DEPARTMENT OF HEALTH & HUMAN SERVICES

Division of Biological Standards & Quality Control, Office of Compliance & Biologics Quality,
Center for Biologics Evaluation & Research, Food & Drug Administration, 10903 New Hampshire Avenue, Silver Spring MD 20993

MEMORANDUM

To: Administrative file for STN 125659

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OCBQ/CBER

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Subject: STN 125659/0 – Review of chemistry related analytical methods used for Plasminogen (Human) RYPLAZIM. Drug Substance and Drug Product

Applicant: Prometic Biotherapeutics, Inc.

Through Lokesh Bhattacharyya, Ph.D.
Chief, LACBRP/DBSQC/OCBQ

James Kenney, D.Sc.
Acting Division Director, DBSQC/OCBQ

Recommendation: Review indicated deficiencies in Drug Product method for (b) (4), (b) (4) method for Glycine by (b) (4), (b) (4) Method for Sucrose by (b) (4) and (b) (4) Drug Product Method for Purity-(b) (4). Recommendations for Complete Review letter items have been made. These are detailed in the descriptive reviews for these specific methods.

Summary:
A new BLA was submitted for a Plasminogen (Human) Drug Product. The following test methods and validations were reviewed for their intended purpose in determining Drug Substance and Drug Product release specifications:

Drug Substance

(b) (4)

(b) (4)

(b) (4)

Drug Product
pH
Appearance
(b) (4)
Particulate Matter
(b) (4)
Reconstitution / Dissolution
(b) (4)
Purity - (b) (4)

Deficiencies in the methods and validations for (b) (4) in Drug Product, Glycine and Sucrose in (b) (4) and Purity by (b) (4) Drug Product were identified. Items recommended for inclusion in a planned Complete Review letter to the sponsor are listed under the reviews for each specific Test Method.

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.

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

Drug product is prepared from the DS (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.4.1 Control of Drug Substance – Specifications
- 125659/0 – 3.2.S.4.2.3 Analytical Procedures – Drug Substance Summary
- 125659/0 – 3.2.S.4.2.3 SOP: AM-009 (b) (4)
- 125659/0 – 3.2.S.4.2.3 SOP: AM-017 (b) (4)
- 125659/0 – 3.2.S.4.2.3 SOP: AM-018 (b) (4)
- 125659/0 – 3.2.S.4.2.3 SOP: AM-038 (b) (4) (b) (4) Assay
- 125659/0 – 3.2.S.4.2.3 SOP: AM-021 (b) (4) (b) (4)
- 125659/0 – 3.2.S.4.2.3 SOP: AM-040 (b) (4)
- 125659/0 – 3.2.S.4.2.3 SOP: AM-041 (b) (4)
- 125659/0 – 3.2.S.4.2.3 SOP: AM-36 (b) (4)
- 125659/0 – 3.2.S.4.2.3 SOP: AM-025 (b) (4)
- 125659/0 – 3.2.S.4.2.3 SOP: AM-044 (b) (4)
- 125659/0 – 3.2.S.4.3 Control of Drug Substance – Validation of Analytical Procedures
- 125659/0 – 3.2.S.4.3.2.1 Validation Report: AMT-001 (b) (4), (b) (4)
- 125659/0 – 3.2.S.4.3.2.1 Validation Report: AMV-010 (b) (4)
- 125659/0 – 3.2.S.4.3.2.1 Validation Report: AMV-015 (b) (4)
- 125659/0 – 3.2.S.4.3.2.1 Validation Report: AMV-016 (b) (4)
- 125659/0 – 3.2.S.4.3.2.1 Validation Report: AMV-007 (b) (4) (b) (4)
- 125659/0 – 3.2.S.4.3.2.1 Validation Report: AMV-018 (b) (4)
- 125659/0 – 3.2.S.4.3.2.1 Validation Report AM-014 (b) (4) (b) (4)
- 125659/0 – 3.2.P.5.1 Control of Drug Product - Specifications
- 125659/0 – 3.2.P.5.2 Analytical Procedures – Drug Product - Summary
- 125659/0 – 3.2.P.5.2 SOP: AM-039 Particulate Matter
- 125659/0 – 3.2.P.5.2 SOP:AM-028 (b) (4)
- 125659/0 – 3.2.P.5.3 Validation of Analytical Procedures – Summary
- 125659/0 – 3.2.P.5.3 Validation Report: AMQ-009 Particulate Matter
- 125659/0 – 3.2.P.5.3 Validation Report: AMQ-004 (b) (4)

pH (b) (4) Drug Product)

Method AM-009 is performed according to (b) (4) pH requirements. pH (b) (4) used are (b) (4) .

Validation of pH measurement was described in document AMT-001, Analytical Method Transfer Report for (b) (4) and

Plasminogen. The method was evaluated for repeatability and reproducibility. Repeatability was evaluated on (b) (4) replicates by (b) (4) analyst; a (b) (4) was obtained. Reproducibility was evaluated by comparing results from (b) (4) laboratories (PBT – ProMetic Biotherapeutics (b) (4) using the (b) (4) sample. Bias obtained was (b) (4).

Conclusion: As a standard (b) (4) procedure this method and qualification are suitable for use.

Appearance (b) (4) Drug Product)

AMV-017 "Appearance of (b) (4) " is based on (b) (4) This method is applied to Plasminogen (b) (4) (b) (4) DP. Evaluation of appearance includes visual inspection, (b) (4)

Validation of appearance was described in document AMT-001. The method was evaluated for repeatability and reproducibility. Repeatability was evaluated on (b) (4) replicates by (b) (4) analyst; a (b) (4) was obtained for Plasminogen. Reproducibility was evaluated by comparing results from (b) (4) laboratories using the (b) (4) sample. Visual inspection, (b) (4) Plasminogen were similar and samples met specifications.

Conclusion: As a standard (b) (4) procedure this method and qualification are suitable for use.

(b) (4)

(b) (4)

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(b) (4)

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Sucrose Concentration (b) (4)

As described in SOP AM-038, sucrose concentration in Plasminogen Drug Samples is determined by an (b) (4)

(b) (4)

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Validation of method AM-038 was described in report AMV-014. (b) (4)

(b) (4)

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Conclusion: Validation of linearity and range were performed (b) (4) the following was recommended for inclusion in a Complete Review letter.

a. For method for Sucrose in (b) (4) by (b) (4), the following deficiency was identified in the validation report AMV-14:
Linearity and Range have been evaluated using (b) (4). Please submit data assessing these characteristics using (b) (4).

Glycine Concentration (b) (4)

Glycine in Plasminogen (b) (4) is determined by (b) (4)

(b) (4)

(b) (4)

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Conclusion: This reviewer's evaluation of the method and validation information for the Glycine method resulted in the following recommendations for inclusion in a Complete Review letter:

b. (b) (4)

c. Linearity and range have been evaluated using (b) (4)
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d. Repeatability was evaluated using (b) (4)

e. Intermediate precision was evaluated by (b) (4)

f. Robustness was evaluated (b) (4)
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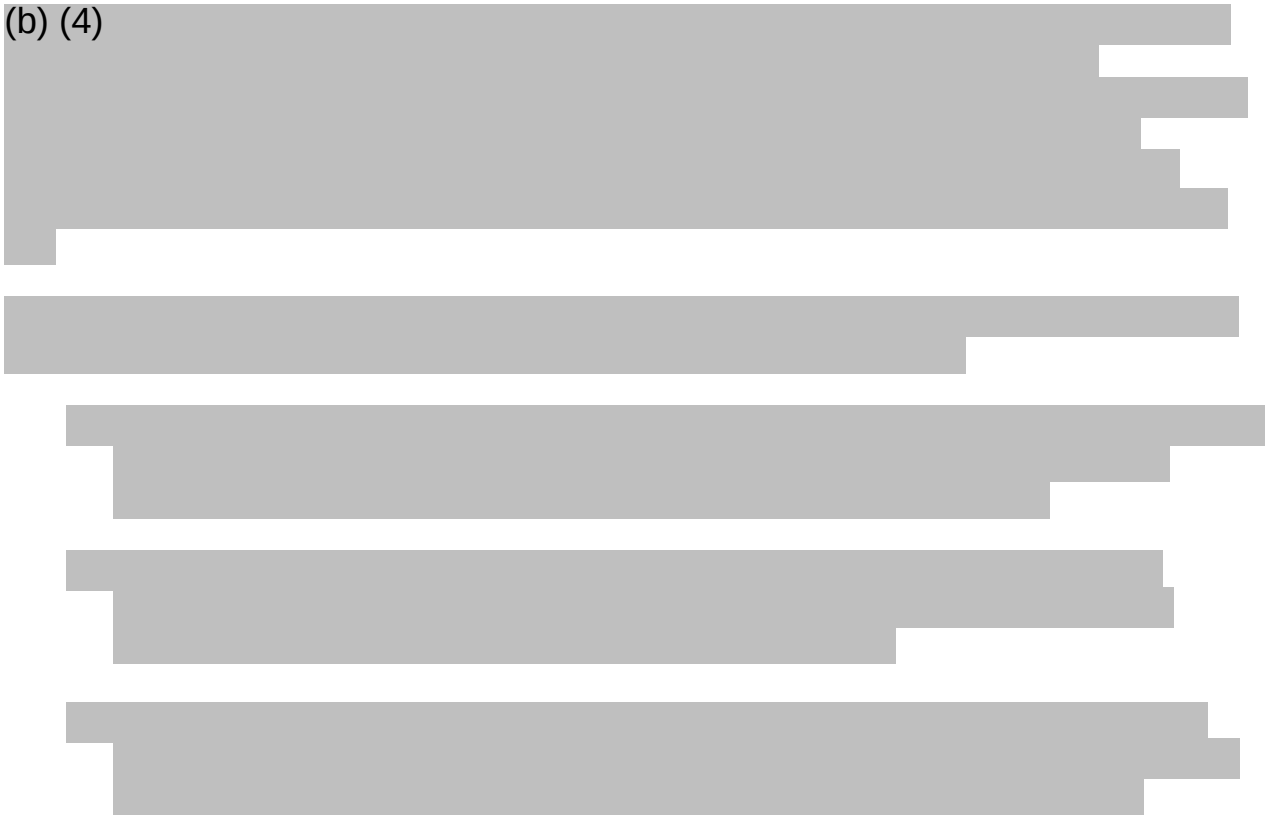
8 pages have been determined to be not releasable: (b)(4)

(b) (4)



Particulate Matter (Drug Product)

The test for Particulate matter in Drug Product is based on (b) (4) The instrument used is a (b) (4) Specifications for Particulate Matter are (b) (4)

As described in AM-039, "Determination of Particulate Matter in (b) (4) .

It is noted by this reviewer that Sample Preparation for Plasminogen product is specifically described in the method attachment AM-039-F2.V2. Section 3.7.2 specifies that "Pg Drug product samples are reconstituted and (b) (4) as per SOP QC-030.Vx 'Reconstitution Procedure for Lyophilized Human Plasminogen (Intravenous)' ". (b) (4) prior to testing is inconsistent with (b) (4) and is inappropriate for a particulate determination assay.

Method validation was reported in document AMQ-009.01-R. Validation was performed for the characteristics repeatability, intermediate precision and specificity. Specificity

(b) (4)

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Intermediate precision was (b) (4)

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Robustness was evaluated for sample preparation parameters. (b) (4)

Conclusion:: The inclusion of a (b) (4) in sample preparation, while intended to reflect clinical administration, is problematic in terms of providing a meaningful product evaluation. This issue has been noted by the Chair of this BLA and at the time of this review is addressed as part of the draft Complete Review letter.