DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: Administrative file for STN 125659/0.18

From:

Name	Role	Date finalized	Stamp	Supervisor/Lab Chief LACBRP	Stamp
Salil K Ghosh, Ph.D.	Lead Reviewer	04/22/21		Tao Pan, Ph.D, Team Lead	
				Kori Francis, Acting Lab Chief	
Ritu Agarwal, Ph.D.	Reviewer	04/21/21		Tao Pan, Ph.D, Team Lead	
				Kori Francis, Acting Lab Chief	

Through: Maryna Eichelberger, Ph.D., Director, DBSQC/OCBQ/CBER

Applicant: Prometic Biotherapeutics, Inc.

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

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Recommendation: Approval

Summary:

The responses to the CR letter of BLA STN 125659 for RYPLAZIM, Plasminogen (Human) were submitted on 01 September 2020. The CR responses related to analytical methods and their validations and/or qualifications were reviewed and found to be acceptable.

This product is intended for replacement therapy in children and adults with plasminogen deficiency. The analytical methods and their validations were reviewed and found to have deficiencies, which were summarized in the Complete Response (CR) Letter, dated 09 April 2018. The sponsor has provided responses to the deficiencies listed in the CR Letter as Amendment 18, which was received on 01 September 2020. This document constitutes the review memo for the CR responses to the deficiencies identified related to the following test methods and validations:

1. [Sucrose content for (b) (4) [Salil Ghosh]

2. (b) (4) in DP], [Ritu Agarwal]
3. [Glycine Concentration in (b) (4) DP], [Ritu Agarwal]
4. (b) (4) DP], [Ritu Agarwal].

Documents Reviewed

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

125659/0.18 – Cover letter dated 4 September 2020

- CR letter dated 09 April 2018
- 3 Quality
  - 3.2 Quality overall Summary
    - 3.2.S.4 Control of Drug Substance (DS)
    - 3.2.S.4.1 Specification
    - 3.2.S.4.2 Analytical Procedures-Drug Substance Summery
      - SOP No. AM- 038.05 (b) (4) test
      - SOP: AM-021 (b) (4) , (b) (4)
      - SOP:AM-028 vs. 03 (b) (4)
      - SOP: AM-041 (b) (4)
    - 3.2.S.4.3 Validation of analytical procedure
      - Validation Report: AMV-037.01-R (b) (4) (b) (4)
    - 3.2.P.5.1 Control of Drug Product – Specifications
    - 3.2.P.5.2 Analytical Procedures – Drug Product - Summary
    - 3.2.P.5.3 Validation of Analytical Procedures (DP)
      - Method Validation Protocol AMV-036.01-R: Sucrose (b) (4) DP
      - Validation Report: RPT_VAL-(b) (4)
      - Validation Report: AMV-035.01-R (b) (4)
    - 3.2.P.5.4 Batch Analyses (DP)

125659/0.22 – 1.11.1 Quality Information Amendment; Response to IR dated 15 January 2021; Received on 28 January 2021

125659/0-PDR_Memo-DBSQC-LACBRP-125659.pdf

Background:

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

The plasminogen Drug Substance (DS) is derived from human donor plasma; drug product is prepared from the DS by sterile filtration, filling and lyophilization in glass

vials. The final container is a 50 mL vial with 68.8 mg of lyophilized plasminogen, and to be used for intravenous administration after reconstitution with 12.5 mL of sterile water for injection.

1. [Sucrose Concentration in (b) (4): [Salil Ghosh]

Introduction

DBSQC reviewer identified a deficiency in the validation of the (b) (4) for sucrose in the original submission and recommended in the CR letter: Linearity and Range have been evaluated using standard curves. Please submit the data assessing these characteristics using analyte (sucrose) in the product mix. In the amendment (125659/0.26), the sponsor assessed the linearity of the method (AM-038.05) (b) (4) sample containing sucrose following the validation protocol, AMV-036.01-P; the study was performed at the (b) (4) site of the company. The release specification for sucrose in (b) (4), remains unchanged.

Review of Method:

The analytical method AM-038 was updated to include the newly validated assay range, tighter system suitability acceptance criteria and minor method clarifications. In the method, sucrose concentration in (b) (4) is determined by an (b) (4)

New and tighter system suitability criteria are included in this amendment and percent bias was calculated from an equation using the nominal value (or reference value) and the experimental value: i) the difference in (b) (4) readings of replicates (duplicates) of standards must be (b) (4) ii) percent bias of the (b) (4) for standard replicates must be (b) (4) and iii) standard curve (b) (4). Acceptance criterion for the (b) (4). Sample acceptance criteria are that (b) (4) and that individual (b) (4) readings be within the range of the standard curve.

Review of Method Validation for Linearity:

First, the sponsor determined the concentration of sucrose in (b) (4) sample (b) (4) occasions by (b) (4) analysts, the mean result was (b) (4) sucrose from (b) (4) reportable results (b) (4) in (b) (4) following the protocol AMV-036.01-R.

Linearity was evaluated (b) (4) . Hence, the linearity of the method is demonstrated.

The working range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample. According to linearity, precision and accuracy criteria, range was defined as (b) (4) .

Conclusion:

The responses to the deficiency identified in the CR letter are acceptable; the sucrose method is suitably validated for its intended use.

2. (b) (4) **in DP]: [Ritu Agarwal]**

The specification for (b) (4) is set at (b) (4) for plasminogen drug product.

Method
(b) (4)

Validation
Method validation was described in AMV-035.01-R "Method Validation Report – Determination of (b) (4) in Lyophilized Plasminogen by (b) (4) . Characteristics evaluated were linearity, accuracy, precision (repeatability and intermediate precision) and LOQ. The review is documented in DBSQC's review memo (dated April 9, 2018). At that time, several deficiencies were identified, and were included in the CR letter dated April 9, 2018. The responses to the CR letter comments are reviewed as below.

a. The (b) (4) method for (b) (4) in Drug Product (b) (4) does not include a specification for (b) (4) of the (b) (4) Please revise the procedure to include an upper limit specification.

Review of response: In the revised testing instruction, the acceptance criteria for (b) (4) was added, as (b) (4) The sponsor's response is acceptable.

b. In the qualification report for the (b) (4) assay (b) (4), intermediate precision was evaluated by a total of (b) (4) experiments. Please submit data to cover a minimum of (b) (4) assays.

Review of response: The sponsor re-evaluated the assay precision. The assessment of the repeatability was performed using the data generated for the accuracy assessment (as below, from (b) (4) reportable results at (b) (4)). The (b) (4) for Pg DP met the predetermined acceptance criteria of (b) (4) on mean recovery.

Intermediate precision assessment was performed on the Pg DP vials by (b) (4) analysts on (b) (4) days. The reportable results generated during the accuracy assessment for Pg DP were also used. For another (b) (4) occasions (in addition to the accuracy run at (b) (4)), only (b) (4) with (b) (4) reportable results was analyzed. The intermediate precision (b) (4) at the (b) (4) met the predetermined acceptance criteria (b) (4) for mean recovery).

c. Accuracy for (b) (4) was evaluated only at (b) (4), and this point exceeded the product specification. Please provide data establishing accuracy to cover the intended reporting range of (b) (4) concentration in the sample.

Review of response: The data for accuracy validation were submitted by the sponsor. The Pg DP samples with known (b) (4) were prepared at (b) (4) The sponsor's response is acceptable.

Conclusion: The method is clearly described and validated and is acceptable as a quality control test for the quantitation of (b) (4) .

3.(b) (4) /DP]: [Ritu Agarwal]

The specification for the purity of plasminogen (b) (4) /drug product is set at (b) (4) for the (b) (4) , and for (b) (4) impurities, is set at (b) (4) respectively.

Method
The percentage of plasminogen (b) (4) drug product, is determined by a (b) (4) method, following the procedure described in SOP AM-041. The method employs an (b) (4) . The system suitability was determined using a (b) (4) Acceptance criteria for the system suitability check is (b) (4)

Validation
Method Validation was described in report, RPT_VAL-(b) (4) . The method is validated by evaluating specificity, accuracy, precision, linearity, range and robustness (b) (4) and specificity, accuracy, precision, linearity, range and LOQ for (b) (4) . The review is documented in DBSQC's review memo (dated April 9, 2018). At that time, several deficiencies in method validation were identified, and were included in the CR letter dated April 9, 2018. The responses to the information request are reviewed as below. Some of the information requests were not addressed in the resubmission, and an additional request was sent on 15 January 2021. The responses were received on 28 January 2021 and are reviewed as below.

a. The (b) (4) values from the (b) (4) /DP (b) (4) presented in the analytical method are above (b) (4), which is beyond the (b) (4) you selected. In general, the measurement of (b) (4) higher than (b) (4) should be avoided.

Review of response: In the revised version of the test method SOP submitted by the sponsor, (b) (4) he sponsor's response is acceptable.

b. Your assay does not include a positive control. Please include a suitable positive control with established (b) (4) percentage limits for (b) (4) (based on your historical data, preferably from (b) (4) independent

measurements) in your analytical method to assure the consistency of the assay performance.

Review of response: As requested by CBER, the sponsor qualified a positive control sample. The established (b) (4) percentage limits for (b) (4) control, were used to ensure consistency of the assay performance.

c. We do not agree the integration provided in page 380 of the validation report, which uses (b) (4) approach and is known to result in underestimation of impurities. (b) (4) with a (b) (4) for all (b) (4) and (b) (4) approach for (b) (4) is considered a preferable method.

Review of response: In the revised version of test method SOP, as requested by CBER, the integration approach was changed from (b) (4) to using a (b) (4) for all (b) (4), and then a (b) (4) for (b) (4).

d. (b) (4) is observed in the (b) (4)/DP (b) (4) in the validation report, which usually is an indication of (b) (4) Please provide data to justify your choices of (b) (4) and (b) (4) for this method.

Review of response: In response to CBER IR, the sponsor submitted the method development report, document ADR-5026.005 (as Amendment 22, dated 28 January 2021), which includes the details for the choice of (b) (4). The sponsor's response is acceptable.

e. Provide data to show that (b) (4) in your product are not (b) (4) under the proposed (b) (4) condition described in the analytical method.

Review of response: In the method development report ADR-5026.005, submitted by the sponsor as Amendment 22 (dated 28 January 2021), describes the recovery of (b) (4) plasminogen aggregates, obtained under different stressed conditions. As per the data, (b) (4) species could be effectively recovered using the current (b) (4) method. The sponsor's response is acceptable.

f. The linearity (b) (4) failed to meet the acceptance criterion of correlation coefficient (b) (4). Please provide justification.

Review of response: In the original validation, this discrepancy was reported, and according to this report, due to the (b) (4) of the (b) (4), the volumes used for the assay could lead to some variability in results. The linearity study was repeated, and the results were acceptable. Also, this assay was re-validated, and the linearity was again demonstrated in the resubmission package that was submitted by the sponsor.

g. Provide accuracy results based on (b) (4) from appropriate samples because purity specifications are expressed in (b) (4) percentages.
h. Provide assay range based on satisfactory results of linearity, accuracy and precision.
i. Limits of Quantitation (LOQs) of (b) (4) should be expressed in terms of the reportable results, which are (b) (4) percentages. They are the lowest reportable values that (b) (4) /DP samples have satisfactory precision and accuracy outcome. Provide LOQ in terms of (b) (4) .

Review of responses: The (b) (4) method was revalidated to incorporate the purity specifications. Linearity, accuracy and precision was evaluated (b) (4)

(b) (4)

(b) (4)

Method Transfer: The (b) (4) assay was re-validated at Prometic Biotherapeutics Inc (b) (4)), and the but release testing for (b) (4)/DP is performed at the Prometic Bioproduction Inc. site (PBP), located in Laval, Quebec, Canada. The transfer report, document AMT-021.01-R, was submitted by the sponsor as Amendment 22 dated 28 January 2021. A partial validation was performed at the PBP site. (b) (4) The sponsor's data is acceptable.

j. Provide robustness evaluation results for (b) (4).
Review of response: The method robustness data were submitted by the sponsor. Robustness was assessed with the following variations: (b) (4) obtained from the modified parameters ((b) (4)) were comparable to the (b) (4) results at the nominal conditions.

(b) (4)

Conclusion: An adequate description of the (b) (4) method is provided, and the method is satisfactorily validated.

4.[Glycine Concentration (b) (4) [Ritu Agarwal]

The specification for glycine in drug product is set at (b) (4).

Method

Glycine in Plasminogen (Pg) (b) (4) drug product is determined by (b) (4) .

During the review of the original submission, as described in AMV-037.01-R, validation of method AM-021 was assessed for characteristics of accuracy, precision, specificity, linearity, range and robustness. The review is documented in DBSQC's review memo (dated April 9, 2018). At that time, several deficiencies in method validation were identified, and were included in the CR letter dated April 9, 2018. The responses to the information request following re-submission were received on 01 September 2020 and are reviewed as below.

a. In method AM-021, (b) (4) are assigned acceptance criteria of (b) (4) (AM-021 11.1.1)." Please adopt criteria for these parameters based on the actual measured values obtained in addition to their precision.

Review of response: The test method SOP was revised by the sponsor, to include the system suitability criteria that were requested in the IR. The average (b) (4) was included to be within (b) (4) and (b) (4) The sponsor's response is acceptable.

b. Linearity and range have been evaluated using standard curves. Please submit data assessing these characteristics using (b) (4) in the (b) (4) .

Review of response: To assess linearity, (b) (4)

(b) (4)
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The accuracy was evaluated (b) (4)
The sponsor's data is acceptable.

c. Repeatability was evaluated using (b) (4). Repeatability should include all aspects of sample preparation. Please evaluate repeatability to cover either (b) (4)

d. Intermediate precision was evaluated by (b) (4) analysts on (b) (4) days, for a total of (b) (4) separate experiments. Please submit results for (b) (4) based on a minimum of (b) (4) separate assays.

Review of responses: The assessment of the repeatability was performed using the data generated for the accuracy assessment for each sample type. The (b) (4) for Pg DP and (b) (4) met the acceptance criteria (b) (4) thus confirming the repeatability of the method within the tested range. Intermediate precision assessment was performed on the Pg (b) (4) only, in a total of (b) (4) occasions (different days, analysts, equipment). The Intermediate precision (b) (4) met the acceptance criteria (b) (4)

e. Robustness was evaluated only for (b) (4) by (b) (4) analysts and (b) (4) suppliers. Please provide data for the evaluation of method robustness with respect to critical (b) (4) parameters to include (b) (4)

Review of response: Robustness was assessed with the following variations: (b) (4)
Results were compared with the Pg (b) (4) sample obtained during normal condition. The recoveries for the samples tested under different conditions were within (b) (4)

Conclusion: The method is clearly described and validated and is acceptable as a lot release test for the quantitation of glycine.