Our STN: BL 125659/0

LATE-CYCLE MEETING MEMORANDUM
April 4, 2018

Prometic Biotherapeutics, Inc.
Attention: Ms. Danielle Craig
(b) (4)

Dear Ms. Craig:

Attached is a copy of the memorandum summarizing your March 8, 2018 Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number STN BL 125659/0 in future submissions related to the subject product.

If you have any questions, please contact Pratibha Rana at (240) 402-8433.

Sincerely,

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

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Late-Cycle Meeting Summary

Meeting Date and Time:	March 8, 2018, 3:00 pm - 4:30 pm
Meeting Location:	Bldg. 71, Room 1208
Application number:	BLA 125659/0
Product name:	Plasminogen (Human)
Proposed Indication:	Replacement therapy in adults and children with plasminogen deficiency
Applicant Name:	Prometic Biotherapeutics, Inc. (Prometic)
Meeting Recorder:	Pratibha Rana, MS

FDA ATTENDEES

Wilson Bryan, MD, CBER/OTAT
Basil Golding, MD, CBER/OTAT/DPPT
Mahmood Farshid, PhD, CBER/OTAT/DPPT
Alexey Khrenov, PhD, CBER/OTAT/DPPT
Tim Lee, PhD, CBER/OTAT/DPPT
Theresa Chen, PhD, CBER/OTAT/DCEPT
Laurie Norwood, MS, CBER/OCBQ/DMPQ
Steve Winitsky, MD, CBER/OTAT/DCEPT
Qiao Bobo, PhD, CBER/OCBQ/DMPQ
Jie He, CBER/OCBQ/DMPQ
Pratibha Rana, MS, CBER/OTAT/DRPM/B2
Anthony Lorenzo, CBER/OCBQ/DMPQ
Ze Peng, MD, PhD, CBER/OTAT/DPPT
Bethany Baer, MD, CBER/OBE/DE/PB
Anthony Hawkins, MS, CBER/OCBQ/DIS/BMB
John Eltermann, RPh, MS, CBER/OCBQ/DMPQ
Kimberly Benton, PhD, CBER/OTAT
Boris Zaslavsky, PhD, CBER/OBE
Ilan Irony, MD, CBER/OTAT/DCEPT

APPLICANT ATTENDEES

Danielle Craig, Associate Director Regulatory Affairs
Dr. John Moran, Chief Medical Officer
Dr. Joseph Parker, Senior Director Clinical Development
Maria Rubinacci, Manager Clinical Affairs
Davida Blackman, Senior Director Process Development
Anthony Adson, Director Assay & QC Support
Nathalie Rousseau, Manager Regulatory Affairs CMC
Gordon Harris, Vice President Manufacturing
Rachel Duguay, Vice President Quality
Bill Bees, Vice President Plasma Technologies
Thomas Loisel, Director Manufacturing Sciences

Bruce Pritchard, COO
Pierre Laurin, President & CEO

BACKGROUND

STN BL 125659/0 was submitted on August 11, 2017, for Plasminogen (Human).

PDUFA goal date: April 14, 2018.

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on February 27, 2018.

DISCUSSION

1. Discussion of Substantive Review Issues – 30 minutes

   FDA started with the introduction, and outlined the current state of the review. FDA acknowledged that Plasminogen (Human) is intended for an unmet medical need, and qualified for Orphan and Rare Pediatric Disease designations. FDA also acknowledged that there were no major issues identified in the clinical part of the BLA, but emphasized that good clinical results cannot compensate for major CMC and facilities issues, which are serious and systemic and must be resolved prior to licensure.

   FDA acknowledged receiving Prometic's proposed timeline for resolution of the manufacturing and product quality issues. FDA noted that the timeline includes the submission of multiple amendments beyond the April 14, 2018 goal date for the BLA. FDA commented that the proposed timeline is not binding, and emphasized that diligent and complete resolution of the issues are more important than following the timeline, considering that of the steps are contingent on the success of the others, and that both facilities and process design issues need to be resolved.

   FDA and Prometic agreed that there will be no itemized discussion of the issues presented in the Late-Cycle Meeting Materials. Instead, Prometic gave a presentation regarding the current status of their efforts to address FDA's review and inspectional concerns (see attached presentation).

   During the presentation, FDA made the following comments:

   a. In their recent submission, Prometic stated that inspectional Observation # 9 was addressed by introducing an SOP instructing staff to monitor the state of the facility. However, FDA was interested if the defects described in this observation (peeling paint and plaster) were actually repaired. Prometic responded that repairs were completed.

   b. Prometic described their efforts to control aggregation by developing and introducing new analytical methods. FDA commented that while appropriate

methods are critical, it is also necessary to address the role of aggregation, its impact on product quality and safety, as well as the impact of process parameters on aggregation. Prometic acknowledged these concerns, and assured FDA that they plan to address them.

c. Prometic explained the planned response to the process validation issues. Prometic stated that the (b) (4) for the lyophilization is fixed, and depending on the batch size, (b) (4) will be used. FDA commented that the current PPQ batches do not support the proposed (b) (4) batch and Prometic acknowledged the deficiency, and indicated that it will be addressed in the new PPQ study. FDA further suggested that a (b) (4) plan should be considered for the lyophilization study, and Prometic acknowledged FDA's point.

Additional Discussion:
While discussing the qualification of drug product (DP) manufacturing equipment, Prometic acknowledged the issue communicated in the Late-Cycle Meeting Materials. FDA stated that the qualification for some critical DP manufacturing equipment was not done with plasminogen-related materials, and no risk assessment or rationales were provided. Prometic acknowledged the deficiencies, and planned to address these issues.

2. Additional Applicant Data – 15 minutes (Applicant)

In the second part of the presentation, Prometic showed a brief summary of the 48-week clinical data that have been generated from continued treatment of subjects subsequent to the submission of the original BLA.

Additional Discussion:
The applicant asked whether the 48-week clinical data could support full approval, as previously discussed with the FDA during the development program and the pre-BLA interaction. FDA replied that the 48-week primary efficacy outcome measure (ligneous lesion resolution) is a clinically meaningful endpoint that is suitable for providing information about the durability of treatment effects and can therefore support traditional approval. However, the determination of the adequacy of the 48-week clinical outcomes to demonstrate substantial evidence of effectiveness and safety to support approval will be a review item.

3. Review Plans – 5 minutes (Applicant)

FDA is reviewing Prometic's amendments submitted to date. The PDUFA goal date of the BLA is April 14, 2018.

Additional Discussion: The applicant inquired about their options for withdrawal, and resubmission of the BLA after they have collected the additional information to address the major deficiencies. FDA recommended that the applicant keep the file active in order to preserve the review work that has been

completed to date. FDA also pointed out that in the event that a Complete Response (CR) letter is issued, the applicant's complete response to the CR letter would be reviewed in 6 months, which is a shorter timeframe than for a priority review of a new BLA.

The applicant asked whether FDA could extend the review clock for the BLA. FDA explained that there are no provisions for extending the clock except for classifying an amendment as a Major Amendment to add three months on the current clock. However, a Major Amendment would need to be received prior to the goal date of April 14, 2018, and address all of the outstanding issues, which is not feasible with Prometic's proposed timeline (December 2018, or later).

The applicant inquired about the appropriate way to submit the additional clinical data. FDA replied that the additional clinical data should be submitted as a final study report after the final analyses of the data have been completed.

Prometic asked if labeling discussions are going to be scheduled. FDA responded that, considering the state of the review, it is unlikely.

FDA informed Prometic that in the future, please only submit final reports when one or more 483 observation items are complete, and refrain from sending interim updates.

4. Applicant Questions –20 minutes

   No further questions from Prometic were raised.

5. Wrap-up and Action Items – 10 minutes

This application has not yet been fully reviewed by the signatory authorities, Division Directors, and Review Committee Chair, and therefore, this meeting did not address the final regulatory decision for the application.

END