M E M O R A N D U M

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

To: Administrative File for BLA (**STN 125659/0**)
Crystal Melendez, RPM, RPMB/DRPM/OTAT

From: Alexey Khrenov, PhD, Hemostasis Branch (HB)/ Division of Plasma Protein Therapeutics (DPPT)/ Office of Tissues and Advanced Therapies (OTAT)

Through: Tim Lee, PhD, Chief, HB/DPPT/OTAT

Basil Golding, MD, Director, DPPT/OTAT

Subject: Final CMC review of Prometics's original BLA for Plasminogen (Human) STN 125659/0 submitted August 14, 2017

Contents

1. Executive Summary

STN 125659/0 is an original biologics license application (BLA) submitted by Prometic Biotherapeutics for Plasminogen (Human) with the proposed proprietary name RYPLAZIM. Prometic Biotherapeutics is a wholly owned subsidiary, and a US agent for Prometic Life Sciences Inc. headquartered in Laval, Canada. As all Prometic companies operate essentially as part of a single company, the term Prometic is used in the memo, unless it is necessary to use the name of a particular subsidiary.

This is the second submission of the BLA. It was originally submitted under STN 125647/0, which received a "Refuse To File" letter due to a significant amount of information missing from the submission.

The active ingredient of RYPLAZIM is a human plasma-derived plasminogen. The protein is purified from human blood plasma using Prometic's (b) (4) . The manufacturing process for RYPLAZIM is a (b) (4)

The drug product is supplied as a preservative-free, lyophilized formulation presented in one dosage strength of 68.8 mg lyophilized plasminogen per vial in single-use glass vials of 50 mL nominal capacity. RYPLAZIM is reconstituted with sterile Water for Injection (sWFI) giving a final volume of 12.5 mL.

RYPLAZIM is indicated for replacement therapy in adults and children with plasminogen deficiency.

STN 125659/0 was reviewed under the priority review schedule of the PDUFA V Program. Prometic submitted the BLA on 14 August 2017, and the PDUFA V action due date is 14 April 2018.

The scope of my review covers all CMC topics except the evaluation of safety regarding adventitious agents (reviewed by Dr. Ze Peng), and Endotoxin and Bioburden test methods (reviewed by the Division of Biological Standards and Quality Control (DBSQC) in the Office of Compliance and Biologics Quality).

Substantive CMC deficiencies related to the validation of the manufacturing process, characterization of the drug substance (DS) and drug product (DP), specifications, and facilities and equipment were discovered during the review of the BLA, and inspection of Prometic's facility at Laval, Canada. Due to these issues, the manufacturing process for RYPLAZIM cannot be considered validated.

These deficiencies were communicated to Prometic, and Prometic has initiated additional studies for the development of the manufacturing process and analytical methods, with the purpose of re-designing the validation studies, and performing a new Process Performance Qualification (PPQ) campaign. Prometic estimated that the PPQ campaign would not be completed until November 2018, which will fail to meet the action due date for this BLA. Therefore, I recommend issuing Prometic a Complete Response Letter.

2. Background

RYPLAZIM was developed for the US market under IND 16186 for replacement therapy in adults and children with congenital plasminogen deficiency.

Plasminogen deficiency is a disorder that results in the development of fibrin-rich pseudo membranes that impair normal tissue and organ function. The lesions are commonly described as ligneous membranes. Most commonly, ophthalmologic lesions have been described, however, other physiologic systems are affected, including the gingiva, otic, renal collecting system, respiratory tract, and female genitourinary system. Plasminogen deficiency is extremely rare, and the true prevalence is unknown. Based on available data, a predicted prevalence of homozygous or compound heterozygous plasminogen deficiency is approximately 1.6 per 1,000,000 people. No replacement therapy is currently available for these patients, and no other plasminogen products are licensed for other indications.

For the purpose of consistency, the name RYPLAZIM is used throughout the memo. In the BLA, the product is referred to as "*plasminogen*", "*Plasminogen Intravenous (Human)*" or the acronym *Pg*. The FDA proper name is "*Plasminogen (Human)*".

RYPLAZIM is purified from human plasma, and acts as a replacement for natural plasminogen missing in plasminogen deficiency patients. Plasminogen is the zymogen of plasmin that is synthesized in the liver and circulates in the blood. The native form of plasminogen, Glu-plasminogen, contains 791 amino acids, 24 disulfide bridges, no free sulfhydryls, and five regions of internal sequence homology, known as kringles, between Lys77 and Arg560. Glu-plasminogen has a molecular weight of about 90 kD and a pI of approximately 7, although differential glycosylation and/or removal of the N-terminal activation peptide can result in a pI range of 6-9. There is one N-linked glycosylation site and two O-linked sites. Approximately 70% of the plasminogen in circulation contains only O-linked glycosylation, while the rest contains both N- and O-linked sugars. Glu-plasminogen is readily converted to Lys-plasminogen by plasmin hydrolysis of the Lys77-Lys78 peptide bond.

Plasminogen is distributed throughout the body, and when the conditions are present for activation, the plasminogen zymogen is converted to the active enzyme, plasmin, by t-PA or by u-PA. Plasmin then degrades fibrin clots to fibrin degradation products and D-dimers; and converts latent matrix metalloproteinases (pro-MMPs) into active MMPs, which in turn further degrade extracellular matrix (ECM) as part of the tissue healing/remodeling process.

3. Review History

A BLA for Plasminogen (Human) was first submitted under STN BL 125647/0 as a rolling BLA. The final modules were submitted on 4 April 2017, and a "Refuse To File" (RTF) letter was issued on 1 June 2017 due to significant amount of information missing from the submission. The current BLA, STN 125659/0, was submitted on 14 August 2017, which included an itemized response to the deficiencies outlined in the RTF letter. The BLA was reviewed under the priority 8-month schedule of the PDUFA V program, as the indication for RYPLAZIM was granted Orphan designation, and Rare Pediatric Disease designation.

Because numerous major deficiencies were identified during the review of the BLA and facility inspection, it was decided at the Mid-Cycle meeting that the reviewers will not send any substantive Information Request (IR) regarding CMC issues to the company. We will instead convey the deficiencies in a CR letter. Significant review issues were discussed with the company during the pre-license inspection (PLI) of the Prometic facility in Laval, Canada on 14-21 November 2017, and during the Late-Cycle Meeting on 8 March 2018.

4. Manufacturing Process

4.1. Manufacturers

The manufacture of RYPLAZIM is divided into two main stages (see Figure 1) conducted at two manufacturing facilities (Table 1). Production of the Bulk Drug Substance (BDS) takes place at the Prometic Bioproduction facility in Laval, Canada, which was not FDA-licensed, and was inspected during the review of this BLA. Prometic Bioproduction is another wholly owned subsidiary of Prometic Life Sciences Inc. (b) (4) is used for some of the tests. Production of the Final Drug Product (FDP) is performed at the FDA-licensed contract manufacturing facility of (b) (4) Additionally, two contract laboratories are used for testing of FDP samples

Reviewer's Comments (all italicized text in the rest of the memorandum represents this reviewer's comments):

The split manufacturing approach (BDS production by one manufacturer, and FDP filling at contract facility) is common and acceptable. Split manufacturing takes advantage of (b) (4) *expertise in lyophilization, and availability of lyophilization and fill equipment.*

CBER conducted a PLI of Prometic's Laval manufacturing and testing facility 14-21 November 2017. The inspection team consisted of DMPQ inspectors Jie He and Lily Koo, ORA inspector Susan Jackson, and OTAT product reviewer Alexey Khrenov. At the end of the inspection, a Form FDA 483 with 12 observations was issued. The firm is still in the process of addressing the observations, and implementing corrective actions.

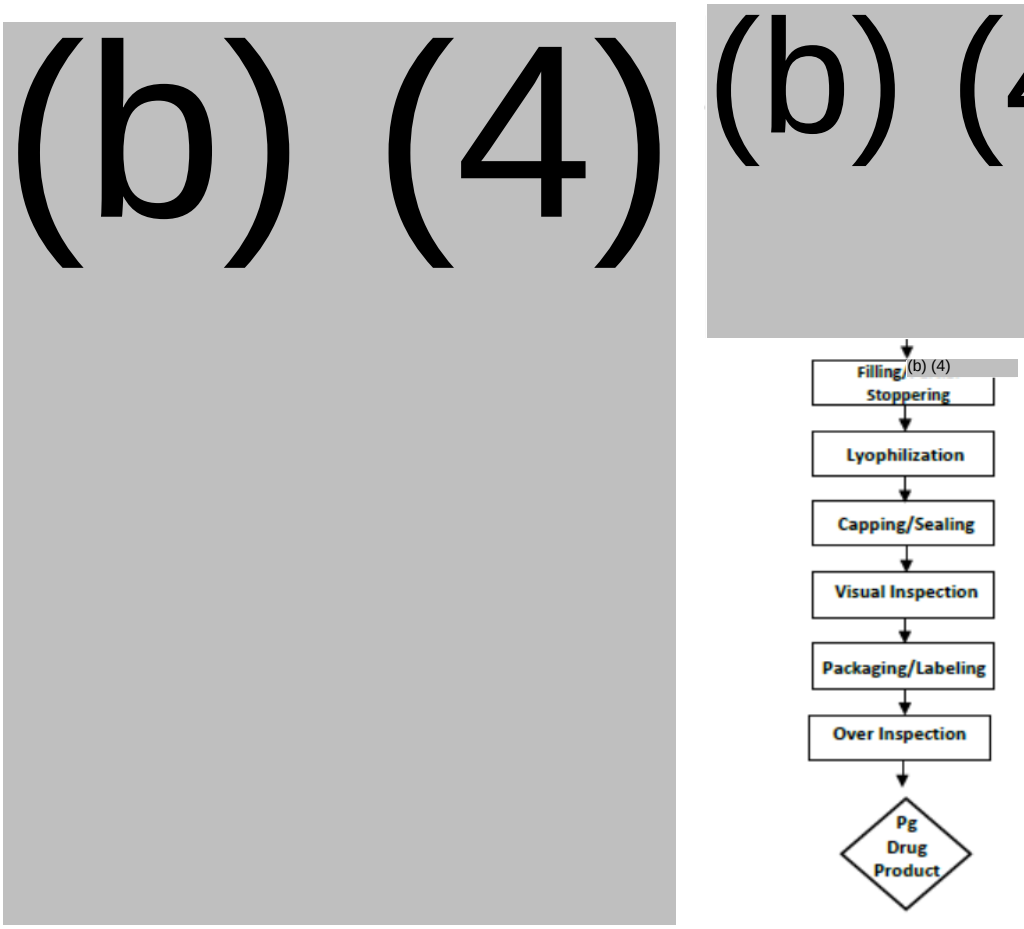
Table 1: Manufacturing Facilities for RYPLAZIM

Facility	Responsibility
Prometic Bioproduction Inc. 531 des Prairies Blvd Building (b) (4) Laval, Quebec H7V 1B7 Canada FEI: 3010550055 DUNS: 202985149	RYPLAZIM BDS manufacturing, Quality Control in-process, release and stability storage and testing of commercial product; and Quality Assurance oversight (including contract facilities)
(b) (4)	Method development and characterization testing, stability storage and testing of clinical products
(b) (4)	FDP aseptic filling, lyophilization, inspection, labeling and secondary packaging. FDP sterility, endotoxin and (b) (4) particulates matter testing
(b) (4)	FDP general safety testing
(b) (4)	Stability samples sterility testing

My overall impression was that the deficiencies were major and systemic. Both process design and execution were deficient. The manufacturing staff demonstrated a disregard for GMP rules and regulations, and the instruction and advice from Quality Assurance were routinely ignored. Risk assessments were superfluous, and serious risks were downplayed in order to continue production. The people in production management lacked the knowledge of the manufacturing process, and could not provide the critical information about the process operations. I would not recommend an approval of any submission without a re-inspection of these facilities, and assurance that the issues observed are adequately addressed.

Considering that (b) (4) FDP manufacturing facility was previously inspected, the decision was made by DMPQ, and supported by DPPT, to waive the PLI for this facility.

Figure 1: RYPLAZIM manufacturing process. The production of BDS includes (b) (4) . The FDP is manufactured in (b) (4) . Release testing is performed on the (b) (4) FDP.



Batch and Scale Definition

Plasma pools of approximately (b) (4) are manufactured into plasminogen intermediate (Intermediate), which is then (b) (4) batches of intermediate are (b) (4) and manufactured into (b) (4) batch of BDS. Thus, (b) (4) batch of BDS is manufactured from (b) (4)

(b) (4) BDS batches (approximately (b) (4) are used to manufacture (b) (4) batch of FDP. Accordingly, the FDP batch size varies between (b) (4) vials.

4.2. Intermediate and Bulk Drug Substance

The RYPLAZIM manufacturing process (Figure 1) is relatively standard for plasma-derived coagulation factor products. RYPLAZIM is purified using a (b) (4) *designed to reduce the levels of product- and process-related impurities, and undergoes three viral clearance steps. The main difference from other products is that* (b) (4) *step*

does not use an (b) (4) *, but uses Prometic's* (b) (4)

(b) (4)

(b) (4)

4.3. Final Drug Product

(b) (4) batches of DS are combined to manufacture a (b) (4) DP (b) (4) . (b) (4) lots of BDS are (b) (4) filled in 50 mL vials, lyophilized, stoppered, capped/sealed, inspected, labeled and packaged to form the FDP.

The FDP is reconstituted with 12.5 mL Sterile Water for Injection (sWFI) and passed through a disc syringe filter before administration.

The RYPLAZIM package includes the FDP vial only. All the supplies including sWFI, syringe/needle and filter are supposed to be provided by the patient or healthcare provider.

Table 2: Nominal composition of reconstituted RYPLAZIM

Ingredient	Quantity, mg/mL	Function
Plasminogen	5.5	Active Substance
Sodium citrate		
Sodium chloride		
Sucrose		
Glycine		

(b) (4)

4.4. Controls of Materials, and Extractables and Leachables

Most of reagents and materials used in the manufacture of RYPLAZIM are supplied by vendors and conforms to (b) (4) *specifications. Prometic performs testing to confirm the Certificate of Analysis provided by the supplier. No issues are discovered regarding third-*

party supplied reagents and materials. The materials, control of which required a separate review are (b) (4) *which are manufactured by Prometic.*

4.4.1. Plasma

Prometic claims that human source plasma used in the production of RYPLAZIM was collected from healthy, non-immunized donors in FDA or Health Canada licensed and (b) (4) certified facilities in the United States (US) and Canada. Donor qualification, quality assurance, donor deferral, education and training of personnel, and (b) (4) guidelines as provided by the (b) (4)

Prometic provided a list of plasma centers used for plasma collection. The only center which is not from the United States is (b) (4) *which is also FDA-licensed.*

All plasma suppliers, test laboratories, transport companies and storage companies have supplier quality agreements (SQA) and are qualified by Prometic. These SQAs align the quality systems between both parties and facilitate the communication of quality requirements for each of the control systems. Supplier agreements include elements such as Supplier Qualification and Audit process, Record Retention, Donor Selection and Exclusion, Unit Collection (e.g., (b) (4)), Processing and Storage, Plasma Documentation and logistics, Notification requirements (e.g., Lookback/Post Donation Information), Changes/Compliance (e.g., (b) (4)), Issue and Compliant Resolution, and Communication plan.

FDA did not verify the SQAs, however during the PLI, it was noted that on receipt of plasma units, multiple occurrences of (b) (4) *with* (b) (4) *were registered over an extended period of time. It is recommended that Prometic's* (b) (5), (b) (7)(E)

Donors are initially tested, and then every (b) (4) months thereafter, tested for syphilis and the presence of other potential adventitious agents via (b) (4)). All donations are tested for the presence of human immunodeficiency virus (HIV), hepatitis (A, B and C) prior to release. Additional precautions taken to ensure the safety and quality of the plasma used for the manufacture of RYPLAZIM are (b) (4) Collected plasma is (b) (4) of plasma based on post-donation disqualifiers such as high-risk behavior, testing reactive for HIV, HBV or HCV or international travel.

In general, plasma collection, handling and testing appear to follow the regulations and accepted practices, and may be considered acceptable.

(b) (4)

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(b) (4)

[redacted]

5. Analytical Methods, Release Specifications, and Reference Standards

Due to the significant amount of information, this section outlines only the issues raised during the review, and does not contain descriptive information. If a particular method or specification is not mentioned, it is because no issues were identified.

5.1. Specifications for the Intermediate, Bulk Drug Substance, And Final Drug Product

Specifications for RYPLAZIM Intermediate, BDS, and FDP are presented in Tables 6, 7, and 8, respectively.

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

(b) (4)

Table 7: Specifications for the RYPLAZIM FDP

Parameter monitored	Category	Test Method	Acceptance criteria
pH	General	(b) (4)	(b) (4)
Appearance		Visual Inspection (b) (4)	Clear or slightly opalescent and colorless liquid, essentially free of visible particulates (reconstituted)
			White to off-white cake (lyophilized)
(b) (4)		(b) (4)	
(b) (4)		(b) (4)	
Particulate Matter		(b) (4)	
(b) (4)		(b) (4)	
Reconstitution /Dissolution Time		Visual inspection and timer	NMT (b) (4) minutes
(b) (4)	Identity	(b) (4)	
Total Plasminogen		(b) (4)	
(b) (4)		(b) (4)	
Total Proteins	Concentration	(b) (4)	
Plasminogen Activity	Potency	(b) (4)	
(b) (4)		(b) (4)	

Parameter monitored	Category	Test Method	Acceptance criteria
(b) (4)	Purity	(b) (4)	
Sterility	Safety	(b) (4)	No growth
Endotoxin		(b) (4)	

5.1.1. General Approach to Justification of Specification and setting of acceptance criteria

Prometic claimed that for the Intermediate, the specification was reviewed based on manufacturing experience and batch analysis data and the proposed specification is based on (b) (4) For the BDS and FDP, their specifications are based on the calculation of (b) (4) tolerance limits (b) (4) confidence interval (CI)] for Plasminogen BDS and Plasminogen FDP CQAs based on an assumed normal distribution of the parameters.

The statistical approaches used to justify the acceptance criteria are inadequate, and resulted in excessively wide ranges, which do not allow for adequate control of manufacturing consistency. Also, conflicting information was provided in the BLA and during the inspection regarding the precise statistical approaches used in these studies: Prometic personnel were not sure if (b) (4) SD or (b) (4) tolerance limits were used for the calculations of acceptance criteria.

To perform this analysis, data from both the Plasminogen BDS and Plasminogen FDP batches were combined. This was deemed acceptable by Prometic since all quantitative datasets of Plasminogen FDP and BDS were comparable from a biochemical and statistical point of view (the means were not significantly different at the (b) (4) CI).

Establishing acceptance criteria by combining the data from the testing of the BDS and FDP, is inappropriate. While the means may not be statistically different, the statistical parameters of the distributions for the BDS and FDP were significantly different (usually the FDP had tighter distributions). The issue was exacerbated by the fact that Prometic did not just combined the data, but they averaged the SDs for the FDP and BDS to calculate the final ranges. Thus, in some cases, the specification range became excessive for the FDP, but insufficient for the BDS. In case of (b) (4) , the ranges of values observed in the BDS (minimum and maximum observed values for the BDS and FDP were presented) exceeded the proposed specification ranges.

Also, for (b) (4) (tested in BDS only), the maximum observed values exceeded the proposed limits. When this fact was pointed out to Prometic staff during the inspection, I was informed that the data from early versions of the manufacturing process were included in the justification, which is also inappropriate.

5.1.2. Specifications found to be inadequate and non-informative

a. Visual Inspection of FDP and Particulate Matter

The acceptance criterion for Visual Inspection of the reconstituted solution is listed as "Clear or slightly opalescent and colorless liquid, essentially free of visible particulates (reconstituted)".

While the Prometic specification does not expressly claim compliance to (b) (4) *the use of language "essentially free of visible particulates" implies that testing is performed according to* (b) (4)*, which is not the case as I found out during the inspection. The release testing for Visible Particulates in the FDP is performed* (b) (4) *, therefore, it does not accurately represent the amount of particulates, and allow for its proper control in the FDP. The release testing for Particulate Matter (*(b) (4) *) in the FDP is also performed* (b) (4) *therefore, and does not allow for its proper control as well.*

b. Reconstitution Time

The acceptance criterion for reconstitution/Dissolution time is listed as "NMT (b) (4) minutes". The actual times observed ranged between (b) (4) minutes, with an apparent increase of this parameter in recently manufactured batches. Prometic claimed that compilation of historical reconstitution times as presented in report Pg_0028 has identified intra-analyst variability as a cause of the variability in time. Prometic also states that the proposed time is adequate for preparation and administration of lyophilized drug product and that the proposed specification was based on the upper limit of the (b) (4) CI.

At the same time in report Pg_0028, it is sated that "The IND specifications for reconstitution time were set at NMT 10 minutes but were (b) (4) to NMT (b) (4) minutes for the BLA, based on a (b) (4) of the Plasminogen FDP release data. This also allows the assay to account for human variability.

The Specification is excessive and not justified. Prometic may correctly attribute the variability to the way the operators perform the test, but did not address the issue. Instead of reassessing the procedure and introducing the necessary controls to improve consistency, Prometic included all the data in the calculation of the acceptance criteria pushing the limit to (b) (4) *minutes, well over* (b) (4) *minutes, which was the maximum observed.*

c. Excipients

Prometic tests for two excipients present in the FDP: sucrose and glycine. No tests are proposed for sodium chloride and sodium citrate. The reasoning for testing only two excipients is that sodium chloride and citrate are components of the (b) (4) used in the process, and unlikely to be significantly variable. On the other hand, sucrose and glycine are (b) (4) . This approach is justified. However, the testing of sucrose and glycine is performed on the (b) (4); (b) (4) the FDP.

Excipients content is part of the labeling of the FDP. As such, the excipients which are tested should be controlled at the FDP stage, especially considering that (b) (4) *batches of BDS are* (b) (4) *to manufacture* (b) (4) *of RYPLAZIM FDP.*

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

5.4. In-support testing

As our review team concluded that the process is not properly validated, CBER decided not to conduct any in-support testing until the FDP manufactured by a properly validated process becomes available.

5.5. CBER Lot Release

RYPLAZIM is a plasma-derived product, which will be a subject for CBER Lot Release. Lot release protocol will be developed and approved after Prometic addresses the deficiencies in release testing and specifications identified during the current review cycle.

6. Process Development, Validation and Qualification

6.1. Process Development

The RYPLAZIM BDS manufacturing process was developed by Prometic at its Research and Development (R&D) facility in (b) (4) The process was (b) (4) by Prometic Bioproduction Inc. at its manufacturing facility in Laval, Canada. According to Prometic, the process has been refined during (b) (4) and clinical material manufacturing to improve process robustness in the following ways:

(b) (4)

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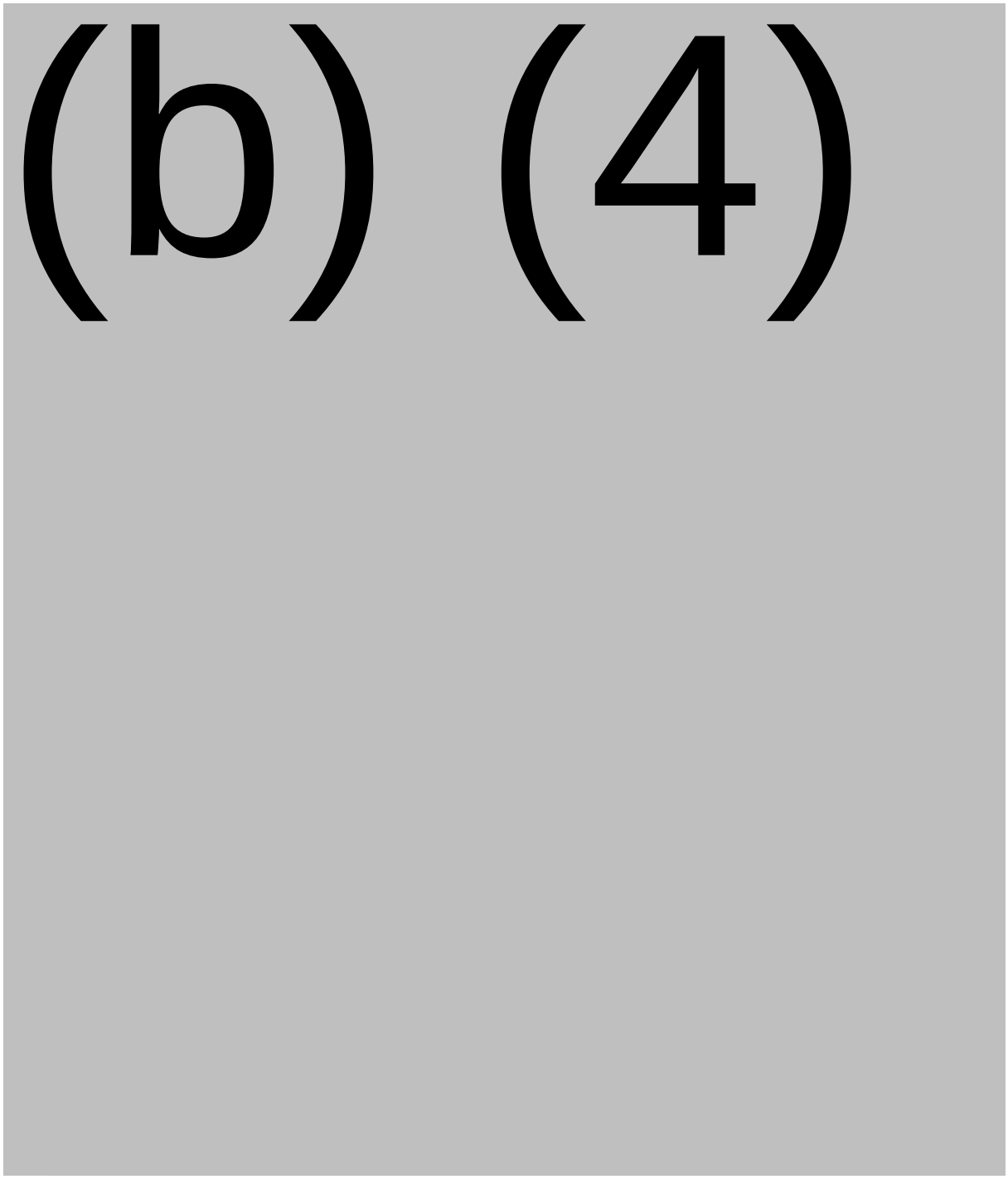
These various process developments are grouped into three categories.
1. Pre-Clinical process
2. Development Process Drug Substance (b) (4)
3. Development Process Drug Substance (b) (4)

The main developments across these three processes are shown in Figure 2.

Prometic described the developments made to each process manufacturing step and the impact on product quality and process performance. For each manufacturing step, all process modifications within the step are described, including the effects of these process modifications and summary data. Conclusions are drawn about the impact of the effects of the process modifications.

As the BDS is fully formulated, for FDP manufacturing process development, studies were mostly limited to the development and optimization of lyophilization, and shipping qualification. These studies were performed by (b) (4) and reviewed by DMPQ.

Figure 2. RYPLAZIM BDS manufacturing process development stages.



Due to the significant amount of information, this section outlines only the issues raised during the review, and does not contain descriptive information.

There were several issues observed in the process development document. In particular, an (b) (4) *was observed* (b) (4) *. This may indicate* (b) (4) *which was not investigated or controlled.*

Prometic stated that the reason for the (b) (4) *from the final process was "that the* (b) (4) (b) (4) *increases the tendency of purified Plasminogen to form aggregates (particulates)* (b) (4) (b) (4) (b) (4)*, which assists in minimizing particulate formation". As mentioned above, aggregation is not controlled in-process and neither are the hold times.*

Finally, Prometic changed the container closure system for the Intermediate and BDS without proper qualification or risk assessment. In the Pre-clinical process, the BDS was collected and stored in (b) (4) *by the manufacturer and have* (b) (4) *From* (b) (4) *BDS is collected and* (b) (4)*, which are made from the* (b) (4)*, but are not intended for* (b) (4) *by the manufacturer. Multiple instances of* (b) (4) (b) (4) *were discovered during the PLI.*

Prometic also provided several reports of studies to support manufacturing development.

Multiple deficiencies were identified in these reports, undermining the usability of the data in further process development. Specifically:

a. (b) (4) **5026-001 Analytical Comparability of Plasminogen.**
The purpose of this document is to establish analytical comparability of (b) (4) samples (at (b) (4)) and (b) (4) process samples (b) (4) (b) (4), performed in (b) (4)).

Prometic claimed analytical comparability, however it could not be established for the BDS, as out of the (b) (4) *BDS batches produced by the new process,* (b) (4) *failed* (b) (4) *due to* (b) (4) *" of* (b) (4)*, and the other batch was OOS for* (b) (4) *batch was not tested for this parameter).*

b. PBL/114/R22/261115/01 (b) (4)
The purpose of this study was to monitor the performance of the (b) (4)

No rationale was provided for the choice of (b) (4) *runs as the study limit. No acceptance criteria were established to define satisfactory performance of the* (b) (4)*. The* (b) (4)*, which is not a part of the actual manufacturing process.*

c. PBL/PC3452 Interim (b) (4)
An interim report on the (b) (4) study at (b) (4) . Currently, the (b) (4) study is at (b) (4) .

(b) (4)

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(b) (4)

The issue of the criticality of these product–related impurities, and the lack of validated assays, was already discussed above.

8. Methods Used in Clinical Trials

The following assays were used and validated in house by Prometic for the evaluation of clinical study samples:

(b) (4)

All assays use (b) (4) (b) (4) and were validated by the clinical laboratory performing the tests (b) (4)). The validation reports were submitted in the BLA.

My review of the assays used in the clinical trials did not identify significant issues.

9. Stability

9.1. Intermediate

During clinical material manufacturing, the (b) (4)

The proposed Intermediate storage time is not supported by available stability data, as only up to (b) (4) *of data are provided.*

The proposed storage temperature and associated stability study conditions are not adequately defined. The storage temperature is listed as (b) (4) *" whereas the stability data are available for* (b) (4) *This tolerance for storage temperature* (b) (4) *is excessive. The latter issue is also observed for BDS storage conditions.*

9.2. Bulk Drug Substance

(b) (4)

Also, considering the deficiencies found in the assays and product specifications, stability of the BDS should be re-assessed after Prometic corrects these deficiencies. This issue is also applicable to the FDP stability results.

9.3. Final Drug Product

The intended storage condition of RYPLAZIM FDP is 2°C to 25°C. Stability data for the FDP have been collected at both refrigerated storage condition (5°C ± 3°C), room temperature storage condition (25°C (b) (4)(b) (4) and (b) (4) stability condition (b) (4)) to support the RYPLAZIM label statement with a (b) (4) month shelf-life when stored at 2°C to 25°C. The FDP was tested per release specification and testing time-points include T = 0, 3, 6, 9, 12, 24 (b) (4) months.

There were no OOS results observed, except for the initial clinical lot # (b) (4) , which did not meet specifications for particulate matter at Time = 0 and 3 months. Lot # (b) (4) had over (b) (4) particles larger than (b) (4) at the 3-month time-point. Based on these observations, a (b) (4) was employed prior to testing in all subsequent release or stability indicating assays, with the exception of sterility or endotoxin testing since it may interfere by removing potential contamination.

The particulates/aggregation issue is discussed above.

(b) (4) stability was tested on FDP Lot (b) (4) , in the drug product primary packaging, which were exposed to (b) (4)

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Another study evaluated the in-use stability of FDP (Lots (b) (4) When used at the clinical site or in the home environment, Plasminogen is reconstituted and infused intravenously through a filter within 3 hours. This study examined the stability of the Plasminogen drug product in this window, as well as potential deviations beyond 3 hours. These studies specifically examined (b) (4) Prometic tested (b) (4) conditions; (b) (4) scenario is currently being practiced in the clinical setting. In the Phase 2/3 clinical trial, a vial of plasminogen is reconstituted, and then infused intravenously into a subject. Immediately prior to infusion, plasminogen is filtered through a (b) (4) filter. It is conceivable in a home environment that a patient would not follow the protocol strictly, and the (b) (4) situation could occur where the material is reconstituted and filtered immediately, but not infused directly. This study showed that (b) (4) situations, even when the Plasminogen is (b) (4) remain within specifications.

Although there was some variability in particulates in the (b) (4) condition, the levels were still within specification. In addition, (b) (4) showed no changes at any time-point. There were also no populations of viable microorganisms present within the (b) (4) testing window following (b) (4) . There were no stability-related failures in any lot under either condition during the (b) (4) testing window.

Considering the deficiencies found in the assays and product specifications, the stability results should be re-assessed after Prometic corrects these deficiencies. Until then, FDP stability cannot be confirmed.

10. Chemistry, Manufacturing and Controls - Conclusion

Based on the review of the information in the BLA and observations made during the inspection of the BDS manufacturing facility, the manufacturing process of RYPLAZIM is not considered to be adequately validated and sufficiently controlled to ensure consistent manufacture of the commercial product.

I found the CMC information inadequate to support the quality, identity, purity, potency and safety of RYPLAZIM, and recommend issuing a Complete Response (CR) Letter in which all CMC deficiency items will be listed.

11. Proposed CMC Deficiency Items to be included in the Complete Response Letter

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 and (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 (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 plasminogen activity 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)

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. 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.

c. 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.

d. 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.

e. 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.

f. 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.

g. 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.

h. 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)

(b) (4)

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

ADDITIONAL COMMENTS

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.