Our STN: BL 125659/0

MID-CYCLE COMMUNICATION SUMMARY
January 24, 2018

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

Dear Ms. Craig:

Attached is a copy of the summary of your December 14, 2017 Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to STN BL 125659/0 in your future submissions related to Plasminogen (Human).

If you have any questions, please contact 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

Mid-Cycle Communication Teleconference Summary

Application number:	BLA 125659/0
Product name:	Plasminogen (Human)
Proposed Indication:	Replacement therapy in adults and children with plasminogen deficiency
Applicant:	Prometic Biotherapeutics, Inc. (Prometic)
Meeting date & time:	December 14, 2017, 10:00 am - 11:00 am
Committee Chair:	Alexey Khrenov, PhD
RPM:	Pratibha Rana, MS

Prometic Attendees:
Danielle Craig, Associate Director, Regulatory Affairs
Nathalie Rousseau, Manager, Regulatory Affairs, CMC
Rachel Duguay, Vice President, Quality
Joseph Parker, Senior Director, Clinical Development
John Moran, Chief Medical Officer
Gordon Harris, Vice President, Manufacturing
Bill Bees, Vice President, Plasma Technologies
Bruce Pritchard, COO
Pierre Laurin, President & CEO

FDA Attendees:
Jie He, MS, CBER/OCBQ/DMPQ/MRBII
Alexey Khrenov, PhD, CBER/OTAT/DPPT/HB
Pratibha Rana, MS, CBER/OTAT/DRPM/B2

Agenda:

1. Multiple major issues in the BLA have been identified by the review committee to date in the following disciplines:

Chemistry, Manufacturing, and Controls:

a. The process is not properly controlled. In-process controls are not sufficient to control the unit operations of the manufacturing process.

b. The process is not properly validated. 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.

c. Changes had been introduced to the process steps, 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. When the comparability assessments were performed, some

parameters failed to meet the pre-determined acceptance criteria, but no investigations were performed.

d. The studies to support process development are deficient. For example, the (b) (4) studies lacked appropriate acceptance criteria, and multiple results were excluded from analysis without investigations. The (b) (4) studies were performed after the PPQ campaign, and revealed that the (b) (4) used are insufficient to (b) (4) as evident from an (b) (4)

e. The potency assay is not suitable for its intended purpose due to a lack of product-specific standard or other appropriate reference material. As such, the assay could not be properly validated, and its performance has not been verified and monitored over time.

f. The characterization and control of product aggregation are inadequate.

g. Most of the specifications for the Drug Substance Intermediate, Bulk Drug Substance (BDS) and Final Drug Product (FDP) are not properly justified. The statistical approaches used are deficient, and the datasets used to establish the specifications are inadequate. The release testing for Visible Particulates in the FDP is performed (b) (4), therefore, it does not allow for proper control for the presence of foreign particles.

h. The qualifications of critical manufacturing equipment are inadequate. Examples include, but are not limited to:

    i. Cleaning validation for BDS processing (b) (4) were inadequate.

    ii. Some FDP manufacturing equipment PQ studies (filling line, depyrogenation oven, autoclave, vial washer) were not done with the 50 mL vials used for the FDP.

    iii. The cleaning validation for the (b) (4) lyophilizer was not done using the plasminogen product, and no risk assessment or justifications were provided.

i. For lyophilization process validation, insufficient information was provided in the BLA. Deficiencies include, but are not limited to:

    i. No sampling plan was provided for the developmental study and PPQ runs.

    ii. (b) (4) was performed for the (b) (4)

iii. No information was provided on the (b) (4) used during lyophilization, which may depend on the (b) (4) .

iv. Batch sizes expected during commercial scale manufacturing and test results for the developmental runs are not provided.

v. The proposed maximum batch size (b) (4) is not supported by the PPQ batches (b) (4)

j. BDS and FDP shipping validations are inadequate because BDS shipping was validated using an obsolete protocol, and FDP shipping was validated with a (b) (4) .

2. Information regarding major safety concerns

   No major safety concerns have been identified to date.

3. Preliminary Review Committee thinking regarding risk management

   The applicant's Pharmacovigilance Plan has been reviewed and an Information Request has been sent. Initial safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) at this time, but the review is still ongoing.

4. Any information requests sent and responses not received

   a. An Information Request for additional clinical data was sent on 12/11/2017.

   b. An Information Request regarding the Pharmacovigilance Plan was sent on 12/8/17.

5. Late-Cycle meeting (LCM)

   a. The tentative date for the LCM between you and the Review Committee will be late February 2018.

   b. We intend to send the LCM materials to you approximately 10 days in advance of the LCM.

   c. If these timelines change, we will communicate updates to you duringthe course of the review.

6. The current thinking of the review committee is that this BLA will not be presented at the Blood Products Advisory Committee meeting.

Discussion summary

Prometic requested clarification on the CMC issue 1.i.iv., **"***Batch sizes expected during commercial scale manufacturing and test results for the developmental runs are not provided."* FDA explained that it is not clear from the data provided what the planned batch size is for the commercial scale lyophilization process.

Prometic did not have other questions or requests.

END