Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

TO: To file BLA STN 125659/0

FROM: Jie He, M.S., CSO, CBER/OCBQ/DMPQ/MRB2

THROUGH: Qiao Bobo, PhD., Chief, CBER/OCBQ/DMPQ/MRB2

CC: Pratibha Rana, RPM, CBER/OTAT/DRPM/RPMBII

APPLICANT: Prometic BioTherapeutics, Inc [US. Lic# Pending]

PRODUCT: Plasminogen (Human) Intravenous, RYPLAZIM

SUBJECT: DMPQ CMC Primary Review Memo

ADD: Aril 14, 2018

REVIEWER SUMMARY AND RECOMMENDATION

A. SUMMARY

Prometic BioTherapeutics, Inc (Prometic) re-submitted this original application under STN 125659/0 for the licensure of Plasminogen (Human) Intravenous (Plasminogen) for the replacement therapy in adults and children with plasminogen deficiency on 8/11/2017. The preparatory name for the product is RYPLAZIM. Prometic previously submitted a BLA submission (STN125647/0, submitted on April 4, 2017) for the same product, and it was issued a RTF by CBER on June 1, 2017 due to deficiencies in the submission.

The manufacture of plasminogen drug substance (DS) is performed in the Prometic BioProduction, Inc.'s facility in Laval, Quebec (Canada); and the manufacture of the drug product (DP) is in (b) (4) .

The Plasminogen DP is formulated as a sterile, nonpyrogenic, white or off-white, lyophilized powder preparation for intravenous injection. The Plasminogen final drug product (FDP) is supplied in single-dose 50 mL glass vials, reconstitution with liquid diluent (sWFI), which is not provided with the DP package. Each vial is reconstituted with 12.5 mL Sterile Water for Injection (WFI) and passed through a disc syringe filter before administration. Upon reconstitution, Plasminogen DP contains 5.5 mg/mL plasminogen in (b) (4) sodium citrate, (b) (4) sodium chloride, (b) (4) glycine, and (b) (4) sucrose.

A recommendation for waiver of Pre-Licensing Inspection (PLI) memo for the contract DP manufacturing facility (b) (4) facility was prepared. The PLI for the Prometic Bioproduction Inc.'s Laval facility was inspected by CBER during November 14 to 21, 2017. There were multiple deficiencies noted during the inspection and a 12 item 483 observation was issued covering facility, equipment, processing, quality system to Prometic upon conclusion of the PLI.

There were multiple issues noted during reviewing of the BLA with regard to the process validation, equipment validation.

B. RECOMMENDATION

I recommend a Complete Response (CR)

1. For equipment cleaning validation studies at PBP, the QC tests for (b) (4) were not properly qualified for the tests. Prometic needs to conduct cleaning validation again using qualified QC test methods.

2. Hold-times and process times are not validated for unit operations for Drug Substance manufacturing process. Prometic needs to 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.

3. For lyophilization process validation, insufficient information was provided regarding the commercial scale PQ study, information for production loading configuration is missing, and the claimed production batch size of up to (b) (4) is not supported by the PPQ campaign. Prometic needs to provide more specific information on commercial production loading process, including position and number of (b) (4) will be used for all claimed batch sizes. The PPQ campaign should include all sizes claimed as well.

4. The proposed storage temperatures and associated stability study conditions for the Drug Substance Intermediate and BDS are not adequately defined. For the Intermediate, the storage temperature is listed as (b) (4) whereas the stability data are available for (b) (4) For the Intermediate and BDS, the storage and stability program conditions are listed as (b) (4) . This tolerance is excessive, considering the storage conditions and the observed difference between the stability of the BDS stored at (b) (4) (b) (4) . Prometic needs to have a consistent storage conditions or perform studies to establish the stability of the materials stored under the worst-case scenario conditions.

5. The performance qualifications for some drug product manufacturing equipment, including the filling line, (b) (4) and lyophilizer, are inadequate because the PQ studies were conducted without using either the 50 mL vials used for Ryplazim or not using plasminogen as (b) (4) . Prometic needs to provide sufficient risk assessment or justifications for the omission, or conduct PQ again using Ryplazim related materials.

6. Shipping validation for (b) (4) stored final drug product is inadequate with (b) (4) validation run conducted in (b) (4) . The shipping validation should be done under the worst-case condition, and also establish a defined shipping time.

7. The observations noted in the FDA-Form 483 during the pre-license inspection have not been resolved completely. Refer to DMPQ 483 response review memo for details.

SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Jie He	Concur	
Qiao Bobo	Concur	
Jay Eltermann	Concur	

The review is organized as the following sections:

I. REVIEW NARRATIVE
II. ENVIRONMENTAL ASSESMENT
III. MANUFACTURE
IV. DRUG SUBSTANCE
V. DRUG PRODUCT
VI. 483 OBSERVATION
VII. REVIEW ISSUES AND CONCLUSION

I. REVIEW NARRATIVE

Items Reviewed

Date Received	Submission	Review Completed (Yes/No)
8/14/2017	STN125659/0	Yes
9/21/2017	STN125659/0.2 (response to IR of 9/6/2017)	Yes
12/12/2017	STN125659/0.6 (initial response #1 to 483)	Yes
1/12/2018	STN125659/0.9 (update response #2 to 483)	Yes
1/22/2018	STN125659/0.10 (update response #3 to 483)	Yes
3/6/2018	STN125659/0.11 (update response #4 to 483)	Yes

I reviewed the manufacturing processes of Ryplazim including the drug substance (DS) (plasma pooling, chromatography purification, solvent detergent treatment, nanofiltration, (b) (4)) performed at Prometic BioProduction Inc. (PBP) facility in Laval, Canada, and drug product (DP) (filling, and lyophilization) performed at (b) (4)

My review focuses on the facilities, equipment, container closure, filling and lyophilization processes for Ryplazim manufacturing.

II. ENVIRONMENTAL ANALYSIS (CATEGORICAL EXCLUSION)

Prometic requested categorical exclusion from environmental analysis for this BLA with respect to the manufacture of Plasminogen under 21 CFR 25.31(c). Prometic stated that the Plasminogen (Human) product is:

1. derived from a naturally occurring source material whose environmental presences will not be increased through manufacture of the product and
2. indicated for treatment of a rare disease, the exemption according to 21 CFR 25.31 (c) "Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment." is appropriate.

Reviewer comment:

Based on the information submitted and the nature of this product, I concluded that the sponsor's request for Categorical Exclusion from an Environmental Assessment under 21 CFR 25.31(c) is justified as this product is composed of naturally occurring substances and manufacturing of this product will not alter significantly the concentration and distribution of the natural substance, its metabolites, or degradation products in the environment, and no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment.

III. MANUFACTURE

Facilities for RYPLAZIM Manufacturing

The following facilities in Table 1 are associated with the manufacture of RYPLAZIM DS, DP, storage and testing.

Table 1: Facilities Associated with the Manufacturing of RYPLAZIM Drug Substance, Drug Product, storage and testing

1	**Prometic BioProduction, Inc.,** (PBP) 531 des Prairies BLVD, Building (b) (4), Laval, Quebec, Canada H7V1B7 FEI #**3010550055**; DUNS #202985149	
	DS Manufacturing, DS & DP QC in process, release and stability testing, QA oversight	No FDA inspection history. PLI conducted by CBER/ORA 11/14-21/2017. A 12 item 482 issued
2	(b) (4)	

	DP aseptic filling, lyophilization, inspection, QC testing, labeling and secondary packaging	(b) (4) item 483 was issued, and classified as VAI. (b) (4) Inspection by CDER (b) (4) (b) (4)
3	(b) (4)	(b) (4) NAI, (b) (4) VAI) (b) (4) NAI
4	(b) (4)	(b) (4) NAI, (b) (4) VAI, (b) (4) OAI) by CDER/CVM (b) (4)
5	(b) (4)	
	Stability storage and testing	No FDA inspection history

Except the Prometic BioProduction (PBP) facility in Laval, Quebec, all other facilities inspections were waived or were not subject to an inspection.

Product Description

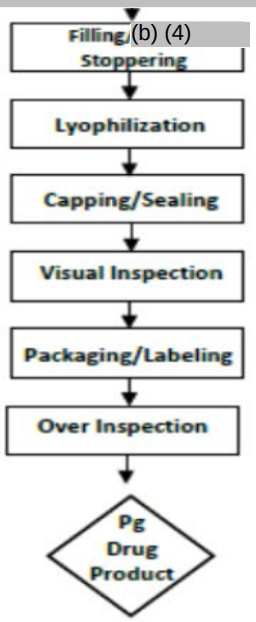
Plasminogen (Pg) is a glycoprotein that is synthesized in the liver and circulates in the blood. The plasminogen molecule contains 790 amino acids, 24 disulfide bridges, no free sulfhydryls and 5 regions of internal sequence homology, known as kringles, between Lys77 and Arg560. These five triple-looped, three disulfide bridged, kringle regions are homologous to the kringle domains in t-PA, u-PA and prothrombin. Native glu-Pg (Mr = 90,000) is readily converted to Lys-77-Pg (Mr = 83,000) by plasmin hydrolysis of the Lys76-Lys77 peptide bond. Prometic has developed a (b) (4) . Plasminogen (Human) and the proposed proprietary name RYPLAZIM for the replacement therapy in adults and children with plasminogen deficiency.

The formulation for Plasminogen (Human) is (b) (4) Sodium Chloride, (b) (4) Glycine, (b) (4) Sucrose. This material is (b) (4) to produce a lyophilized product. Plasminogen (Human) is reconstituted in 12.5 mL Water for Injection prior to administration. Plasminogen (Human) is administered to patients through the intravenous route of administration.

Figure 1. Overview of Manufacturing

(b) (4)

(b) (4)



Human source plasma collected from FDA licensed plasma collection facilities is (b) (4). At the beginning of DS manufacturing, (b) (4) until it is shipped to manufacture Plasminogen Drug Product (DP) at (b) (4)

(b) (4) lots of Plasminogen (b) (4) are (b) (4), aseptically filled in 50 mL vials, lyophilized, stoppered, capped/sealed, inspected, labeled and packaged to form the final Plasminogen DP, Plasminogen (Human).

IV. DRUG SUBSTANCE

1. **ESTABLISHMENT DESCRIPTION**
   - **A. Facility**
   - **B. Utilities**
   - **C. Facility Cleaning & Sanitization**
2. **MANUFACTURING PROCESS**
3. **EQUIPMENT AND THEIR VALIDATIONS**
4. **PROCESS CONTROL AND TEST SPECIFICATIONS**
5. **VALIDATION FOR BDS MANUFACTURING PROCESS**
6. **PROCESS PERFORMANCE QUALIFICATION STUDIES (PPQ)**
7. **CONTAINER CLOSURE SYSTEM FOR BULK DS**
8. **SHIPPING VALIDATION FOR DS FROM LAVAL QUEBEC TO** (b) (4)

1. ESTABLISHMENT DESCRIPTION

Ryplazim DS is manufactured by Prometic at the Laval facility listed in the Table 2 below:

Table 2: Establishment information

FACILITY	RESPONSIBILITY
Prometic BioProduction Inc. 531 des Prairies Blvd Building (b) (4) Laval, Quebec H7V 1B7 Canada FEI: 3010550055 DUNS: 202985149 Contact person: Mowafak Nassani, Director, Quality Telephone: 450-781-0115	Plasminogen DS manufacturing, Quality Control in-process, release and stability storage and testing of commercial product; and Quality Assurance oversight (including of contract facilities)

The production process for Ryplazim DS at the Prometic BioProduction Laval site involves from (b) (4) (b) (4) steps. This site has no previous FDA inspection history, and a pre-licensing inspection (PLI) has been conducted from November 14 to 21, 2017, and a 12 item 483 was issued upon conclusion of the PLI.

A. Facility

The PBP manufacturing and support facilities are located on the *Institut national de la recherche scientifique* (INRS) in Laval, Canada. A site plan is provided in the BLA.

(b) (4)

Building (b) (4) is the main facility for DS manufacturing, and Building (b) (4) provides for the storage of raw materials, process materials, Quality Control, testing laboratories and offices to support manufacturing operations. PBP is registered as a manufacturer with the FDA CBER, Drug Listing Branch, HFN-315. The FEI number for this facility is **3010550055**. The facility is also used to manufacture other plasma derivatives and all the products currently being manufactured are listed in the Table 3 below:

Table 3: Substances Manufactured in the Plasminogen Production Area

Substance	Current Substance Status	Final Substance Stage
Human Plasminogen	Investigational	Intermediate and Drug Substance

(b) (4)

PBP will not manufacture or consider the manufacturing of penicillin, live vaccines or highly toxic or potent products in its multi-product use facility at the Boulevard des Prairies facility. All products are manufactured from human source plasma and have been collected and tested per US FDA standards.

Main manufacturing areas in Building (b) (4)

The manufacturing areas in Building (b) (4) have been classified into (b) (4) zones as the followings:

(b) (4)

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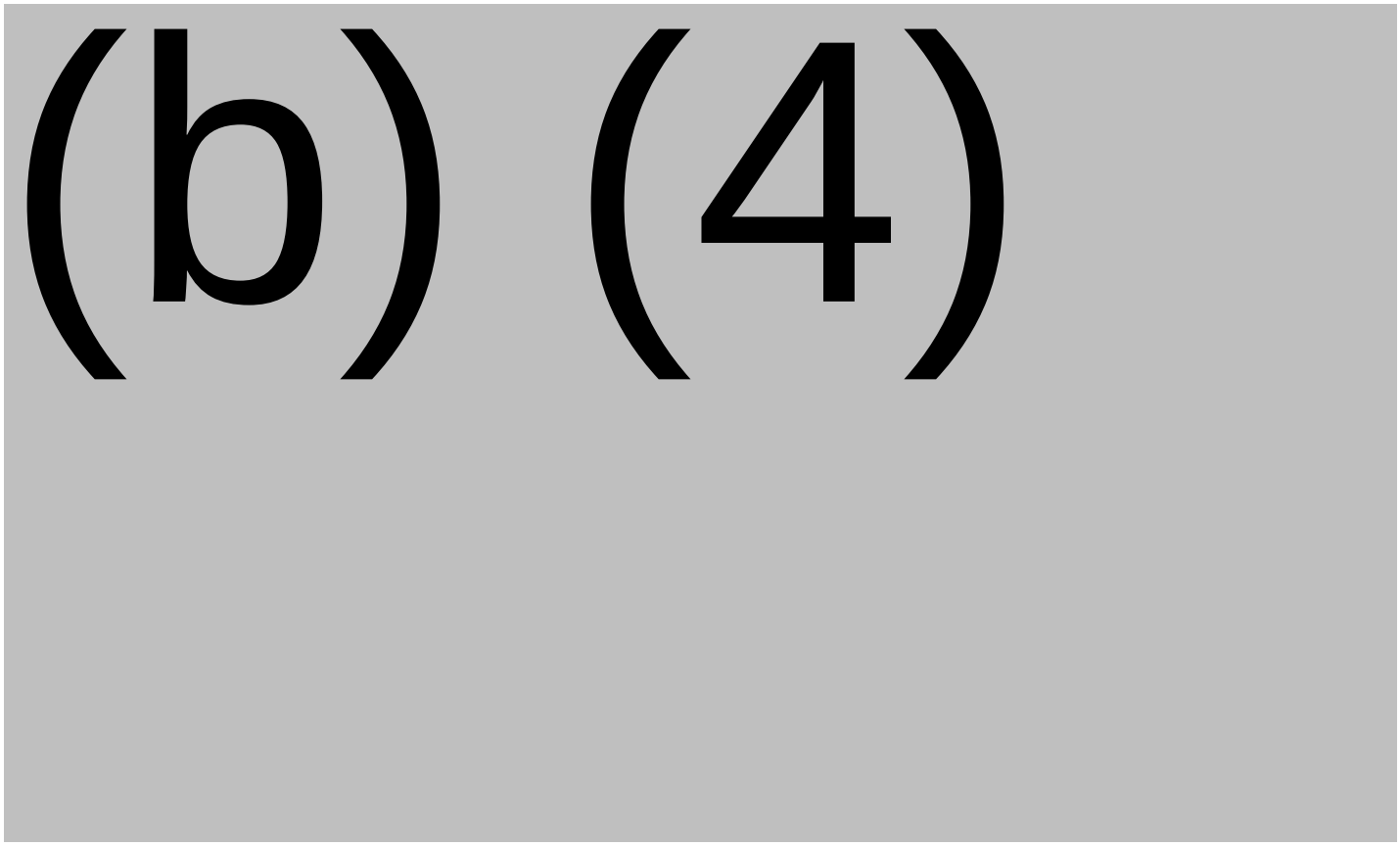
Figure 3. Building (b) (4) core manufacturing facility layout



The DS Manufacturing process follows a linear sequence of steps that progress from (b) (4), to Manufacturing Zone (b) (4) through to Manufacturing Zone (b) (4) with substance dedicated equipment. All Manufacturing Zones operate as Grade (b) (4) The BLA provided diagrams for flow paths for the source plasma and for the substance as it moves through the DS manufacturing process.

Reviewer comment:
The production zoning appears adequate, more detailed review of facility flow paths is also reviewed during PLI and in EIR.

B. Utilities
The BLA does not contain information regarding the utility system at PBP, and these systems were reviewed during the PLI. Refer to EIR for details.

Water
(b) (4)
Water for Injection (WFI), USP (b) (4)

(b) (4)

Water for Injection (WFI)" and SOP QC-020.RR (b) (4) *WFI Sampling".*

WFI is produced from a (b) (4) . The WFI (b) (4)

Table 4: Specifications for Water for Injection (b) (4)

Test	Test Method	Alert Limit	Action Limit	Specification Limit
(b) (4)				

There is a comprehensive monitoring program for the water system. The BLA stated that IQ/OQ for the system has been conducted successfully.

(b) (4)

(b) (4) .

(b) (4)

(b) (4)

Reviewer comment:

The BLA contains limited information on utility systems. The utility systems were reviewed and inspected during PLI. See EIR for more details.

C. Facility Cleaning & Sanitization

The PBP manufacturing areas are cleaned and disinfected using (b) (4) agents. Disinfectants are alternated to reduce the risk of microbial resistance and include (b) (4) agents. Firm stated that disinfectants are alternated to reduce the risk of microbial resistance and include (b) (4) agents. Disinfectant solutions are prepared per the manufacturer's instructions, using (b) (4) . There are SOPs for area specific cleaning requirements for manufacturing areas and ensure the effectiveness of cleaning and disinfectant agents. Production Area corridor floors are cleaned (b) (4). The Production Zone cleanroom (b) (4) cleaned (b) (4) The cleaning and sanitization of manufacturing spaces is governed by procedure *M-006.RR "Cleaning of a Cleanroom*" which was provided in Amendment 2.

Reviewer comment:

There is minimum information provided in the BLA related to facility cleaning. Facility cleaning is reviewed during PLUI, and refer to EIR for details.

2. MANUFACTURING PROCESS

35 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

V. DRUG PRODUCT

1. **ESTABLISHMENT DESCRIPTION**
   - **A. Facility**
   - **B. Utilities**
   - **C. Materials, Components, Product and Equipment Flow**
   - D. **Contamination/Cross-Contamination Prevention**
2. **ENVIRONMENTAL MONITORING**
3. **MANUFACTURING PROCESS**
4. **EQUIPMENT AND EQUIPMENT VALIDATIONS**
5. **VALIDATION FOR FDP MANUFACTURING PROCESS**
6. **CONTAINER CLOSURE SYSTEM FOR BULK DS**
7. **SHIPPING VALIDATION FOR DS FROM LAVAL QUEBEC TO** (b) (4)

1. ESTABLISHMENT DESCRIPTION

The Plasminogen Drug Substance (DS) is (b) (4) for drug product manufacturing. Plasminogen Drug Product (DP) contains 68.8 mg lyophilized plasminogen per vial. The lyophilized Plasminogen DP cake contains (b) (4) of glycine and (b) (4) of sucrose per vial, which are present as (b) (4). The lyophilized cake also contains (b) (4) of sodium citrate and (b) (4) of sodium chloride per vial as part of the drug formulation. Plasminogen DP is supplied in a 50 mL glass vial. Each vial is reconstituted with 12.5 mL Sterile Water for Injection (WFI) and passed through a disc syringe filter before administration. Upon reconstitution, Plasminogen DP contains 5.5 mg/mL plasminogen in (b) (4) sodium citrate, (b) (4) sodium chloride, (b) (4) glycine, and (b) (4) sucrose.

Table 60: Composition of Plasminogen (Human) DP after Reconstitution

Component	Quantity (mg/mL)	Function
Plasminogen	5.5	Therapeutic agent
Sodium citrate	(b) (4)	
Sodium chloride	(b) (4)	
Glycine	(b) (4)	
Sucrose	(b) (4)	

A. Facility

Plasminogen (Human) Drug Product is manufactured by:
(b) (4)

(b) (4) is a GMP compliant facility for the formulation, filtration, filling, lyophilization, packaging, and labeling of parenteral drugs, devices, and biological pharmaceutical products for developmental purposes, clinical trials, and full-scale commercial manufacturing operations. (b) (4) has FDA compliance history, and currently holds a US license or US registration with US license No.: (b) (4). The recent FDA inspections are summarized below:

- (b) (4) inspection by CDER (b) (4) VAI.
- (b) (4) Surveillance Inspection by CDER (b) (4) VAI.

A waiver of inspection for this facility has been recommended.

The overall facility was designed to provide compliance to European and US GMP for the formulation/compounding, filtration, filling, lyophilization, packaging and labeling of parenteral drugs, biologics and medical devices. This facility is designed to be a multi-product contract manufacturing facility for aseptically filled and sterile injectable vial and syringe products in either liquid or lyophilized forms up to (b) (4). Current operations including formulation, filtration, filling, lyophilization, packaging, and labeling are carried out in a (b) (4) multi-product facility constructed in (b) (4). The principal presentations associated with parenteral fills within the plant include vials and syringes. The facility consists of approximately (b) (4) of classified manufacturing space. (b) (4) only has (b) (4) operational manufacturing building (b) (4), the multi-product contract manufacturing facility at (b) (4) will not manufacture or consider manufacture of penicillin, beta lactams, live vaccines or highly toxic products. The current products manufactured in the facility are listed in the table below:

Table 61: List of Product Groups Manufactured Within (b) (4) Building (b) (4)

(b) (4)

(b) (4)

Building (b) (4) is the only manufacturing building used by (b) (4) of interior space including warehousing, manufacturing, quality control testing, pharmaceutical processing, packaging and clerical support/administrative activities. The principal presentations associated with parenteral fills within the plant include vials and syringes. The facility consists of approximately (b) (4) of classified manufacturing space. Air provided to the manufacturing areas is HEPA-filtered.

(b) (4)

(b) (4)

B. Utilities

Facility Heating, Ventilation, and Air Conditioning (HVAC)

Suitable HVAC for the production facility is provided by (b) (4) main air-handling systems, and the BLA provided HVAC plan diagrams. The aseptic core of the manufacturing facility consists of (b) (4)

(b) (4)

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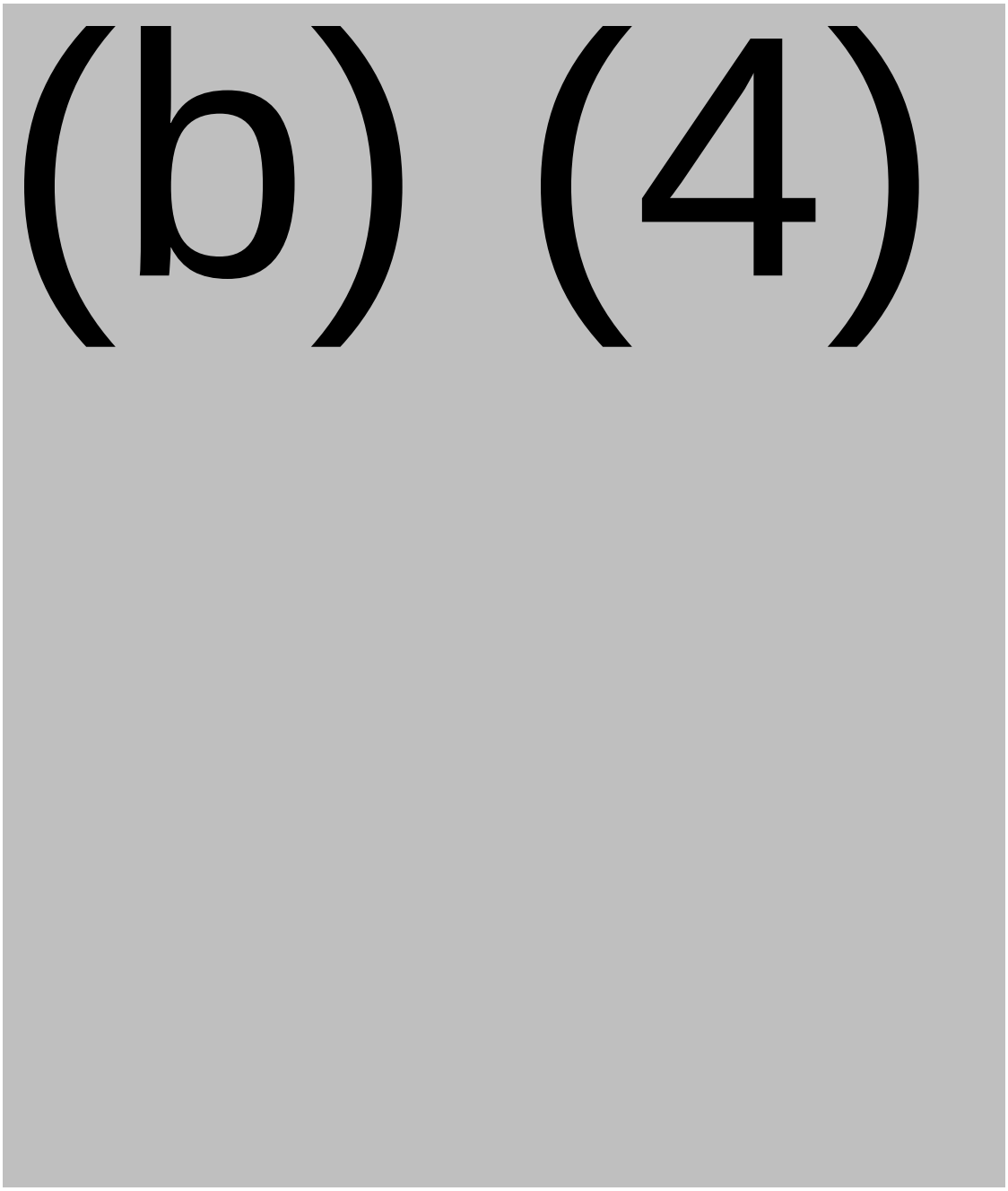
The classifications for the core manufacturing facility is shown in the figure below:



26 pages have been determined to be not releasable:(b)(4)

(b) (4)

PPQ lots samples tested by Prometic are summarized in table below:

Table 95: Prometic Final Product Testing

Test	Sample	Specification	Results (b) (4)				
Appearance <cake)	Final Product Units (Quantities and locations specified by Client)	White to off-white powder	Conforms	Conforms	Conforms	Conforms	Conforms
Particulate Matter		(b) (4)					
(b) (4)							
Reconstitution Time		<10 minutes	(b) (4)				.
(b) (4)		(b) (4)					

Table 96: Prometic Final Product Testing

Test	Sample	Specification	Results (b) (4)				
DH	Final Product Units (Quantities and locations specified by Client)						
Appearance (reconstitution)		Clear or slightly opalescent and colorless liquid	Conforms	Conforms	Conforms	Conforms	Conforms
(b) (4)		(b) (4)					
(b) (4)							
(b) (4)							
Total Protein (b) (4)							
(b) (4)							
(b) (4)							

The bioburden test results for final DP tested by Prometic are summarized in the table below:

Table 97: Prometic Final DP safety testing

Test	Sample	Specification	(b) (4)				
General safety	**Final Product Units**	21 CFR 610.11	confirm	confirm	confirm	confirm	confirm
Rabbit Pyrogen		Meet requirement	confirm	confirm	confirm	confirm	confirm

Final Product Evaluation (Batch (b) (4) sample testing as well as (b) (4) samples were pulled and tested at Prometic for primary product homogeneity and quality (b) (4) Results were evaluated and the resulting degree of variability is not significant for these samples from different locations.

(b) (4) for all (b) (4) lots were also evaluated without any issue. CCIT (b) (4)) was also conducted with the PPQ lots using (b) (4) method (b) (4) and examined (b) (4) random samples from each manufactured lot.

There were 8 deviations associated with the PPQ campaign, as briefly summarized below:

Table 98: Non-conformances

Deviation	Description	Lot impacted
2100000734	Volume and sampling change requested by Prometic in the middle of PPQ. No impact.	(b) (4)
3100000323	1 Cracked vial. Root cause undetermined.	
3100000626	Incorrect carton and label used. Personnel error.	
3100000727	A discrepancy was identified in the expected quantity of labeled cartons. Personnel error.	
3100001051	The incorrect volume per filter was tested during final product sterility testing. Personnel error.	
3100001131	The quantity of units missing stoppers exceeded the (b) (4) action limit. Wrong stopper (b) (4) used. Equipment error.	
3100001153	During 100% inspection, 196 defects were found out of (b) (4) units inspected which exceeded the (b) (4) major defect (b) (4) action limit. Method error.	
3100001171	Temperature and (b) (4) data did not record at the normal (b) (4) increment on two occasions during manufacturing of the lot. Equipment error.	
3100001194	An absence of (b) (4) of vials was observed during set-up. Human error.	

None of the deviation is considered having impact to the validation study.

Reviewer comment:
The PPQ study was conducted for (b) (4) lots. All (b) (4) lots manufactured per the PPQ protocol yielded acceptable in-process testing and final product testing results demonstrating robustness and consistency in the manufacturing processes. All critical process parameters indicate a uniform process that is under control. The (b) (4) final DP tests of bioburden and endotoxin results all met acceptance criteria, other in-process parameters are reviewed by product office. But the (b) (4) PPQ FDP lots (b) (4) were manufactured using (b) (4) manufacturing process has been being validated and locked, so the associated data from these (b) (4) lots are not considered for PPQ purpose.

For lyophilizer (b) (4), it seems for the ~(b) (4), only (b) (4) were used, and for the (b) (4), (b) (4) were used. It is not clearly stated what (b) (4) were used for the PPQ lots, and if these (b) (4) are fixed for production. The lyophilization (b) (4) sampling is not in a (b) (4), but from (b) (4) with just (b) (4) vial each. The lots (b) (4) manufactured (b) (4) manufacturing process was validated, so these (b) (4) lots were not being

considered valid and the data can't be used as PPQ lots. There is a discrepancy for the batch sizes stated in "Description of manufacturing Process and Process Control" in 3.2.P.3.3 and "Batch formula" in (3.2.P.2). The proposed commercial production batch size range has not been validated properly since only the (b) (4) *size has been validated. This issue is addressed in the CR recommendation.*

DP risk assessment

(b) (4) conducted an extractables risk evaluation for the Plasminogen drug product as directed by SOP017633 (SOP3154), "*Evaluation of Extractables from Product Contact Surfaces in the* (b) (4) *for Products*". The report "*Extractables Risk Evaluation Product: Human Plasminogen, Lyophilized Client Prometic Project:2388*" assessed risk of each component used in the fill finish of Plasminogen (Human). Review of this report is deferred to product office.

6. CONTAINER CLOSURE SYSTEM

Primary container

The primary container closure consists of a 50 mL (b) (4) glass tubing vial with a 20 mm opening, a 20 mm (b) (4) stopper and a 20 mm aluminum seal with a flip-off cap. The primary container system is (b) (4), sterilized and filled under aseptic conditions at (b) (4). This type of primary container closure system is standard for (b) (4) biological products and widely used in the biologics.

Table 99: Plasminogen DP Primary Packaging Components

Package Component	Description	Source
Glass Vial-50cc/20mm clear vial	(b) (4), clear borosilicate glass serum bottle, (b) (4) expansion tubing, 73.03 ± 0.79 mm (height) x 42.44 ± 0.79 mm (outside diameter), ready to wash and sterilize	(b) (4)
Stopper-20mm (b) (4) closures	Elastomeric bromobutyl grey rubber bung, (b) (4) (Ready to Sterilize), (b) (4)	(b) (4)
Cap/Seal-20mm, (b) (4)	Flip-off matte finish plastic cap, aluminum seal, (b) (4)	(b) (4)

Figure 11: Drawing of the Plasminogen DP 50cc Glass Vial

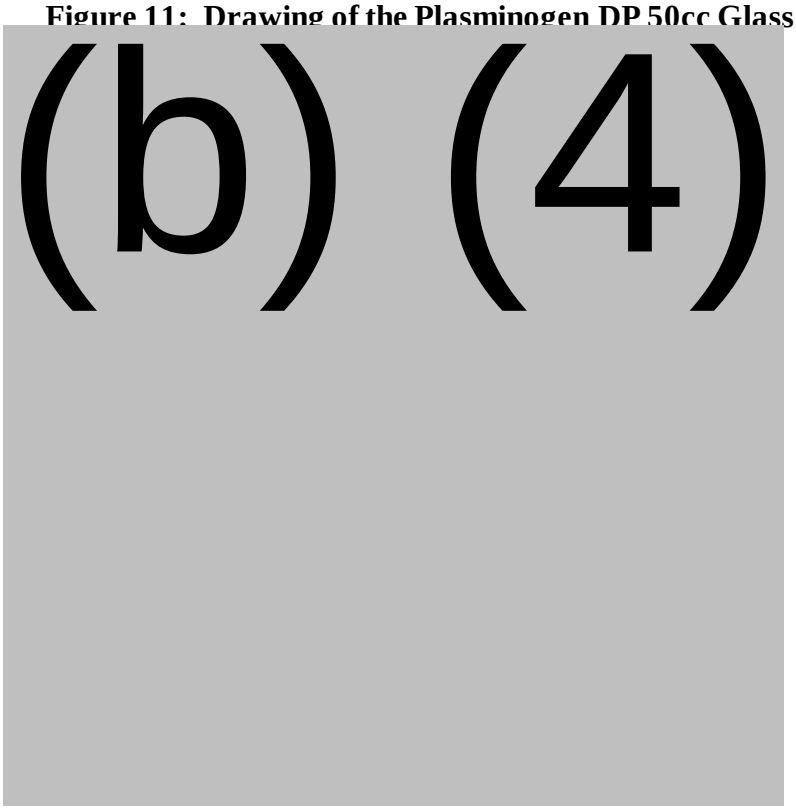


Figure 12: Drawing of the Plasminogen DP Stopper

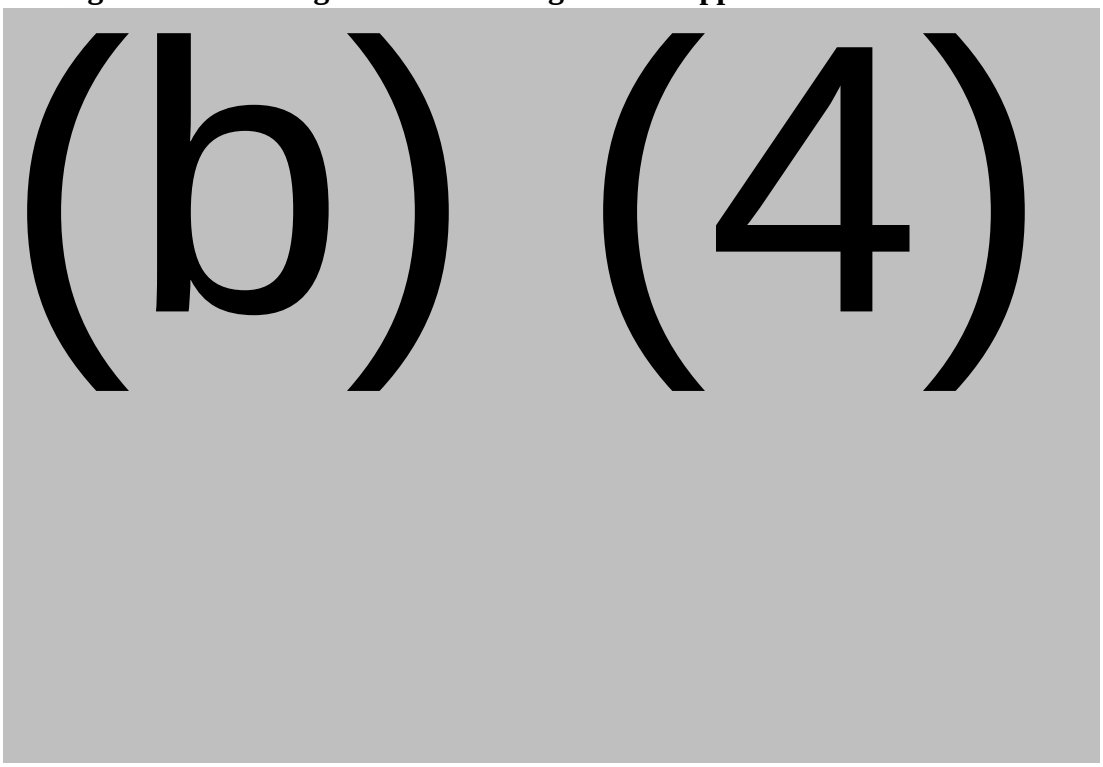


Figure 13: Drawing of the Plasminogen DP Seal

(b) (4)

The Primary Container Closure of vialed, lyophilized and capped Plasminogen DP are individually labeled, packaged into secondary cartoon packaging and inspected by trained personnel at (b) (4) per protocol and per approved batch packaging record.

CCIT

Container closure integrity tests (CCIT) were conducted for this 50 mL vial as summarized in the table below:

Table 100: Drug Product Container Closure Integrity Testing

Category	Test Method	Acceptance Criteria	Results	Clinical Lots Tested
(b) (4)				

For the (b) (4) vials from (b) (4) lots of Pg DP vials (Lot# (b) (4)) were tested using a (b) (4) . The vials containing Plasminogen DP are (b) (4) . All samples met specifications and passed the (b) (4) . The CCIT report "(b) (4) Study Report of the Plasminogen Vial & Stopper Container Closure System" PDR-5026.020 is included in the BLA. Firm also conducted (b) (4) test for the stopper after (b) (4) . (b) (4) vials of Plasminogen Drug Product lots (b) (4) each were removed from (b) (4) The flip-off caps were (b) (4) . For all vials selected for testing, each stopper was (b) (4) . Each (b) (4)

(b) (4) . The vials were then (b) (4) (b) (4) (b) (4)

Results indicated there was no (b) (4) vial.

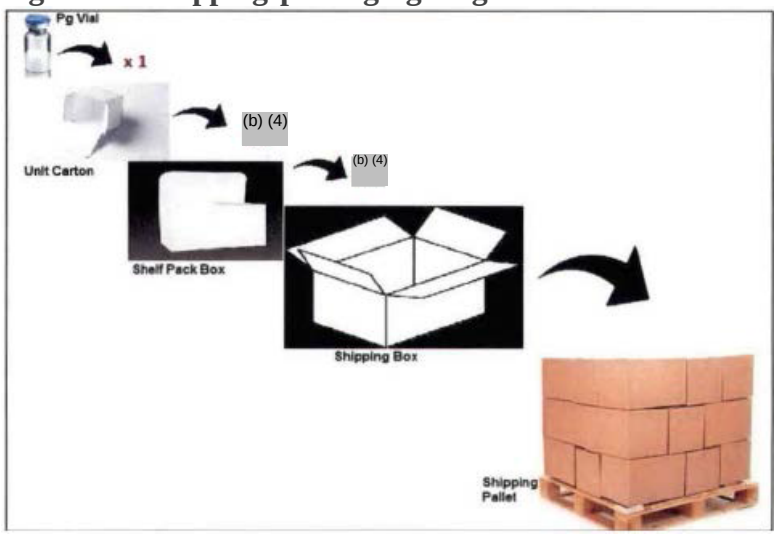
Reviewer comment:
Firm used two methods for CCIT studies using PPQ FDP vials. Both the (b) (4) *on paper appear adequate for the CCIT study except there was no information provided on the types of controls used for these tests, thus it is not possible to evaluate the sensitivity for the test.*

Secondary packaging of FDP vials
The Primary Container Closure of vialed, lyophilized and capped Plasminogen DP are individually labeled, packaged into secondary packaging and inspected by trained personnel at (b) (4) per protocol and per approved batch packaging record. The Plasminogen DP secondary packaging includes a; pre-printed individual unit carton (1¾ x 1¾ x 3.17 inches) manufactured by (b) (4) Labeled Drug Product vial units are manually packaged into the pre-printed unit cartons. Tracking information is printed on the smallest saleable unit of Plasminogen (Human), the bulk shipping box and shipping pallets in both human readable and in two-dimensional data matrix bar code form. The tracking/serialization platform provides visibility and traceability of Plasminogen (Human) as the product moves through the supply chain between Prometic, contract manufacturers, distributors and pharmacies. Prometic has contracted with (b) (4) to provide the logistics and support for the Plasminogen (Human) tracking and serialization program.

Labeling review is deferred to CBER APLB.

7. SHIPPING OF FDP
Final Drug product (FDP) shipping validation was conducted per protocol SPV-006.01-P, and shipping validation report SPV-006 .01 -R "Shipping Validation Report of Plasminogen Drug Product from (b) (4) Under Controlled Temperature (b) (4) was provided in the BLA. The standard packaging was qualified without any defect. (b) (4) transport service and a temperature-controlled active (b) (4) system were used to transport the Pg DP. The (b) (4) has adequate insulation, active temperature control with heating/cooling unit and an interior design optimized for adequate air circulation to maintain product temperature in the (b) (4) range. Packaging of the FDP vials is described and shown in the figure below:

Figure 14: Shipping packaging diagram



- Each filled vial of Pg DP was inserted into an individual unit carton
- (b) (4) unit cartons were combined into a shelf pack box or separators
- (b) (4) shelf pack boxes were packaged into a shipping box or separators
- (b) (4) shipping boxes were attached to a single pallet and secured inside (b) (4)

(b) (4) data-loggers were included in the shipping configuration to monitor the temperature inside strategically selected shipping boxes. (b) (4) data-loggers were used to monitor the temperature both inside and outside the (b) (4).

(b) (4) validation run for US domestic standard shipping packaging configuration for Pg FDP was conducted per the validation protocol. Upon delivered, Pg DP samples taken from the (b) (4) were sent to ProMetic BioProduction Inc. (in Laval, Quebec) to be QC tested. All temperature data recorded by the data-loggers was reviewed by PBP validation personnel. Details of the shipping run is shown in the table below:

Table 101: Validation run for SP shipping

(b) (4)

The temperature information recorded by all the (b) (4) showed that the temperature inside the shipping packages met the (b) (4) requirement and the temperature inside the (b) (4) maintained an average (b) (4) throughout the duration of the shipment. QC test of the FDP that product quality was not compromised during the shipment.

Reviewer comment:
Prometic claimed that since the FDP is shipped in an active shipping container, and there is no need to do more than just (b) (4) *run for the shipping validation. But this shipping run was done in* (b) (4)*, and may not represent the worst-case situation. This issue is addressed in CR recommendation.*

VI. VIII. 483 OBSERVATION

CBER and ORA conducted a Pre-License Inspection of Prometic's DS manufacturing facility in LAVAL Quebec from Nov. 14 to 21, 2017. A 483 with 12 items was issued to Prometic on Nov. 21, 2017 and copied below:

1. The manufacturing process for the plasminogen bulk drug substance (BDS) is not adequately validated or controlled. Specifically,
   a. The in-process controls (IPC) used during process validation, and implemented currently, do not provide adequate control of the process to allow the demonstration of process consistency. Specifically,
      i. The assay for (b) (4) is not suitable for its intended use. Prometic uses, but does not qualify, the (b) (4) , but Prometic does not use an (b) (4) . As such, the results from previously performed assays cannot be verified, and assay performance over time cannot be monitored.
      ii. A subset of the IPC tests was classified in the BLA as "characterization" tests. 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 normal operating ranges.
      iii. No controls are provided for (b) (4) in in-process intermediates, BDS or final drug product (FDP) despite multiple indications showing the (b) (4)
      iv. Analytical methods were modified after the production of the PPQ lots without bridging studies. For example, method (b) (4) determination was changed to method AM-044. Despite the change in (b) (4) , no bridging studies were performed.
      v. No in-process acceptance specifications for (b) (4) were established during the manufacturing of the PPQ lots in support of the BLA. The in-process (b) (4) acceptance specifications were not established until March 2017.
      vi. During the manufacturing of the PPQ lots, the in-process (b) (4) test methods were not verified, and no in-process (b) (4) acceptance criteria were established.

   b. Process steps and materials have been changed between the time of BLA submission and this inspection due to incomplete process knowledge. Specifically,

i. On March 9, 2017, it was discovered (INR 17-271.01) that materials for (b) (4) (b) (4) were used together with (b) (4) despite the manufacturers' warning of incompatibility. Changes to the process are (b) (4).
ii. On June 15-16, 2017, it was discovered (INR-17-265.01 and INR-17-266.01) that the modified procedures to prepare (b) (4) for the solvent/detergent treatment step were inappropriate, and could not (b) (4).

c. Development studies to support the process validation are inadequate. Specifically,
i. Some acceptance criteria for (b) (4) studies (past and ongoing) are not specific enough. For example, acceptance criteria for (b) (4) study include (b) (4) In most cases, the acceptance criteria were not justified.
ii. Multiple results in the studies were labeled as outliers and excluded from analysis.
iii. Incidents observed during the studies were not investigated. For example, particulates were observed during the study of (b) (4) (report MPV-026), but no investigation was performed.
iv. There are no validated hold-times and process step times.

d. Planned deviations were performed during the PPQ batch manufacturing. Specifically, (b) (4) was allowed according to report QAR-001.01-R.

e. BDS lots manufactured from plasma pools with out-of-specification (OOS) (b) (4) test results were released without adequate investigation. For example, among the (b) (4) lots of plasma pools with OOS (b) (4) test results manufactured from May through September 2017, (b) (4) lots were released for further manufacturing into BDS and the contaminating (b) (4) have not been quantitated and identified.

f. There is no procedure or documentation to guide and document the setting of FDP and BDS specifications. It is not clear how the specifications are approved. As a result, the following deficiencies were noted in the specifications:
i. Specifications for the parameters tested for both BDS and FDP were established based on the combined data for BDS and FDP, which is statistically inappropriate.
ii. Testing procedure AM-017 (b) (4) is not compliant to the (b) (4) requirements of (b) (4), as only (b) (4) sample is tested but (b) (4) acceptance criteria (b) (4)" is used.
iii. It is not clear what statistical approaches were used to establish each acceptance criteria. Justification of Specification in the BLA states that (b) (4) tolerance interval for (b) (4) confidence interval was used for all criteria, however during the interview Prometic staff indicated that it may not be true for all acceptance criteria. As specification setting

process was not properly documented it was not clear what acceptance criteria used different approach.

iv. For several specification parameters, minimum and maximum results reported are outside or coincide with proposed specification ranges.

g. BDS shipping validation is inadequate. (b) (4) shipping validation runs for BDS used obsolete protocols with the incorrect fill volume and (b) (4). In addition, the shipping time range was not established.

h. The system for monitoring environmental conditions in Building (b) (4) during the manufacture of the Plasminogen PPQ drug substances batches was inadequate. Specifically,

i. The (b) (4) was not qualified for its intended use.

ii. (b) (4) was disabled during the period of November 2015 to November 2016, which covered the period when the Plasminogen PPQ batches were manufactured.

iii. The (b) (4) settings did not provide adequate control for activities involving operators and equipment in rooms where manufacturing occurred. For example, during the period of November 2015 to June 2016, the (b) (4); during the period of June 2016 to March 2017, (b) (4) The limit settings were not executed under change control.

iv. There is no system or backup plan established for when power outages and wireless outages occur to ensure continuous monitoring of (b) (4), (b) (4) within the manufacturing area. (b) (4) wireless outages were recorded for (b) (4), used to store (b) (4) wireless outages were recorded for (b) (4) from July 2016 to August 2017. No monitoring data were recorded during wireless outages.

2. Regarding quality assurance oversight of the quality systems operation, the following was observed:

a. The SOP QA-007 "Incident notification deviation and investigations" is deficient. Specifically,

i. The SOP states that the procedure does not applied to planned deviations, but also states that planned deviations are deemed acceptable following change control procedure.

ii. The SOP does not provide clear requirements for situations where CAPA is required.

b. Deviations, investigations and incidents are not managed appropriately. Specifically,

i. SOP QA-007 requires incidents to be reported within 72 hours. However, multiple incidents were not reported to the QA within allowed timeframe

ii. There are 426 incidents reported in 2016 and 428 incidents reported by the time of FDA inspection in 2017, including several recurring incidents. For example, multiple recurring

incidents were observed related to (b) (4) (b) (4) broken (b) (4) as well as insect intrusions.

iii. Risk assessment for deviations is inadequate and absence of impact on product quality is often assumed without proper evaluation. For example, deviation DEV-16-111.01 was issued for the (b) (4) (exceeding the (b) (4) limit specified in the batch record) and the implemented CAPA was to increase the limit to (b) (4) The risk assessment did not adequately evaluate the increased (b) (4) impact on the (b) (4) integrity. Following this increase, the rupture of (b) (4) in the following (b) (4) BDS shipments was observed at (b) (4)

iv. Corrective actions are not effective or documented. For example, incident report INR-17-06.01 was open on 24 March 2017 for incomplete (b) (4). Corrective action implemented included verification of the (b) (4) and adjustment of the (b) (4) (no formal CAPA was open). However, on 17 May 2017, another incidence of incompletely (b) (4) occurred and was reported to QA on 28 June 2017. Also, starting from August 2016, there were 11 incidents of observations of insects inside the production areas before investigation INV-16-028.01 was opened. Some of the CAPA resolution plans have been executed, but insect intrusions are still being observed. The associated CAPA effectiveness is projected to be evaluated in August 2018.

v. Incident/deviation reports are not always issued for unscheduled production equipment repairs or maintenance. For example, no incident report was issued for multiple unscheduled repairs for (b) (4) during 2017. The repairs include (b) (4).

c. OOS for in-process (b) (4) test results were not adequately managed per SOP QA-007.02 "Incident Notifications, Deviation and Investigations", effective Dec. 15, 2016. For example, there were 26 deviations for in-process samples from (b) (4) lots manufactured from May 4, 2017 through June 1, 2017 without any QA notifications and investigations being generated within the SOP requirement.

d. The SOP QC-015.02 "Handling of Out-of-Specification Test Results" is inadequate, leading to deficient investigations of OOS results. Specifically,

i. If the Phase 1 laboratory investigation did not identify the root cause of OOS result, the procedure instructs the QC staff to perform Phase 2 investigation by retesting/resampling of samples without explicit requirement for QA approval. If OOS is not confirmed in this retesting, no investigation is performed by the Manufacturing Department. Several such investigations reviewed (for example, INR-16-424.01 and INR-17-297.01) did not include documented investigations from the Manufacturing Department and root cause of the OOS result was not identified. Incident INR-17-007.001 indicated that after (b) (4)

DP (b) (4), but this was not brought to attention of other departments and corrective action was limited to better (b) (4).

ii. The SOP does not specify the procedure for identifying out of trend (OOT) results.

iii. The SOP allows to remove outliers results from analysis without specifying clear criteria for identifying result as an outlier.

3. The cleaning validation of critical equipment is inadequate. Specifically,

a. The cleaning validation for (b) (4) performed in May 2015 failed. This (b) (4) continued to be used as a shared equipment for the manufacture of plasminogen drug substance and (b) (4) until July 2016. The testing for (b) (4) carryover after each campaign was inadequate because the potentially (b) (4) cannot be detected by the (b) (4)

b. The clean hold time assigned to the (b) (4) was not supported by sufficient data. Specifically, the assigned clean hold time of (b) (4) was established base on a (b) (4).

c. The analytical methods used for (b) (4) cleaning validation were not qualified for their intended use. Specifically,

i. The (b) (4) method SOP AM-010.04 has not been validated for recovery of (b) (4) from the (b) (4) after cleaning with a (b) (4).

ii. The (b) (4) method ((b) (4)) SOP AM-002.05 has not been validated for recovery of (b) (4) from the (b) (4) after cleaning with a (b) (4)

4. Disinfectants used to clean the cleanroom have not been appropriately qualified. Specifically,

a. The Detergent and Disinfectant Validation (CVP-0.18.01-R) performed to validate the effectiveness of (b) (4), used to disinfect the cleanroom during the PPQ batch manufacture, was inadequate. Specifically,

i. The validation study did not establish criteria for (b) (4).

ii. The validation study did not evaluate disinfectant effectiveness against (b) (4)

iii. The validation study did not consider the cleanroom surfaces, such as the (b) (4)

b. (b) (4) the current disinfectant used to clean the cleanrooms since June 2017 according to SOP M-006-09, has not been validated for its intended use.

c. (b) (4) used to clean the cleanrooms, has not been validated.

5. Batch record does not provide sufficient description of the manufacturing steps and no separate SOPs for manufacturing steps were observed in the manufacturing area or referenced in the batch record. For example,
   a. During the walkthrough of Zone (b) (4) the firm could not explain the details of the process of (b) (4) even after reading batch record.

   b. Batch record has no instructions on how (b) (4) should be attached to the (b) (4). Inconsistency was observed in using (b) (4) in production Zone (b) (4).

   c. Per SOP QC-020.03 (b) (4) Water for Injection", a (b) (4) is needed for (b) (4) in production areas. However, this requirement is not specified in the (b) (4) preparation batch records.

6. The (b) (4) have not been adequately qualified because no performance qualification was performed on (b) (4) to demonstrate adequate and consistent performance ((b) (4) under conditions simulate those used during actual manufacturing.

7. Control of materials is inadequate. Several (b) (4) observed in the storage area has "released" labels with the expired retest date. Per SOP QC-014 "GMP Materials Sampling, Testing and Release" materials past their retest date should be quarantined. No evidences were observed that the materials were retested. The use log for item (b) (4) states that it was used in October 2017 while it was due to retest in April 2017.

8. The preventative maintenance plan is inadequate in that Quality Assurance does not always provide oversight and/or there is no responsible person assigned to perform a specific task. Specifically,
   a. The 2016 (b) (4) preventative maintenance plan for the WFI system was not executed. There was no QA evaluation of the missing preventative maintenance.
   b. There is no preventative maintenance plan for the (b) (4) No deviations were initiated and no product impact was evaluated by the Quality Unit.

   c. Preventative maintenance plans for (b) (4) do not include all components of the equipment (e.g., (b) (4)).

   d. Temperature alarms and abnormal patterns in the (b) (4) are not always evaluated by the Quality Unit for impact to the contents inside the (b) (4), which include (b) (4), (b) (4) Similarly, temperature alarms in (b) (4) which was used for the storage of drug substance intermediates until June 2016, were not always evaluated by the Quality Unit for the impact to the contents of the (b) (4)

e. (b) (4) in Building Room (b) (4) was observed to be worn out and partially disassembled. In 2017, there were 2 incidents of (b) (4) due to inadequate (b) (4). No evidence of PM of this equipment is provided.

f. (b) (4) was repaired twice (March 2015 and November 2017). No evidence of PM of this equipment is provided.

g. During the observation of the SBDS (b) (4) procedure the battery in the (b) (4) used to measure the (b) (4) was dead and (b) (4) was not functional. No spare batteries were available in Zone (b) (4) which caused delay in the process.

h. The use log for (b) (4) between March 6 – April 7 2017. The log book stated that in one instance the (b) (4) was "broken" and in another instance "damaged (b) (4) Despite multiple request to provide the history of the (b) (4) for the (b) (4) used, this was not done and this information is not readily available.

9. Regarding the manufacturing facility, the following was observed:
   a. In Zone (b) (4) at least four instances of (b) (4) on the walls were noticed.

   b. Below the (b) (4) between Zone (b) (4) room, the (b) (4) was falling off.

   c. (b) (4) between and around (b) (4) was rough/incomplete in multiple places.

10. Equipment identification is inadequate. Specifically,
   a. There was no lot information on shared equipment. Specifically, during the walkthrough in Zone (b) (4) have no labels on what lots is being manufactured.

   b. The SBDS (b) (4) is still labeled as "(b) (4) " and is labeled for (b) (4) " zone. The (b) (4) is used in Zone (b) (4) since December 2016 and was not re-labeled for use in Zone (b) (4)

11. Operator was observed inappropriately working inside the (b) (4) in Zone (b) (4) blocking airflow not following procedure SOP MM-012 "(b) (4) .

12. (b) (4) has been used for nanofiltration process without a (b) (4) . No (b) (4) test is done by vendor or Prometic for this product contact (b) (4) used at the (b) (4) processing step.

Reviewer comment:
See separate DMPQ and product office memos for reviewing of the 483 responses from Prometic.

VI. REVIEW ISSUES AND CONCLUSION

Review issues:

1. The CCIT for FDP has no information on positive and negative controls used.
2. For equipment cleaning validation studies at PBP, the QC tests for (b) (4) were not properly qualified for the tests.
3. For BDS and FPD manufacturing process, the in process hold time and process time for each step has not been established or specified.
4. The performance qualifications of some critical manufacturing equipment for drug product, including: filling line, depyrogenation ovens, autoclave, vial washer and lyophilizer, are inadequate. Some of the PQ studies were conducted without using Ryplazim related materials or product, and no sufficient risk assessment or justifications provided.
5. For lyophilization process validation, insufficient information was provided regarding commercial scale PQ study, information regarding production batch sizes and load configurations is not sufficient.
6. Shipping validation for FDP is inadequate with (b) (4) run and not under worst-case conditions.
7. Prometic claims the storage condition for Plasminogen DS is determined to be (b) (4) . But the BLA indicted Plasminogen DS storage conditions at PBP is (b) (4) (shipping condition and storage condition) at (b) (4) for up to (b) (4) This means the DS could possibly be stored at (b) (4) which conflicts with the claimed storage condition. This issue was discussed during PLI.

Inspection issues:

8. There were a 12 item 483 issued to PBP at the conclusion of PLI at Laval Quebec facility. Prometic has since submitted 4 amendments in response to the 483. Prometic is planning to conduct the PPQ validation again once all other issues have been addressed. Among the 12 observations, only #9 related to facility repair has been closed, and the other 11 items have not been closed as of this review. Prometic is not able to address all the outstanding 483 issues by Action Due Date of the BLA.

Considering the review and inspection issues outline in this memo, I recommend a Complete Response for this BLA.