 months
  - (b) (4) of the (b) (4) DP lots were part of a comparability study for assessment of transfer of DP manufacture from LWI to LBSS.
  - (b) (4) of the DP lots were used in extended characterization studies
  - (b) (4) of the (b) (4) DP lots manufactured were full scale process development lots, which included proposed process improvements.

Test for Visual Inspection and (b) (4) Sampling was not implemented at the time of DP testing of these lots. All (b) (4) lots tested negative for in-process and final DP sterility. Results for all (b) (4) DP lots endotoxin were (b) (4), meeting the endotoxin specification of (b) (4).

- Full scale GMP commercial process development DP lots for evaluation of process improvements and stability (DP Lots: (b) (4)). In-process and final DP sterility and endotoxin release specifications were met.

- (b) (4) full scale GMP commercial process DP lots manufactured for Process Performance Qualification (PPQ). In-process and final DP sterility and endotoxin release specifications were met.

### 3.2.P.5.5 Characterization of Impurities

Defer to PO.

### Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

The data provided was incomplete: it was stated elsewhere in the submission that a total of (b) (4) batches were manufactured. PO was notified. Issues within DMPQ purview (sterility and endotoxin failures) are addressed above (see 3.2.P.2, IR of 5/4/2020, Q.4). Review of any other issues is deferred to PO.

### 3.2.P.6 Reference Standards or Materials

Defer to PO and DBSQC.

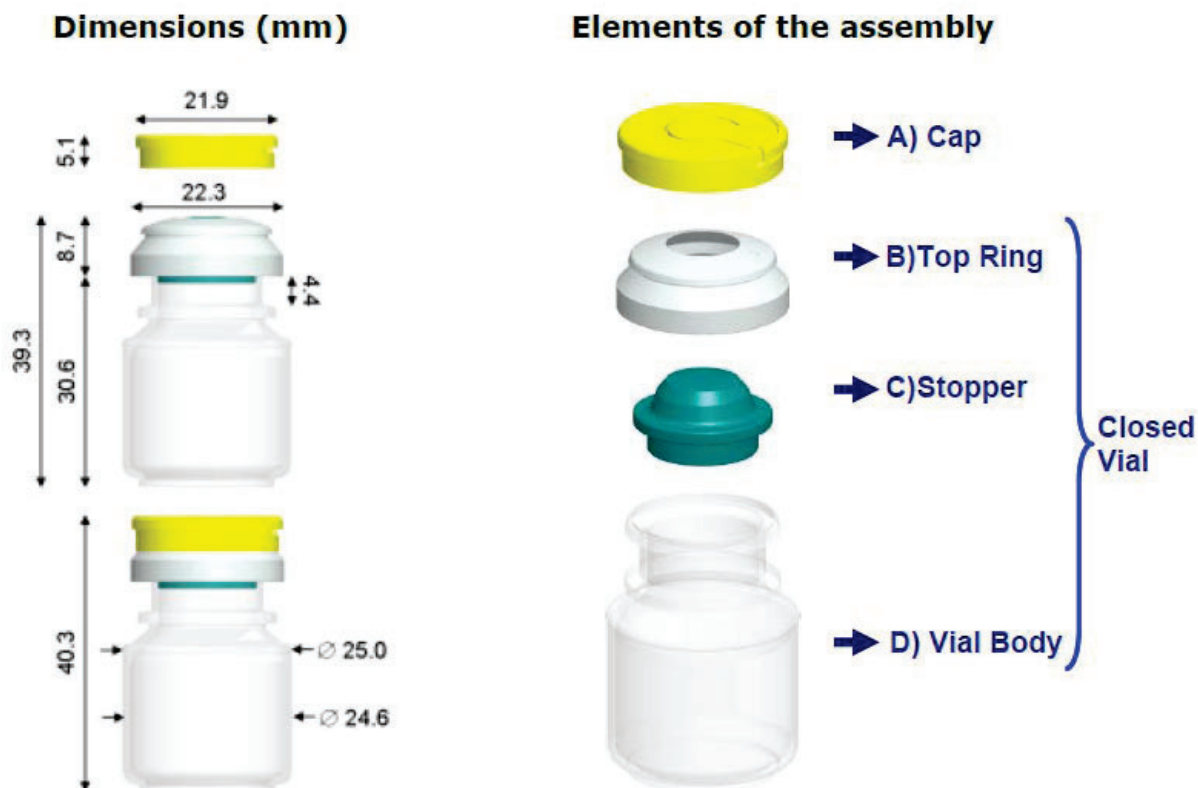
### 3.2.P.7 Container Closure System (CCS)

Additionally, refer to 3.2.P.2.4 Container Closure System for general description of CCS, use, and CCIT.

CCS is a 6.0 mL ready-to-fill closed vial manufactured by (b) (4) and it consists of the following components:

1. Vial body (product contact)  
Material of construction: Cyclo-Olefin Copolymer (COC) of very high purity, animal-free origin  
Specification/Compliance: (b) (4)
2. Stopper (product contact)  
Material of construction: proprietary Thermoplastic elastomer (TPE), animal-free origin  
Specification/Compliance: (b) (4)
3. Top ring (non-product contact)  
Material of construction: Acrylonitrile Butadiene Styrene (ABS)
4. A yellow flip away cap (non-product contact; ensures sterility assurance level of the (b) (4) area)  
Material of construction: high density polyethylene (HDPE)  
Specification/Compliance: (b) (4) derived materials meet (b) (4) and Note for Guidance (b) (4)

Components 1-3 are preassembled and caps are supplied separately. A diagram of the vial and its dimensions is included below:



Container closure components meet the following specifications:

Vial:

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

Cap:

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

At LBSS each batch of vials and caps is visually inspected and identified by (b) (4) [REDACTED]. The following additional testing is performed at LBSS on the (b) (4) unique vendor lots of closed vials and (b) (4) thereafter:

- (b) (4)

### **Overall Reviewer's Assessment of Section 3.2.P.7:**

The scope of inspection and testing of incoming lots of CCS is not clear. Clarification was requested on 6/2/2020. The response to the IR will be reviewed in the addendum memo. The IR is shown in bold below.

**Q.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.)**
- b. Whether the (b) (4) of the vial body or the stopper or both is performed**
- c. What in house testing of caps is performed**

### **3.2.P.8 Stability**

#### **3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data**

The proposed shelf-life of the DP stored in closed vials at  $\leq -135^{\circ}\text{C}$  in liquid nitrogen vapor phase is 48 months.

The following stability studies were performed using DP filled in 6 ml (b) (4) closed vial: long-term, accelerated, and short-term. Stability testing within DMPQ purview included endotoxin (NMT (b) (4)), sterility (negative), and container closure integrity (Pass). Endotoxin and sterility testing were performed at the release testing facility, (b) (4) or, for earlier studies, at LBSS. CCIT by (b) (4) was done at (b) (4), where tested.

Proposed shelf-life is supported by long-term real time stability studies conducted at  $\leq -135^{\circ}\text{C}$  in liquid nitrogen vapor phase for up to 48 months. A total of (b) (4) batches of drug product stored in closed vials were evaluated across 2 completed (48 months; SP-011 and SP-008) and one ongoing (6 month data available, SP-013) studies. Testing schedule for these studies is 0, 3, 6, 9, 12, 18, 24, 36, 48, and 60 (SP-013 only) months.

SP-008 (b) (4) lots): Endotoxin testing at 0, 12, 24, 36, 48 months. Testing at 24 months was not performed due to shipping delays. Sterility testing at 0, 12, 24, 36, 48 months. Lot (b) (4) not sterility or endotoxin tested past 24 month due to limited product availability (planned deviation).

SP-011 (b) (4) lots): Endotoxin testing at 0, 12, 24, 36, 48 months. Testing not performed at 24 month due to sample shipping issues. Sterility testing at 0, 12, 24, 36, 48 months.

SP-013 (b) (4) lots): Endotoxin, sterility testing, and CCIT planned at 0 (except CCIT), 12, 24, 36, 48, 60 months. Only 6 months of data is available.

The stability of (b) (4) DP lots (PPQ lots) has been studied following storage at accelerated conditions (SP-015): at (b) (4)

A short-term post thaw formulation study (SP-014) was conducted on (b) (4) batches (PPQ lots) of DP, to evaluate stability of a clinical dose for infusion over the 5 hour formulated expiration period (infusion time limit). The DP was thawed and diluted in Plasma-Lyte A similarly to clinical delivery process used for the Phase III studies and planned for commercialization. The DP was held at room temperature post-formulation and samples were taken for viable cell concentration and cell viability at 0, 30, 90, 180, and 300 minutes post formulation. Specifications within DMPQ were not included in this study.

All available sterility and endotoxin results met their respective specifications.

### 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

The post approval stability protocol was provided for cryopreserved final product [ex vivo cultured adult human mesenchymal stromal cells (ce-MSCs)] contained in 6 mL (b) (4) closed vials with a target fill volume of (b) (4) mL and manufactured at LBSS according to the proposed manufacturing process.

All lots will be stored at  $\leq -135^{\circ}\text{C}$  in liquid nitrogen vapour phase for the duration of the studies. All product testing will be performed at contract testing organizations (CTO) qualified by Mesoblast. Assays used in the proposed post approval stability commitment will be either validated or verified to be suitable for use.

The following testing (with respective specification) within DMPQ purview is proposed for long-term study protocol:

- Sterility (negative) at 0, 12, 24, 36, 48, 60 months
- Endotoxin (NMT (b) (4)) at 0, 12, 24, 36, 48, 60 months
- Container closure integrity by (b) (4) test (pass) at 12, 24, 36, 48, 60 months

Mesoblast committed to the following:

- The (b) (4) lot of final product manufactured from each new DCB lot will be placed into the long-term stability program stored at  $\leq -135^{\circ}\text{C}$  in liquid nitrogen vapor phase).
- A minimum of one commercial scale production batch of final product per year will be placed into the long-term stability program.
- The impact of any significant manufacturing process changes on the stability will be assessed via a change control process. Additional final product from (b) (4) donors may be required to be placed in both Long Term and Accelerated (b) (4) (Freezer)] stability programs.
- Data from at least 6 months on long term stability and (b) (4) accelerated will be required for comparability to current marketed product.

**Overall Reviewer's Assessment of Section 3.2.P.8:**

Provided stability data and stability protocol/commitment are acceptable from DMPQ perspective.

**3.2.A APPENDICES****3.2.A1 Facilities and Equipment**

Mesoblast submitted information about three facilities, Lonza Walkersville, Lonza Singapore, and Integrated Commercialization Solutions. This review is limited to the last two facilities as it has been determined that Lonza Walkersville is the cell bank manufacturer.

**Lonza Bioscience Singapore (LBSS).** The information included in the BLA is limited to the following:

- Facility overview (building description and flows)
- Facility systems (HVAC, EM and facility classification, utilities and process gases, computer systems)
- Equipment
- Contamination and cross-contamination controls
- Facility floor plans (air classification, HVAC zoning; personnel, product, waste, and raw material flows)

Additionally, Mesoblast submitted a letter from Lonza Bioscience Singapore Pte. Ltd. authorizing cross-referencing of their Master File, MF (b) (4), Lonza Bioscience Singapore Cell Therapy Facility in support of the BLA STN 125706/0 filing with the FDA. All information relevant to the DP and included in MF was reviewed below.

**Description.** LBSS is designed to be a multi-product facility for the manufacture of allogeneic cell therapy products. The facility constructed in 2009 is a (b) (4) building consisting of mechanical and cGMP production areas

dedicated to the production of human cells for therapeutic use, administrative offices, warehouse (b) (4) and laboratories. It is directly adjacent to (b) (4) contract manufacturing facility producing recombinant monoclonal antibodies and other proteins. Both facilities are located in the Lonza Singapore campus in Tuas Biomedical Park, share the same address and FEI number, 35 Tuas South Avenue 6, Singapore 637377. LBT and LBSS are connected via two separate “linkways”.

LBSS started manufacturing and testing operations in compliance with PIC/S (Singapore), ICH Q7, and 21 CFR in Q4 2012. Regulatory inspection history includes three inspections performed by Singapore regulatory authority in 2013, 2016, and 2019. All inspections resulted in GMP certificate issuance.

The following areas are located on each floor of the building:

(b) (4)

(b) (4)

None of these spaces are used for storage, testing, or manufacture of ce-MSCs or other cell therapy products.

(b) (4)

(b) (4)





- (b) (4)

Quality control laboratories are located in the (b) (4) Building next to the adjacent LBT facility.

**Finishes** used in LBSS:

*Walls:*

- Grade (b) (4)

*Door frames:* (b) (4)

frame.

*Doors:* (b) (4)

Both doors, frames, and interior windows in the facility have features to ensure pressurization/air classification control (e.g. gasket seals, flush mounting, interlocks and door closers, etc.)

*Floors:* Concrete slab (b) (4) (manufacturing and support areas) or concrete slab with (b) (4) (mechanical space) to ensure chemical and water resistance.

**Flows.**

***Product and process flow.*** Production steps of ce-MSC manufacture take place in the following areas:

(b) (4)

(b) (4)

For products manufactured in Production Suite (b) (4) (not used for ce-MSD), intermediates similarly enter from (b) (4)

Finished product flows are the same for products manufactured in both production suites.

Cell culture media production flow is as follows:

(b) (4)

**Raw material flow.** All materials arrive at the dock in LBT building, where identity (label check) and quantity is verified, and goods are transferred to LBSS warehouse for receipt and storage. Receipt, unique Lonza batch number assignment, and QA release for production is performed electronically via (b) (4) system. Materials that require sampling and testing prior to release are transferred in (b) (4).

Materials arrive on/leave the (b) (4) floor of LBSS via (b) (4). Material flow between various areas on the (b) (4) floor of LBSS is as follows:

- (b) (4)

At the warehouse, raw materials are (b) (4) using (b) (4) prior to transfer into the manufacturing areas via MALs.

All materials enter the controlled areas of the facility from Storage/Tech Area (b) (4) in one of the following ways:

- (b) (4)

All other material flows through the clean rooms or between Clean Corridor and clean rooms are (b) (4), through either material airlocks, gown-in/gown-out, or pass-throughs. Materials are brought directly from (b) (4)

**Control of raw materials** is performed via (b) (4). All materials for GMP operations are checked against the delivery note, visually examined, and entered into (b) (4) upon receipt. Materials are marked as “quarantined” and stored in warehouse. Toxic materials are segregated in a designated lock cage during storage. Samples of raw materials are collected based on item-specific sampling plan and are tested by QC. QA performs disposition of materials and updates (b) (4). Released materials are either stored in the warehouse or used immediately. Rejected materials are secured by locks and access control.

For materials of animal origin, suppliers are required to provide information on the source(s), which should be in compliance with BSE/TSE guidelines and meet Lonza requirements regarding sourcing and traceability of such materials (assessed via a questionnaire). A full Certificate of Analysis with virus and mycoplasma testing results is required for each lot of animal derived materials. Alternatively, a risk assessment must

be in place prior to the receipt. Certificate of Origin is required for each lot of animal-derived material and supplier's Certificate of Suitability or an equivalent documentation should be available for any primary animal-derived material of ruminant specification.

The following animal/human origin materials are used in LBSS facility: donor or working cell banks (cell culture), fetal bovine serum (media component), (b) (4), (b) (4), trypsin (cell detachment), and human albumin (excipient).

**Control of cell banks.** All cell banks to be introduced in the facility require adequate qualification documentation, including a traceable history, testing reports for adventitious agents from either the customer or other Lonza site. Sampling and testing plans for cell banks are agreed upon with customers. A typical testing plan includes (b) (4), 9 CFR testing (porcine, bovine in vitro assays), retrovirus testing, (b) (4) testing, testing for viruses of human origin (unless fully covered by donor testing program), and infectivity assay using a human cell line. Sterility tests and Mycoplasma tests are performed on (b) (4). CofA and shipping documentation are reviewed prior to authorizing cell bank receipt into the facility. QA releases cell banks into the appropriate cell bank storage (b) (4).

All consumable materials with product-contact surfaces are sterile, single use materials (b) (4) by either vendor or manufacturer. Consumables that are not wrapped or single wrapped are sanitized with (b) (4) with (b) (4) and transferred to manufacturing areas for use. (b) (4) wrapped materials are (b) (4) with (b) (4), and the consumable is transferred to the required manufacturing area for use.

**Equipment flow.** Mesoblast stated that equipment flow follows that of raw materials.

**Personnel flow.** Personnel access to manufacturing areas and to different classified zones is controlled by a computerized badge access system. Only trained and qualified personnel can enter manufacturing areas.

Personnel enter/exit the facility through sequential (b) (4). Visitors enter through (b) (4). Unlike personnel entry, visitor entry is (b) (4) (i.e. it is unclear how visitors leave the facility). Gowning rooms and airlocks have compartmentalized interlocking doors.

Personnel flow is (b) (4) through the following manufacturing suites: (b) (4)

(b) (4) For each of these suites, personnel enter from (b) (4) Production Suite (b) (4); exit from this suite is

through (b) (4)

(b) (4) flow is allowed between Clean Corridor and the following clean rooms:  
(b) (4).

Additionally, (b) (4) flow is allowed between:

- (b) (4)

**Waste flow.** Flows for general waste, bio waste and soiled gowns were provided.

General waste and soiled gowns flow from (b) (4)

Bio waste (includes used materials with product contact) from Final Fill leaves via (b) (4)

(b) (4) described above. The waste is segregated operationally and is removed after all filled vials have been passed out of the Final Fill room.

Remaining clean rooms' bio waste exits (b) (4)

General waste from production rooms follows (b) (4)

General waste and bio waste from (b) (4)

Raw materials and bio waste (b) (4)

(b) (4) Additionally, the following airlocks are shared between materials and bio waste: (b) (4) Suite), MAL between Production Suite (b) (4).

General waste from the facility is collected daily by contract cleaners and transported to external general waste open-top containers for disposal.

[illegible]

All AHUs except (b) (4) supply partially recirculated air with at least (b) (4) fresh air. (b) (4) provides (b) (4) fresh (b) (4) pass air to final fill, inspection room and associated airlocks.

The air supplied to clean rooms (Grade (b) (4) ) is HEPA-filtered via (b) (4) terminal HEPA mounted on the ceiling and return air exhaust grille at low level wall. (b) (4) are also in place for (b) (4). Temperatures of the rooms are maintained at (b) (4) except Production Suite (Room (b) (4)) and Media Fill at (b) (4) maximum relative humidity.

Air change information (as designed) was provided for (b) (4) only. Grade (b) (4) areas supplied by these AHUs are designed to have (b) (4)

**Pressure Differentials.** The facility adopts a (b) (4) airlock where air flows from (b) (4). Final fill and Production suite (b) (4) are at the (b) (4) overall relative pressure (approximately (b) (4)). All airlocks are designed to the (b) (4). All doors in classified areas are interlocked. Containment of certain rooms is achieved by using (b) (4) airlocks, where a (b) (4) is maintained. (b) (4) are used for all open processes except for (b) (4) which is performed in a Grade (b) (4) environment.

Per the provided air classification diagram pressure differential of at least (b) (4) (as designed, under static conditions) is set up at each door to ensure air (b) (4) from (b) (4).

Pressure differentials on doors to Storage/Tech Area are (b) (4). In all classified areas, there is no space that is zero or negative pressure with respect to atmospheric pressure.

Air from Production Suite (b) (4)

all other pressure differentials are set to (b) (4).

A similar pressure differential set up is implemented for the Final Fill: (b) (4)

. Pressure differentials at each door are at least (b) (4).

There is no pressure differential between Production Suite (b) (4)

Pressure differential at each door is (b) (4)

Both Airlock and Gown (b) (4)

MAL (b) (4)

difference).

Air from Clean Corridor (Grade (b) (4)

difference).

Pressure differential is monitored by calibrated sensors, connected to Building Automation System, continuously maintained, monitored, and alarmed. All alarms are reviewed and followed up. Records are archived electronically.

**Air Classification and Environmental Monitoring (EM).** Grade (b) (4) areas are used for media fill, final fill, and other open aseptic operations. Provided by (b) (4) (b) (4) Operated with Grade (b) (4) background and are not tied in to an AHU (standalone exhaust fan only).

Grade (b) (4) areas are used as background for Grade (b) (4) for closed manufacturing processes and other less critical manufacturing steps.

Grade (b) (4) are used for less critical manufacturing steps, such as closed processes, staging, inlet for raw materials.

Material pass throughs meet either Grade (b) (4) requirements, depending on the location. Pass through qualification consists of IOQ to ensure proper installation and air (b) (4) operation post-opening. PQ of pass throughs is included in the EMPQ. They are also a subject to routine EM.

**EMPQ** was performed over a period of (b) (4) consecutive days during which the total airborne particulates, surface-viable and viable airborne particulates are monitored under routine operating conditions.

**EM program** includes sampling for total airborne particulates (by (b) (4) ), viable airborne bioburden (by (b) (4) ) and viable surface bioburden (by (b) (4) ).

The following action limits (in operation) are implemented in LBSS facility:

(b) (4)

Sampling frequency for routine monitoring depends on room classification. Routine EM of Grade (b) (4) and Grade (b) (4) rooms is performed (b) (4) . This is in addition to dynamic EM and personnel monitoring (prior to exit of Grade (b) (4) areas) performed during (b) (4) aseptic operation. Alert levels and EM trending data are regularly evaluated.



**Facility Cleaning and Sanitization.** Cleaning is performed (b) (4) unless production activities span over the (b) (4), in that situation, the minimum cleaning requirements are as follows:

- (b) (4)

Cleaning is performed using (b) (4) disinfectants. Per Mesoblast, all cleaning agents and disinfectants were qualified for their use (concentration, method of application, frequency of use and rotation).

Effectiveness of cleaning agents was verified during EMPQ.

Several disinfectant effectiveness summary reports testing various disinfectants on all facility surfaces and against different microorganisms (mostly in-house isolates) were provided in MF (b) (4)

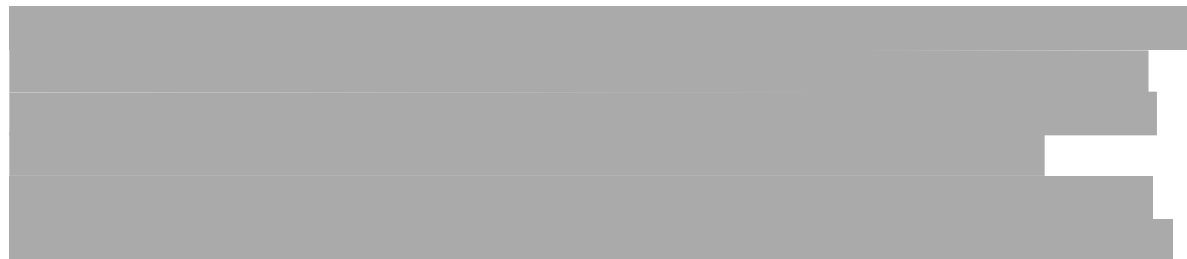





1. SGTS-6434 effective 10/30/2011
2. SGTS-9630 effective 1/11/2012
3. SGTS-13185 effective 2/16/2015
4. SGTS-14813 effective 3/12/2015
5. SGTS-19905 effective 4/25/2018

All studies evaluated (b) (4) contact time for all disinfectants and surfaces tested. I evaluated the provided results. In all cases the acceptance criterion of (b) (4) reduction for fungi and spore-forming organism, and (b) (4) reduction for vegetative bacteria was met. Some studies evaluated (b) (4) with regards to effect on sporeformers for information only, as it was not expected (and did not demonstrate) to have sporicidal effect. The details of each study are provided below.

(b) (4)



(b) (4)



**Water Systems.** Source water is supplied by Singapore's Public Utilities Board where the quality meets WHO standards for drinking water. It is (b) (4) into the WFI generator.

(b) (4) WFI supplied from the generator is circulated (b) (4)



Piping of the distribution system is

(b) (4)

Source water, pre-treated water, and WFI are monitored by QC (microbial and chemical testing). Water used for direct manufacturing purposes meets the (b) (4) of water-for-injection (WFI):

(b) (4)

WFI (b) (4) in LBSS is monitored (b) (4) for (b) (4), and (b) (4) for all other tests. WFI from (b) (4) is monitored (b) (4) for all microbial and chemical tests. (b) (4) point is sampled (b) (4) for (b) (4). Water monitoring data are regularly evaluated and trended.

**Clean Steam.** Clean steam is produced by (b) (4) as feed water. The quality meets the (b) (4). Acceptance criteria. Clean steam is supplied (b) (4).

**Clean Compressed Air (CCA)/Instrument Air.** CCA is produced by the (b) (4)

**Process gases.** Process gases such as (b) (4) are obtained from qualified suppliers according to LBSS supplier and contractor qualification procedures. They are supplied in (b) (4).

**Computer systems.** Mesoblast stated that all systems used in GMP manufacture are 21 CFR Part 11 compliant. The following computer systems are used at LBSS:

Quality Management:

- (b) (4): managing GMP document creation, approval, and distribution

- (b) (4) workflow management (deviations, investigations, commitments, change control, customer complaints, audit observations, CAPAs)
- (b) (4) Training module: managing training plan, logging training record, and maintaining training history for all employees engaged in GMP activities.

#### Quality Control

- Laboratory Information Management System (LIMS): lab management (e.g. sample receiving, tracking, disposition, instrument management), data management (e.g. data logging, result reviewing), generation of worksheet and test reports.
- (b) (4) Inventory Manager and Laboratory Execution System: module-based software for laboratory inventory and data management, managing Form templates and generating (b) (4) Worksheets.
- Mobile Acquisition Data (MODA): LIMS for EM data logging, trending, and reporting

#### Logistics

- (b) (4) system designed to plan, track and control material purchases and product production; maintain inventories; control the release of raw materials, quarantined goods, and finished products; and process customer orders.

#### Equipment, Facilities, and Utilities Monitoring

- Plant Wide Control System (PWCS): system for equipment monitoring and control that allows operators to control equipment by communicating with PLCs, monitoring and displaying equipment status on graphic user interface GUI, logging process data including all alarms, and provide audit trails to all linked equipment.
- Building Automation System: control and monitor HVAC and on/off alarms of environmental chambers (e.g. cold rooms, freezers, incubators, dewars)
- (b) (4): monitor and execute instrument calibration.

**Equipment.** No product contact equipment is used in manufacture of Remestemcel-L. All product contact materials are single use and made of either inert plastics or stainless steel. A list of major non-product contact equipment is included below. Equipment IDs are included for qualified equipment based on the information provided in LBSS MF:

Equipment	Use/Process Step	ID	Room
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Additional qualified equipment used for Remestemcel-L projects and not listed in the table above include

- (b) (4)

Per information included in LBSS MF all equipment at the facility is shared except (b) (4) (can be either dedicated or shared), (b) (4), and (b) (4)

Equipment qualification activities (IOPQ) are governed by LBSS validation master plan. Appropriate validation activities are determined based on the system impact assessment/ component criticality review.

Preventive maintenance program is in place at the facility. Equipment requiring calibration is placed on the calibration program as well.

**Equipment Cleaning/Sanitization.** Cleaning and changeover are proceduralized. Non-product contact surfaces of equipment are routinely cleaned using the qualified cleaning and sanitizing agents (b) (4). More extensive equipment cleaning is performed during change over (b) (4)

Small apparatuses for (b) (4) preparation are manually cleaned using validated cleaning procedures. They are then sterilized in an (b) (4). After cleaning, (b) (4) samples are tested for (b) (4) for cleaning verification.

Details of each cleaning method include defined soiled holding time, cleaning agent contact time, rinsing time, and clean hold time.

**Contamination and Cross contamination controls.**

The following measures to prevent contamination and cross-contamination at LBSS are in place (see above for more details):

- (b) (4)

- (b) (4)

**Contract Service Providers.** LBSS primarily subcontracts the following services:

- Laboratory services (routine raw material testing, in-process, release, and stability testing)
- Calibration/metrology services

Material suppliers and contractors are qualified either directly or through Lonza global network. Assessment is performed by either on-site or desktop audit based on risk assessment. In addition to customer-specific contract laboratories, the following contract laboratories are used:



- (b) (4)

**Operator training.** Operators are trained in all relevant SOPs and performance measures prior to carrying out cGMP activities. Operators who work aseptically within Grade (b) (4) environment must pass their individual aseptic qualification requirements (Basic Operator Aseptic Process Simulation, Advanced Cell Therapy Operator Aseptic Process Simulation, and Aseptic Technique in the Cell Therapy Manufacturing Areas) as well as the Training Program.

Aseptic process simulations are designed to simulate the worst case scenario of production process, repetitive processing steps, and operator fatigue.

**Gowning Requirements.** Initial gowning for facility entry (Grade (b) (4) areas) consists of the following steps:

- (b) (4)

**Products Manufactured at the Facility.** In addition to Remestemcel-L, the facility manufactures the following clinical products:

(b) (4)

**Integrated Commercialization Solutions (ICS)** is a multi-product storage, secondary packaging and distribution facility for cell-therapy products, small molecules, biologics, devices and drug/device combination products. It has a footprint of (b) (4) of warehousing and storage space within a single building. Separate areas are dedicated for specific storage requirements, by temperature and/or regulatory controls:

(b) (4)

A segregated (b) (4) area bounded is dedicated for GMP activities including labeling, relabeling, packaging, repackaging, kitting, gross inspections of external containers or packaging, and serialization activities.

At ICS, the ce-MSD DP vials and packaged finished DP are stored in (b) (4) adjacent to the GMP Solutions Area]. Inbound product is received, cryostored, then transported from the (b) (4) to the GMP Solutions area for packaging, and then returned to cryostorage until distribution.

**Drug Product Vial Receipt and Storage Process.** (b) (4)

(b) (4)

**Secondary Packaging and Shipment to Customer Process.** The final packaging configuration consists of either a single vial or four vials enclosed in a carton, with each configuration having a separate product code and batch record.

Prior to packaging, a (b) (4)

at  $\leq -135^{\circ}\text{C}$ .

### **Facility Systems**

**Temperature Control Systems.** Temperatures within the warehouse are maintained by (b) (4) AHU spaced throughout the warehouse. The number of units provides (b) (4) redundancy in the event of a HVAC unit failure. All AHU are supported by an emergency generator that can support the HVAC units for up to (b) (4) days on a full fuel tank in the event of a power loss. The tanks can be replenished as needed and the fuel level is maintained at not less than (b) (4) of a tank.

The (b) (4) temperature is maintained by liquid nitrogen that fills the (b) (4) automatically.

**Inventory Control Systems.** Inventory tracking (location, i.e. (b) (4) ) and status (e.g. quarantined) at ICS is managed using a validated and 21 CFR Part 11 compliant (b) (4) system. Quarantined stock is physically segregated from released stock.

Goods receipt is performed and documented in an Incoming Receipt Inspection Record (IRIR), in the (b) (4) System and the ICS inventory management system, (b) (4) operating software, which is specific for the management of product in (b) (4)

storage. The (b) (4) operating software communicates directly with the (b) (4) system.

Packaged vials are returned to the (b) (4) and received in as a new part number and lot number, tracked in (b) (4). The lot number is the Lonza generated lot number plus a letter suffix relevant to the number vials in the packaged carton presentation (1 or 4 vials). The packaged vials are stored as quarantine until the final executed batch record is approved by Mesoblast. ICS systematically changes the stock status to match the disposition provided by Mesoblast in (b) (4). Released product is then available for distribution.

**Equipment.** There is no product contact equipment at the ICS facility. The following key non-product contact equipment was listed:

- (b) (4) : storage of DP vials and cartoned product
- Cryoshippers: shipment/movement of finished product
- Liquid nitrogen vapor container: (b) (4)

No qualification reports were provided for any equipment.

**Controls to Prevent Contamination and Cross Contamination.** The following controls were listed:

- (b) (4)

### **Overall Reviewer's Assessment of Section 3.2.A1:**

**LBSS facility:** Overall the information provided in the BLA is high level and, excluding floor plans, is insufficient for review. Qualifications of none of the equipment (including HVAC and EMPQ) or utilities was included. No routine monitoring (EM or utilities) was described. Based on the information included in the DMF for LBSS facility, qualification studies were performed; however, the DMF only contains summaries of qualification

reports that do not include study/testing/sampling description, acceptance criteria or results. As such, this information was requested in a series of IR below.

**Integrated Commercialization Solutions facility:** Provided information is high level and is insufficient for review. As such, this information was requested in a series of IR below.

The response to the IR will be reviewed in the addendum memo. The IR is shown in bold below.

**Q.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.**
- 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.**
- 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)**
- d. Please clarify how WFI supplied by LBSS water system is used in DP manufacture, facility or equipment cleaning, incubator/facility air humidification, etc.**
- 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)**
- 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.**
- g. A description of routine monitoring programs for water and process gases, including frequency and type of testing performed.**
- 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).**

**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

The response to the IR of 6/2/2020 will be reviewed in the addendum memo. The IR is shown in bold below.

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

- a. (b) (4) room (floor plans)
- b. (b) (4) wall panel system
- c. (b) (4) (AHU zoning diagram)

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

- a. (b) (4) room
- b. (b) (4)
- c. (b) (4)

**Q.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).
- b. A clarification whether the pass throughs are active or passive.
- c. A representative qualification report, including description of testing performed, acceptance criteria and results. Please specify differences in qualifications of different passthroughs, if any.
- d. Qualification completion dates and summary of deviations/ investigations/ CAPAs associated with qualification of all pass throughs.

**Q.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.**

**Q.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
- b. Please clarify if your storage areas room classification are CNC or not-controlled
- c. Visitor entry into the facility is shown as (b) (4). Please clarify how visitors exit the facility.

- d. Please explain the use/purpose of the facility doors on the floor plans that have no flow shown through them (e.g. Production Suite (b) (4) to Utility Area, Clean Corridor to Services Corridor, Kitting Room to Corridor). If these are fire doors, please explain what controls are in place to ensure they are only opened in case of an emergency.
- e. There is a material flow shown from Storage/Tech to Utility area. However, there is no personnel flow between these areas.
- f. General waste flow from Production Suite (b) (4) was not shown

**Q.9. Regarding your on-site media production:**

(b) (4)

**Q.10. It was stated in the LBSS MF that (b) (4) is used in (b) (4) [REDACTED]. Please confirm that this is not applicable to Remestemcel-L process.**

**Q.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.

**Q.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.

**Q.13.** Please provide the description of your HVAC system including a diagram of 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

**Q.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.

**Q.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.

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

**Q.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)
- b. An explanation when each type of the sealer/welder is used
- 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
- d. Please explain if you allow tubing reuse for welding
- e. A list of any tubing weld/seal deviations and associated CAPAs



**Q.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)

**Q.19. Regarding your computerized systems:**

- a. It appears that your LIMS and (b) (4) systems are redundant please clarify the use of each system
- b. Please provide a brief description of your change control and back-up procedures (including back-up storage location) for all computerized systems

**Q.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

**Q. 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.
- 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.)
- c. You stated that (b) (4) . Please define “open workstation” and “production line”. Provide photographs if needed for clarity.
- 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.

**Q.22. Please clarify difference 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.**

**Q.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.**

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

**Q.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.**

The response to the IR of 5/4/2020 will be reviewed in the addendum memo. The IR is shown in bold below.

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

### **3.2.A2 Adventitious Agents Safety Evaluation**

Defer to PO.

#### **□ Viral Clearance Studies**

Defer to PO.

### 3.2.A3 Novel Excipients

NA

### 3.2.R Regional Information (USA)

#### ❑ Executed Batch Records

The following regional information was provided in this section:

- Manufacturing establishment information
- Executed batch records for DCB (b) (4), (b) (6) and DP batch (b) (4).
- Batch certification for bulk product batch (b) (4)
- Certificate of testing for batch (b) (4)
- Certificates of analysis for BMA lots (b) (4), (b) (6)
- Certificates of analysis for DCB (b) (4), (b) (6) issued by Osiris (2012) and Mesoblast (2020)
- Certificate of compliance for DP lot (b) (4)
- Cell bank retest certification for DCB (b) (4), (b) (6)
- Lot traceability from bone marrow donor to final product for lot (b) (4)
- Quality assurance control sheet for lot DCB (b) (4), (b) (6)
- Clinical bone marrow donor program summary of records for BMA lots (b) (4), (b) (6)

#### ❑ Method Validation Package

NA

#### ❑ Combination Products

NA

#### ❑ Comparability Protocols

NA

### Overall Reviewer's Assessment of Section 3.2.R:

Information within DMPQ purview appears acceptable. Evaluation of batch records from Quality System perspective will be performed during PLI.

### **Module 1**

#### **A. Environmental Assessment or Claim of Categorical Exclusion**

Defer to PO.

#### **B. Labeling Review**

#### **Full Prescribing Information (PI):**

Defer to PO.

**Carton and Container Label:**

Defer to PO.

**Modules 4 and 5**

**Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints**

Defer to PO.