DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

CBER REGULATORY REVIEW MEMORANDUM

Date 02 January, 2018

From Simleen Kaur
Laboratory of Microbiology, *In-Vivo* Testing and Standards (LMIVTS)
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To Biologics License Application Submission Tracking Numbers 125659/0

Subject BLA: Review of Bioburden, Sterility and Endotoxin Test Method Qualifications for Plasminogen (Human)

Through James L. Kenney, D.Sc., Chief, LMIVTS
Maryna Eichelberger, Ph.D., Director, DBSQC

Applicant Prometic Biotherapeutics Inc. (Prometic)

Product Plasminogen (Human)

Biologics License Application (BLA) Submission Tracking Number (STN) 125659/0

Submission Received by CBER 14 August, 2017

Review Completed 02 January, 2018

Material Reviewed

Method qualifications for: 1) bioburden; 2) sterility; and 3) endotoxin tests performed on Plasminogen (Human) and response to CBER's information request, received 18 October of 2017, were reviewed.

Executive Summary

After a thorough review of the this BLA, this reviewer finds the bioburden, sterility and endotoxin test methods were qualified in accordance with (b) (4) respectively, and the Plasminogen product (b) (4) DP matrixes were demonstrated to be suitable for these intended test methods.

Background

On 14 August, 2017, Prometic submitted this BLA for Plasminogen (Human) indicated for replacement therapy in adults and children with plasminogen deficiency. Plasminogen drug product (DP) contains 68.8 mg lyophilized plasminogen supplied in a 50-mL glass vial. Each vial is reconstituted with 12.5 mL sterile water for injection and passed through a disc syringe filter before administration. Upon reconstitution, the vial contains 5.5 mg/mL plasminogen. The recommended dosage for plasminogen was initially assigned as (b) (4) but was lowered to 6.6 mg/kg during clinical trial studies. Plasminogen is infused intravenously, as bolus, at a rate of 5 mL/min in 10-30 minutes and is given every 2-4 days to maintain a plasma plasminogen activity level of at least 10% above patient's baseline level.

Plasminogen drug substance (DS) is manufactured by Prometic and tested for (b) (4) prior to release for DP formulation. The formulated DP is shipped to (b) (4) where it filled, lyophilized and packaged for final release. The final container is tested for sterility and endotoxin by (b) (4) prior to release.

The DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews endotoxin release specifications to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are released per their product's licensed test method specifications. Therefore, this review will focus on the bioburden, sterility and endotoxin test method qualifications to ensure the Plasminogen (b) (4) DP matrixes are suitable for these intended test methods.

Review

(b) (4)

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(b) (4)

(b) (4)

Sterility Test Qualification for DP

(b) (4) qualified their sterility test for Plasminogen DP matrix using the (b) (4) method by performing (b) (4) qualification studies to demonstrate the matrix is suitable for the intended test method. The test was performed using (b) (4) lots of DP final container (i.e., lot numbers: (b) (4)).

(b) (4)

(b) (4)

(b) (4) Bacterial Endotoxin Test (b) (4) BET) Qualification for DP
(b) (4) qualified (b) (4) BET method for Plasminogen DP to verify their product matrix is suitable for the intended test method in accordance with (b) (4)

(b) (4)

Prometic submitted the endotoxin results for several DP lots, which met their endotoxin test specification of (b) (4) . CBER finds these proposed specifications acceptable.

Conclusions

Based on the review of Prometic's qualification studies for bioburden, sterility and endotoxin submitted in this BLA, this reviewer finds the test methods were qualified in accordance with (b) (4) respectively, and Plasminogen (Human) (b) (4) drug product matrixes are suitable for the intended test method. Therefore, this reviewer recommends approval of these tests in the production of Plasminogen (Human).