



DEPARTMENT OF HEALTH & HUMAN SERVICES

Division of Biological Standards & Quality Control, Office of Compliance & Biologics Quality,
Center for Biologics Evaluation & Research, Food & Drug Administration, 1401 Rockville Pike, Rockville, MD 20852

MEMORANDUM

To: Administrative file for STN 125659

From: Noel Baichoo, Ph.D.
Laboratory of Biochemistry, Virology and Immunochemistry (LBVI)
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)

Subject: STN 125659/0 – Review of analytical methods used for testing Identity by (b) (4)
[REDACTED] for Plasminogen (Human) Drug Product
RYPLAZIM.

Applicant: Prometic Biotherapeutics, Inc.

Through Muhammad Shahabuddin, Ph.D.
Chief, LBVI/DBSQC/OCBQ/CBER/FDA

Maryna Eichelberger PhD.
Division Director, DBSQC/OCBQ/CBER/FDA

Recommendation: Acceptable

Summary:

A new BLA was submitted for a Plasminogen (Human) Drug Product. This document constitutes the Primary Review Memo from DBSQC for the (b) (4) [REDACTED] method used for determining identity and its validation for use in lot release.

Conclusion: On the basis of the review of the original submission the test for identity by (b) (4) [REDACTED] is approvable for quality control testing.

Background:

On August 11, 2017 Prometic Biotherapeutics submitted a BLA (STN 125659) for a Drug Product (DP) RYPLAZIM, Plasminogen (Human). This drug product is indicated for replacement therapy in children and adults with plasminogen deficiency.

Plasminogen is expressed as an 810 amino acid zymogen. After removal of the signal peptide it becomes 791 amino acids in length with an approximate molecular weight of 90 kDa. This form of plasminogen is referred to as Glu-plasminogen. Cleavage between Lys77 and Lys78 yields Lys-plasminogen which is

around 83 kDa in size. Plasminogen can be converted to plasmin by cleavage at an activation site by various enzymes including tissue plasminogen activator, urokinase plasminogen activator, kallikrein, and factor XII. Plasminogen is secreted in a closed conformation which is resistant to activation. Upon binding to clots or the cell surface, plasminogen changes conformation which allows conversion to plasmin. Plasmin is a serine protease that targets several blood proteins including fibrin to dissolve clots.

The plasminogen Drug Substance (DS) is derived from human donor plasma. Plasma is (b) (4)

Drug product is prepared from the DS by (b) (4), filling and lyophilization in glass vials. The final container is a 50 ml vial which contains 68.8 mg of lyophilized plasminogen along with sodium citrate, sodium chloride, sucrose and glycine. The vial is reconstituted with 12.5 mL of sterile water for injection. The reconstituted drug is administered intravenously.

Documents Reviewed

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

- 125659/0 - 3.2.S.4.2 SOP: AM-024: (b) (4) Identification of Plasma Derived Proteins by (b) (4)
- 125659/0-3.2.S.4.3 Validation Report: AMV-013.01-R: Identification of human Pg (b) (4) Drug Product samples by (b) (4) for release and stability evaluation
- 125659/0-3.2.S.4.3 Validation Report: RPT_PRT(b) (4) (b) (4). 01: Method Validation Report for Identity of (b) (4) Plasminogen, and (b) (4)
- 125659/0-3.2.S.4.3 Validation Report: AMV-003.01-R: Identification of (b) (4) Plasminogen by (b) (4)

(b) (4)

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