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**)
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Subject: Addendum to the Final CMC review of Prometic's BLA for plasminogen, human-tvmh – Review of Prometic's Response to the *Complete Response Letter*

Contents

1. Executive Summary

This memorandum is an addendum to the final review of the Chemistry, Manufacturing and Controls (CMC) sections in the BLA submitted by Prometic Biotherapeutics Inc. (Prometic) for plasminogen, human-tvmh. The proposed proprietary name is RYPLAZIM, and the

proposed indication is for the treatment of patients with type 1 plasminogen deficiency (hypoplasminogenemia).

A Complete Response Letter (CRL) was issued to the BLA on April 9, 2018. Prometic submitted a complete response to the CRL on September 4, 2020 in an amendment under STN 125659/0.18.

This addendum summarizes my review of Prometics's responses to the deficiencies described in the CRL. The scope of my review covers all CMC information except 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 (OCBQ)).

Prometic has adequately responded to the CRL, providing sufficient information to address the deficiencies within the CMC sections in the BLA.

Since the issues raised in the previous review have been resolved, I recommend APPROVAL for this BLA from the CMC perspective, with the Postmarketing Commitments listed in the Appendix.

2. Background

The BLA is submitted by Prometic Biotherapeutics Inc., a wholly-owned subsidiary of, and US agent for Liminal Biosciences Inc. (Liminal; formerly Prometic Life Sciences Inc.) headquartered in Laval, Canada. As all the Prometic and Liminal entities operate essentially as parts of a single company, we refer to the applicant as Prometic in this memo unless it is necessary to specify a particular subsidiary.

The active ingredient of RYPLAZIM is a human plasma-derived plasminogen. The protein is purified from human plasma using Prometic's proprietary (b) (4) technology based on a (b) (4) . The manufacturing process for RYPLAZIM is part of Prometic's (b) (4) designed to (b) (4) . No (b) (4) product has yet been licensed.

RYPLAZIM is supplied in one dosage strength of 68.8 mg lyophilized plasminogen in a 50-mL single-dose glass vial. It is reconstituted with 12.5 mL sterile Water for Injection (sWFI) for intravenous administration. RYPLAZIM contains no preservative.

RYPLAZIM is indicated for the treatment of patients with type 1 plasminogen deficiency (hypoplasminogenemia) *(NOTE: the exact language describing the indication was changed several times over the duration of the BLA review per FDA requests).*

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. Ophthalmologic lesions are most often encountered, 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.

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 either tissue-type or urokinase-type plasminogen activator. Plasmin degrades fibrin clots to fibrin degradation products and D-dimers; and converts latent matrix metalloproteinases (pro-MMPs) into active MMPs, which further degrade extracellular matrix (ECM) as part of the tissue healing/ remodeling process.

For the purpose of consistency, the name RYPLAZIM is used throughout this memo. In the BLA, the product is referred to as "*plasminogen*", "*Plasminogen Intravenous (Human)*" or the abbreviation *Pg*. The FDA suggested proper name was initially "*Plasminogen (Human)*" but was changed by the Advertising and Promotional Labeling Branch (APLB) in OCBQ to "*plasminogen, human-tvmh*" in the current review cycle.

3. Review History

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

A BLA for RYPLAZIM was first submitted under STN 125647/0 as a rolling BLA. The final modules were submitted on 4 April 2017, and a "Refuse To File" (RTF) Letter was issued to Prometic on 1 June 2017 due to a 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 review schedule (8 months) of the PDUFA V Program, as the indication for RYPLAZIM was granted Orphan Drug and Rare Pediatric Disease designations.

Numerous major deficiencies were identified during the review of the BLA, and conveyed to Prometic during the Late-Cycle Meeting on 8 March 2018.

Substantive CMC deficiencies related to the validation of the manufacturing process, characterization of the bulk drug substance (BDS) and final drug product (FDP), specifications, facilities and equipment were identified during the review of the BLA, and pre-license inspection (PLI) of the Prometic facility in Laval, Canada on 14-21 November 2017. As a result, a CRL was issued to the applicant on 9 April 2018. Prometic responded to the CRL on 4 September 2020 in an amendment under STN 125659/0.18.

4. Overview of Manufacturing

Reviewer's Comments (all italicized text in the rest of the memorandum represents this reviewer's comments): *The CMC overview in the section was updated with the information presented in Prometic's Responses to the CRL and amendments received and reviewed in the second review cycle.*

The manufacture of RYPLAZIM is divided into (b) (4) main stages (see Figure 1) conducted at two manufacturing facilities (Table 1). Production of the BDS takes place at Prometic Bioproduction Inc. in Laval, Canada. Prometic Bioproduction Inc. is another wholly-owned

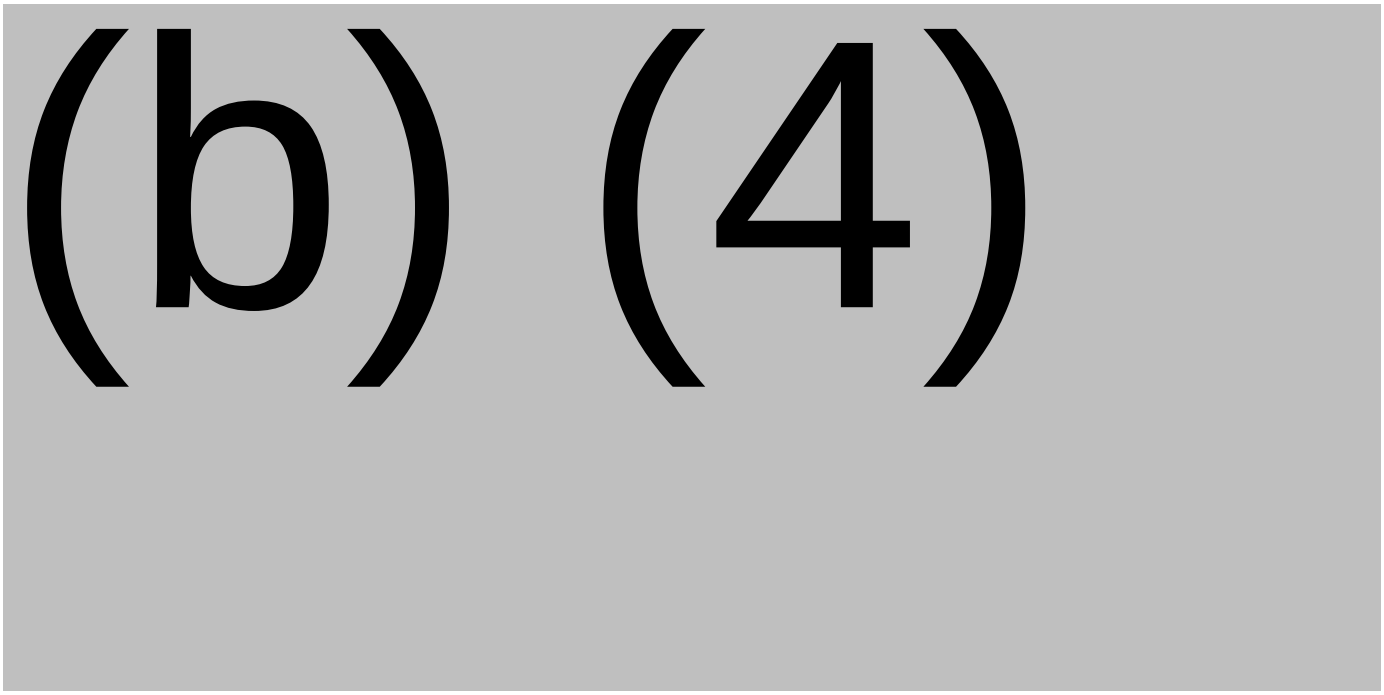
subsidiary of Liminal. Production of the FDP is performed at the FDA-licensed contract manufacturing facility of (b) (4)
Additionally, two contract laboratories are used for testing of the FDP.

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	• BDS manufacturing • Quality Control: – In-process control testing – Release testing – Stability storage and testing • Quality Assurance oversight (including of contract facilities)
(b) (4)	• Drug product aseptic filling • Lyophilization • Inspection • Labeling and secondary packaging • In-process control testing • Release testing (Drug product sterility, endotoxin, (b) (4) particulate matter testing and (b) (4))
(b) (4)	• Release testing for (b) (4)-Plasminogen determination • Stability testing for (b) (4)-Plasminogen determination
(b) (4)	Stability samples sterility testing Stability samples storage (b) (4) conditions)

Plasma pools of approximately (b) (4) are manufactured into plasminogen intermediate (Intermediate), which is then stored (b) (4). (b) (4) batches of Intermediate are (b) (4) manufactured into one batch of BDS. Thus, one batch of BDS is manufactured from (b) (4) of plasma. (b) (4) BDS batch (b) (4) is used to manufacture (b) (4) batch of FDP. The FDP batch size varies between (b) (4) vials. (*NOTE: Previously, up to* (b) (4) *BDS batches were used to produce one single FDP batch, which resulted in significantly larger FDP batches*).

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



RYPLAZIM is purified from plasma using a series of chromatographic steps designed to reduce the levels of product- and process-related impurities, and the process also includes three viral clearance steps. The special feature in this process is that the (b) (4) affinity chromatography step does not use an (b) (4), but it uses Prometic's proprietary (b) (4) specific for plasminogen.

To manufacture the FDP, (b) (4) BDS batch is (b) (4), aseptically filled in 50-mL vials, lyophilized, stoppered, capped/sealed, inspected, labeled and packaged.

The FDP is reconstituted with 12.5 mL sterile Water for Injection (sWFI) and passed through a disc syringe filter before intravenous administration. The RYPLAZIM package includes the FDP vial only. All the supplies including sWFI, syringe/needle and filter are to be provided by the patient or healthcare provider. The nominal composition of reconstituted RYPLAZIM is shown in Table 2.

Table 2: Nominal composition of reconstituted RYPLAZIM

Ingredient	Quantity, mg/mL	Function
Plasminogen	5.5	Active Substance
Sodium citrate	(b) (4)	
Sodium chloride	(b) (4)	
Sucrose	(b) (4)	
Glycine	(b) (4)	

4.1. In-support testing

During the first review cycle of the BLA, CBER decided not to conduct any in-support testing until FDP batches manufactured by a properly validated process becomes available because the review team concluded that the process at that time was not properly validated. During the review of Prometic's responses to the CRL, in-support testing was also not performed by OCBQ/DBSQC due to restrictions in the laboratory functions imposed during the COOVID-19 pandemic.

4.2. CBER Lot Release

RYPLAZIM is a plasma-derived product, which will be a subject for CBER Lot Release. A lot release protocol was developed by OCBQ/DBSQC based on the final release specification shown below.

5. Changes in the manufacturing process in the resubmission

The CRL enumerated many major CMC issues, which are attributable to the weaknesses in the design and control of the manufacturing process. These include poor analytical methods and operating procedures that cause inconsistent performance of manufacturing steps. Large variability in the results of in-process control and release testing made it impossible to effectively control the process and to evaluate its performance. While Prometic's responses to particular CRL items are reviewed below, addressing them also required multiple modifications made to many manufacturing steps. These changes were made in stages (Prometic's names for the development stages are in parenthesis) based on the feedback in the Form FDA 483 and the issues observed post-PPQ 1 campaign (**Post–PPQ 1**), feedback from the CRL (**Engineering**) and results from engineering studies (**PPQ 2-Commercial**).

The following changes were introduced at the (b) (4) stage:

(b) (4)

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

(b) (4)

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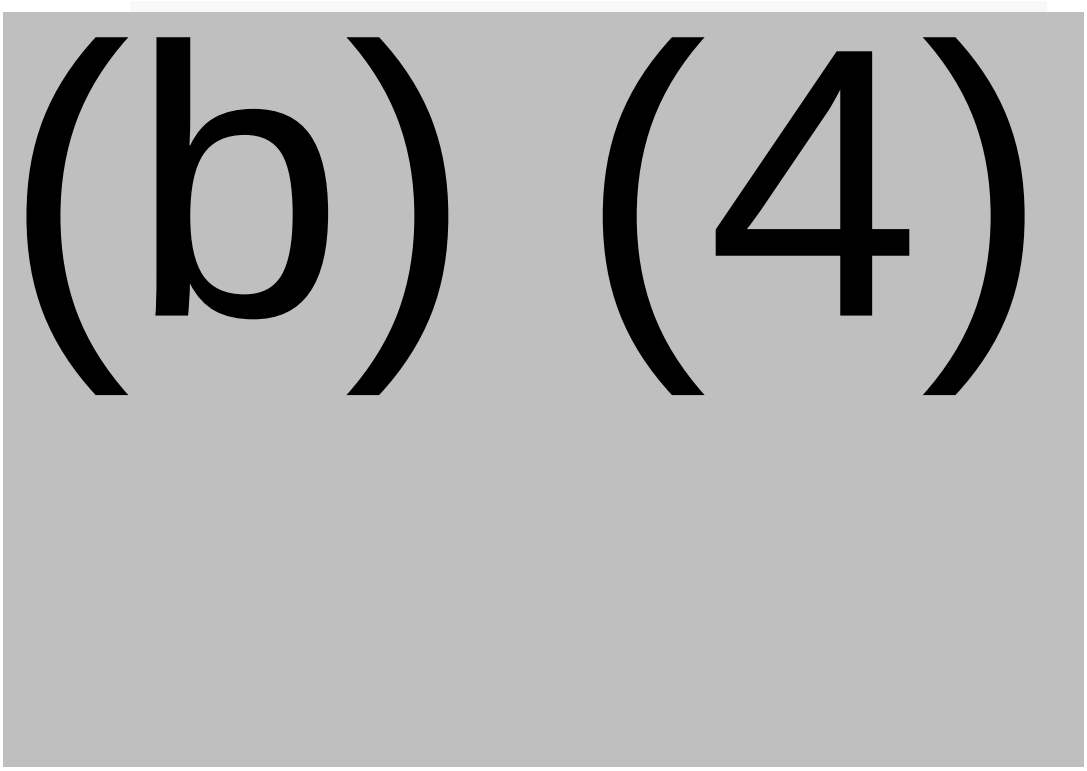
(b) (4) (b) (4)(b) (4) :

(b) (4)

The changes listed above along with the improvements in analytical methods greatly improved the consistency and controllability of the manufacturing process. For example, Figure 2 shows the plasminogen activity measured at step(b) (4) ("retains" stand for retain samples retested by updated activity assay) at different process development stages. The profile of result variability across the stages is typical for other manufacturing steps and process parameters, with consistency of results being greatly improved in the commercial process.

Figure 2. Effect of Process Changes on the Pg Activity at Step (b) (4)



The large number of process changes listed above necessitated the evaluation of comparability between the product produced by the current commercial process and those manufactured earlier and used in most of the patients in the clinical trials. Prometic submitted two comparability reports (Attachment 3.2.S.2.6-1 *PDR-5026.079.02-A Comparability Report Pg Int* and Attachment 3.2.S.2.6-2 *PDR-5026.079.01-B Comparability Report_Pg DS and DP*). In the studies described in the reports, each step of the process to produce the RYPLAZIM Intermediate, BDS and FDP was assessed for comparability based on confirmation that the critical process parameters (CPPs), in-process control (IPC) testing, monitoring, and release results satisfied the process control ranges, action limits or specifications in place at the time of the PPQ 2 campaign. Where possible, the data generated in the process stages were also evaluated for statistical equivalency to the PPQ 2 stage. Since multiple analytical methods were revalidated prior to the PPQ 2 campaign, retain samples from the Post-PPQ 1 process stage or samples from engineering lots generated after the last Post-PPQ 1 process stage were assessed in these assays. Where available, this retain, and engineering lot sample data were also included for assessment of comparability.

All release assays at the PPQ 2 process stage for the RYPLAZIM Intermediate, BDS and FDP demonstrated comparability. The data demonstrate statistically-driven comparability between lots manufactured at the PPQ 2 and Post-PPQ 1 process stages, as well as those at all process development stages, including lots used for the pivotal clinical trial and lots intended to support shelf life claims.

Prometic significantly improved the manufacturing process and performed a large number of development and comparability studies. The data provided demonstrate major improvements in process consistency, and the results obtained are within the ranges established for the materials manufactured by earlier versions of the process. I agree with Prometic's

assessment that the material manufactured by the current process is comparable to material used in the clinical trials, and the results of these trials can be used to support the approval of this BLA.

6. Review of responses to CRL

Only responses to the CRL items listed in my original CMC memo are reviewed here. Reviews of responses to the CRL items provided by other reviewers are documented in their respective addendum memos. The items are numbered as they were in the CRL.

Also, the extent and significance of most CRL items required the performance of a number of studies, extensive changes to the manufacturing process, and corresponding revisions to the CMC sections of the BLA. As a result, Prometic did not provide detailed responses to the CRL items in a separate document, but rather submitted very brief responses in a table format, referencing the revised sections of the BLA and relevant documents. Considering that this table is over 20 pages long, Prometic's approach is acceptable. Accordingly, Prometic's responses listed below are not the exact statements made by the company, but rather a summary of the information provided to support the resolution of the CRL issues.

6.1. CRL item 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.

Prometic's response: Prometic re-evaluated the CQAs for RYPLAZIM and their utilization in the control strategy. The company performed new risk assessments to determine the CQAs based on different risk assessment methodologies and provided revised report *PDR-009.03 Risk Assessment of Prospective Quality Attributes for Prometic Plasminogen*. Both risk assessments used the approach described in the CASSS A–Mab: A Case Study in Bioprocess Development, however, the previous one used QA Assessment Tool # 2, based on the Preliminary Hazard Analysis approach, which is not appropriate for commercial stage product. The new risk assessment used QA Assessment Tool # 1, which is based on the ICH Q9 methodology. As a result, a significant number of additional CQAs were identified (Table 3).

As a result of the re-evaluation, analytical procedures for the evaluation of (b) (4) Plasminogen (b) (4) were added to the release and stability specifications for (b) (4) FDP.

Table 3: RYPLAZIM Critical Quality Attributes (CQAs)

CQA in the original application	CQAs in the CRL response
Product concentration (reconstituted product)	Protein concentration
(b) (4) (reconstituted product)	Plasminogen activity
(b) (4) (b) (4)	Plasminogen Activity
(b) (4) : Particulate Matter (reconstituted product)	pH
Endotoxin / Pyrogenicity (reconstituted product)	Appearance of cake and reconstituted
Sterility (reconstituted product)	(b) (4)
(b) (4)	(b) (4)-plasminogen
Reconstitution time	Plasminogen purity
Aggregation: molecular association, potentially leading to (b) (4)	Aggregates could affect efficacy and or safety.
Fragments, (b) (4)	Fragments
Freedom from adventitious agents (viruses, and prions)	Aggregates
	Conformation (b) (4) structure
	Plasma protein impurities
	Endotoxin
	Sterility
	Adventitious viruses
	(b) (4)
	Foreign particles
	(b) (4)
	(b) (4)
	Glycine
	Sucrose

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.

Based on the re-assessment of CQAs (see above), Prometic re-evaluated the control scheme of the manufacturing process for RYPLAZIM. The assessment is summarized in two-part report *PDR-001 Critical Process Parameter Assessment in Plasminogen (Human) Manufacturing* (*Part A: Pg Intermediate Manufacturing Process, Part B: Pg DS and DP Manufacturing Process)*. Prometic re-evaluated both number and placement of IPCs and CPPs and their respective acceptable ranges. To further improve process control, both Proven Acceptable Ranges and narrower Process control Ranges were established for the CPPs. Similarly, Prometic set both Alert and Action limits for the IPCs.

The reestablished control scheme for the manufacturing process is a significant improvement over the previous one. The acceptable ranges for the IPCs and CPPs are statistically justified and reasonable. Additional IPCs and CPPs allow adequate control over the performance of the manufacturing process steps and ensure its ability to verify their outputs. The inclusion of (b) (4) *for plasminogen is especially helpful. The previous concerns regarding inconsistency between the ranges of plasminogen* (b) (4) *in the consecutive process steps had been addressed, as the ranges are now consistent.*

I consider this CRL item to be adequately addressed.

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 Prometic (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.**

In their re-evaluated control strategy, Prometic still listed multiple IPC tests (including many of the same IPCs listed as "characterization" tests in the original BLA) as "Monitoring" in Sections 3.2.S.2.4 Controls of Critical Steps and Intermediates, and 3.2.P.3.4 Controls of Critical Steps and Intermediates. The company stated that these are *"In-process testing to generate process history and knowledge."* Prometic also sets Alert and Action limits for these IPCs.

The intent of Prometic's approach to separate the IPCs in two categories: "IPC" and "Monitoring" is not clear. Considering that Alert and Action limits are set, these IPCs are clearly important for monitoring process performance. From the regulatory standpoint, it is not material how the IPC is classified if it is handled as an IPC in the quality system. As such, in the Information Request (IR) sent to Prometic on 18 February 2021, the following request was made:

Please note that regardless of your intended use of the data and how you define controls ("IPC" or "Monitoring"), all tests described in Sections 3.2.S.2.4 and 3.2.P.3.4 have to be performed on each batch of Drug Substance (DS) and Drug Product (DP). Failure to meet

action limits for any of the controls listed in these sections should trigger appropriate investigations per your quality system. Compliance with the procedure will be subject to verification at cGMP inspections. Any post-approval change to the control scheme described in Sections 3.2.S.2.4 and 3.2.P.3.4 will require an appropriate regulatory submission. Please acknowledge your understanding of these requirements.

In the response to IR submitted 8 March 2021 under STN 125659/0.23, Prometic confirmed their understanding of the requirements. The company also confirmed that all batches are tested per current Continuous Process Verification protocol, which was also submitted.

In the CRL responses, Prometic also addressed the issue of validation of "characterization methods". All methods currently used in the control of RYPLAZIM manufacturing are currently validated and performed at Prometic's Laval facility (except for tests performed at (b) (4) or contract labs). No testing for commercial process is performed at Prometic (b) (4) .

One of the issues identified in the CRL responses was the fact that before and during the PPQ 2 campaign, a number of tests were still performed at Prometic (b) (4) *where they were validated. At this time, all the methods have been transferred to the Laval facility. Prometic did not provide method transfer reports for* (b) (4) *. These reports were requested in the same IR and submitted under STN 125659/0.23 (except for the SEC report which was already submitted earlier in response to an IR from DBSQC). No issues were identified in the method transfer reports.*

Considering that all IPCs are currently treated the same way, measured by validated methods, and have acceptance criteria, and Prometic committed to follow appropriate regulations, the issue is adequately addressed.

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 particulates after** (b) (4) **of the sample does not accurately represent the amount of protein aggregation in the product.**

To address this CRL, Prometic performed additional studies. They concluded that Plasminogen has an intrinsic propensity to form aggregates, and that the aggregation process occurs by way of hydrophobic interactions between intact plasminogen monomers and is readily reversible. The propagation and/or reversal of aggregates is dependent upon variables such as (b) (4) .

Studies performed on the (b) (4) , that is observed in the samples, show that when (b) (4)

(b) (4)

Prometic developed an aggregate control strategy utilizing (b) (4) analytical techniques: (b) (4) The company performed the studies comparing the aggregation in various samples by these methods and found that the results from these techniques do not correlate completely, but are complementary. The combination of (b) (4) is employed to monitor and control particles of various sizes, and each technique is used to quantitate or monitor the aggregates present in the in-process control samples, (b) (4) and reconstituted FDP. Specifically, (b) (4) . Prometric also investigated the use of (b) (4) but found these (b) (4) methods to be unsuitable for QC application.

The combination of (b) (4) , thus covering the whole range of the particles that may potentially be present. (b) (4) are used as quantitative tools to monitor aggregation while (b) (4) can only be used in a qualitative manner and is only used as a confirmatory tool for aggregate monitoring to complement (b) (4) .

Aggregation is measured at the following stages mostly by all (b) (4) methods: (b) (4) , FDP (b) (4) Prometic also developed statistically-justified acceptance criteria for all in-process control and release tests.

Prometic also verified the effect of various (b) (4) factors, including (b) (4) on particulates in RYPLAZIM. The company performed several new studies, investigating the effect of these factors on RYPLAZIM, updating a set of stability-indicating assays, including (b) (4) and confirming that the assays are indeed stability-indicating. (b) (4) (b) (4) (b) (4) were the factors most affecting the number of particles, and in some cases, (b) (4) was observed. However, all conditions under which these effects were visible were extreme. Notably, (b) (4) was able to consistently detect the effects of (b) (4) in most cases, but in case of (b) (4) , it did not show any increase in aggregation, while (b) (4) showed significant increase in particulates.

The main issue in the original BLA was related to a lack of understanding and control of protein aggregation in RYPLAZIM. This issue was only briefly mentioned in the submission, but even the limited data showed that plasminogen tends to aggregate, and under some circumstances, (b) (4) *. Moreover, aggregation was completely overlooked when the control strategy was developed.*

In CRL response, Prometic provided a comprehensive investigation of aggregation in in-process control, (b) (4) *FDP samples.* (b) (4)

samples were tested, and it was demonstrated that the quantity and size of the aggregates vary between process stages in normal (b) (4) *samples. The data also show that normal storage does not increase aggregation.*

The current control strategy for aggregation allows for robust control of this parameter by multiple analytical methods. This CRL item is adequately addressed.

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.**

Prometic established and validated hold and processing times for all manufacturing steps. For BDS manufacturing, the study was performed at full manufacturing scale to verify the maximum processing times (Action Limits) for intermediates. (b) (4) Intermediate lots were produced at maximum processing times for all the process steps. (b) (4) BDS lots were also produced using maximum hold times, (b) (4) using Intermediate lots manufactured under standard process times, and (b) (4) using the (b) (4) Intermediate lots described above which were manufactured under extended processing times. The study is described in report *PDR-098.03 Serial Hold Processing Time of Pg* (b) (4) *intermediates at* (b) (4) *(Pg-intermediate) and* (b) (4) *(BDS) in Laval.* Prometic also performed a similar study *(PDR-099.02 Serial Hold Processing Time of Plasminogen* (b) (4) *during DP manufacturing at* (b) (4) on FDP using the latter BDS (b) (4) from the above study. Finally, the study (*PDR-5026.080.01 Effect of Extended Processing Time on the CQAs of Plasminogen During DP Manufacturing – Additional Studies*) was conducted to confirm the hold time for the FDP process using the remaining lots from study PDR-098 and extended analytical characterization.

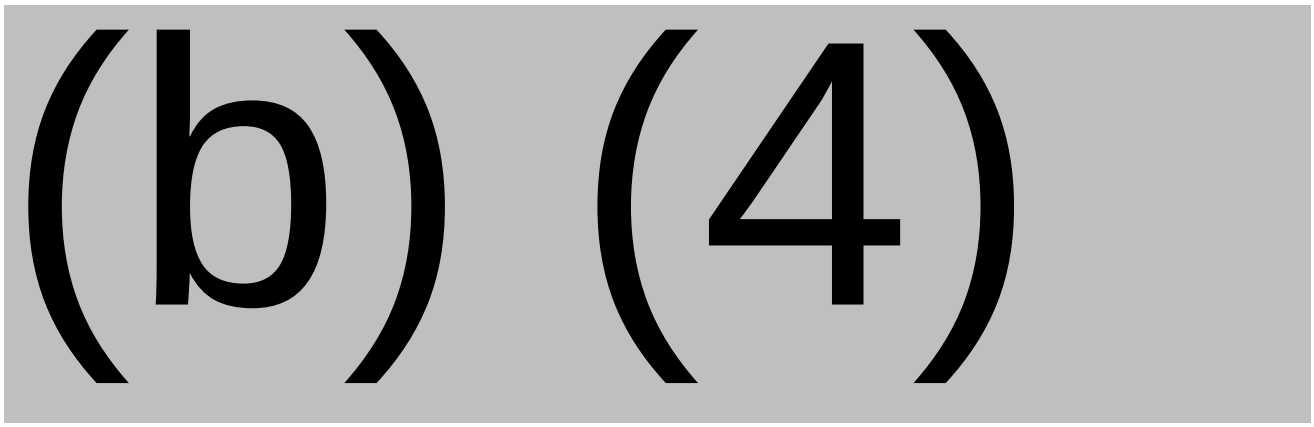
Additionally, another study was conducted (*PDR-078.01 Evaluation of Plasminogen (Human) process intermediate hold time at* (b) (4) *(Pg Intermediate) and* (b) (4) *(BDS)*). In this study, Prometic investigated the potential maximum hold times ("(b) (4) ") for each independent process intermediate. The design of the study included sampling the process intermediates at (b) (4) . The samples were then (b) (4) There were no (b) (4) " studies performed for the FDP manufacturing steps

It is not clear how relevant are the latter study to the manufacturing process, except for providing additional assurance that the current validated hold times are adequate.

The hold times established and validated for the RYPLAZIM BDS and FDP manufacturing processes are shown in Table 4

Table 4. Hold and process times in RYPLAZIM manufacturing process

Process Step	Maximum Processing Time Validated During the Serial Processing Times (b) (4))		(b) (4) Established for each Independent Step (b) (4)
	Alert Limit	Action Limit	
(b) (4)			



Prometic established and validated hold and process times for all manufacturing steps and adequately addressed this CRL item.

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 commercially obtained 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 commercial kits used over time. Please develop an appropriate reference standard for plasminogen potency and validate the assay using this standard.

To ensure reliable and accurate measurement of plasminogen activity, Prometic significantly revised their use of the (b) (4) , performed on the (b) (4) .

First, the company established and qualified an in-house Plasminogen Reference Standard. The (b) (4) standard was sourced (b) (4) and used from (b) (4) , through the completion of the manufacturing process validation/PPQ 2 campaign. Each working reference standard (b) (4) through (b) (4)) was qualified by (b) (4) . In contrast, the (b) (4) standard is sourced from a (b) (4) Plasminogen Reference Standards.

Notably, Prometic uses these new reference standards in all analytical procedures which requires a reference material: (b) (4)

The current primary (b) (4) standard, (b) (4) is sourced from (b) (4) , which was manufactured after the PPQ 2 campaign using the proposed commercial manufacturing process. Reference standard lot (b) (4) also supports the analytical program as the in-use standard since its implementation (b) (4) and will continue to support the analytical program until the qualification of a subsequent reference standard lot, (b) (4) , which is to be adopted for in-use reference standard purposes upon qualification.

Reference Standard (b) (4) is currently monitored via two programs:

1. Reference standard trend/drift monitoring program, applicable for in-use reference standard only.
2. Reference standard stability monitoring program based on ICH guidance with increased frequency of every (b) (4) for the life of the reference standard lot.

Prometic also submitted a protocol for the qualification of future reference standard (b) (4) .

The new reference standard is adequately qualified and maintained. Of note, Prometic performed a significant number of additional characterization tests on the (b) (4) *including* (b) (4) *The proposed qualification protocol for future standard is also adequate.*

To improve the assay, Prometic also introduced a procedure to qualify critical reagents: (b) (4) Each newly acquired or newly produced critical reagent lot or batch is qualified prior to being used for routine testing purposes.

Specifically, for the qualification of any new batch of plasminogen control, the (b) (4)

For the qualification of any new lot of the commercially obtained reagent (b) (4) is conducted, comparing an (b) (4) qualified reagent kit lot.

The changes to the system suitability and qualification procedures are adequate and allowed for significant improvements in the assay performance.

Prometic optimized and re-validated the assay with the changes described above 3 times, before finally addressing all the issues encountered during validation attempts. The issues were related both to method performance and validation studies design. Prometic made other changes to the method to address the former, including changing to (b) (4) (previously done by the (b) (4) . As not all validation parameters were affected in all validation studies, successive re-validations were performed for each parameter. The latest validation report AMV-048.01-R, submitted with the BLA, includes all data gathered during the validation exercises. The data submitted show that the acceptance criteria were met for all parameters and the assay demonstrated good performance in general.

Notably, in the course of method optimization and validation, Prometic acquired deep understanding and knowledge with regards to the various factors affecting assay performance and robustness, as well as established its fitness for stability studies using stressed samples.

The measures taken by Prometic to improve assay performance, especially establishing a proper reference standard program, greatly improved assay performance and quality and consistency of manufacturing data. The knowledge acquired by Prometic with regards to this assay adds assurance that the company is able to appropriately use it for plasminogen activity measurement in various types of samples. This CRL item is adequately addressed.

ii. The method for determining (b) (4) was validated using (b) (4) in lieu of plasminogen, whereas the validation protocol specified that plasminogen, along with (b) (4) should be used for validation. Please validate the method using plasminogen.

Prometic re-validated the method using samples of RYPLAZIM (b) (4) FDP, and several in-process samples. Additionally, the calibration curve was made using the plasminogen in-house references standard. All acceptance criteria were met, and the assay is now properly validated and fit for use.

This CRL item is adequately addressed.

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 reference standard for plasminogen and validate the assay using this standard.

Prometic re-validated the method using the new in-house reference standard (described in the method validation report AMV-039.01-R). All acceptance criteria were met, and the assay is now properly validated and fit for use.

This CRL item is adequately addressed.

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 reconstituted FDP that has not been (b) (4).**

iv. **Testing for excipients is performed on (b) (4) not on FDP. Please perform testing for excipients on FDP.**

Prometic reevaluated the whole control strategy for RYPLAZIM, including specifications. The revised specifications and their justification addressed all issues mentioned in CRL item 1.d and are reviewed together.

In the resubmission, Prometic re-evaluated a number of specification acceptance criteria and added several new specification parameters. To address the CRL, Prometic proposed to perform FDP release testing on (b) (4) product, except for Particulate Matter. The testing for excipients (glycine and sucrose) was added to FDP release specification as well.

As RYPLAZIM is filtered before infusion, it is acceptable and relevant to test filtered FDP for Particulate Matter. However, considering the properties of this product and its tendency to aggregate (see above), testing (b) (4) product for Particular Matter is also necessary to assess its quality. This testing was already performed at (b) (4) . In the IR sent to Prometic 18 February 2021, Prometic was requested to add the Particulate Matter test for (b) (4) FDP to the release specification.

In responses to our IR, Prometic agreed to add the Particulate Matter test for (b) (4) FDP and revised the specification accordingly.

In the resubmission, the company also clarified the statistical methodology used to justify the acceptance criteria. The proposed specification limits and ranges were based on the historical release test results or retain sample datasets for the new and substantially optimized methods, which are calculated as a (b) (4) release and stability datasets, assuming a normal distribution. To confirm the appropriateness of each specification limit or range, predictive intervals (PI) were also calculated assuming a normal distribution.

Prometic argued that for the improved process, the variability in the release test results could not be established, as only (b) (4) batches have been produced to date with this process (b) (4) PPQ lots and (b) (4) post-validation lots). These (b) (4) batches, in conjunction with the understanding of the above-described process improvements, were used for setting the specification range midpoint, but were insufficient for the calculation of a (b) (4) , due to the limited sample size. Therefore, to give a midpoint representative of the proposed commercial process, yet taking into account the overall historical variability, (b) (4) of the results from the (b) (4) lots produced post-process improvement was (b) (4) calculated from the standard deviation of the historical batches.

It was inappropriate to justify the acceptance criteria of BDS and FDP specifications based on variability values calculated using data from batches manufactured prior to process improvement. At the same time, the limited number of batches manufactured using the current commercial process made establishing variability difficult. To address this concern, Prometic was requested to establish alert limits based on the variability observed in the batches manufactured using the current process (PPQ 2 and later batches). Prometic was also requested to propose a Post-Marketing Commitment (PMC) to review additional commercial manufacturing data, and revise the acceptance criteria based on the variability data of the commercial process, specifying the timeframe or number of batches necessary to acquire sufficient data for this review and analysis.

In the response to IR submitted under STN 125659/0.23, Prometic recalculated the internal release limits (IRL) (alert limits) for the quantitative specification parameters for the RYPLAZIM Intermediate, BDS and FDP, using a (b) (4) Predictive Interval from the PPQ 2 and Post-PPQ 2 batch release data (the commercial process). Prometic also stated that the acceptance criteria will be evaluated after (b) (4) batches are produced for Intermediate, BDS and FDP. Post-marketing commitment #1 is listed in the Appendix.

Finally, Prometic was requested to revise the acceptance criterion for Reconstitution Time. The proposed limit of (b) (4) minutes (same as originally) was not justified. As the reconstitution time varied significantly for FDP, due to both changes in the manufacturing process and changes in the reconstitution procedures, the resulted (b) (4) value significantly exceeded the maximum observed reconstitution time ((b) (4) minutes). The product manufactured by the current commercial process can be dissolved within (b) (4) minutes. Accordingly, we considered the proposed release specification limit inappropriate even when paired with the alert limit.

Prometic revised the acceptance criteria to "NMT 10 minutes" and made the respective changes to the product labeling.

Tables 5, 6 and 7 below show the specifications for the Intermediate, BDS and FDP, respectively, comparing the specifications proposed in the original BLA to the final specifications. The new or changed acceptance criteria and specification parameters are shown in red. The last column in these tables lists the proposed alert limits.

Prometic re-evaluated the specifications and addressed FDA concerns. This CRL item is adequately addressed.

(b) (4)

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

(b) (4)

Table 7: Specification for the RYPLAZIM FDP

Parameter monitored	Test Method	Acceptance criteria (old)	Acceptance criteria (new)	Alert limits
pH	pH Measurement (b) (4)	(b) (4)		
Appearance	Visual Inspection (b) (4)	Clear or slightly opalescent and colorless liquid, (reconstituted)		
		White to off-white cake (lyophilized)		
Appearance – Particulates (b) (4))	(b) (4)		Essentially free of visible particulates	
(b) (4)				
(b) (4)				
Particulate Matter (b) (4)	(b) (4)	(b) (4)		
Particulate Matter	(b) (4)			
(b) (4)				
Reconstitution /Dissolution Time	Visual inspection and timer	NMT (b) (4) minutes	NMT 10 minutes	NMT (b) (4) minutes
(b) (4)				
Total Plasminogen	(b) (4)			

Parameter monitored	Test Method	Acceptance criteria (old)	Acceptance criteria (new)	Alert limits
(b) (4)				
Total Proteins	(b) (4)			
Plasminogen Activity	(b) (4)			
(b) (4)				
Sterility	(b) (4)	No growth	No growth	
Endotoxin	(b) (4)	(b) (4)		
Sucrose Concentration	(b) (4)			
Glycine Concentration	(b) (4)			
	(b) (4)			

6.2. CRL item 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) (b) (4) studies lacked appropriate acceptance criteria, in multiple reports results were labeled "outliers" 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.**

c. **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.**

d. **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.**

e. **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.**

f. **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.**

g. **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.**

h. **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.**

i. **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.**

Considering the severity and systemic nature of the issues related to process validation, we did not expect Prometic to specifically address each of the items above. It was rather expected that the company would modify their practices in general, optimize the manufacturing process and analytical controls, and conduct a new PPQ campaign. Accordingly, the state of process validation as submitted in the CRL response is reviewed below, without reference to the previously identified deficiency items.

Prometic conducted additional process development and validation studies which informed the process improvements listed in Section 5 of this memo.

The studies included:

- (b) (4) Validation: Evaluate the (b) (4) performance within the production (b) (4) to achieve the required levels of (b) (4)
- Plasminogen Intermediate (b) (4) Evaluation: Evaluate the effectiveness of Intermediate (b) (4) and duration
- (b) (4) Hold Studies: Evaluate the (b) (4) quality of (b) (4) used in the manufacturing process

- Processing Time Studies: Evaluate the maximum processing times for the process intermediates

The company also initiated new full-scale (b) (4) studies to be run starting with the PPQ 2 batches. The protocols for these studies are provided in the BLA.

The lack of completed full-scale (b) (4) *studies is a minor issue. However, as the process and analytical methods were improved and changed, Prometic did not have the opportunity to manufacture a large number of batches. It is also unreasonable to request such studies to be completed, considering that the previously established* (b) (4) *were over* (b) (4) (b) (4). *The issue is mitigated by the existing data from previously performed studies which, while deficient, established the baseline for the* (b) (4) (b) (4) *Prometic also provided the protocols for new* (b) (4) *studies, which are adequate.*

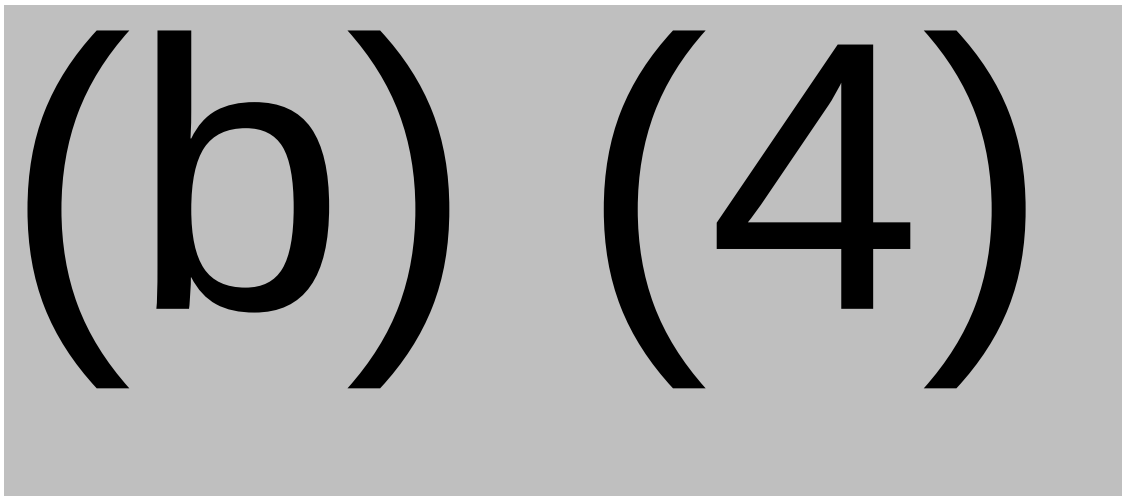
The PPQ studies took place during the manufacturing of the (b) (4) , described in *MPV-037.01-R_PPQ Report_* (b) (4) described in *MPV-038.02-R_PPQ Report_*(b) (4) and FDP (b) (4) , described in *MPV-039.02-R_PPQ Report_Pg DP* (b) (4) The campaign was performed in May-September 2019.

The lots used in the execution of the PPQ study, with their dates of manufacture (DOM) are shown in Table 8. Each BDS lot was manufactured from (b) (4) Intermediate lots, and each FDP lot was manufactured from (b) (4) BDS lot.

While the actual validated range of (b) (4) *vials is narrower than the proposed batch size* (b) (4) *) the difference is minor and acceptable. Notably, the upper value is limited by the capacity of the lyophilizer* (b) (4).

Table 8. PPQ Lot History and Use

FDP Qualification Batch Number	**FDP Lot Number** Number of Vials (DOM)	**BDS Used Lot Number** (DOM)	**Intermediate Used Lot Number** (DOM)
(b) (4)			



The following approach was used to analyze all collected data to confirm the state of control of the process and update normal operating ranges for subsequent batches, if needed:

1) Analysis of the process performance to execute critical process parameters (CPP) within each pre-established process control range using Mean, STDEV, 95% confidence interval from the mean and by plotting the data in time series charts. The output process parameter measurements were also plotted and analyzed. Recommendations were issued by the Manufacturing Sciences group in case of non-random variation observed as well as investigating the impact on product quality.

2) Analysis of the process performance to reliably produce product meeting IPC or Release result specifications within pre-established limits or product meeting monitoring assay results within pre-established limits:

- Plotting the data in time series charts: The fit of release, IPC and monitoring measurements within normal operating range (NOR) for all batches in the study were assessed using time series charts. Charts and trends were examined to assess the level of control. Recommendations were provided to include PPQ results to improve the level of control, if applicable.
- PPQ 2 release, IPC or monitoring data were compared with the historical data in time series charts.
- For "for information only" plasma pool measurements, the values obtained are representative of the variation inherent to the plasma source and to the analytical methods variability (not representative of the stability or consistency of the process). Measurements were compared to historical data and established ranges using time series charts to acquire more knowledge of the starting material.

3) Analysis of the process performance to reliably capture active plasminogen with high purity and remove product- and process-related impurities: this is done using time series charts for the stepwise removal of the process-related impurities. The charts were evaluated to monitor lot-to-lot variation.

4) Analysis of the process performance to yield consistent plasminogen: this was done using Mean, STDEV, 95% CI, and control charts. Consistency between yields observed prior to PPQ 2 (in (b) (4) was done similarly to what is described in 2).

5) Analysis of the process performance was evaluated using the Ppk (Process performance index) for each numerical release test quality attributes. Ppk acceptance criteria is (b) (4) Capability was assessed using (b) (4) tools.

6) Alert ((b) (4) and Action (b) (4) Predictive Intervals were refined (using (b) (4) software) by adding PPQ 2 results into the evaluation.

In general, the results of the PPQ 2 campaign were acceptable. Very few attributes demonstrated Ppk below (b) (4), but this were due to inclusion of historical data (pre-PPQ 2 batches) in the calculations. The process demonstrated consistent performance and all the acceptance criteria were met except for the cases described below.

For Intermediate manufacture no out-of-limit (OOL) results (defined as results outside of the alert or action limits) were observed.

For BDS manufacture, (b) (4) OOL results were observed for IPC and (b) (4) for a release specification parameter, including (b) (4) results outside alert limits and (b) (4) results outside action limits. The IPC OOL results were for (b) (4) The release OOL (but not OOS) result was for (b) (4)

For FDP manufacture, (b) (4) OOL results were observed for IPC and (b) (4) for release specification parameters, including (b) (4) results outside alert limits and (b) (4) results outside action limits. The IPC OOL results were for (b) (4) . For the release OOL (but not OOS) results, (b) (4) were for (b) (4) (Note that (b) (4) samples ((b) (4)) were taken from FDP batches during the PPQ 2 campaign, so the (b) (4) results are from (b) (4) lots) and (b) (4) result was for (b) (4)

All OOL results were not significantly outside of the predetermined limits (being mostly within (b) (4), or the next significant decimal figure) and did not affect the quality of the BDS. Prometic assessed all OOL results and concluded that these results were caused by the established limits being too tight. This was caused by the lack of a sufficient amount of data from the improved process to establish process variability. For some parameters, including release tests for Sucrose and (b) (4) for which the data from earlier process were used to establish the limits, the OOL were caused by changes in values due to process improvements. Specifically, for Sucrose, the change in the procedure for sucrose addition reduced the loss during this process and increased the measured sucrose concentration compared to the earlier process. For (b) (4) the changes in sampling used for calculation of the final dilution, caused an increase in the plasminogen content in the FDP, which became closer to the target value, whereas historically, the sucrose concentration was below the target. Prometic used the data from the PPQ 2 campaign to adjust the limits for future manufacturing.

There were some deviations and discrepancies from the protocols observed during the PPQ 2 campaign, as well. The discrepancies were mostly related to incorrect information in the protocol (editorial errors) and are not significant. The deviations were mostly related to either human errors or equipment malfunctions. In several deviations, the equipment (b) (4)) were found to be out of calibration either during routine check-ups, or when checked after the malfunction during manufacturing. The causes of some malfunctions were not identified, as the equipment function (e.g., (b) (4)) returned to normal spontaneously. Two notable deviations

which were not related to malfunctions: First, the action limit for (b) (4) processing time has been exceeded during the BDS manufacturing of lot # (b) (4) , which was attributed to "the lack of official information transmission methodology across QC and Production and among Production staff". Second, a total of (b) (4) units were culled out of the total (b) (4) units inspected with (b) (4) cake defects in the (b) (4) 100% IPC visual inspection of FDP lot (b) (4) . The action limit for (b) (4) cake rejects is (b) (4) whereas the results were (b) (4). The root cause of the (b) (4) cake defect appeared to be related to the (b) (4) due to PPQ sampling. The position of the (b) (4) was changed for lots (b) (4) , and only (b) (4) cake vial in lot (b) (4) and none in lot (b) (4) were found.

Finally, Prometic reported a significant number of incidents (Prometic classifies as such the deviations which are not directly related to manufacture) which occurred at the Laval facility during the time of the PPQ 2 campaign.

The PPQ 2 campaign appeared to be successful from the data provided in the BLA. Considering the significance and extent of the issues identified during the PLI (which also affected the decision to invalidate the original PPQ campaign), there are still some potential concerns regarding the level of general cGMP compliance, equipment maintenance and Quality System, as reflected in the reported deviations and "incidents". However, these issues cannot be ascertained from document review and are to be assessed and documented by inspectors conducting a re-inspection of the Laval facility on 17-24 May 2021. Otherwise, this CRL item is considered adequately addressed.

6.3. CRL item 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.**

    i. **For the Intermediate, the storage temperature is listed as (b) (4) " whereas the stability data are available for (b) (4) Please establish that the Intermediate is stable at (b) (4)**
    ii. **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) and (b) (4) Please ensure consistent storage conditions, or perform studies to establish the stability of the materials stored under the worst-case scenario conditions.**

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

As Prometic re-assessed product stability in general after changes in the manufacturing process, analytical procedures and specifications to address item 3.a, the stability data provided in the response to CRL are reviewed below, without emphasis on the previously

identified deficiency items. In response to our IR, Prometic submitted updated stability data in amendment STN 125659/0.23, these data are referenced below where available, instead of the ones submitted in response to the CRL.

Prometic incorporated all stability data including those generated for the original BLA in the new stability reports. In many cases, the quality of the old data was poor (e.g., for Plasminogen Activity or (b) (4) *due to the extreme variability of these methods at the time) and their usefulness is limited. The review below is based mostly on the new data generated using the PPQ 2 batches and tested by the optimized methods.*

Stability of Intermediate

The Intermediate is stored (b) (4) (proven acceptable range of (b) (4)) for a maximum of (b) (4) until (b) (4) to manufacture (b) (4) batch of BDS. In addition to the original stability data, Prometic provided data for (b) (4) additional Intermediate batches manufactured during the PPQ 2 campaign which were stored at (b) (4) . The Intermediate was tested according to the revised specification, which includes (b) (4) . There were no visible trends observed during the storage period in any of the parameters tested.

The proposed Intermediate storage time and conditions are supported by the available stability data.

Stability of BDS

The intended storage condition of BDS is (b) (4) . Stability data for Plasminogen BDS have been collected under (b) (4) storage conditions (b) (4) to support the BDS stability claim of a (b) (4) shelf life when stored at (b) (4) . Similar to the Intermediate, in addition to the original stability data, Prometic provided data for (b) (4) additional BDS batches manufactured during the PPQ 2 campaign which were stored at (b) (4) . The BDS was tested according to the revised specification. Of note, the BDS is not stable for longer than (b) (4) when stored at (b) (4) Therefore, no accelerated condition was included in the BDS stability program. There were no visible trends observed during the storage period in any of the parameters tested.

Notably, in Section 3.2.S.7.1 Stability Summary and Conclusion, Prometic did not perform statistical trend analysis. Instead, trend analysis was reported to be captured in Report PDR-5026.089_Summary of Stability Data. In response to our IR, Prometic submitted the report, accompanied by a statement that trend analysis is not required per ICH Q1E. Indeed, no trend analysis was found in the report. Nevertheless, as there were no obvious trends observed, it is a minor issue.

The proposed BDS storage time and conditions are supported by the available stability data.

Stability of FDP

The intended storage condition of FDP is 2°C to 25°C. Stability data were collected under both refrigerated (5°C ± 3°C), room temperature (25°C (b) (4) and (b) (4) stability storage conditions to support the label statement of a 24-month shelf life when stored at 2°C to 25°C. In addition to the original

refrigerated and room temperature FDP data for T = 0, 3, 6, 9, 12, 24 (b) (4) months, Prometic provided data for (b) (4) additional FDP batches manufactured during the PPQ 2 campaign for 1, 2, 3, 4 6, 9 and 12 months (the study is intended to continue to (b) (4) months). All (b) (4) conditions studies were conducted for 6 months. The PPQ 2 batchers were tested per the new release specification. There were no visible trends observed during the storage period in any of the parameters tested for any storage conditions. No OOS results were observed as well.

Prometic provided FDP stability data for up to 12 months for the batches manufactured by the current commercial process during the PPQ 2 campaign, while claiming a shelf life of 24 months. At the same time, there were no adverse trends observed and there were no adverse trends in the (b) (4) stability studies for up to 6 months. Also, most of the variability observed appears to be related to the variability of the analytical procedures, as the profiles are similar for all batches and conditions tested. That likely indicates good long-term FDP stability. The data from the earlier batches (at least for some specification parameters) are somewhat supportive for product stability as well. Based on this factor, it is acceptable to approve a 24-month shelf life at 2°C to 25°C for the RYPLAZIM FDP.

Prometic did not perform any new in-use stability studies using PPQ 2 batches, and only submitted the original data to support the 3-hour in-use stability for the reconstituted FDP. So, in-use stability was not established based on the most recent tests and specifications acceptance criteria. In the IR sent to Prometic 18 February 2021, we requested the company to establish in-use stability using FDP batches manufactured by the current process. In their response, Prometic proposed to perform these requested studies post-marketing. As the original in-use stability studies were much less affected by poor intermediate precision variability of the analytical methods due to the nature of the studies, the new studies is confirmatory in nature, and should not critical for approval, so the proposal is acceptable.

In summary, the stability data provided are sufficient to support the requested shelf lifes of the RYPLAZIM Intermediate, BDS and FDP. The Stability-related items in the CRL are adequately addressed.

7. Chemistry, Manufacturing and Controls - Conclusion

The information in the response to the CRL and subsequent amendments adequately addressed the issues raised in the CRL. The BLA was thoroughly revised and improved in major ways. Prometic generated a significant amount of additional data on product characterization and process development. These data informed the optimization and improvement of the manufacturing process and associated control strategy along with key analytical procedures. The improved process was adequately validated in the new PPQ campaign. Based on the review of the information in the BLA, the manufacturing process of RYPLAZIM is adequately validated and sufficiently controlled to ensure consistent manufacture of the commercial product. The remaining minor issues may be resolved post-marketing.

I found the CMC information adequate to support the quality, identity, purity, potency and safety of RYPLAZIM, and recommend approval of this BLA with the PMCs listed in the Appendix.

8. Appendix – Proposed Postmarketing Commitments

1. Prometic Biotherapeutics Inc (Prometic) commits to revise the acceptance criteria of the specifications for RYPLAZIM Intermediate, Bulk Drug Substance (BDS) and Final Drug Product (FDP) by analyzing the data generated from the manufacture of (b) (4) batches of RYPLAZIM using the current commercial process. Prometic commits to perform an interim statistical re-assessment of all the alert limits in the current commercial process by analyzing the data from the manufacture of all commercial batches up to 31 May 2022, and submit the interim study report as a *Changes-Being-Effected Supplement* by 31 July 2022. Prometic commits to submit the Final Study Report as a *Prior Approval Supplement* by 30 September 2023.

   Final Study Report Submission: 30 September 2023

2. Prometic commits to perform in-use stability studies to confirm the stability of the reconstituted RYPLAZIM FDP under real-world use conditions. The RYPLAZIM FDP batches used in the studies should be manufactured by the current commercial process that meet the acceptance criteria of the current FDP specification. Prometic commits to submit the final study report as Postmarketing Commitment – Final Study Report by 31 May 2022.

   Final Study Report Submission: 31 May 2022