Our Reference: BLA 125659/0
CRMTS # 11347

MEETING SUMMARY
October 11, 2018

Prometic Biotherapeutics, Inc.
Attention: (b) (4)

Dear (b) (4) :

Attached is a copy of the memorandum summarizing your September 13, 2018, BLA 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 as soon as possible.

Please include a reference to CRMTS #11347 or BLA 125659, in your future submissions related to the subject product.

If you have any questions, please contact Nevitt Morris at (240) 402-8269.

Sincerely,

Ebla Ali Ibrahim, MS
Acting Branch Chief 2
Division of Regulatory Project Management
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Meeting Summary
(Includes Preliminary Meeting Responses)

Meeting ID #:	CRMTS #11347
Submission type & #:	BLA #125659
Product name:	Plasminogen (Human)
Proposed Indication:	Placement therapy in adults and children with plasminogen deficiency
Applicant:	Prometic Biotherapeutics, Inc.
Meeting type:	Type C
Meeting category:	BLA
Meeting date & time:	September 13, 2018 3:00 pm to 4:00 pm
Meeting format:	Face-to-Face
Meeting Chair/Recorder:	Nevitt Morris, RN, BSN BS
RPM:	Nevitt Morris, RN, BSN, BS
Preliminary Meeting Responses:	September 7, 2018

FDA Attendees:
Ebla Ali Ibrahim, MS, OTAT/DRPM
Kimberly Benton, PhD, OTAT
Nevitt Morris, RPM, OTAT/DRPM
Alexey Khrenov, PhD, OTAT/DPPT
Nicole Trudel, PhD, CBER/OCBQ/DMPQ
Jie He, M.S., CBER/OCBQ/DMPQ
Ze Peng, PhD, OTAT/DPPT
Basil Golding, MD, OTAT/DPPT
Mahmood Farshid, PhD, OTAT/DPPT

Prometic Biotherapeutics Attendees:
Rachel Duguay, B.S., Prometic Biotherapeutics
Anthony Adson, M.Sc., Prometic Biotherapeutics
Davida Blackman, Ph.D., Prometic Biotherapeutics
Stacy Plum, Ph.D., Prometic Biotherapeutics
Nathalie Rousseau, M.Sc. Prometic Biotherapeutics
Stephane Gonnard, Manufacturing Sciences Manager, Prometic Biotherapeutics
(b) (4)
(Telephone)
Bill Bees, VP (Telephone)

Background and Objectives:

Prometic Biotherapeutics, Inc., submitted a meeting request on June 22, 2018, to discuss and receive FDA agreement on Prometic Therapeutic's approach to several key CMC issues listed in the Agency's Complete Response Letter dated April 9, 2018. The pre-meeting materials were submitted on July 27, 2018.

FDA provided its preliminary meeting responses to Prometic Therapeutic's questions on September 7, 2018. After reviewing the preliminary meeting responses, Prometic Therapeutics notified FDA on September 10. 2018, of its decision to limit the meeting to discuss only question numbers #4c and #3.

Sponsor Questions

Sponsor Question #1a:
Prometic has re-evaluated the list of Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) to define a comprehensive strategy for setting the In-Process Controls (IPCs). These revised parameters are used to establish the control strategy to ensure consistency of the manufacturing process. In addition, the IPC limits will be revised using data obtained during the engineering runs from the optimized analytical methods, and the limits will be imposed during Process Performance Qualification (PPQ).

Does the FDA agree with our list of CQAs for the plasminogen Drug Product (DP) and their justifications?

FDA Preliminary Meeting Response to Question #1a:
FDA agrees with your list of CQAs. However, assessment of the adequacy of the IPCs to ensure the consistency of the manufacturing process will be made during the review of the information regarding justification of the CQAs in your complete response to the CRL. Please note that while the meeting package stated "*the details of the assay ranges, and acceptance criteria for each CQA are described in Appendix A*", this information could not be located in Appendix A or other appendices.

Meeting discussion for Sponsor Question #1a:
Prometic acknowledged FDA responses and feedback. FDA emphasized that due to the amount of information submitted and limited time allotted for review of meeting package, responses should not be interpreted as agreement with the choice of particular CQAs and IPCs, but rather as a feedback for general approach. FDA also noted that, the approach used in original BLA was not itself deficient, but the implementation was, including multiple inconsistencies between different documents related to development of control strategy and how it was implemented in the manufacturing process. Prometic acknowledged FDA comments.

Applicant Question #1b:
Does the FDA agree with our strategy of identifying the CPPs in the manufacturing process, listed by Unit Operation (with Process Flow Diagram of each Unit Operation in Appendix A), and implementing the IPCs stated for each, including Normal Operating Range (NOR) and justifications of NORs?

FDA Preliminary Meeting Response to Question #1b:
FDA agrees with your strategy of identifying the CPPs, and implementing IPCs. Again, the adequacy of the CPPs, IPCs, and their relevant acceptance criteria to control the manufacturing process will be determined during the review of the data and justifications provided in your complete response to the CRL. This determination may also be affected by the outcome of the proposed Comparability/Change validation studies. FDA recommends that you take (b) (4) samples after the (b) (4) step to assist in investigation in case of process failure or out-of-specification results.

Meeting discussion for Sponsor Question #1b:
There was no discussion of this question during the meeting.

Applicant Question #2a:
Does the FDA agree that a combination of (b) (4) can be used to effectively monitor lower-order and higher-order aggregation?

FDA Preliminary Meeting Response to Question #2a:
FDA agrees with your approach to use multiple orthogonal methods to monitor aggregation. However, the suitability and effectiveness of the proposed methods to monitor and control aggregation will be determined based on our review of the validation packages provided in your complete response to the CRL.

Meeting discussion for Sponsor Question #2a:
There was no discussion of this question during the meeting.

Applicant Question #2b:
Does the FDA agree with Prometic's proposed approach to monitor aggregation in the (b) (4) DP, and (b) (4) (b) (4) by (b) (4), while controlling particulate count in the (b) (4) drug product by (b) (4) analysis?

FDA Preliminary Meeting Response to Question #2b:
FDA agrees with the general analytical approach to monitor aggregation. FDA cannot comment on details of your proposed control strategy before reviewing the validation study reports and justifications to support the use of the different analytical methods at the various stages of product manufacture and relevant acceptance criteria.

Meeting discussion for Sponsor Question #2b:
There was no discussion of this question during the meeting.

Applicant Question #3:
Does the FDA agree that the revised (b) (4) method and implemented strategy are adequate to establish the Performance Qualification (PQ) of the (b) (4) assay to measure Pg activity, and to monitor and verify the performance of successive (b) (4) overtime?

FDA Preliminary Meeting Response to Question #3:
The revised (b) (4) method and implemented strategy appear adequate. However, the final determination will be made upon our review of the validation package for the new method. Please include in the validation package, statistical analysis and comparison of plasminogen activity in (b) (4) samples measured by the old and new assays.
FDA recommends Prometic to predict the usage of the potency reference standard, and establish a protocol to qualify future batches, and a plan to preserve the unitage of the reference standard.

Meeting discussion for Sponsor Question #3:
Prometic provided additional information regarding their plans to demonstrate that the (b) (4) assay is adequate to measure Pg activity and support method bridging studies. The plan includes testing of (b) (4) samples from representative PPQ1 and subsequent batches with the old and new assay to show batch-to-batch consistency of plasminogen activity. Prometic has engaged a contract statistical consulting firm to assist with determining an appropriate statistical methodology to demonstrate consistency. Prometic stated that variability of the old method will be reduced for this study relative to historical data by using a (b) (4) lot of (b) (4) . The old and the new assay will both be run using (b) (4) (b) (4) .
However, the old assay will use the (b) (4) , whereas the new assay will use the in-house qualified reference standard and control.

FDA requested clarification regarding the meaning of (b) (4) ".
Prometic explained that during development of new method, significant variability was found in (b) (4) between batches of testing (b) (4). It necessitated development of the procedures to qualify the quality of (b) (4) and warrants the use of (b) (4) batch of qualified (b) (4) in the bridging study.

Prometic plans to use the data from the new assay only to set specifications for PPQ. FDA agreed.

Prometic acknowledged FDA's advice to establish procedure to qualify future batches of reference standard against the current batch of reference standard. Prometic plans to establish appropriate SOPs and stated that all future batches of reference standards will be trended to control for drift in the unitage of the reference standard. FDA agrees with proposed approach and suggested to Prometic to submit protocol/SOP for future in-house standard qualification as part of the Complete Response. FDA explained that otherwise, as a change in critical reagent, all future standards batches will need to be approved through Prior Approval Supplements (PAS). With an approved protocol FDA

still recommended to submit the first new batch of standards for approval. Prometic acknowledged FDA's comment.

Applicant Question 4a:
Does the FDA agree with the proposed stability-indicating assays and the approach described in the Comparability Protocol Outline (Appendix I)?

FDA Preliminary Meeting Response to Question 4a:
FDA agrees with the proposed stability-indicating assays and the approach described in the comparability Protocol Outline. However, the suitability of these assays and study to assess product stability will be determined upon our review of the validation packages.

Meeting discussion for Sponsor Question #4a:
There was no discussion of this question during the meeting.

Applicant Question #4b:
Does the FDA agree with the proposed stability protocols for Plasminogen Intermediate, DS, and DP going forward?

FDA Preliminary Meeting Response to Question #4b:
FDA agrees with the proposed stability protocols.

Meeting discussion for Sponsor Question #4b:
There was no discussion of this question during the meeting.

Applicant Question #4c:
Does FDA agree with the proposed plan to bridge the data acquired before revalidation of the analytical methods and those acquired after method re-validation to allow usage of stability data from the initial BLA to support a major amendment to the current BLA using stability data from the new PPQ batches with less than (b) (4) batches of DP?

FDA Preliminary Meeting Response to Question #4c:
FDA agrees, in principle, with the proposed plan to bridge the data, however, would point out that the plan lacks acceptance criteria and description of statistical approaches to establish comparability. The ability to use previously acquired stability data will depend on the outcome of the comparability exercise. FDA cannot comment on the need for a major amendment at this time.

Meeting discussion for Sponsor Question #4c:
Prometic acknowledged FDA's feedback and stated that acceptance criteria will be included in the protocol when resubmitting the BLA. The comparability protocol will be in place prior to the PPQ2 run.

Prometic's proposed approach to bridge the stability data for Drug Product (DP) is as follows:

- Test contingency stability samples with revised and re-validated methods, including additional stability indicating methods (eg. (b) (4)
- Generate stability comparability report to bridge old data with the new data.
- Continue to assess stability samples using the revised and re-validated methods.
- Put DP from the recent engineering lot (pre-PPQ2) on stability.
- Set appropriate acceptance criteria for the analytical release and stability indicating assays prior to the upcoming PPQ2 runs.

Prometic inquired if FDA agrees, with the assumption of comparability, with the approach that the existing stability database, in addition to available stability data from PPQ2 runs, will support the BLA resubmission.

FDA responded that the definitive answer to this question can't be given until comparability is indeed established. FDA can't agree based on "assumption of comparability". Final determination regarding the use of stability data from batches manufactured by earlier processes will be made during the review of Complete Response. FDA emphasized, that both product comparability and analytical method comparability will need to be established. The results of comparability studies and the data provided will determine to what degree earlier stability data can be leveraged to establish product shelf-life. FDA also noted that amount of available stability data will depend on the date of BLA resubmission. As it is not clear at this point when resubmission will occur, shelf life discussion is premature at this time. Additionally, FDA explained that with approved stability protocol in place shelf-life may be extended after BLA approval.

Additional Discussion:

FDA asked Prometic regarding the timeframe of the resubmission. Prometic responded that it is not yet determined, but it is likely to be in the first half of 2019. FDA stated that the question is asked strictly to facilitate workload and resources planning at the Agency and Prometic is not bound by their responses. FDA asked Prometic to provide this information as soon as resubmission date is determined. Prometic agreed and noted that prior to resubmission, an additional meeting may be requested to get feedback on the comparability results before commencing PPQ2. FDA advised Prometic that if the planned date of resubmission will be after April 9, 2019 (one year after issuing of CR Letter) Prometic will need to notify FDA, formally confirming that they still intend to submit a Complete Response. See further information in CFR 601.3(c)(1).

Prometic asked FDA if another inspection of the Laval facility will be performed. FDA responded that the resubmission will be a Class II resubmission with a 6 month review clock, and considering the magnitude and

significance of the issues outlined in the Form 483 and CR Letter, it is highly likely that an inspection will be required. FDA noted that Prometic acknowledged the existence of issues and the need to address them and explained that major effort was put both into addressing facilities issues and revising the BLA. Per Prometic, most of the Quality sections of the BLA are going to be revised completely. FDA asked Prometic to include a reviewer's guide with the resubmission, outlining the changes in the BLA. Prometic agreed.