

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file [STN 125706/0.65]

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
M. Nahid Parvin, Ph.D.	Lead Reviewer	07/07/2023		Muhammad Shahabuddin, Ph.D.	
Claire H. Wernly, Ph.D.	Reviewer	05/04/2023		Simleen Kaur, M.S.	
Salil Ghosh, Ph.D.	Reviewer	07/12/2023		Kenneth S Phillips, Ph.D.	

Through Maryna Eichelberger, Ph.D.
 Division Director, DBSQC/OCBQ

Applicant: Mesoblast Inc.

Subject: Review of Analytical Methods used for Ryoncil™ (Remestemcel-L) Drug Product (DP) Lot Release

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release of Ryoncil™ (Remestemcel-L) and the associated analytical method validations or qualifications, were reviewed:

1. Residual Bovine Serum Albumin (BSA) by (b) (4) for DP (M. Nahid Parvin)
2. Mycoplasma test for DP (Claire H. Wernly)
3. Quantitation of Residual rTrypsin using (b) (4) for DP (Salil Ghosh)

Conclusion: The analytical methods and their validations and/or qualifications reviewed for the Ryoncil™ (Remestemcel-L) drug product were found to be adequate for their intended use.

Documents Reviewed:

Information in sections of the complete response (CR) submission that describe control of Drug Product (DP) (3.2.P.5) including descriptions of DP specifications, analytical procedures of DP and validation of analytical procedures were reviewed. Additional information in amendments #125706/0.72, #125706/0.75, and #125706/0.81 received on April 13, May 01, and May 23, 2023, respectively, were also reviewed.

Background:

Mesoblast Inc. submitted their response on the complete response (CR) letter (September 30, 2020) of original BLA for Remestemcel-L for the treatment of acute Graft versus Host Disease (aGVHD) on January 30, 2023. The proposed indication is steroid refractory (SR)-aGVHD (grade B-D) in pediatric patients. Remestemcel-L is a liquid cell suspension of ex-vivo culture-expanded adult human mesenchymal stromal cells (ce-MSCs) derived from allogeneic bone marrow. It is sterile, preservative free and formulated in 3.8 mL of cryo-medium composed of 70% v/v Plasma-Lyte A, 20% v/v human serum albumin (HSA) solution (25%) and 10% v/v dimethyl sulfoxide (DMSO), to a nominal cell concentration of 6.68×10^6 viable cells/mL for each DP unit vial. The recommended dose of Remestemcel-L is 2×10^6 hMSC/kg (body weight).

The active agent in the Remestemcel-L Drug Substance (DS) is ex vivo cultured human mesenchymal stromal cells (ce-MSCs), derived from the bone marrow aspirates of unrelated and human leukocyte antigen (HLA) unmatched healthy adult donors. The first stage process is the production of the intermediate drug substance, also referred to as the Donor Cell Bank (DCB), which is manufactured at Lonza Walkersville, Inc (LWI), MD, USA. The (b) (4)

and seeded into plastic cell factories. The MSC population is selected through their adherence to the plastic surface. This primary culture is grown to confluence and passaged to expand cell numbers. At passage 2, cells are harvested and cryopreserved to form a DCB.

The DS is produced as part of the second stage process. DCB is transported to Lonza Bioscience Singapore Facility (LBSS) for manufacture of the DS and DP. DCB are thawed and following a series of 5 cell culture expansions ce-MSC are harvested as DS and formulated into DP at a concentration of 6.68×10^6 viable cells/mL. The DP is filled into vials and cryopreserved for storage in liquid nitrogen vapor phase at $\leq -135^\circ\text{C}$.

DBSQC completed the review of residual BSA, Sterility, Endotoxin, Mycoplasma, residual Trypsin and Appearance analytical methods for DP in the original BLA submission. Please refer to DBSQC consolidated review memo dated August 05, 2020. There was no change to Sterility, Endotoxin and Appearance methods and the tests remain suitable for their intended purpose. In the CR submission, Mesoblast submitted a new validation/qualification report of the above-listed analytical methods.

The following facilities perform the methods reviewed:

1. (b) (4)
2. (b) (4) (Lonza Bioscience Singapore Facility)
3. (b) (4)

In this review memo, the analytical method and validation and/or qualification for determination of residual BSA by (b) (4), Mycoplasma, and quantitation of residual rTrypsin using (b) (4) for DP is reviewed.

1. Determination of residual BSA by (b) (4), M. Nahid Parvin

Introduction

Raw materials used in the manufacturing process of ce-MSD are potential sources of process-related impurities in the final DP. These include (b) (4), Fetal Bovine Serum (FBS) and trypsin. (b) (4)

(b) (4) residual FBS may be in DP in trace amounts and present risks of product contamination with adventitious agents, and of immune reactions in patients who are allergic to bovine proteins. However, these risks are minimized by control of FBS material prior to introduction into the manufacturing process and by (b) (4) steps, (b) (4), and (b) (4) that remove FBS from ce-MSD.

Residual levels of BSA in the ce-MSD DP are controlled through measurement of residual BSA in (b) (4). In the original BLA submission, residual BSA was measured utilizing (b) (4). Residual levels of BSA in the current (b) (4) lots of commercial DP were trended using this (b) (4) and a tightening of the specification from (b) (4) was recommended.

(b) (4)

The updated analytical method and validation for determination of residual BSA by (b) (4) is reviewed below.

Analytical method is a (b) (4) for quantitation of residual BSA present in the ce-MSD final drug product. Mesoblast Inc contracted (b) (4) to perform lot release testing using a commercially available quantitative (b) (4). There are two testing sites (b) (4). The assay was validated at both sites.

Method

(b) (4)



(b) (4)



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

(b) (4)



Conclusion:

Based on the data reviewed, the analytical procedure and validation of analytical procedure for determination of residual BSA by (b) (4) is acceptable and appropriate for intended use.

2. Mycoplasma Method (DP), Claire H. Wernly

Introduction

Mesoblast subcontracted mycoplasma assay qualification and routine testing to (b) (4) and submitted the initial qualification study performed by (b) (4), site which was reviewed in the original submission and found acceptable.

In the CR submission, Mesoblast submitted a new qualification study report and test details for mycoplasma performed at (b) (4) site as an alternate mycoplasma testing site.

This review will focus on the qualification of mycoplasma test method for Ryoncil™ DP at (b) (4) site, to indicate if the method is suitable under the actual conditions of use. Acceptance criteria of (b) (4) must be met for the release of (b) (4).

Method

(b) (4)



(b) (4)



(b) (4)



(b) (4)

Conclusion

(b) (4) methods were performed, and the results were compliant with (b) (4), thus demonstrating the methods are suitable under the actual conditions of use.

3. Quantitation of Residual rTrypsin using (b) (4) (DP), Salil Ghosh

Introduction

During the manufacture of ceMSC DP, recombinant trypsin is used (b) (4) during the production of final product. (b) (4). The (b) (4) method to measure residual rTrypsin was validated by evaluating specificity, precision, accuracy, linearity, range, and limit of quantitation (LOQ); review of the information showed that the assay was suitable for its intended purpose and documented in DBSQC Consolidated review memo for analytical methods, dated August 6, 2020. At that time, the specification of residual rTrypsin was (b) (4) but has been tightened to (b) (4) for proposed commercial DP lots. The lowest concentration of standard in the calibration curve is (b) (4) rTrypsin, and all validation criteria are met at this concentration including linearity. Therefore, the assay remains suitable for measuring residual rTrypsin with a specification of (b) (4).

In Amendment 0.65, additional residual rTrypsin assay characteristics (stability of (b) (4) were validated following protocol c24236-3. The use of (b) (4) in the assay is the only change in the description of Quantitation of Residual rTrypsin in ceMSC using (b) (4) (SOP 00799 version 9).

Method Validation

(b) (4)

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

(b) (4)



Conclusion

Based on the information provided in the original BLA submission, as well as in Amendment 65, it is concluded that the Quantitation of Residual rTrypsin in ceMSC using (b) (4) is still suitable for lot release testing.