Our STN: BL 125659/0

BLA COMPLETE RESPONSE
April 9, 2018

ProMetic BioTherapeutics, Inc.
Attention: Ms. Danielle Craig
1330 Piccard Drive, Suite 201
Rockville, MD 20850

Dear Ms. Craig:

This letter is in regard to your Biologics License Application (BLA) for Plasminogen (Human) manufactured at your Laval, Quebec, Canada, location and at your contract manufacturer, (b) (4) , submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in the amendments dated March 6 and March 13, 2018. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

CHEMISTRY, MANUFACTURING, AND CONTROLS

1. The product and the manufacturing process control strategies are not adequately developed and validated. Please address the following deficiencies by providing relevant data to establish appropriate controls.

    a. Please re-evaluate all Critical Quality Attributes (CQAs) and develop, with justifications, a consistent list of CQAs. Your current list of CQAs does not include all attributes needed to control product quality; furthermore, your different reports list different attributes as CQAs. For example, (b) (4) plasminogen (b) (4) are listed as CQAs in report PDR-001 "Critical Process Parameters Assessment in Plasminogen Drug Substance Manufacturing," but these CQAs are not controlled anywhere in the process. In report PDR-009 "Risk Assessment of Prospective Quality Attributes for Prometic Plasminogen," the identified CQAs are insufficient to control product quality.

    b. Please re-evaluate in-process controls (IPCs) to address the following issues:

        i. The current IPCs do not allow control of the performance of the unit operations. For many manufacturing steps, the chosen IPCs are likely to stay within the "normal operating ranges" (NORs) even if the operation of the step fails.

ii. "Control of critical steps and Intermediates" section of the BLA includes a set of tests labeled as "characterization." Per Prometic, these tests are not intended to be a permanent part of IPC, and are performed in the laboratory at (b) (4) which had not validated these methods. For these tests, no action is taken when the results are outside of the NOR, but even NORs for some of these parameters show very significant variabilities. However, some of these tests are indicative of product quality and the performance of the unit operations. Please reassess these "characterization" tests for their utility to control process performance and make them permanent IPCs, validating analytical methods.

iii. Protein aggregation is not controlled or monitored in (b) (4) final drug product (FDP), despite indications of the protein's propensity to aggregate. Please note that your approach to perform assessments of (b) (4) of the sample does not accurately represent the amount of protein aggregation in the product.

iv. Hold-times and process times are not validated for unit operations. We note that for the entire process, the only hold times reported in the BLA are for (b) (4) storage of the Drug Substance Intermediate and the BDS.

c. Analytical procedures that are used for the release and/or IPC testing are unsuitable for their intended purpose, or are not adequately validated; specifically:

i. You have not established the performance qualification of the (b) (4) assay for (b) (4) for your product. No qualified in-house standard or control sample was used to monitor and verify the performance of successive (b) (4) used over time. Please develop an appropriate (b) (4) and validate the assay using this (b) (4) .

ii. The method for determining total protein by (b) (4) was validated using (b) (4) , whereas the validation protocol specified that (b) (4) , should be used for validation. Please validate the method using (b) (4) .

iii. The assay for plasminogen by (b) (4) was validated without using an in-house primary or working reference standard. In addition, the linearity and range of the assay were not sufficiently established during validation, as demonstrated by significantly lower than expected results for the linearity. Please develop an appropriate (b) (4) for plasminogen and validate the assay using this (b) (4)

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

v. In the qualification report for the (b) (4) assay (AM-004.01-R), Intermediate Precision was evaluated by a total of (b) (4) experiments. Please submit data to cover a minimum of (b) (4) separate assays.

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

vii. For the method for Glycine in Drug Substance by (b) (4) AM-021 and the validation report AMV-10, the following deficiencies were identified:

(b) (4)

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viii. For method for Sucrose in (b) (4) by (b) (4), the following deficiency was identified in the validation report AMV-14.

1. Linearity and Range have been evaluated using standard curves. Please submit data assessing these characteristics using (b) (4)

ix. For the method for Purity Determination by (b) (4) AM-041 and the validation report AMV-016, the following deficiencies were identified:

1 page has been determined to be not releasable: (b)(4)

d. Most of the specifications for the Drug Substance Intermediate, BDS, and FDP are not properly justified. Please reevaluate the data, and re-establish the specifications to address the following issues:

i. The datasets used to establish the acceptance criteria are inadequate. Many acceptance criteria are established by combining the data from the testing of the BDS and FDP, which is inappropriate. In addition, the data from early versions of the manufacturing process are included in the justification. Some of the test results presented are outside of the proposed specification ranges.

ii. The statistical approaches that were used to justify the acceptance criteria (b) (4) Standard Deviations or (b) (4) tolerance limits) have resulted in wide acceptance ranges, leading to inadequate control of manufacturing consistency. The exact statistical approaches used in these studies need to be clearly explained.

iii. The release testing for Visible Particulates in the FDP is performed (b) (4) therefore, the results do not accurately estimate the level of visible particulates in FDP. Please perform testing for Visible Particulates on (b) (4) FDP that has not (b) (4) .

iv. Testing for (b) (4) is performed on BDS, and not on FDP. Please perform testing for (b) (4) on FDP.

2. The manufacturing process is not properly validated. Please address the following issues regarding process validation:

a. The studies to support process development are deficient. For example, the (b) (4) studies lacked appropriate acceptance criteria, in multiple reports results were labeled (b) (4) and excluded from analysis without investigations. The (b) (4) studies were performed after the Process Performance Qualification (PPQ) campaign, and revealed that the (b) (4) used are insufficient to (b) (4) , as evident from an excess of (b) (4) . Please ensure that conditions of use of the process materials are confirmed by appropriate studies.

b. For lyophilization process validation, insufficient information was provided regarding the commercial scale PQ study, information for (b) (4) is missing, and the claimed (b) (4) is not supported by the PPQ campaign.

c. During the comparability assessment after changes in the manufacturing process, some parameters failed to meet the pre-determined acceptance criteria, but no investigations were performed.

d. There are no validated hold-times and process times for individual manufacturing steps. Conflicting information on process times was described in the BLA, and provided to FDA during the pre-license inspection. Please establish the hold-times between manufacturing steps, as well as the time limits for the manufacturing steps, where appropriate, and validate the respective durations in prospective validation studies.

e. Changes had been introduced to the manufacturing process, materials and equipment after the completion of the PPQ campaign, but they were not reported in the BLA. Some of these changes were made without proper comparability assessments. Additional comparability studies are needed.

f. Multiple deficiencies were identified in the Process Performance Qualification (PPQ) reports, e.g., out-of-specification (OOS)/out-of-trend (OOT) results were not properly investigated.

g. As discovered during facility inspection and outlined in Form FDA 483, multiple facility issues were present during the PPQ campaign for the BDS. These issues need to be resolved.

h. The (b) (4) used for the (b) (4) storage of the Drug Substance Intermediate and BDS are not intended for (b) (4) and are not suitable for this use, as evident by (b) (4) . No prospective validation studies were performed to confirm the suitability of the (b) (4) for storage of (b) (4) materials. Please ensure that a suitable container closure system is used for the Intermediate and BDS.

i. Due to the above issues, the PPQ campaign does not support the commercial process submitted in the BLA, or process performance. Please conduct a new PPQ campaign for the BDS and FDP after you have addressed all the deficiencies.

3. The stability of the Drug Substance Intermediate, BDS and FDP is not fully established. Please address the following issues:

a. Please re-assess the stability results and specifications after you have corrected the deficiencies in the assays and product specifications as stated in item 1 above.

b. The proposed storage temperatures and associated stability study conditions for the Drug Substance Intermediate and BDS are not adequately defined.

(b) (4)

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(b) (4)

c. Proposed Intermediate storage time is not supported by available stability data.

4. For adventitious agents safety evaluation, please address the following issues:

(b) (4)

5. The QC tests used for equipment cleaning validation at PBP facility have not been qualified during cleaning validations.

6. The performance qualifications for some drug product manufacturing equipment, including the filling line, depyrogenation ovens, autoclave, vial washer, and lyophilizer, are inadequate. Some of the associated PQ studies were conducted without using Ryplazim related materials or product, and no sufficient risk assessment or justifications provided.

7. There are no data provided for the positive and negative controls used for the container closure integrity tests for final drug product vials.

8. Shipping validation for final drug product is inadequate with (b) (4) run and not under the worst-case condition.

9. The observations noted in the FDA-Form 483 during the pre-license inspection have not been resolved completely.

LABELING

10. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

ADDITIONAL COMMENTS

11. FDA is concerned about your record-keeping and documentation practices. We noted a significant portion of the reports, including those related to process development, were prepared in the Summer of 2017, and are not contemporaneous with the studies described in these reports.

Within one year after the date of this letter, you are required to resubmit or withdraw the application (21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval.

For PDUFA products, please submit your meeting request as described in our guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants*, dated May 2009. This document is available on the internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf, and CBER's *SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*. This document is available on the internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm. Both documents may be requested from the Office of Communication, Outreach, and Development, at (240) 402-8020.

We acknowledge receipt of your amendments dated March 6, and March 13, 2018. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable sections of the amendment(s) dated March 6, and March 13, 2018, in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Ms. Pratibha Rana, at (240) 402-8433 or pratibha.rana@fda.hhs.gov.

Sincerely,

Basil Golding, MD
Director
Division of Plasma Protein Therapeutics
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research