



DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file: STN 125706/0

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
Most Nahid Parvin	Lead Reviewer	07/09/2020		Muhammad Shahabuddin	
Claire Wernly	Reviewer	07/14/2020		James Kenney	
Salil Ghosh	Reviewer	08/03/2020		Kori Francis	

Through: Maryna Eichelberger PhD.
Division Director, DBSQC

Applicant: Mesoblast Inc.

Subject: Review of Analytical Methods used for Ryoncil (Remestemcel-L, ex vivo culture expanded mesenchymal stromal cell) Drug Product Lot Release

Recommendation: Approval

Summary:

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

1. Residual BSA by (b) (4) for DP (M. Nahid Parvin)
2. Sterility for DP (Claire Wernly)
3. Endotoxin for DP (Claire Wernly)
4. Mycoplasma for DP (Claire Wernly)
5. Quantitation of Residual rTrypsin using (b) (4) for DP (Salil Ghosh)
6. Appearance for DP (Salil Ghosh)

Conclusion:

The analytical methods and their validations and/or qualifications reviewed for the Ryoncil drug product were found to be adequate for their intended use.

Documents Reviewed:

This is an electronic submission. Information submitted and reviewed includes:

- 1.2 Cover letter, dated 29 May 2019
- 1.2 Cover letter, dated 04 September 2019
- 2.2. Introduction
- 2.3.P. Drug Product
- 3.2.S.4. Control of Drug Substance
 - 3.2.S.4.1 Specifications
 - 3.2.S.4.2 Analytical Procedures
 - 3.2.P.5.2. Analytical Procedures
 - TM 21355 Analytical Procedure of Determination of residual BSA by (b) (4) for Mesoblast (GMP)
 - SOP 00799- Quantitation of Residual rTrypsin in ceMSC using (b) (4)
 - SOP 33578.01: Determination of Appearance According to the (b) (4) for Mesoblast
 - 3.2.P.5.3. Validation of Analytical Procedures
 - Test Validation Report C21315.01 Method Validation Report for Determination of residual BSA by (b) (4) for Mesoblast (GMP)
 - Method Validation C16766.1: Biologics License Application (BLA) Validation of SOP ACF-0300; Quantitation of Residual rTrypsin in ceMSC using (b) (4)
 - Method Validation Report C21897.00: Verification of Determination of Appearance According to the (b) (4) for Mesoblast
 - 3.2.P.5.4. Batch Analysis
 - 3.2.P.5.6. Justifications of Specifications
 - 3.2.P.6. Reference Standards or Materials

- 125706/0.26 (Amendment)-Recd 05/14/2020-DATS#890795
- 125706/0.37 (Amendment)-Recd 06/30/2020-DATS#901441

Background:

Mesoblast Inc. submitted their original BLA for Ryoncil (Remestemcel-L) for the treatment of acute Graft versus Host Disease (aGVHD) on January 31, 2020. The proposed indication is steroid refractory (SR)-aGVHD (grade B-D) in pediatric patients. Ryoncil is a liquid cell suspension of ex-vivo culture-expanded adult human mesenchymal stromal cells (ce-MSCs) derived from allogeneic bone marrow. It is supplied as a sterile, preservative free and formulated in 3.8 mL of cryo-medium composed of Plasma-Lyte A (70% v/v), human serum albumin (HSA) 25% solution (20% v/v, comprising 5% HSA and 15% buffer) and dimethyl sulfoxide (DMSO) (10% v/v) with 6.68×10^6 viable cells/mL. The recommended dose of Ryoncil is 2×10^6 hMSC/kg (actual body weight).

The sponsor requested priority review under the Fast Track designation of the Federal Food Drug and Cosmetic Act 506 (a) for Ryoncil for use in SR-aGVHD. SR-aGVHD is a serious and life-threatening condition which has a devastating effect on pediatric patients and a high mortality rate. The only FDA approved treatment for SR-aGVHD is Jakafi® (ruxolitinib) for ages 12 and older. There is currently no approved treatment available for children with SR-aGVHD younger than 12 years of age.

The active agent in the Ryoncil 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 $\leq -135^\circ\text{C}$.

In this review memo, the analytical method and validation and/or qualification for determination of residual BSA by (b) (4), sterility, endotoxin, mycoplasma,

quantitation of residual rTrypsin using (b) (4) and appearance for DP is reviewed.

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

Introduction

Analytical method explained in Section 3.2.P.5.2. is a (b) (4) for quantitation of residual BSA present in the ce-MSD final drug product. Mesoblast Inc contracted a test lab (b) (4) for testing and validation for this assay. (b) (4) uses commercially available quantitative (b) (4) for determination of residual BSA.

Review of Method:

(b) (4)

[Redacted content]

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

(b) (4)

(b) (4)

Review of Response:

The sponsor's response is acceptable.

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. Sterility (Drug Product) (Claire Wernly)

Introduction

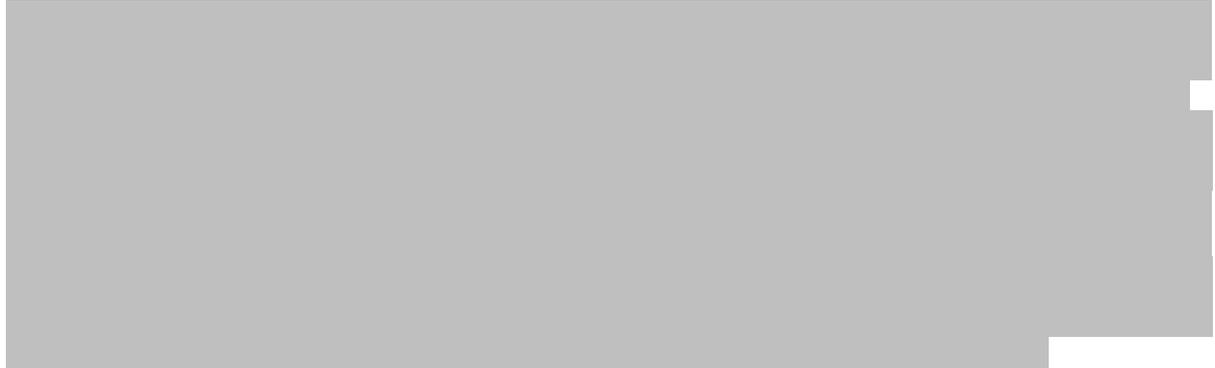
DP is tested for sterility at (b) (4) using SOP#00006.03 "Sterility testing by (b) (4)". The test is designed to detect the presence of micro-organisms in the test article by (b) (4). The method is described below, together with the tests that were performed to demonstrate suitability of the test method.

Review of Method:

(b) (4)

Sterility Test Qualification:

(b) (4)



Conclusion:

The sterility test is adequately described and appropriately qualified under the actual condition of use for the DP.

3. Endotoxin (Drug Product) (Claire Wernly)

Introduction

The test is performed (i.e., qualified via (b) (4) bacterial endotoxin test (b) (4) method) by (b) (4) to ensure the method can detect or quantitate bacterial endotoxins that may be present in the test samples.

Review of Method:

(b) (4)



(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Information Request and Review

The following question was sent in an IR to the sponsor on June 11, 2020 and response was received on June 30, 2020.

- a. Protocol number 00004.02 discusses use of both the (b) (4) Assay as well as the (b) (4) assay for Endotoxin testing in accordance to (b) (4) We have received qualification report for (b) (4) assay; however, qualification study for (b) (4) assay was not submitted as part of section 3.2.P. Please provide the missing qualification report for review, to ensure method is suitable under the actual conditions of use.

Review of the Response

Mesoblast clarified that only the (b) (4) Assay is qualified and utilized for testing of DP. The response was found acceptable.

Conclusion:

The (b) (4) test is adequately described and appropriately qualified according to the actual condition for use for detection or quantitation of bacterial endotoxins present in DP.

4. Mycoplasma (Drug Product) (Claire Wernly)

Introduction

The test is performed (i.e., (b) (4) methods) by (b) (4) to ensure the method can detect the presence of mycoplasma in the DP.

Review of Method:

(b) (4)



(b) (4)



(b) (4)



(b) (4)





Information Request and Review

The following question was sent in an IR to the sponsor on June 11, 2020 and response was received on June 30, 2020.

- b. A (b) (4) of the (b) (4) assay (b) (4) method are considered the (b) (4) for mycoplasma testing for biologics produced in cell substrates in accordance to (b) (4). We have received qualification report for (b) (4) assay; however, studies for (b) (4) methods were not submitted as part of section 3.2.P. Please provide the missing qualification reports for review to ensure methods are suitable under the actual conditions of use.

Review of the Response

A detailed qualification report was provided in the response. The reviewer found all requested information from the report. The response was found acceptable.

Conclusion:

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

5. Quantitation of Residual rTrypsin in ceMSC using (b) (4) [redacted] (Salil Ghosh)

During the manufacture of ceMSC DP, recombinant trypsin (rTrypsin) is used in (b) (4) [redacted]

Method:

(b) (4) [redacted]

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

(b) (4)

Conclusion

Based on the information provided in the BLA submission, it is concluded that the Quantitation of Residual rTrypsin in ceMSC using (b) (4) assay is suitable for lot release testing of Ryoncil DP.

6. Appearance (Drug Product) (Salil Ghosh)

The verification for the (b) (4) method was designed according to Mesoblast's test article ceMSC (b) (4). This assay is an appearance test, which visually evaluates physical state, presence of particulates, color and clarity of the DP. The test is verified and performed for lot release at (b) (4)

Method:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Conclusion:

Test Article ceMSC (b) (4) is a simple assay and has been successfully verified for lot release testing of Ryoncil DP.