U.S. Food & Drug Administration
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**To:** Administrative File STN BL125659/0.26 (DATS #917883)

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CBER/OCBQ/DMPQ/MRB2

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**Applicant:** Prometic Biotherapeutics Inc. (Prometic) (US License # 2065)

**Facilities:** Prometic Bioproduction Inc. - 531 des Prairies Boulevard Building (b) (4)
Laval, Quebec, Canada (FEI #: 3010550055)
(b) (4)

**Product:** Plasminogen (Human) Intravenous, Ryplazim®

**Indication:** Treatment of clinical signs and symptoms associated with congenital plasminogen deficiency in pediatric and adult patients (Hypoplasminogenemia disorder)

**Subject:** Review Memo for Responses Associated to the Complete Response Letter (CRL) for Biologics License Application (BLA) for Ryplazim® [Plasminogen (Human) Intravenous] in Support of the Manufacture for the Plasminogen Drug Substance (DS) at Prometic Bioproduction Inc. in Laval, Quebec, Canada and the Manufacture for the Plasminogen Drug Product (DP) at (b) (4)

**ADD:** June 05, 2021

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## RECOMMENDATION:

Approval.

## RESPONSE TO CRL FOR BLA REVIEW TABLE OF CONTENTS:

**(FIRM RESPONSES TO 483 OBSERVATIONS IN SUPPORT OF PLI CONDUCTED ON NOVEMBER 14-21, 2017 AT PROMETIC BIOPRODUCTION INC. IN LAVAL, QUÉBEC)**

## SUMMARY:

On September 04, 2020, CBER received the Amendment STN BL125659/0.26 from Prometic in support of the responses to a CRL that was issued to them on April 09, 2018. This CRL is associated with the original BLA under STN BL125659/0 in support for the manufacture of Plasminogen (Human) DS at Prometic Bioproduction Inc. in Laval, Québec, Canada, and the manufacture of Plasminogen (Human) DP at (b) (4)

## BACKGROUND:

CBER received a BLA from Prometic on August 14, 2017 under STN BL125659/0 in support for the manufacture of Plasminogen (Human) Intravenous DP.

Plasminogen (Human) DP is used for the treatment of symptoms associated with Hypoplasminogenemia disorder, which is congenital plasminogen deficiency in pediatric and adult patients.

Plasminogen (Human) DP is a sterile, non-pyrogenic, lyophilized white or off-white powder preparation for intravenous injection. The DP is supplied in a single use 50mL glass vial, which is reconstituted with 12.5mL of Sterile Water for Injection (WFI) (not included in DP package). The reconstituted DP is passed through a disc syringe filter prior to administration intravenously. Upon reconstitution, Plasminogen (Human) DP contains 5.5mg/mL plasminogen in (b) (4) sodium citrate, (b) (4) sodium chloride, (b) (4) glycine and (b) (4) sucrose.

In this BLA, Prometic proposed to manufacture the Plasminogen (Human) DS at Prometic Bioproduction Inc. in Laval, Québec and the Plasminogen (Human) DP at (b) (4) .

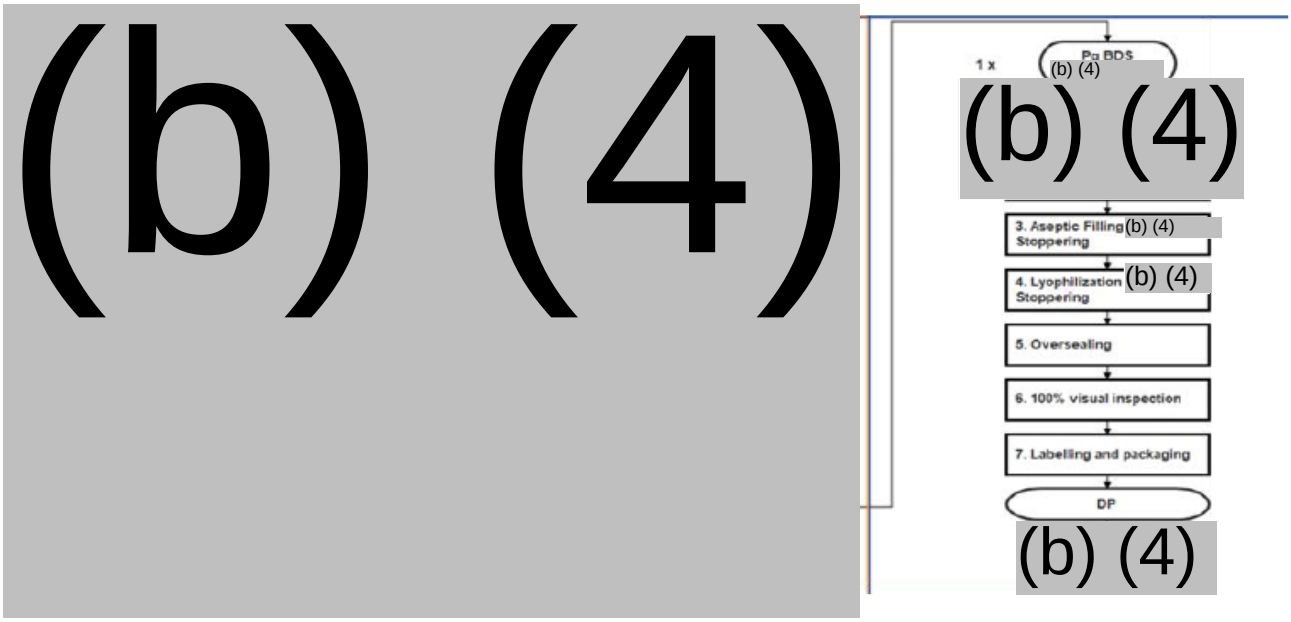
Prometic explained that (b) (4) human source plasma from US Licensed collection facilities is the main material used for the manufacture of the Plasminogen (Human) DS. They indicated that the manufacture of the Plasminogen (Human) DS started with the (b) (4)

(b) (4)

The manufacture of Plasminogen (Human) DP starts with the (b) (4) batches of Plasminogen (Human) DS for a total volume of (b) (4). Then the (b) (4) Plasminogen (Human) DS (b) (4), filled into 50mL vials, (b) (4) stoppered, lyophilized, capped, visually inspected, labeled and packaged. The Plasminogen (Human) DP is stored at a temperature between 2°C to (b) (4) C.

The manufacture of Plasminogen (Human) DS and DP is illustrated in the following flow chart diagram:

**Figure 1: Manufacturing Flow Diagram of Plasminogen DS and DP**




A Pre-License Inspection (PLI) (eNSpect Operation ID# 197508) was conducted at Prometic Bioproduction Inc. in Laval, Québec on November 14-21, 2017 in support for the manufacture of Plasminogen (Human) DS and the original BLA. At the end of this PLI, a 12-item FDA Form 483 was issued for the following objectionable conditions:

- The manufacturing process for the Plasminogen (Human) DS was not adequately validated or controlled;
- Inadequate oversight of the quality system operation;
- Inadequate cleaning validation of critical equipment;
- Disinfectants used for the cleaning of rooms had not been qualified;
- Batch records did not provide sufficient description of the manufacturing steps and no separate SOPs for manufacturing steps were observed in the manufacturing area or referenced in the batch record;
- The (b) (4) used for nanofiltration had not been qualified;
- Inadequate control of materials;
- Inadequate oversight of the preventive maintenance;
- Peeling paint, loose plaster on the walls and rough surfaces observed in the manufacturing areas;
- Not all manufacturing equipment in (b) (4) were identified during production;
- Operator working inappropriately inside (b) (4) and blocking the (b) (4);
- Product contact (b) (4) without (b) (4) had been used for nanofiltration process.

The inspectional findings from this PLI were documented in the Establishment Inspection Report (EIR). The firm provided the responses to these observations on the following dates:

**Table 1: Prometic Responses to 483 Observations**

| Date Received | Amendment No. | Sequence |
|---|---|---|
| December 12, 2017 | STN 125659/0.6 (DATS #713443) | 0007 |
| January 12, 2018 | STN 125659/0.9 (DATS #717153) | 0010 |
| January 22, 2018 | STN 125659/0.10 (DATS #719188) | 0011 |
| February 12, 2018 | STN 125659/0.12 (DATS #723317) | 0013 |
| March 13, 2018 | STN 125659/0.14 (DATS #727883) | 0015 |

Prometic provided satisfactory responses that resolved and closed Observation #9.a, #9.b and #9.c. However, they did not provide satisfactory responses to resolve and close Observations #1, #2, #3, #4, #5, #6, #7, #8, #10, #11 and #12.

A decision was made to waive the PLI in support of the manufacture of Plasminogen (Human) DP in (b) (4) during the initial BLA review cycle and it was addressed in a separate inspection waiver memo.

On April 09, 2018, a CRL was issued to Prometic to address deficiencies observed during the PLI and deficiencies found in the review of this BLA; specifically, in the

Chemistry, Manufacturing and Control (CMC) Sections for the DS and DP manufacturing facilities, equipment and manufacturing processes.

On September 08, 2020, Prometic submitted an amendment STN BL125659/0.26 (DATS #917883) in responses to the above CRL.

The scope of this review memo consists of the evaluation of Prometic's CRL responses to the deficiencies identified in the DMPQ CR review memo issued on April 13, 2018 and the discussion of the actions implemented by Prometic for the resolutions and closures of Observations #1, #2, #3, #4, #5, #6, #7, #8, #10, #11 and #12 in response to the CRL item #9 issued on April 09, 2018.

The actions implemented by Prometic for the resolutions of Observations #1, #2, #3, #4, #5, #6, #7, #8, #10, #11 and #12 were reviewed during the second PLI conducted at Prometic Bioproduction Inc. in Laval, Québec on May 17 - 24, 2021. This PLI was conducted in support for the manufacture of Plasminogen (Human) DS. The results from this PLI are discussed in the Establishment Inspection Report (EIR).

Additional information discussed in this memo includes the firm's responses received on October 26, 2020 and April 12, 2021 under amendments STN BL125659/0.19 (DATS #929541) and STN BL125659/0.24 (DATS #1036578 in response to two Information Requests (IRs) submitted on October 08, 2020 and March 26, 2021. The IR from October 08, 2020 requested clarification regarding the content of the amendment under STN BL125659/0.26 and the responses to the CRL item #9 in support of above Observations that were not satisfactorily resolved and closed. The IR from March 26, 2021 requested additional clarification regarding the firm's responses to the CRL.

It has been determined that an inspection of Prometic Bioproduction Inc. (FEI #3010550055) in Laval, Québec is required before the approval of this application, to assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to pandemic restrictions on travel, the second PLI of this facility was scheduled late in the review cycle. FDA/ORA/OBPO conducted this inspection on May 17-24, 2021 (eNSpect Operation ID# 200437). The observations listed in the Form FDA 483 from the first PLI on November 2017 were evaluated in this second PLI and they were remediated, resolved and closed. No outstanding objectionable issues were found in this second PLI. No Form FDA 483 was issued to Prometic Bioproduction Inc. at the conclusion of this PLI on May 24, 2021. The inspectional findings from this PLI were documented in the Establishment Inspection Report (EIR).

***Reviewer Comments:*** *Based on the review of Prometic's responses to resolve and close the deficiencies addressed in the DMPQ review memo issued on April 13, 2018 and the responses in support of the IRs submitted on October 08, 2020 and March 26, 2021, I conclude that the issues reviewed in this review memo were resolved and closed properly. Also, based on the outcome from the second PLI conducted by FDA/ORA/OBPO of Prometic Bioproduction Inc. at Laval, Québec on May 17-24, 2021, I recommend the approval of this BLA.* ***See Recommendation Section.***

**REVIEW OF RESPONSES TO CRL ITEMS:**

This review memo is the evaluation of Prometic's responses to the deficiencies identified in the DMPQ review memo issued on April 13, 2018 and the CRL item #9 from the CRL issued on April 09, 2018. These responses to the CRL issued to Prometic on April 09, 2018 were received on September 04, 2020 under Amendment STN BL125659/0.26 (DATS #917883). Also, the responses in support of the CRL item #9 were receive on October 26, 2020 under amendment STN BL125659/0.19 (DATS #929541.)

The CR items appear *italicized* and a summary of the firm response and reviewer commentary appear in regular text.

The CR items discussed in this memo were identified and cross-referenced as "CRL Item #" from the CRL issued on April 09, 2018 and "DMPQ Memo CR Item #" from the DMPQ Memo dated April 13, 2018.

- ✓ ***Reviewer Comments:*** *The firm did not specify if the information in the resubmitted BLA is new or updated.* ***See IR Question #1 – 10/08/2020 (Below).***

1. *Regarding the BLA resubmitted under amendment STN 125659/0/18 on September 04, 2020;*

   *It is unclear if some of the information resubmitted in this BLA is new or updated. Please enumerate those sections and documents in the resubmitted BLA that are new or updated and have not been reviewed previously.*

**Firm Responses:** In amendment STN BL125659/0.19 received on October 26, 2020, Prometic explained that the documentation provided in the resubmitted BLA under amendment STN 125659/0/18 are new or updated. They indicated that changes were done in Modules 2 and 3 to address the responses to the CRL questions. The firm stated that Module 5 was updated to include 48-week clinical data.

- ✓ ***Reviewer Comments*****:** *The firm's response is acceptable. New and updated items from the resubmitted BLA in support for the response of the deficiencies in the DMPQ Memo dated April 13, 2018 and the CRL issued on April 08, 2018 are discussed below in this memo.*

**RESPONSES TO CRL ITEMS:**

- ***CRL Item #1.b.iv. -*** *Hold times and process times are not validated for unit operations. We noted 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.*
- ***CRL Item #2.d. –*** *There are no validated hold-times and process times for individual manufacturing steps. Conflicting information on process time 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 the prospective validation studies.*

- ***DMPQ Memo CR Item #2 –*** *For BDS and FPD manufacturing process, the in-process hold time and process time for each step has not been established or specified.*

❖ ***Note:*** *CRL Items #1.b.iv. and #2.d were included in the PO review memo dated on April 06, 2018. The response to these CRL items were reviewed from the DMPQ standpoint.*

❖ ***Note:*** *Firm's responses in support for CRL Items #1.b.iv. and #2.d,; in addition, to DMPQ Memo CR Item #2 discussed below are the same as submitted under amendment STN BL125659/0.19 and received on October 26, 2020 in support for the actions taken for correction, resolution and closure of the Observation #1.c.iv. associated to the PLI conducted in the Prometic Bioproduction Inc. in Laval, Quebec on November 14-21, 2017.*

**Firm Response:** Prometic stated that hold and process times in support for the manufacture of BDS and FDP were established and validated to resolve and close the above CRL Items.

In Section 3.2.S.2.5.3.5 from Module 3.2.S.2.5 of the resubmitted BLA, Prometic stated the following studies were conducted for the implementation of the hold and process times in support for the manufacture of Pg Intermediate and BDS:

o PDR-078.01, "*Evaluation of Pg*(b) (4) *Intermediates Hold Time at* (b) (4) *(Pg-Intermediate) and* (b) (4) *Pg Intermediate* (b) (4) *(BDS) in Laval,*" reports the results for the determination of maximum hold times for the process steps conducted during the manufacture of Pg Intermediate and BDS. They indicated that the process times determined in PDR-098.02 were verified in this Study.

Prometic explained in this study that Pg Intermediate Batch No. (b) (4) was manufactured at (b) (4) plasma scale and BDS Batch No. (b) (4) was manufactured at (b) (4) Pg Intermediate plasma scale, for a total of (b) (4) scale.

The firm indicated that the results from this Study will be used for the implementation of maximum hold times and process times in support for the manufacture of Pg Intermediate at (b) (4) plasma scale and BDS at (b) (4) Pg Intermediate at (b) (4) scale.

Prometic stated that the alert and action limits for the process times and the maximum hold times are the following:

**Table 2: Process Times and Hold Times in Support for the Manufacture of Pg Intermediate and BDS**

| Pg Intermediate Process Step | Process Time - Alert Limit | Process Time - Action Limit | Maximum Hold Time |
|---|---|---|---|
| (b) (4) | | | |

| Pg DS Process Step | Process Time - Alert Limit | Process Time - Action Limit | Maximum Hold Time |
|---|---|---|---|
| (b) (4) | | | |

- PDR-098.03, "*Serial Hold Processing Time of Pg-IV Intermediates at* (b) (4) *Plasma Scale (Pg-Intermediate) and* (b) (4) *Pg Intermediate Scale (BDS) in Laval*," reports the results from the implementation of the process times during the manufacture of Pg intermediate at (b) (4) plasma scale and BDS at (b) (4) Pg Intermediate at (b) (4) scale.

  Prometic indicated that Pg Intermediate (b) (4) batches were manufactured as follows: Batches No. (b) (4) . These batches were named as batches (b) (4) . They stated that (b) (4) BDS batches were manufacture as follows: Batches No. (b) (4) . These batches were named as batches (b) (4)

  The firm explained that Batches (b) (4) were manufactured at (b) (4) Pg Intermediate (b) (4) scale were manufactured and according to the average process times as determined in PDR-098.02 and verified in PDR-078.01.

  Prometic indicated that Batch (b) (4) was manufactured using Pg Intermediate Batches (b) (4) . They stated that this batch was manufactured according to the process time alert limits as determined in PDR-098.02 and verified in PDR-078.01.

  The firm stated that the alert and action limits for the process times and the maximum hold times are the following:

**Table 3: Process Times and Hold Times in Support for the Manufacture of Pg Intermediate**

| Pg Intermediate Process Step | Step From | Step To | Average Process Time | Process Time Alert Limit | Process Time Action Limit |
|---|---|---|---|---|---|
| (b) (4) | | | | | |

| Pg Intermediate Process Step | Step From | Step To | Average Process Time | Process Time Alert Limit | Process Time Action Limit |
|---|---|---|---|---|---|
| (b) (4) | | | | | |

**Table 4: Average Process Time, Process Time Alert and Action Limits in Support for the Manufacture of Pg Intermediate**

| | |
|---|---|
| **Average Process Time** | (b) (4) |
| **Process Time Alert Limit** | (b) (4) |
| **Process Time Action Limit** | (b) (4) |

**Table 5: Process Times and Hold Times in Support for the Manufacture of BDS**

| BDS Process Step | Step From | Step To | Average Process Time | Process Time Alert Limit | Process Time Action Limit |
|---|---|---|---|---|---|
| (b) (4) | | | | | |

**Table 6: Average Process Time, Process Time Alert and Action Limits in Support for the Manufacture of BDS**

| | |
|---|---|
| **Average Process Time** | (b) (4) |
| **Process Time Alert Limit** | (b) (4) |
| **Process Time Action Limit** | (b) (4) |

Prometic indicated that (b) (4) testing were conducted to the Pg Intermediate and BDS at the following process steps:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

In Section 3.2.P.3.5.3.4 from Module 3.2.P.3.5 of the resubmitted BLA, Prometic stated the following studies for the implementation of the hold and process times in support for the manufacture of the FDP:

- PDR-058.01, *"Evaluation of Hold Time of Plasminogen BDS* (b) (4) *During DP Manufacturing*," reports the results from the determination of the maximum processing hold time during the manufacture of the FDP at (b) (4). This Study was conducted in (b) (4)

  The hold times evaluated during the manufacture of the FDP are the following:

(b) (4)

(b) (4)

  The following testing were conducted at the above holding times: (b) (4) . According to the results from the above testing conducted at the mentioned holding times, Prometic indicated that a maximum processing hold time of (b) (4) is recommended (b) (4)

- PDR-099.02, "*Serial Hold Processing Time of Plasminogen BDS* (b) (4) *During DP Manufacturing at* (b) (4)," reports the results in support for the increase in the process times in the (b) (4) steps of the FDP. Prometic stated that BDS Batch (b) (4) from PDR-098.03 was used to manufacture FDP Batch No. (b) (4) They indicated that approximately (b) (4) vials of 50mL were filled with (b) (4) of FDP.

The firm stated that the determined alert and action limit process times from each process step are the following:

**Table 9: Process Times in Support for the Manufacture of FDP**

| FDS Process Step | Process Time Alert Limit | Process Time Action Limit |
|---|---|---|
| (b) (4) | | |

Prometic indicated that (b) (4) testing were conducted when the BDS was (b) (4) and at the (b) (4) (b) (4). They stated that the (b) (4) testing results complied with the criteria of (b) (4) The firm explained that sterility and endotoxin testing were conducted for the FDP at (b) (4) and (b) (4) step. They stated that the sterility and endotoxin testing results [[complied with the criteria of no growth and (b) (4), respectively.

- PDR-5026.080, "*Effect of Extended Processing Time on Pg DP Manufacturing on the CQA's"*, reports the results from the verification of the process times during the manufacture of FDP Batches No. (b) (4) at the following conditions:

**Table 10: FDP Batches Manufactured in PDR-5026.080**

| FDP Batch No. | Pg Intermediate and BDS |
|---|---|
| (b) (4) | |

Prometic explained that FDP Batches No. (b) (4) were (b) (4) that were manufactured at the following processing times:

**Table 11: Process Times in Support for the Manufacture of FDP**

(b) (4)

The firm stated that PDR-5026.080 complied with the same alert and action limit process times as reported in PDR-099.02.

- ✓ ***Reviewer Comments:*** *The hold and process times reported in PDR-078.01, PDR-098.03, PDR-058.01, PDR-099.02 and PDR-5026.080, in support for the response of the CRL Items #1.b.iv. and #2.d; in addition, to DMPQ Memo CR Item #2 were reviewed from DMPQ standpoint. They were found acceptable, since there were no excursions in the* (b) (4) *testing conducted to the Pg Intermediate, BDS and FDP as reported in the above Reports.*

- ***CRL Item #2.b****: For lyophilization process validation, insufficient information was provided regarding the commercial scale PQ study, information for production loading configuration is missing and the claimed production batch size of up to* (b) (4) *is not supported by the PPQ campaign.*
- ***DMPQ Memo CR Item #5*** **–** *For lyophilization process validation, insufficient information was provided regarding commercial scale PQ study, information regarding production batch sizes and* (b) (4) *configuration is not sufficient.*

**Firm Response:** Prometic stated that the validation of the lyophilization step was conducted during the manufacture of the FDP batches in support for the PPQ2 campaign. They indicated that the results from this validation study were reported in PPQ 2390-12, (b) (4) *Process Performance Qualification Report*." The firm clarified that PPQ 2390-12 was included as attachment of MPV-039.02, "*Process Performance Qualification Report for Plasminogen (Human) Part 3 – Pg DP Process*."

Prometic indicated that the following FDP lots were manufactured in the PPQ2 campaign:

**Table 12: FDP Batches Manufactured in PPQ2 Campaign**

| FDP PPQ2 Batch No. | BDS Volume | Batch Filling Volume per Vial | Number of Vials Filled | Date of Manufacture |
|---|---|---|---|---|
| (b) (4) | | | | |

The firm indicated that these lots were manufactured using BDS at a volume between (b) (4) which is considered as the BDS batch size for commercial manufacturing. They explained that the previous BDS batch size used for the manufacture of the FDP batches PPQ1 lots was between (b) (4) . Prometic indicated that the BDS batch size was (b) (4) due the following reasons:

- Implementation of a (b) (4)
- (b) (4) in the (b) (4) ;
- Implementation of (b) (4)
- (b) (4) of the FDP from (b) (4) ;

- (b) (4) in the number of BDS batches to be use in the manufacture of a single FDP batch. Previously, a maximum of (b) (4) BDS batches were used for the manufacture of a single FDP batch. It was decided to use (b) (4) BDS batch to manufacture one FDP batch;
- Implementation of a process time of (b) (4) from the (b) (4) of the BDS (b) (4) . Previously, this process time was not defined;
- Implementation of a process time of (b) (4) from the (b) (4) Previously, this process time was (b) (4) according to media fill studies.

Prometic clarified that there are no changes in the (b) (4) parameters in support for the manufacture of the PPQ2 batches, since they are using the same ones as in PPQ1 batches.

The firm explained that a lyophilization mapping run was conducted to demonstrate that there are no changes in the homogeneity of the FDP vials placed in the (b) (4) locations of the shelf in the lyophilizer. They indicated that (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

(b) (4)

(b) (4)

- ✓ ***Reviewer Comments*****:** *The validation of the lyophilization step conducted during the manufacture of the FDP batches associated to the PPQ2 campaign and in support for the response CRL Item #2.b. and DMPQ Memo CR Item #5 was reviewed from DMPQ standpoint and found acceptable.*

- ***CRL Item #3 / DMPQ Memo CR Item #4 -*** The stability of the Drug Substance Intermediate, BDS and FDP is not fully established. Please address the following issues:

- **CRL Item #3.a. / DMPQ Memo CR Item #4.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.*

- ***Note:*** *CRL Item #3.a. was repeated in the PO review memo dated on April 06, 2018. The response to this CRL item was reviewed from the DMPQ standpoint.*
- ***Note: (****clarification) CRL Item #1 (item 1 above) in the CRL issued to Prometic, addressed critical quality attributes (CQA's), in-process controls (IPC's), hold-times and process times, analytical procedures for standards, in-process and release testing and specification for the Drug Substance Intermediate, BDS and FDP that were not developed and validated.*

**Firm Response:** Prometic stated that the stability results and specifications were re-assessed after correcting the deficiencies in the assays and products specifications in the above CRL Items.

The firm explained that PDP-5026.079.02-A, "*Comparability Protocol (Part A): Comparison of Data Generated Following Improvements to the Manufacturing Process: Pg Intermediate Manufacturing Process*" and PDP-5026.079.02-B, "*Comparability Protocol (Part B): Comparison of Data Generated Following Improvements to the Manufacturing Process: Pg Intermediate to Plasminogen DP,"* consist in a comparison of the critical process parameters (CPPs); in-process and release specifications from the historical data and the PPQ data reported in Reports MPV-037.01-R, "*Process Performance Qualification Report for Plasminogen (Human): Part 1 Intermediate Process – Product Codes* (b) (4) *Plasma Scale Manufactured by Prometic in Laval, Québec, Canada,"* MPV-038.02-R, "*Process Performance Qualification Report for Plasminogen (Human) Part 2 - Pg DS Process - Product Codes* (b) (4) *Plasma Scale Manufactured by Prometic in Laval, Québec, Canada*" and MPV-039.02-R, "*Process Performance Qualification Report for Plasminogen (Human) Part 3 – Pg DP Process- Product Codes* (b) (4) *Batch Size Manufactured by* (b) (4)

- ***Note:*** (b) (4) *stability results and specifications in support for the BDS and Endotoxin and sterility stability results and specifications in support for the FDP are discussed under the scope of this memo. The review of the other stability specifications and results are deferred to the Product Office reviewer.*

In Modules 3.2.S.4.1, "Specifications," and 3.2.S.4.5, "Justification of Specifications, Prometic indicated the following (b) (4) release specifications for the BDS:

(b) (4)

(b) (4)

The firm stated that the above specifications are applicable to the stability of the BDS at storage temperature of (b) (4) at time points (b) (4).

In Module 3.2.S.7.3, "Stability Data," Prometic provided the following (b) (4) testing results conducted in the Stability Study for the BDS:

**Table 18: Storage Temperature and Time Points in Support for the Stability of the BDS**

| Batch | Temperature | Time Points |
|---|---|---|
| (b) (4) | | |

The firm stated that the (b) (4) testing for BDS PPQ2, BDS (b) (4) PPQ1 and Post-PPQ1 Batches complied with specifications of (b) (4) respectively.

In Modules 3.2.P.5.1, "Specifications," and 3.2.P.5.6, "Justification of Specifications," the firm indicated the following endotoxin and sterility release specifications for the FDP:

**Table 19: Bioburden and Endotoxin Specifications for FDP**

| Testing | Specifications | Reference | Rationale |
|---|---|---|---|
| Endotoxin | (b) (4) | (b) (4) | (b) (4). The endotoxin specification of (b) (4) was established according to the historical data of the current BDS process and BDS PPQ2 release data |
| Sterility | No Growth (Sterile) | (b) (4) | (b) (4). The bioburden specification of No Growth is according to the historical data of the current BDS process and BDS PPQ2 release data |

The firm stated that the above specifications are applicable to the stability of the FDP at the following storage conditions and time points:

**Table 20: Storage Temperature and Time Points in Support for the Stability of the FDP**

| Storage Temperature (b) (4) | Time Points |
|---|---|
| 5°C ± 3°C | 0, 12, 24 (b) (4) |
| 25°C (b) (4) | 0, 12, 24 (b) (4) |
| (b) (4) | 0 months |

In Module 3.2.P.8.3, "Stability Data," Prometic provided the endotoxin and sterility testing results conducted in the Stability Study of the FDP PPQ2 Batches No. (b) (4) at time point 0 at the above storage temperature; in addition to the Post-PPQ1, (b) (4) -PPQ1 and (b) (4) Batches at the following time points and storage conditions:

**Table 21: Storage Temperature and Time Points in Support for the Stability of FDP Post-PPQ1, (b) (4) -PPQ1 and (b) (4) Batches**

| Batches | Storage Temperature (b) (4) | Time Points |
|---|---|---|
| Post-PPQ1 Batches No. (b) (4) | 5°C ± 3°C<br>25°C (b) (4) | 0, 12 and 24 months |

| Batches | Storage Temperature (b) (4) | Time Points |
|---|---|---|
| (b) (4)-PPQ1 Batches No. (b) (4)<br>(b) (4) Batches No. (b) (4) | 5°C ± 3°C<br>25°C (b) (4) | 0, 12, 24 (b) (4) months |
| (b) (4)-PPQ1 Batches (b) (4)<br>(b) (4) Batches No. (b) (4) | (b) (4) | 0 month |
| (b) (4) Batch No. (b) (4) | (b) (4) | (b) (4) |

The firm stated that the endotoxin and sterility test results from the FDP PPQ2, Post-PPQ1, (b) (4)-PPQ1 and (b) (4) Batches complied with a specification (b) (4) and no growth.

Prometic indicated that PDR-092-A.01, "*Revision of Plasminogen (Human) Specifications: Part - A, the Pg Intermediate"* and PDR-092-B.03*, "Revision of Plasminogen (Human) Specifications: Part – B, the* (b) (4) *the Pg-DP" were* reviewed and updated to include the above endotoxin, bioburden and sterility specifications.

- ✓ ***Reviewer Comments*****:** *The above* (b) (4) *stability results and specifications from the BDS; in addition, to the endotoxin and sterility stability results and specifications from the FDP in support for the response to CRL Item #3.a. and DMPQ Memo CR Item #4.a. were reviewed from DMPQ standpoint. They were found acceptable, since there were no excursions in the endotoxin and bioburden sterility testing conducted to the* (b) (4) *FDP from the PPQ batches. The discussion of the other stability specifications and results are deferred to the Product Office reviewer.*

- **CRL Item 3.b. / DMPQ Memo CR Item #4.b**. *The proposed storage temperatures and associated stability study conditions for the Drug Substance Intermediate and BDS are not adequately defined.*

  - **CRL Item 3.b.i. / DMPQ Memo CR Item #4.b.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)*.*

  - **CRL Item 3.b.ii. / DMPQ Memo CR Item #4.b.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.*

- **CRL Item #3.c. / DMPQ Memo CR Item #4.c**. Proposed Intermediate storage time is not supported by available stability data.

- ***Note:*** *CRL Items #3.b, #3.b.i, #3.b.ii. and #3.c were repeated in the PO review memo dated on April 06, 2018. The response to these CRL items were reviewed from the DMPQ standpoint.*
- ***Note:*** *A single firm response will be provide in support for CRL Items #3.b., #3.b.i, #3.b.ii and #3.c / DMPQ Memo CR Items #4.b., #4.b.i, #4.b.ii and #4.c, since Prometic is referring to the same sections and document in support for the response to these CRL responses.*

**Firm Response:** In Module 3.2.S.2.4, "Controls of Critical Steps and Intermediates," Prometic explained that the storage temperature of Pg Intermediate and BDS are (b) (4) in support for their shelf-life. They indicated that PDR-5026.089, "*Summary of Stability Data*" is in support for the resolution and closure of the above CRL items.

The firm indicated that two stability studies were conducted in support for the stability of the Pg Intermediate at (b) (4) (b) (4). They explained that the first stability study, STB-SBDS-Pg-001-01-P, "*Stability Protocol of Pg Intermediate*" describes the stability study for (b) (4) Post PPQ 1 Pg Intermediate batches (Lots No. (b) (4) Prometic stated that (b) (4) were conducted at time points (b) (4) which are considered the testing time points during the stability of the Pg Intermediate during routine manufacturing. Also, they explained that (b) (4) Post PPQ 1 Pg Intermediate batch was stored at (b) (4) to evaluate the effects on the temperature excursion during shipping or handling the Pg Intermediate. The firm indicated that (b) (4) are conducted at time points (b) (4).

Prometic stated that the second stability study, STB-INT-Pg-001.02-P, "*Stability Protocol*," describes the stability study for (b) (4) PPQ 2 Pg Intermediate batches (Batch No. (b) (4) in support for the storage temperature of (b) (4). They indicated that (b) (4) were conducted at time points (b) (4). The firm indicated that the PPQ 2 Pg Intermediate lots from stability study, STB-INT-Pg-001.02-P were used for the manufacture of BDS PPQ2 Batches No. (b) (4) as reported in Report MPV-038.02-R.

The firm provided the results from the testing conducted in STB-SBDS-Pg-001-01-P and STB-INT-Pg-001.02-P. They indicated that the Pg Intermediate lots evaluated in both studies complied with the following criteria:

**Table 22: Testing Criteria in Support for the Stability of the Pg Intermediate**

| Protocol | Temperature | Testing | Criteria |
|---|---|---|---|
| STB-SBDS-Pg-001-01-P | (b) (4) | | |
| STB-SBDS-Pg-001-01-P | | | |

| Protocol | Temperature | Testing | Criteria |
|---|---|---|---|
| STB-INT-Pg-001.02-P | (b) (4) | | |
| STB-INT-Pg-001.02-P | | | |
| STB-INT-Pg-001.02-P | | | |
| STB-INT-Pg-001.02-P | | | |
| STB-INT-Pg-001.02-P | | | |
| STB-INT-Pg-001.02-P | | | |

In Module 3.2.S.7.1, "Stability Summary and Conclusions," Prometic stated that stability studies were conducted to the following batches of BDS stored at the following temperatures:

**Table 23: Storage Temperature and Time Points in Support for the Stability of the BDS**

| Batches | Temperature | Time Points |
|---|---|---|
| BDS PPQ2 Bach No. (b) (4) | (b) (4) | |
| BDS (b) (4)-PPO1 Batch No. (b) (4) | | |
| BDS Post-PPQ1 Batch No. (b) (4) | | |

In Module 3.2.S.7.3, "Stability Data," the firm provided the results from the (b) (4) testing conducted at the following time points:

**Table 24: (b) (4) Testing Conducted at Time Point (b) (4) Month in Support for the Stability of the BDS**

| Batches | Temperature | Time Points |
|---|---|---|
| BDS PPQ2 Batch No. (b) (4) | (b) (4) | |
| BDS (b) (4)-PPO1 Batch No. (b) (4) | (b) (4) | |
| BDS Post-PPQ1 Batch No. (b) (4) | (b) (4) | |

Prometic stated that the (b) (4) testing for BDS PPQ2, BDS (b) (4) PPQ1 and Post-PPQ1 Batches complied with specifications of (b) (4) respectively.

- ✓ ***Reviewer Comments*****:** *The temperatures of* (b) (4) *for the stability studies for the Pg Intermediate and BDS in support for the response to CRL Items #3.b., #3.b.i, #3.b.ii and #3.c. and DMPQ Memo CR Items #4.b., #4.b.i, #4.b.ii and #4.c.were reviewed from DMPQ standpoint. They were found acceptable, since there were no excursions in the* (b) (4) *sterility testing conducted to the BDS PPQ2, BDS* (b) (4) *-PPQ1 and Post-PPQ1 Batches.*

- ***CRL Item #5 / DMPQ Memo CR Item #1****:* The QC tests used for the equipment cleaning validation at PBP facility have not been qualified during cleaning validations.

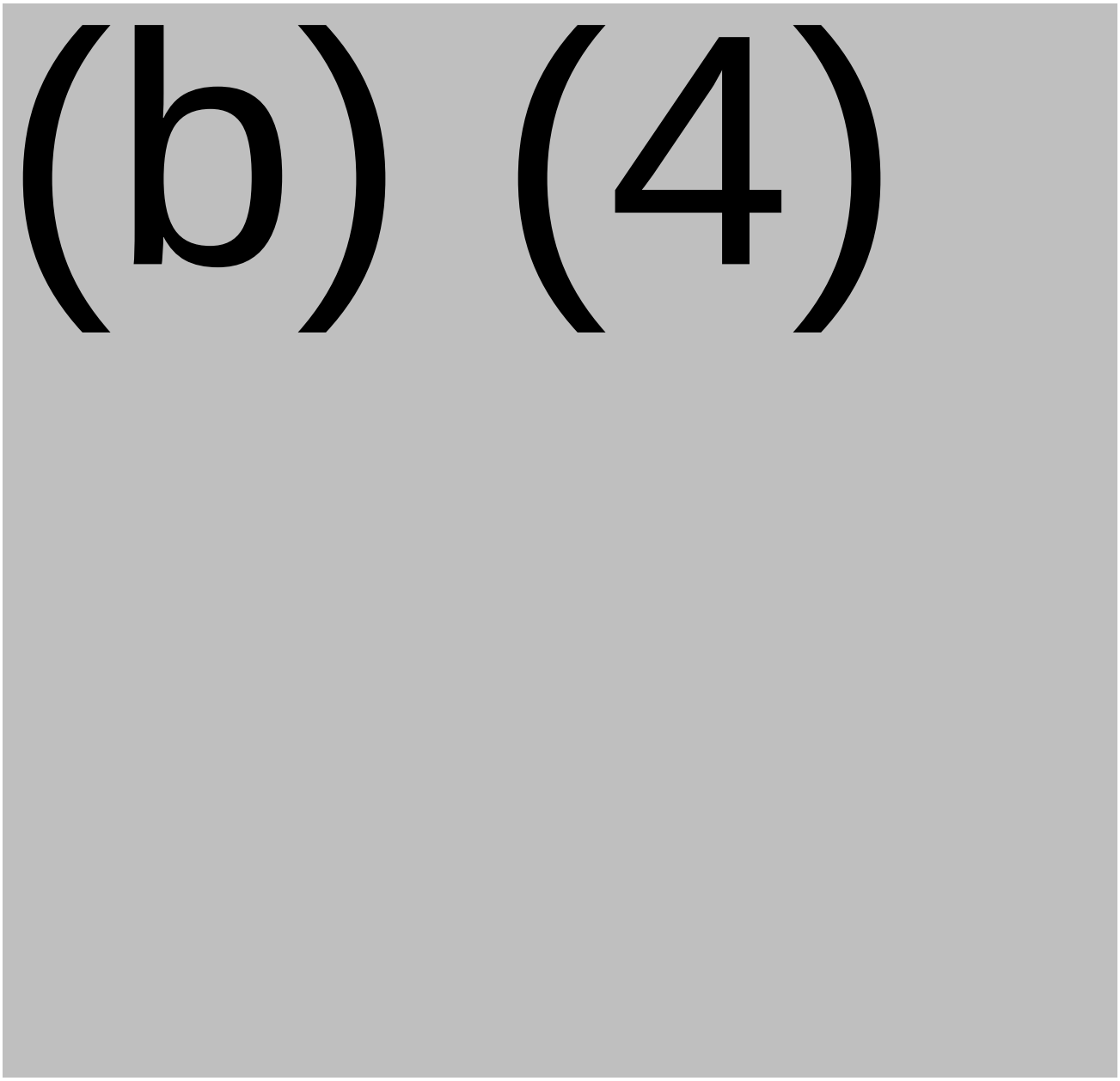
- ❖ ***Note:*** *Firm responses in support for CRL Item #5. and DMPQ Memo CR Item #1, discussed below are the same as submitted under amendment STN BL125659/0.19 and received on October 26, 2020 in support for the actions taken for correction, resolution and closure of the Observations #3.c.i.and #3.c.ii. associated to the PLI conducted in the Prometic Bioproduction Inc. in Laval, Quebec on November 14-21, 2017.*

**Firm Response:** Prometic indicated in the response to above CRL Items that QC test methods used for the equipment cleaning validation at PBP facility have been validated and the SOP in support for the QC test methods has been reviewed and updated. They stated that the following CAPAs were initiated for the validation of the (b) (4) testing method to be use for the cleaning validation of equipment:

- o (b) (4)

The firm explained that the following samples were tested:

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




- ✓ ***Reviewer Comments*****:** *The above deviations with their root causes and actions taken for resolution and closure were reviewed and found acceptable.*

- ***CRL Item #7 / DMPQ Memo CR Item #6 -*** *There are no data provided for the positive and negative controls used for the container closure integrity tests for the final drug product vials.*

**Firm Response:** Prometic stated in the response to the above CRL Item that the positive and negative controls used for the container closure integrity test (CCIT) of the FDP vials were established. They listed QAR-019.01-R, "*Plasminogen Drug Product* (b) (4) *Study Performed by* (b) (4) *Using Positive/Negative Controls Summary Report*" in support for the resolution and closure of these CRL items.

In Section 3.2.P.8.1.3.19 on Module 3.2.P.8.1, "Stability Summary and Conclusion," the firm indicated that the positive control is a FDP vial with a (b) (4) hole size, (b) (4) into the vial. They explained that (b) (4) determined that the positive control vial with a (b) (4) hole size as the smallest hole size to be used in the CCIT of the Plasminogen DP according to QAR-019.01.

The firm stated that the CCIT of the Plasminogen DP using (b) (4) method was qualified according to AMQ-029.01, "*Container Closure Integrity Testing (CCIT) in Plasminogen (Pg) Drug Product (DP).*"

Prometic stated that the negative control is a FDP vial (b) (4) (b) (4) during CCIT.

The firm conducted the CCIT using (b) (4) method to lots manufactured in the studies PPQ-1 and PPQ-2 as part of their stability studies at 5°C and 25°C for (b) (4) months. They indicated that the CCIT was conducted at six months timepoint, according to AM-043.02, "*Container Closure Integrity Testing (CCIT) in Pg DP."*

(b) (4)

(b) (4)

- ✓ ***Reviewer Comments*****:** *Prometic's information regarding the positive and negative controls in support of the response to CRL Item #7 and DMPQ Memo CR Item #6 were reviewed and found acceptable.*
- ***CRL Item #8 / DMPQ Memo CR Item #7:*** *Shipping validation for Final Drug Product (FDP) is inadequate with* (b) (4) *run and not under the worst-case condition.*

**Firm Response:** Prometic stated in the response to the above CRL Items that additional shipping validation study was conducted under worst-case condition. They listed SPV-011.01-R, "*Shipping Validation Report for the Shipping of Plasminogen Drug*

*Product from* (b) (4) *Under Controlled Temperature Conditions* (b) (4) in support for the resolution and closure of these CRL items.

In Section 3.2.P.2.3.8 on Module 3.2.P.2.3, "Manufacturing Process Development," the firm explained that an additional Shipping Validation Study was conducted in support for the (b) (4) transportation of the FDP from (b) (4) which is their tentative commercial distribution center. They indicated that this distribution center is located approximately (b) (4) miles from (b) (4) Prometic indicated that (b) (4) runs were conducted in this study between August 22, 2018 to January 28, 2019, using a temperature-controlled (b) (4) trailer set-up at a temperature of (b) (4) and a minimum load of FDP as worst-case conditions. The firm stated that the results of this Shipping Validation Study were reported in the Summary Report SPV-011.01-R, "*Shipping Validation Report for the Shipping of Plasminogen Drug Product from* (b) (4) *) Under Controlled Temperature Conditions* (b) (4) Prometic claimed that a copy of the Summary Report SPV-011.01-R was provided in the response in support for the CRL item #8. However, copy of this Summary Report was not included in the response for this CRL item.

Prometic indicated that an additional run in support of the Shipping Validation Study SPV-006.01 was conducted from April 30, 2018 to May 02, 2018. They explained that the purpose of this run is to demonstrate that the transportation of the FDP lots from (b) (4) to their clinical distributor centers, (b) (4) and using the (b) (4) shipping container complies with a temperature of (b) (4) . The firm stated that an external contractor (b) (4) was responsible for the transportation of these FDP lots from (b) (4) Prometic indicated that the shipping of FDP from (b) (4) has a duration of (b) (4) with (b) (4) .

The firm explained that a retrospective Shipping Validation Study has been conducted in support for the transportation of the FDP lots used for clinical trials from (b) (4) to their clinical distribution centers, (b) (4) . They indicated that the purpose of this retrospective study is to demonstrate that the (b) (4) shipping container is capable to maintain a temperature of (b) (4) during (b) (4) transportation of these lots and during (b) (4) seasons. The firm stated that (b) (4) was responsible for the transportation of these lots from (b) (4) . They reported in this retrospective study that the temperature of the FDP lots shipped to (b) (4) and (b) (4) complied with a criterion of (b) (4) Prometic indicated that visual inspection was conducted to the (b) (4) shipping container and the FDP lots when they were received in (b) (4) . They stated that no physical damage was observed in the (b) (4) shipping container and the FDP lots.

- ✓ ***Reviewer Comments*****:** *Prometic did not provide the Summary Report SPV-011.01-R in the response in support for the CRL item #8 and DMPQ CRL Item #7. Also, they did not provide a summary that describes the procedure and the results from the* (b) (4) *run conducted in support of the Shipping Validation Study SPV-006.01 and the retrospective Shipping Validation Study in the response in support for the CRL item #8.* ***See IR Questions #3.a., #3.b.i and #3.b.ii. – 03/26/2021 (Below.)***

3. *Regarding Section 3.2.P.2.3.8 in Module 3.2.P.2.3 in support for the response to the CRL item #8 in page 32 of Module 1.2;*

   a. *You stated in Section 3.2.P.2.3.8.1 that Report SPV-011.01-R was included in Attachment 3.2.P.2.3-1. However, Report SPV-001.01-R, approved on September 28, 2015 was included in this attachment instead of Report SPV-011.01-R. Please provide a copy of the Report SPV-011.01-R. Ensure to include a summary that describes how this study was conducted, with a description of the shipping configuration for the load used in this study and the location of the temperature probes placed in the load. Ensure to include a summary of the maximum, minimum and average shipping temperature readings and shipping times in each run conducted in this study. Also, ensure to include a summary that describes any deviation(s) initiated in this study with their action implemented for correction and resolution.*

**Firm Responses:** Prometic provided copy of *Summary Report SPV-011.01-R, "Shipping Qualification Report for the Shipment of Plasminogen Drug Product from* (b) (4) *under Controlled Temperature Conditions* (b) (4) approved on March 02, 2020. They explained that this Summary Report describes the results from (b) (4) shipping validation runs in support for the transportation of the FDP from (b) (4) (FDP manufacturing facility) to their tentative commercial distribution center in (b) (4) at a temperature of (b) (4)

The firm indicated that these runs were conducted using a minimum shipping load as worst-case conditions representative of a (b) (4) Prometic explained that this load consisted of (b) (4) containing (b) (4) 50mL vial with FDP. Then each (b) (4) with the FDP vial and (b) (4) are packaged into a shipping box, for a total of (b) (4) shipping boxes. (b) (4) is used to (b) (4)

Prometic explained that a temperature datalogger is placed in the (b) (4) containing the FDP vial and a (b) (4) temperature datalogger is placed outside of each shipping (b) (4). They stated that these temperature dataloggers record the temperature inside and outside of (b) (4) during each shipping run.

The firm indicated that the shipping (b) (4) were placed in a (b) (4) transfer and secured in the (b) (4). They explained that the (b) (4) has sensors to monitor temperature and alarms during transportation.

Prometic stated that shipping validation runs were conducted at the following dates to simulate (b) (4) shipping conditions:

**Table 51 – Summary of the Shipping Validation Runs**

| Shipping Validation Run # | Season | Date Conducted | Shipping Contents | FDP Lot # |
|---|---|---|---|---|
| (b) (4) | | | | |

The firm indicated that the distance between (b) (4) is approximately (b) (4) miles from (b) (4). They stated that the duration of the shipping validation runs is the following:

**Table 52 – Duration of the Shipping Validation Runs**

| Shipping Validation Run # | Shipping Start Date and Time | Shipping End Date and Time | Duration |
|---|---|---|---|
| (b) (4) | | | |

Prometic provided a summary of the temperature results in support of the shipping validation runs as follows:

**Table 53 – Temperature of the Shipping Validation Runs – Inside of (b) (4) and Outside of (b) (4)**

| (b) (4) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |

**Table 54 – Temperature of the Shipping Validation Runs – Inside of (b) (4)**

| (b) (4) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |

The firm explained that Deviation #1 was initiated due the maximum temperatures recorded inside of the (b) (4) and outside of the (b) (4) exceeded the maximum shipping temperature of (b) (4) for more than (b) (4). These maximum temperatures were stated in Table 53. They indicated that the root causes are the preparation of the (b) (4) for this study and their equilibration period in (b) (4) were between (b) (4). Prometic indicated that the above temperature excursions did not impact this Shipping Study, since the FDP is stored at a temperature of 2°C to 25°C for 24 months according to their stability data. The firm stated that the temperature recorded inside of the (b) (4) and outside of the (b) (4) during shipping did not exceed (b) (4). They indicated that this deviation is considered resolved and closed.

- ✓ ***Reviewer Comments:*** *Summary Report SPV-011.01-R was reviewed and found acceptable.*

b. *You explained in Section 3.2.P.2.3.8.2 that an additional run was conducted in support for the Shipping Validation Study SPV-006.01, to demonstrate the transportation of the FDP lots from* (b) (4) *to your clinical distributor center* (b) (4) *at a temperature between* (b) (4) *Also, you indicated in this section that a retrospective study has been conducted in support for the transportation of the FDP lots from* (b) (4) *to your clinical distribution centers in* (b) (4) *. You stated that the purpose of this retrospective study was to demonstrate* (b) (4) *transportation at a temperature between* (b) (4) *during* (b) (4) *seasons. However, you did not provide a summary that describes this additional run and the retrospective study in support of the CRL Item #8.*

   b.i. *Please provide a summary that describes the additional run in support for the Shipping Validation Study SPV-006.01 and the retrospective study. Ensure to include the following information: the description of the shipping load, including the number of* (b) (4) *, number of FDP vials per* (b) (4) (b) (4) *and number of* (b) (4) *used. Also, ensure to indicate the total number of temperature dataloggers used and their location in the shipping load. Ensure to provide a diagram that illustrates the location of the temperature dataloggers in the load. Please provide a summary of the maximum, minimum and average shipping temperature readings. Ensure to provide the transportation distance and time for the* (b) (4) *transportation conditions. Ensure to include a summary that describes any deviation(s) initiated in these studies with their action implemented for correction and resolution.*

**Firm Responses:** Prometic provided copy of the *Summary Report SPV-006.01-R, "Summary of Shipping Validation Report of Plasminogen Drug Product from* (b) (4) *under Controlled Temperature Conditions* (b) (4) *."* They indicated that this Summary Report describes the (b) (4) shipping validation run conducted from (b) (4) using a (b) (4) . The firm stated that this shipping validation run was conducted on April 30, 2018.

The firm explained that the shipping configuration used in this Study consisted of (b) (4) vials of FDP that were packed in individual (b) (4) . Then (b) (4) (b) (4) were placed inside of a (b) (4) Prometic indicated that (b) (4) were packed into a (b) (4) and (b) (4) were placed in a (b) (4) and secured inside of a temperature-controlled container (b) (4) The firm stated that (b) (4) temperature dataloggers were geometrically distributed in the (b) (4) . They indicated that a temperature datalogger was placed inside of the (b) (4) and other temperature datalogger was placed outside of the (b) (4)

Prometic stated that a courier company was in charge of the (b) (4) transportation of the (b) (4) from (b) (4) at a temperature of (b) (4) They explained that the distance between (b) (4) is approximately (b) (4) miles by (b) (4) and (b) (4) miles by (b) (4) . The firm indicated that the duration of this shipping validation run was (b) (4) with (b) (4) minutes. Prometic stated that the temperature of all

dataloggers complied with a temperature criterion of (b) (4) They indicated that no deviation was initiated in this Study.

The firm provided copy of the Summary Report RAR-089, "Summary of Retrospective Analysis of Ryplazim Clinical Shipments ((b) (4) They explained that this Summary Report describes the results from the retrospective study in support for the shipping of FDB from (b) (4) (clinical distribution centers in US (b) (4)); in addition, to PBP. They indicated that the same shipping configuration discussed in SPV-006.01-R was also used in this study. Prometic stated that (b) (4) were used for the shipment of these clinical lots. They explained that (b) (4) is a small container made of (b) (4) that accommodate (b) (4) at a temperature (b) (4) in (b) (4) conditions.

Prometic indicated that that a courier company was in charge of the (b) (4) transportation of the clinical lots from (b) (4) at a temperature of (b) (4) . They stated that the distance between (b) (4) is approximately (b) (4) miles by (b) (4) and (b) (4) miles by (b) (4) . The firm indicated that the duration of the shipping for the clinical lots was between (b) (4) minutes and (b) (4) minutes. Prometic stated that the distance between (b) (4) is (b) (4) miles by (b) (4) and (b) (4) miles by (b) (4) . They indicated that the duration of the shipping for the clinical lots was between (b) (4) (b) (4) and (b) (4) (b) (4)

The firm stated that temperature dataloggers were placed inside of the shipping boxes to record the temperature during the shipping of the clinical lots. They indicated that the temperature from the dataloggers complied with a temperature criterion of (b) (4) Prometic indicated that no deviation was initiated in this Study.

- ✓ ***Reviewer Comments*****:** *Summary Reports SPV-006.01-R and RAR-089 were reviewed and found acceptable. These studies demonstrate the shipping of the FDP at a temperature of* (b) (4)

  *b.ii. Please indicate the number of lots that were shipped from* (b) (4) *to the clinical distribution centers in support for the retrospective study. Also, please indicate the temperature and conditions representatives of the* (b) (4) *seasons in this retrospective shipping study.*

**Firm Responses:** Prometic explained that (b) (4) clinical lots were shipped from (b) (4) (US clinical distribution center) and (b) (4) clinical lots were shipped from (b) (4) to (b) (4) clinical distribution center) from November 2014 to June 2019 in support for the retrospective study. They indicated that these lots were shipped using (b) (4) and (b) (4) container at a temperature between (b) (4) The firm indicated that the temperature representatives of the (b) (4) seasons in this retrospective shipping study were the following:

**Table 55 – Temperature Representative of the (b) (4) Seasons in the Retrospective Shipping Study**

| Shipping From /To | Season | Maximum Temperature | Minimum Temperature |
|---|---|---|---|
| (b) (4) | (b) (4) | | (b) (4) |

✓ ***Reviewer Comments*****:** *The firm's response is acceptable.*

- ***CRL Item #9 / This CR Item was not included in DMPQ Memo:*** *The observations noted in the FDA form 483 during the pre-licensure inspection have not been resolved completely.*

**Firm Response:** Prometic claimed that observations have been fully addressed.

✓ ***Reviewer Comments*****:** *In the resubmitted BLA, Prometic did not provide information in support of the corrective actions implemented for the resolution and closure of Observations #1.a., #1.b., #1.c., #1.d., #1.e., #1.f., #1.g., #1.h., #2.a., #2.b., #2.c., #2.d., #3.a., #3.b., #3.c., #4.a., #4.b., #4.c., #5.a., #5.b., #5.c., #6, #7, #8.a., #8.b., #8.c., #8.d., #8.e., #8.f., #8.g., #8.h., #10.a., #10.b., #11 and #12.* ***See IR Questions #2.a. and #2.b. – 10/08/2020 (Below).***

2. *You reported in the Action Taken Section for CRL Item #9 on page 33 from Module 1.2, "Reviewer Guide" of the resubmitted BLA under amendment STN 125659/0/18 that the observations noted in the FDA form 483 during the Pre-License Inspection (PLI) have been fully addressed. However, in your responses received on December 12, 2017; January 12 and 22, 2018 and March 06, 2018 in support for the FDA Form 483 Observations made during the PLI at the Prometic BioProduction Inc., Laval, Canada Facility on November 14-21, 2017, you were not able to address all the 483 observations items completely by the Action Due Date of April 13, 2018. Of the 12 observation items in the FDA Form 483, only Observation #9 has been closed completely and 11 other observation items were still open. It is unclear if the corrective actions in support of Observations #1, #2, #3, #4, #5, #6, #7, #8, #10, #11, and #12 have been implemented for their resolution and closure at the time that the BLA under amendment STN 125659/0/18 was resubmitted to the agency.*

   a. *Please provide a summary that describes the corrective actions implemented for the resolution and closure of Observations #1, #2, #3, #4, #5, #6, #7, #8, #10, #11, and #12 when this BLA was resubmitted to the agency. Please justify your response. Please provide supporting documentation in support for the resolution and closure of the above observations.*

   b. *In the case that the documentation in support for the corrective actions implemented for the resolution and closure of Observations #1, #2, #3, #4, #5,*

*#6, #7, #8, #10, #11, and #12 has been provided in the resubmitted BLA, please enumerate the sections and documents that addresses these corrective actions.*

**Firm Responses:** In amendment STN BL125659/0.19 and received on October 26, 2020, Prometic provided a summary that describes the following corrective actions implemented for the resolution and closure of Observations #1.a., #1.b., #1.c., #1.d., #1.e., #1.f., #1.g., #1.h., #2.a., #2.b., #2.c., #2.d., #3.a., #3.b., #3.c., #4.a., #4.b., #4.c., #5.a., #5.b., #5.c., #6, #7, #8.a., #8.b., #8.c., #8.d., #8.e., #8.f., #8.g., #8.h., #10.a., #10.b., #11 and #12.

- ✓ ***Reviewer Comments*:** *The corrective actions implemented for the resolutions and closures of the above Observations are discussed below. A single reviewer comment is provided at the end of the review of these Observations, including IR question(s) to request additional information for clarification.*
- o **Observation #1:** The manufacturing process for the plasminogen bulk drug substance (BDS) is not adequately validated or controlled.
- ❖ ***Note:*** *The corrective action reviewed for the resolution and closure of Observations #1.a., #1.b., #1.c., #1.d., #1.e., #1.f., #1.g., #1.h. were reviewed from the DMPQ standpoint.*

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observation #1 consists in the implementation of the following CAPAs in support for the life cycle of biological products, including development and manufacturing:

- CAPA-17-179 for the implementation of QAR-012.01-R, "*Gap Assessment for SOPs related to Process Development, Process Transfer and Process Qualification at PBT and PBP*." They explained this document is a gap assessment conducted to the SOPs in support for the process development, transfer and qualification in Prometic Biotherapeutics (PBT) and Prometic Bioproduction (PBP) to comply with existing regulatory requirements. This CAPA was closed on December 22, 2017, at the same date as this gap assessment report was approved. This CAPA is also applicable to the Observation #1.f;
- CAPA-17-155 for the review and update of SOP -0272 (SOP CO-003), "*Process Development Studies for Biological Products*" as results from QAR-012.01-R. This SOP describes the requirements and activities to be conducted during the developmental phase in support for the manufacture of biological products. This CAPA was closed on February 27, 2018;
- CAPA-17-156 for the implementation of SOP-0271 (SOP CO-002), *"Process Technology Transfer for Biological Products*," as results from QAR-012.01-R. This SOP describes the requirements and activities to be conducted during the transfer for the manufacture of biological products from the developmental phase to commercial manufacturing. This CAPA is applicable to Observations #1.b.i. and #1.b.ii. This CAPA was closed on February 27, 2018;
- CAPA-18-005 for the implementation of SOP-0273 (SOP CO-004), "*Project Management for Development of Biological Products*," as results from QAR-012.01-R. This SOP describes the requirements for the management of biological products

from their development until their transfer for commercial manufacturing. This CAPA is applicable to Observation #1.b.i. This CAPA was closed on February 27, 2018;

- CAPA-18-002 for the implementation of CQS-023, "*Technology Transfer of New Drug Product*," as results from QAR-012.01-R. This Corporate Quality Standard (CQS) describes the requirements for the transfer of a biological product from the developmental phase to commercial manufacturing. This CAPA was closed on March 02, 2018;
- CAPA-18-003 for the implementation of CQS-011, "*Validation Program*," as result from QAR-012.01-R. This CQS describes the validation requirements for the commercial manufacturing of a biological product. This CAPA was closed on February 19, 2018.

o **Observation #1.a.:** The in-process controls (IPC) used during process validation, and implemented currently, do not provide adequate control of the process to allow the demonstration of process consistency.

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #1.a. consists in the implementation of the following CAPAs:

- CAPA-17-157 for the review and update of PDR-038, "*Quality Target Product Profile (QTPP) – Plasminogen (Human)"* to include specifications in support for the commercial manufacturing of Pg Intermediate, BDS and FDP. This CAPA was closed on March 07, 2019
- CAPA017-158 for the review and update of PDR-009, "Risk Assessment of Prospective Quality Attributes for Prometic Plasminogen (Human)," to determine the CQAs in support for the manufacture of Pg Intermediate, BDS and FDP. This CAPA was closed on March 13, 2019;
- CAPA-17-159 for the implementation of PDR-001-A.06, "*Critical Process Parameter Assessment in Plasminogen (Human) Manufacturing – Part A: Pg Intermediate Manufacturing Process*" and PDR-001-B.06, "*Critical Process Parameter Assessment in Plasminogen (Human) Manufacturing – Part B: Pg DS and DP Manufacturing Process,*" to determine CPPs in support for the manufacture of Pg Intermediate, BDS and FDP. This CAPA was closed on June 04, 2019;
- CAPA-17-160 for the review and update of PDR-029-A.06, "*Control Strategy for Plasminogen (Human) Manufacturing – Part A: Pg Intermediate Manufacturing Process*" and PDR-029-B.07, "*Control Strategy for Plasminogen (Human) Manufacturing – Part B: Pg DS and DP Manufacturing Process,*" for the implementation of additional in-process controls to ensure that the manufacturing process of Pg Intermediate, BDS and FDP is conducted in a controlled and validated state. This CAPA was closed in July 18, 2019. This CAPA is applicable to Observations #1.a.ii., #1.a.iii, #1.a.v., #1.e., #2.d.i., #2.d.ii. and #2.d.iii.

o **Observation #1.a.i.:** The assay for plasminogen activity is not suitable for its intended use. Prometic uses, but does not qualify, the (b) (4) to measure plasminogen activity. The (b) (4) includes a (b) (4), but Protmetic does not use an in-house primary or working reference standards, nor any control

sample in the assay. As such, the results from the previously performed assays cannot be verified, and assay performance over time cannot be monitored.

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #1.a.i. consists in the implementation of the following CAPAs:

- CAPA 17-161 for the revalidation of (b) (4) and Total Protein Content by (b) (4) test methods in support for the use in-house reference standards and Pg control samples. Prometic stated that the in-house reference standards and Pg control samples were developed, validated and implemented in the above test methods in support for the determination of Pg Activity. This CAPA was closed on February 16, 2018;
- CAPA-18-063 for the method comparability and bridging studies for (b) (4) activity and (b) (4) test methods. This CAPA was closed on March 09, 2018.

The firm explained that the following studies were conducted in support for the above CAPAs:

- AMV-030.01-R, "*Total Protein Content by* (b) (4) *for Pg* (b) (4) *DP* (b) (4) *Samples*;"
- AMC-003.02-R, "*Analytical Method Comparability Report for* (b) (4) *Testing for Quantification of Plasminogen Content in Plasminogen Samples* (b) (4) *DP*;"
- AMC-0040.01-R, "Analytical Method Comparability Report for (b) (4) *Assay of Plasminogen Drug Product,* (b) (4) *Samples;*
- AMC-0040.01-R-AMD-01, "*Correction Factor Computation _ Pg Activity* (b) (4) *Assay;"*
- AMV-048.01-R, "(b) (4) *Assay of Plasminogen Drug Product,* (b) (4) *Samples*;"
- AMV-039.01-R, "(b) (4) *Testing for Quantification of Plasminogen Content in Plasminogen Samples* (b) (4) *DP)."*

The firm stated that the following SOPs were reviewed and updated in support for the revalidation of (b) (4), (b) (4) and Total Protein Content by (b) (4) test methods:

- AM-016.07, "*Determination of Total Protein in Plasminogen Samples by* (b) (4)*;*"
- AM-031.07, "(b) (4) *Testing for Quantification of Intravenous Plasminogen (*(b) (4) *DP,* (b) (4)
- AM-029.07, (b) (4) *Assay of Plasminogen Drug Product,* (b) (4) *Samples*."

Prometic indicated that the following studies were conducted in support for the validation of in-house reference standards and Pg control samples:

- RSQ-003.01-R, "*Qualification of Plasminogen Reference Standard (Pg DP* (b) (4) *"*

- RSQ-006.01-R, "*Qualification of In-House Plasminogen Reference Standard Lot* (b) (4) ;"
- STB-DSRS-Pg-001.01-P, "*Stability Protocol of Plasminogen Drug Substance Reference Standard Lot* (b) (4) ."

The firm stated that SOP-0054, "*Preparation and Qualification of Critical Reagents and In-House Reference Standards*" was reviewed and updated to implement additional controls for the qualification of critical reagents used for the determination of Pg Activity and the monitoring of this assay.

o **Observation #1.a.ii.:** A subset of the IPC tests was classified in the BLA as "characterization" test. These tests are not intended to be a permanent part of the IPC and are performed in the laboratory at Prometic Biotherapeutics in (b) (4) , (b) (4) , which had not validated these methods. For these tests, no action is taken when the results are outside of the normal operating ranges.

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #1.a.ii. consists in the implementation of CAPA-17-160. This CAPA is applicable to Observations #1.a, #1.a.iii., #1.a.v., #1.e. and #2.d. This CAPA was discussed in the corrective action in support for Observation #1.a.

o **Observation #1.a.iii.:** No controls are provided for protein aggregation in (b) (4) final drug product (FDP) despite multiple indications showing the protein's propensity to aggregate.

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #1.a.iii. consists in the implementation of CAPA-17-160. This CAPA is applicable to Observations #1.a, #1.a.ii., #1.a.v., #1.e. and #2.d. This CAPA was discussed in the corrective action in support for Observation #1.a.

o **Observation #1.a.iv.:** Analytical methods were modified after the production of the PPQ lots without bridging studies. For example, method AM-027 for (b) (4) determination was changed to method AM-044. Despite the change in (b) (4) and (b) (4) , no bridging studies were performed.

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #1.a.iv. consists in the implementation of the following CAPAs:

- CAPA-17-162 for the implementation of QAR-016.03-R, "*Gap Analysis Report-Validation of Current Analytical Methods Used for the Plasminogen Sample Testing*." The firm explained that this report describes the results from the gap analysis conducted to all analytical methods to ensure proper bridging. They indicated that bridging study under AMC-005.01-R, "*Analytical Method Comparability Report for Determination of* (b) (4) *in Plasminogen Samples by* (b) (4) " was conducted in support for the (b) (4) content analytical method. This CAPA was closed on February 20, 2018.
- CAPA-17-164 in support of the bridging study for (b) (4) and reported in AMC-002-01-R, "*Comparability Between AM-027 and AM-044 for* (b) (4) *Determination in Plasminogen Samples by* (b) (4) ." They indicated that this

study was conducted to conduct equivalency between test methods AM-044 and AM-027 for the determination of (b) (4) in Plasminogen samples using (b) (4). The firm stated that AM-044 replaced AM-027. Prometic explained that the parameters for specificity, accuracy, repeatability linearity range, LOD and LOQ from AM-027 and AM-044 were evaluated in this study for equivalency. This CAPA was closed on February 02, 2018.

- **Observation #1.a.v.:** No in-process acceptance specifications for (b) (4) were established during the manufacturing of the PPQ lots in support of the BLA. The in-process (b) (4) acceptance specifications were not established until March 2017.

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #1.a.v. consists in the implementation of CAPA-17-160. This CAPA is applicable to Observations #1.a, #1.a.ii., #1.a.iii., #1.e., #2.d.i., #2.d.ii. and #2.d.iii. This CAPA was discussed in the corrective action in support for Observation #1.a.

- **Observation #1.a.vi.:** During the manufacturing of the PPQ lots, the in-process (b) (4) test methods were not verified, and no in-process (b) (4) acceptance criteria were established.

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #1.a.vi. consists in the implementation of CAPA-17-184 for the validation of the (b) (4) test method for IPC samples. They indicated that the results from this test method validation were reported in AMQ-011-02-R, "*Analytical Method Qualification and Hold Time Study of* (b) (4) *for* (b) (4) and AMQ-011.03-R, "*Analytical Method Qualification Report on* (b) (4) *Test* (b) (4) *) for In-Process Controls of Manufacturing Process of Plaminogen*." Prometic stated in both studies that the (b) (4) The results of the repeated study were reported in AMQ-019.01-R, "*Analytical Method Qualification Report on* (b) (4) *Technique) for* (b) (4) *Samples*" and AMQ-020.01R, "*Analytical Method Qualification Report on* (b) (4) *Technique) for* (b) (4) *Samples.*" CAPA-17-184 was closed on February 19, 2018. No CAPA was initiated for the (b) (4) testing method qualification under AMQ-019.01-R and AMQ-020.01R. These reports were approved on June 15, 2018.

- **Observation #1.b.:** Process steps and materials have been changed between the time of BLA submission and this inspection due to incomplete process knowledge.
- **Observation #1.b.i.:** On March 9, 2017, it was discovered (INR-17-271.01) that materials for (b) (4) were used together with (b) (4) despite the manufacturer's warning of incompatibility. Changes to process are (b) (4)

- **Observation #1.b.ii.:** On June 15 – 16, 2017, it was discovered (INR-17-265.01 and INR-17-266.01) that the modified procedures to prepare reagents for the solvent/detergent treatment step were inappropriate and could not clarify the solution.

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observations #1.b., #1.b.i. and #1.b.ii consist in the implementation of the following CAPAs:

- CAPA-17-163 for the implementation of QAR-013.01-R, "*Gap Analysis and Risk Assessment of Process Changes Post 2016 PPQ Plasminogen* (b) (4) *Process at* (b) (4) *in Laval, Canada*." The firm explained that this gap analysis and risk assessment was conducted in support for the implementation of the changes in the Plasminogen manufacturing process at (b) (4) after the PPQ Studies of 2016. The changes reported in QAR-013.01-R consists in the preventive action to mitigate the leachable and extractable impact in support of the (b) (4) used for (b) (4) storage and transfer after the removal of the (b) (4) for the (b) (4) testing. Other change reported in QAR-013.01-R consists in the removal of the (b) (4) in the (b) (4) testing. This CAPA was closed on February 08, 2018;
- CAPA-17-173 for bridging studies as result of QAR-013.01-R. A bridging study was conducted in support for the evaluation of two procedures used for the preparation of reagents for the solvent/detergent treatment step. Prometic indicated that these studies were reported in PDP-5026.079.02A, "*Comparability Protocol (Part A): Comparison of Data Generated Following Improvements to the Manufacturing Process: Pg Intermediate Manufacturing Process*" and PDR-5026.079.01-B, "*Comparability Report (Part B): Comparison of Data Generated Following Improvements to the Manufacturing Process: Plasminogen Intermediate to Plasminogen DP*." Additional bridging studies were conducted for the evaluation of two procedures used for the (b) (4) testing after the removal of (b) (4). This CAPA was closed on February 15, 2018;
- CAPA-17-169 and CAPA-17-170 in support for the new Process Performance Qualification Protocols and Reports associated to the manufacture of Pg Intermediate, BDS and FDP. Prometic stated that these PPQ Studies were conducted in support for the changes implemented in the manufacture of Pg Intermediate, BDS and FDP. These CAPAs are applicable to Observation #1.f.i. These CAPAs were discussed in Observation #1.f.i.
- CAPA-17-156 for the implementation of SOP-0271 (SOP CO-002), *"Process Technology Transfer for Biological Products*." This SOP specifies that the impurity profile is conducted to product contact polymer components according to the Technology Transfer Data Package. Also, this SOP specifies that equipment and (b) (4) times for solutions, (b) (4) and products must be documented according to the Technology Transfer Data Package. This above action prevents the recurrence of change manufacturing process with insufficient supporting data. This CAPA is applicable to Observation #1.a. This CAPA was closed on February 27, 2018;
- CAPA-18-005 for the implementation of SOP-0273 (SOP CO-004), "*Project Management for Development of Biological Products*." This SOP describes the

instructions to conduct leachable and extractable studies to the product contact components used in the manufacture of Pg Intermediate, BDS and FDP prior to initiate the PPQ studies. This CAPA is applicable to Observation #1.a. This CAPA was closed on February 28, 2018;

- **Observation #1.c.:** Development studies to support the process validation are inadequate.
- **Observation #1.c.i.:** Some acceptance criteria for the (b) (4) (b) (4) studies (past and ongoing) are not specific enough. For example, acceptance criteria for (b) (4) study include "Consistently (b) (4) " and "Consistent (b) (4) In most cases, the acceptance criteria were not justified.

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #1.c.i. consists in the implementation of the following CAPAs:

- CAPA-17-185 for the implementation of SOP-0269 (SOP MS-001), "*Requirements for Generation of* (b) (4) *Studies for* (b) (4) ." This SOP describes the requirements in support of the (b) (4) studies for the (b) (4) (b) (4) This SOP includes instructions for the handling and investigation of incidents during the (b) (4) studies of (b) (4) . This CAPA is applicable to Observation #1.c.iii.;
- CAPA-17-175 for the evaluation of ongoing (b) (4) (b) (4) studies. Prometic stated that (b) (4) studies were conducted at (b) (4) . This CAPA was closed on February 12, 2018. They indicated that the results of these studies were discussed in the following Reports:
  - PBL/114/R22/261115/01, "(b) (4) *Report*," approved on November 26, 2015.
  - PDR-021.01, (b) (4) *Study* (b) (4) *,"* approved on May 04, 2017;
  - PDR-018.01, (b) (4) Study (b) (4) ," approved on June 26, 2017;
  - PDR-022.02, "(b) (4) *Study of* (b) (4) ," approved on February 12, 2018;
  - PDR-057.01, "*Plasminogen Process* (b) (4) (b) (4) *Study,"* approved on July 17, 2017.

❖ ***Note:*** *The above Reports were not discussed in the corrective action implemented for the resolution of Observation #1.c.i. These reports were discussed in the DMPQ memo issued on April 13, 2018 in support for the review of the BLA under STN 125659/0.*

- CAPA 17-228 and CAPA-17-229 for the (b) (4) studies of the (b) (4) conducted concurrently with the PPQ campaign 2 and during manufacture of Pg Intermediate and BDS. Prometic explained that the reports in support for these studies will be provide to the agency as post-licensure

commitment. These CAPAs were closed on June 04, 2019. The firm provided the following protocols in support for these CAPAs:

- (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

- (b) (4)

(b) (4)

(b) (4)

- **Observation #1.c.ii.:** (b) (4) results in the studies were labelled as outliers and excluded from analysis.

**Firm Responses:** Refer to firm response to the Observation #1.c.i.

- **Observation #1.c.iii.:** Incidents observed during the studies were not investigated. For example, particulates were observed during the study of (b) (4) (report MPV-026,) but not investigation was performed.

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #1.c.iii. consist in the implementation of the following CAPAs:

- CAPA-17-155 for the review and update SOP-0272 (CO-003), "*Process Development Studies for Biological Products,*" to include an instruction for the handling and investigation of incidents during developmental studies. This CAPA is application to Observation #1.a. This CAPA was closed on February 27, 2018;
- CAPA-17-185 for the implementation of SOP-0269 (SOP MS-001), "*Requirements for Generation of* (b) (4) *Studies for* (b) (4) ." This SOP includes instructions for the handling and investigation of incidents during the (b) (4) studies of (b) (4) and (b) (4) . This CAPA is applicable to Observation #1.c.i. This CAPA was closed on February 09, 2018.

o **Observation #1.c.iv.:** There are no validated hold-times and process step times.

❖ ***Note:*** *Firm responses in support of the corrective action for resolution and closure for the Observation #1.c.iv. and received under amendment STN BL125659/0.19 received on October 26, 2020 are the same firm responses received under amendment STN BL125659/0.18 on September 04, 2020 in support for CRL Items #1.b.iv. and #2.d; in addition, to DMPQ Memo CR Item #2. These responses were discussed in the firm responses in support for CRL Items #1.b.iv. and #2.d; in addition, to DMPQ Memo CR Item #2.*

o **Observation #1.d.:** Planned deviations were performed during the PPQ batch manufacturing. Specifically, re-use of (b) (4) was allowed according to report QAR-001.01-R.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observation #1.d consisted in the implementation of CAPA-17-176 for the implementation of SOP CO-005 (SOP-0274,) "*Process Qualification for Manufacture of Biological Products."* This SOP describes the requirements and instructions for the PPQ protocol content, approval process and include a template of the PPQ protocol as reference. This protocol template includes sections in support for the equipment and materials to be used in the PPQ Study and study pre-requisites that prevent the need for planned deviations. This CAPA was closed on February 27, 2018.

The firm indicated that the PPQ protocols in support for the PPQ2 campaign were written using this protocol template.

o **Observation #1.e.:** BDS lots manufactured from (b) (4) test results were released without adequate investigation. For example, among the (b) (4) lots of (b) (4) with (b) (4) test results manufactured from May through September 2017. (b) (4) lots were released for further manufacturing into BDS and the contaminating (b) (4) have not been quantitated or identified.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observation #1.e. consisted in the implementation of the following CAPAs:

- CAPA-17-160. This CAPA is applicable to Observations #1.a, #1.a.ii., #1.a.iii., #1.a.v., #2.d.i., #2.d.ii. and #2.d.iii. This CAPA was discussed in the corrective action in support for Observation #1.a.
- CAPA-17-190 for the review and update of SOP QC-015 (SOP-0048), "*Handling of Out of Specification Test Results*," according to the "*Guidance for Industry, Investigating Out-Of-Specifications (OOS) Test Results for Pharmaceutical Productions*," issued in October 2006. They stated that the investigation of the OOS and OOT are part of the QMS and QA is responsible for them. The firm indicated that QA and the respective departments participate in the Phase 2 investigation and QA must approve any retesting required. Prometic explained that this SOP include instructions for the handling and investigation of OOS and OOT results for release, IPCs and monitoring samples. They stated that the updated SOP does not allows to remove outliners. The firm explained that PDR-121.01, *"Pg Intermediate Specification and Justifications – Commercial Pg-*(b) (4) PDR-122.01, "*DS Specification and Justifications – Commercial Pg*(b) (4) and PDR-123.01, "*DP Specifications and Justifications – Commercial Pg*(b) (4) were reviewed and updated to include the internal specifications for the investigation of OOS and OOT. They explained that IPCs for(b) (4) and other testing are establish according to historical data. This CAPA was closed in November 14, 2018. This CAPA is also applicable to Observations #2.d.i, #2.d.ii and #2.d.iii;
- CAPA-17-192 for the implementation of SOP QC-052 (SOP-0080) (b) (4) *Monitoring for In-Process Control Steps*." This SOP describes the procedure for the(b) (4) in-process testing and actions to be taken if there is (b) (4) OOS. This CAPA was closed on March 20, 2018.

o **Observation #1.f.:** There is no procedure or documentation to guide and document the setting of FDP and BDS specifications. It is not clear how the specifications are approved. As results, the following deficiencies were noted in the specifications.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observation #1.f. consisted in the implementation of the following CAPAs:

- CAPA-17-179 for the implementation of QAR-012.01- R, "*Gap Assessment for SOPs related to Process Development, Process Transfer and Process Qualification at PBT and PBP*." This CAPA was closed on December 22, 2017, at the same date as this gap assessment report was approved. This CAPA is also applicable to the Observation #1.a. This CAPA was discussed in the firm response in support to the Observation #1.a.
- CAPA-17-182 for the implementation of SOP CO-006.01 (SOP-0275), "*Specification Setting for Injectable Biological Products.*" This SOP describes the instructions for the implementation and review of specification for biological products manufactured for clinical and commercial purposes. This CAPA was closed on February 28, 2018.

o **Observation #1.f.i.:** Specifications for the parameters tested for both BDS and FDP were established based on the combined data for BDS and FDP, which is statically inappropriate.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observation #1.f.i. consisted in the implementation of the following CAPAs:

- CAPA-17-166 for the review of the IPC limits and action according to risk assessment, process capability and data from the validated analytical methods. This CAPA was closed on July 18, 2019;
- CAPA-17-167 for the review of the BDS specifications. This CAPA was closed on June 04, 2019;
- CAPA-17-168 for the review of the FDP specifications. This CAPA was closed on June 04, 2019;
- CAPA-17-183 for issuing PDR-092.A-01, "*Revision of Plasminogen (Human) Specifications: Part-A, the Pg-Intermediate*" and PDR-092.B-03, "*Revision of Plasminogen (Human) Specifications.*" These documents describe the updated specifications in support for the BDP and FDP in support of CAPA-17-166, CAPA-17-167 and CAPA-17-168. The firm stated that the updated specification for the BDS and FDP as described in PDR-092.A-01 and PDR-092.B-03 were confirmed during the manufacture of the PPQ-2 campaign. This CAPA was closed on June 04, 2019;
- CAPA-17-169 and CAPA-17-170 in support for the new Process Performance Qualification Protocols and Reports associated to the manufacture of Pg Intermediate, BDS and FDP. The following reports were written in support for these CAPAs:
  - MPV-037.01-R, "*Process Performance Qualification Report for Plasminogen (Human):* (b) (4) *Intermediate Process – Product Codes* (b) (4) *Manufactured by Prometic in Laval, Québec, Canada*", approved on February 26, 2020. This report describes the results from (b) (4) Pg Intermediate batches manufactured at (b) (4) . These lots were manufactured on May 2019;
  - MPV-038.02-R, "*Process Performance Qualification Report for Plasminogen (Human):* (b) (4) *Pg DS Process – Product Codes* (b) (4) *Manufactured by Prometic in Laval, Québec, Canada*", approved on May 01, 2020. This report describes the results from three Pg BDS batches manufactured at (b) (4) . These lots were manufactured on June 2019;
  - MPV-039.02-R, "*Process Performance Qualification Report for Plasminogen (Human):* (b) (4) *Pg DP Process – Product Codes* (b) (4) *Batch Size Manufactured by* (b) (4) approved on June 23, 2020. This report describes the results from (b) (4) Pg FDP batches manufactured using a batch size between (b) (4) . These lots were manufactured on December 2019.

CAPA-17-169 was closed on June 04, 2019 and CAPA-17-170 was closed on May 06, 2020. These CAPAs are applicable to Observation #1.b.

Prometic indicated that the (b) (4) and sterility specifications in MPV-037.01-R, MVP-038.02-R and MVP039.02-R are the following:

**Table 62:** (b) (4) **Specifications in MPV-037.01-R**

| Manufacturing Step | Testing | Specification |
|---|---|---|
| (b) (4) | | |

**Table 63:** (b) (4) **Specifications in MPV-038.02-R**

| Manufacturing Step | Testing | Specification |
|---|---|---|
| (b) (4) | | |

**Table 64:** (b) (4) **Specifications in MPV-039.02-R**

| Manufacturing Step | Testing | Specification |
|---|---|---|
| (b) (4) | | |
| FDP | Sterility | No Growth |

| Manufacturing Step | Testing | Specification |
|---|---|---|
| FDP | Endotoxin | Alert Limit: (b) (4)<br>Action Limit: (b) (4) |

The firm stated that the (b) (4) and sterility results from the batches manufactured and reported in MPV-037.01-R, MVP-038.02-R and MVP039.02-R complied with the above specifications.

- **Observation #1.f.ii.:** Testing procedure AM-017, "(b) (4) " is not compliant to the compendial requirements of (b) (4) as only one sample is tested but (b) (4) acceptance criteria "Essentially free of visible particles" is used.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observation #1.f.ii. consisted in the implementation of CAPA-17-180, to remove the particulate assessment from the analytical method AM-017, "(b) (4) ." The firm explained that the particulate testing is conducted in (b) (4) according to (b) (4) during the second inspection conducted to the filled vials. This CAPA was closed on February 28, 2018.

Prometic indicated that the change in the FDP specification to reflect the reporting of (b) (4) AQL inspection results for particulate testing in the certificate of Analysis was implemented on April 2018.

- **Observation #1.f.iii.:** It is not clear what statistical approaches were used to establish each acceptance criteria. Justification of Specification in the BLA states that (b) (4) tolerance interval for (b) (4) confidence interval was used for all criteria, however during the interview Prometic staff indicated that it may not be true for all acceptance criteria. As specification setting process was not properly documented it was not clear what acceptance criteria used different approach.

  **Firm Responses:** Refer to firm responses to Observation #1.f.

- **Observation #1.f.iv.:** For several specification parameters, minimum and maximum results reported are outside or coincide with proposed specification ranges.

  **Firm Responses:** Refer to firm responses to Observations #1.f. and #1.f.i.

- **Observation #1.g.** BDS shipping validation is inadequate. (b) (4) shipping validation runs for BDS used obsolete protocols with the incorrect fill volume and (b) (4) . In addition, the shipping time range was not established.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observation #1.g. consisted in the implementation of CAPA-17-171 for the review and update of the shipping validation protocol SPV-005.01 and conduct (b) (4) additional shipping validation runs in (b) (4) on 2918. They indicated that the results from these shipping validation runs were reported in SPV-010.01-R, "*Shipping Validation Report for the Shipment of Plasminogen Bulk Drug Substance from PBP to* (b) (4) *under Controlled Temperature Conditions* (b) (4) The firm provided copy of SPV-010.01-R, which is discussed below. This CAPA was closed on April 25, 2019.

SPV-010.01-R was approved on April 24, 2019. This Report describes the results from (b) (4) shipping validation runs in support for the (b) (4) transportation of BDS from PBP to (b) (4) at temperature of (b) (4) They indicated that this (b) (4) transportation is conducted by an external carrier. These runs were conducted at the following dates to evaluate the seasonal changes and their impact on the temperature of the shipped BDS:

(b) (4)

(b) (4)

(b) (4)

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

(b) (4)

.

**Firm Responses:** Prometic explained that the corrective action implemented for the resolution of Observations #1.h.i., #1.h.ii., #1.h.iii and #1.h.iv. includes the implementation of SOP F-034, "*EMS Alarm Handling*" for the notification and handling of (b) (4) excursions and alarms in the manufacturing areas. They indicated that an incident report has to be issue according to SOP-QA-007, "*Quality Events Management and Action Items*," for the notification of these alarms and excursions. The firm stated that Change Controls CCR-17-076.01 and CCR-17-150 were initiated in support to establish the (b) (4) high limit and low limit settings in the manufacturing area. Prometic stated that CAPA-17-186 was implemented for the review and update SOP-0236 (SOP F-035), "*Course of Action for Maintenance, QC and Manufacturing During Power Outage."* This SOP included instructions for the action to be taken in the case of a power outage that affect the QC, Manufacturing and Maintenance areas; including the utilities, (b) (4) clean rooms and others. This CAPA was closed on February 27, 2018.

- **Observation #2:** Regarding quality assurance oversight of the quality system operation, the following was observed:
- **Observation #2.a.:** The SOP QA-007, "Incident Notification Deviation and Investigations" is deficient. Specifically;
- **Observation #2.a.i.:** The SOP states the procedure does not apply to planned deviations, but also states that planned deviations are deemed acceptable following change control procedure;
- **Observation #2.a.ii.:** The SOP does not provide clear requirements for situations where CAPA is required.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observations #2.a.i. and #2.a.ii. consisted in the implementation of the following CAPAs:

- CAPA-17-187 for the implementation of the Quality Management System (QMS), which is an electronic system for the handling of change control requests, deviations, CAPAs and incidents. They explained that the QMS replaces the paper-based system used for the handling of the above items. The firm stated that the paper-based system was migrated to QMS in October 2018. Prometic indicated that this CAPA was closed on March 22, 2019. They stated that this CAPA is applicable to Observations #2.b.i., #2.b.ii., #2.biii., #2.b.iv. and #2.b.v;
- CAPA-17-188 for the review and update SOP-QA-007, "*Quality Events Management and Action Items*," to include instructions that define the requirements for the initiation and handling of planned deviations and CAPAs. They stated that this CAPA was closed in October 25, 2018. The firm indicated that this CAPA is applicable to Observations #2.b.i., #2.b.ii., #2.biii., #2.b.iv. and #2.b.v.

- **Observation #2.b.:** Deviations, investigations and incidents are not managed appropriately. Specifically;

- **Observation #2.b.i.:** SOP-QA-007 requires incidents to be reported within (b) (4) hours. However, multiple incidents were not reported to the QA within allowed timeframe;
- **Observation #2.b.ii.:** There are 426 incidents reported in 2016 and 428 incidents reported by the time of FDA inspection in 2011, including several recurring incidents. For example, multiple recurring incidents were observed related to (b) (4) or (b) (4) (b) (4), (b) (4) ; as well as insect intrusions;
- **Observation #2.b.iii.:** Risk assessments for deviations is inadequate and absence of impact on product quality is often assumed without proper evaluation. For example, deviation DEV-16-111.01 was issued for the (b) (4) (b) (4) (exceeding the (b) (4) limit specified in the batch record) and the implemented CAPA was to increase the limit to (b) (4). The risk assessment did not adequately evaluate the (b) (4) impact on the (b) (4) integrity. Following this (b) (4), the (b) (4) (b) (4) in the following (b) (4) BDS shipments was observed at (b) (4).
- **Observation #2.b.iv.:** Corrective actions are not effective or documented. For example, incident report INR-17-06.01 was open on March 24, 2017 for the incomplete seal of the raw material (b) (4). Corrective action implemented include verification of the (b) (4) room (b) (4) and adjustment of the (b) (4) to a higher (b) (4) (no formal CAPA was open.) However, on May 17, 2017 another incident of incompletely (b) (4) occurred and was reported to QA on June 28, 2017. Also, starting from August 2016 there were 11 incidents of observation of insects inside the production area before investigation INV-16-028.01 was opened. Some of the CAPA resolution plans have been executed, but insect intrusions are still observed. The associated CAPA effectiveness is projected to eb evaluated in August 2018.
- **Observation #2.b.v.:** Incident/deviation reports are not always issued for unscheduled production repairs or maintenance. For example, no incident report was issued for multiple unscheduled repairs for (b) (4) during 2017. The repairs included (b) (4) replacements, (b) (4) replacement and (b) (4) repairs.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observations #2.b.i., #2.b.ii., #2.b.iii., #2.b.iv. and #2.b.v. consisted in the implementation of the following CAPAs:

- CAPA-17-187 for the implementation of the Quality Management System (QMS), which is an electronic system for the handling of change control requests, deviations, OOS, OOT, CAPAs and incidents. This CAPA is applicable to Observations #2.a.i. and #2.a.ii. This CAPA was discussed in the firm responses to the Observations #2.a.i and #2.a.ii;
- CAPA-17-188 for the review and update SOP-QA-007, "*Quality Events Management and Action Items*," to include instructions that define the requirements for the initiation and handling of planned deviations and CAPAs. This CAPA is applicable to Observations #2.a.i. and #2.a.ii. This CAPA was discussed in the firm responses to the Observations #2.a.i and #2.a.ii;

- CAPA-17-189 for the review and update of SOP-0227 (SOP F-026), "*Work Management*" to include an instruction to issue an incident report (INR) according to SOP-QA-007, to determine if the incident affects the product quality. This CAPA was closed on February 05, 2018.

Prometic stated that improvements were conducted in the management of quality event since October 2019. These improvements include the hiring of experienced personnel and training of personnel in the writing and approval of quality events. Other improvements include the implementation of a (b) (4) tracking for the quality events and present the status and trending of the quality events to the senior management as part of the Site Quality Council. They indicated that other improvements include meeting between QA and the respective departments for the handling of investigations and quality events, including backlogs.

- **Observation #2.c.:** OOS for in-process (b) (4) test results were not adequately managed per SOP QA-007.02, "Incident Notifications, Deviation and Investigations," effective December 15, 2016. For example, there were 26 deviations for in-process samples from (b) (4) plasma lots manufactured from May 2, 2017 through June 1, 2017 without any QA notifications and investigation being generated within the SOP requirement.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observation #2.c. consisted in the implementation of the CAP-17-192, for the implementation of SOP 0080 (SOP QC-052.01), "(b) (4) Monitoring for In-Process Control Steps" that describes the procedure for the monitoring of (b) (4) in-process control steps and results. They indicated that this SOP includes instructions for the reporting in-process results in (b) (4) and the tracking of OOS. This CAPA was closed on March 20, 2018.

- **Observation #2.d.:** The SOP QC-015.02, "Handling of Out of Specification Test Results" is inadequate, leading to deficient investigations of OOS results. Specifically;
- **Observation #2.d.i.:** In the Phase I laboratory investigation did not identify the root cause of OOS result, the procedure instructs the QC staff to perform Phase 2 investigation by retesting/resampling of samples without explicit requirement for QA approval. If OOS is not confirmed in this retesting, no investigation is performed by the Manufacturing Department. Several such investigations reviewed (for example INR-16-424.01 and INR-17-297.01) did not include documented investigations from the Manufacturing Department and root cause of the OOS was not identified. Incident INR-17-007.001 indicated that after (b) (4) , (b) (4) , but this was not brought to attention of other departments and corrective action was limited to better sample (b) (4)
- **Observation #2.d.ii.:** The SOP does not specify the procedure for identifying out of trend (OOT) results.
- **Observation #2.d.iii.:** The SOP allows to remove outliers results from analysis without specifying clear criteria for identifying results as an outlier.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observations #2.d.i., #2.d.ii. and #2.d.iii. consisted in the implementation of the following CAPAs:

- CAPA-17-190. This CAPA is also applicable to Observation #1.e. This CAPA was discussed in the firm response in support to the Observation #1.e.
- CAPA-17-160. This CAPA is applicable to Observations #1.a, #1.a.ii., #1.a.iii., #1.a.v. and #1.e. This CAPA was discussed in the corrective action in support for Observation #1.a.

o **Observation #3:** The cleaning validation of critical equipment is inadequate. Specifically;

o **Observation #3.a.:** The cleaning validation for (b) (4) performed in May 2015 failed. This (b) (4) continued to be used as a shared equipment for the manufacture of Plasminogen Drug Substance and (b) (4) until July 2016. The testing for (b) (4) carryover after each campaign was inadequate because the potentially (b) (4) (b) (4) cannot be detected by the (b) (4). Impurity release test assay.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observation #3.a. consisted in the implementation of the following CAPAs:

- CAPA-17-194 to specify that the (b) (4) as dedicated equipment for the Pg (b) (4) process. This CAPA was closed on January 03, 2018;
- CAPA-17-198 for the re-execution of the Cleaning Validation Study for the (b) (4) This CAPA is also applicable to the Observation #3.b. This CAPA was closed on March 14, 2019. The firm provided copy of the Summary Report CVP-032.02-R, "*Cleaning Validation Report for the* (b) (4) " and Summary Report CVP-005.05-R, "*Cleaning Validation Report for the* (b) (4) " in support of this CAPA. Summary Report CVP-005.05-R is discussed in the firm response in support to Observation #3.b. Summary Report CVP-032.02-R is discussed below.
    - CVP-032.02-R, "*Cleaning Validation Report for the* (b) (4) ," approved on March 11, 2019, describes the results from (b) (4) cleaning runs conducted to the (b) (4) ) in support for the (b) (4) step. They indicated that these runs consisted of (b) (4) and the determination of the CHT for this (b) (4). The firm stated that this Study was conducted at the following dates:

(b) (4)

(b) (4)

(b) (4)

Prometic explained that cleaning runs (b) (4) were conducted at the end of the (b) (4) step for the above batches and no (b) (4) step was conducted in support for the cleaning runs (b) (4). They indicated that CHT in support for the cleaning run (b) (4) was conducted before the (b) (4) according to investigation associated to Deviation 3. This deviation is discussed as part of the review of this Summary Report.

The firm explained that (b) (4) of the (b) (4) was conducted using the (b) (4) and according to M-048.A1.V1, (b) (4) *Work Instructions*." They indicated that this (b) (4) consists of the following steps and parameters:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The firm stated that most of the samples from the cleaning run (b) (4) complied with the above criteria. They explained that a (b) (4) sample from the (b) (4) did not comply with the (b) (4) criterion. Prometic indicated that Deviation 3 was initiated to address this issue.

The firm stated that (b) (4) was added to the (b) (4) prior to be store with the (b) (4) in a dry location according to M-048.A1.V1 and until the CHT determination.

Prometic indicated that the CHT consisted (b) (4) They indicated that no residues were observed. The firm provided the CHT times in support for cleaning runs (b) (4) as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The firm stated that five deviations were initiated in this Study. They explained that these deviations are associated to protocol generation errors, (b) (4) for (b) (4) samples were not prepared for cleaning run (b) (4), (b) (4) detected in the (b) (4) samples during the CHT for cleaning run (b) (4), correction in the calculation for the (b) (4) in the (b) (4) samples. Prometic indicated that these deviations were resolved and closed.

- **Observation #3.b.:** The clean hold time assigned to the (b) (4) (b) (4) was not supported by sufficient data. Specifically, the assigned clear hold time of (b) (4) was established based on a single validation run.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observation #3.b. consisted in the implementation of the following CAPAs:

- CAPA-17-193 for the review of SOP VAL-021 (SOP-0268) to include the CHT verification and the use of validated analytical method. This CAPA was closed on January 12, 2018. This CAPA is applicable to Observations #3.c.i and #3.c.ii.
- CAPA-17-198 for the re-execution of the Cleaning Validation Study for the (b) (4) ). This CAPA is also applicable to the Observation #3.a. This CAPA was closed on March 14, 2019. Prometic provided copy of the Summary Report CVP-032.02-R, "*Cleaning Validation Report for the* (b) (4) ," and Summary Report CVP-005.05-R, "*Cleaning Validation Report for the* (b) (4) " in support of

this CAPA. Summary Report CVP-032.02-R was discussed in the firm response in support to Observation #3.a. Summary Report CVP-005.05-R, is discussed below.

- CVP-005.05-R, "*Cleaning Validation Report for the* (b) (4) approved on June 16, 2020 that describes the results from (b) (4) runs conducted to the (b) (4) in support for the (b) (4) of Human Blood Plasma (HBP). They stated that this Study was conducted according to WIN-0127.V06, "*Cleaning Instructions for the* (b) (4) " The firm indicated that these runs consisted of (b) (4) and the determination of the DHT and CHT for this system. Prometic stated that this Study was conducted from March to April 2020 during the (b) (4) of the following batches of HBP:

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

(b) (4)

The firm indicated that the DHT of the (b) (4) was determined since the time that finish the HBP (b) (4) until the beginning of the (b) (4) . They stated that the DHT has to comply with a criterion of (b) (4) . Prometic provided the results from the DHT conducted to this system as follows:

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

(b) (4)

Prometic that the DHT complies with the criterion of (b) (4) .

Prometic stated that the (b) (4) was cleaned using a (b) (4) according to the following steps and parameters:

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

(b) (4)

(b) (4)

(b) (4)

The firm explained that (b) (4) was conducted at the end of the (b) (4) for to verify that there are no residues of corrosion, cleaning agent and product. They stated that (b) (4) testing was conducted to the (b) (4) samples collected from the (b) (4) Prometic indicated that (b) (4) from pre-determined locations in the interior of the the (b) (4) were tested for (b) (4). They indicated that (b) (4) from the cleaning runs (b) (4) complied with the following criteria:

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

(b) (4)

(b) (4)

Prometic explained that the (b) (4) is disassemble, then tubing and small parts are cleaned with (b) (4). They stated this system is (b) (4) (b) (4) prior to store in a dry location and start the CHT. The firm indicated that the CHT consisted in the (b) (4) sampling from predetermined locations in the (b) (4) to be tested for (b) (4) They explained that the (b) (4) from the cleaning runs (b) (4) complied with a (b) (4) criterion of (b) (4) for (b) (4). Also, (b) (4) was conducted in the interior of the (b) (4). They indicated that no corrosion and residues were observed. The firm provided the CHT times in support for cleaning runs (b) (4) as follows:

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

(b) (4)

Prometic stated that the CHT of (b) (4) with (b) (4) and (b) (4) was determined as the maximum CHT for the (b) (4), since it is the minimum CHT determined in this Study.

The firm indicated that Deviation 1 was initiated in this Study, due a protocol generation error in the instruction of when the samples are collected at the end of the (b) (4) and the CHT. They stated that this deviation was resolved and closed.

- CAPA-17-199 for the determination of clean hold time for the (b) (4) This CAPA was closed on March 06, 2019. Prometic provided copy of the Summary Report CVP-005.05-R in support for the Cleaning Validation Study of the (b) (4) and the determination of the CHT associated to this CAPA, which is discussed as part of CAPA-17-198.

- **Observation #3.c.:** The analytical method used for (b) (4) cleaning validation were not qualified for their intended use. Specifically;

- **Observation #3.c.i.:** The (b) (4) method SOP AM-010.04 has not been validated for recovery of (b) (4) from the (b) (4) after cleaning with (b) (4) solution.

- **Observation #3.c.ii.:** The (b) (4) method (b) (4) assay) SOP AM-002.05 has not been validated for recovery of (b) (4) from the (b) (4) after cleaning with (b) (4) solution.

  - ***Note:*** *Firm responses in support of the corrective action for resolution and closure for the Observations #3.c.i. and #3.c.ii. and received under amendment STN BL125659/0.19 on October 26, 2020 are the same firm responses received under amendment STN BL125659/0.18 on September 04, 2020 in support for CRL Item #5 and DMPQ Memo CR Item #1. These responses were discussed in the firm responses in support for CRL Item #5 and DMPQ Memo CR Item #1.*

- **Observation #4:** Disinfectants used to clean the cleanrooms have not been appropriately qualified. Specifically;

- **Observation #4.a.:** The Detergent and Disinfectant Validation (CVP-018.01-R) performed to validate the effectiveness of (b) (4), used to disinfect the cleanroom during the PPQ batch manufacture, was inadequate. Specifically;

- **Observation #4.a.i.:** The validation study did not establish criteria for (b) (4) reduction for bacteria and mold.

- **Observation #4.a.ii.:** The validation study did not evaluate disinfectant effectiveness agains (b) (4) microorganisms and house flora.
- **Observation #4.a.iii.:** The validation study did not consider the cleanroom surfaces, such as (b) (4) .

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observations #4.a.i., #4.a.ii. and #4.a.iii. consisted in the implementation of the following CAPAs:

- CAPA-17-200 to conduct the neutralizing efficacy study for (b) (4) in required surfaces of the manufacturing areas in QAR-017.02, "*Surface Sampling Method Recovery, Neutralization Efficacy and Facility Disinfection Efficacy Challenge Tests*". This CAPA was closed on August 15, 2018;
- CAPA-17-201 and CAPA-202 to include the method recovery qualification for (b) (4) ; in addition, to the disinfectant effectiveness studies on (b) (4) in QAR-017.03, "*Surface Sampling Method Recovery, Neutralization Efficacy and Facility Disinfection Efficacy Challenge Tests*". Both CAPAs were closed on February 04, 2019;
- CAPA-17-203 to re-evaluate the data from the initial Cleaning Validation Study for the (b) (4) cleaning frequencies according to CVP-039.01-R, CVP-038.01-R and CVP-037.01-R, in support for the neutralization, recovery and disinfectant studies for (b) (4) . They indicated that this CAPA supposed to the completed and closed on March 2018. The firm indicated that the closure date of this CAPA was extended several times until October 31, 2022 due the following reasons:

**Table 78: CAPA -17-203 Tentative Closure Dates and Reasons**

| CAPA Tentative Closure Date | Reason |
|---|---|
| June 30, 2018 | Change in the (b) (4) cleaning frequencies and removal of (b) (4) cleaning frequency |
| December 23, 2019 | Cleaning Validation Study (CVP-0061.01) conducted in support for a change in the (b) (4) cleaning frequency, determination of Clean Hold Time (CHT) and the effectiveness of the (b) (4) disinfectant in support for CAPA-19-104. Also, this study was conducted to confirm the (b) (4) disinfectant wet contact time in support for CAPA-19-106 |
| August 31, 2020 | Cleaning Validation Study (CVP-0070.01) conducted for the changes in the (b) (4) cleaning to implement the use of (b) (4) as sporicidal agent after (b) (4) step in Rooms (b) (4) (dedicated for (b) (4) step). Cleaning Validation Study (CVP-063.01) conducted for the implementation of cleaning procedure after mechanical shutdown in support of CAPA-19-109 |
| October 31, 2022 | Cleaning Validation Study is conducted to evaluate the efficacy of the cleaning frequencies ((b) (4) and after mechanical shutdown) in the manufacturing area, after the change in the material of floor surfaces from (b) (4) , named as (b) (4) floor 2020 on June 2020 |

The firm indicated that the following studies were conducted in support for CAPA CAPA-17-203 to evaluate the effectiveness of the (b) (4) in the (b) (4) and (b) (4) cleaning of the manufacturing areas:

- CVP-050.01-R, "(b) (4) *Cleaning of the GMP Manufacturing Areas*;"
- CVP-059.01-R, "*Cleaning Validation Final Report for the* (b) (4) *Cleaning of the GMP Manufacturing Areas*;"
- CVP-061.01-R, (b) (4) *Cleaning of the GMP Manufacturing Area and CHT Determination Under* (b) (4) *Conditions*;"
- CVP-070.01- R, "(b) (4) *Cleaning of the* (b) (4) *Area of the GMP Manufacturing Areas*;"
- CVOP-063.01-INT01, "*Cleaning Validation Interim Report: Cleaning After Mechanical Shutdown of the GMP Manufacturing Areas."*

Prometic provided copies of QAR-017.03 and the summary reports from the above Cleaning Validation Studies in support for the resolution of Observations #4.a.i., #4.a.ii. and #4.a.iii. These summary reports are discussed below.

- QAR-017.03, "*Surface Sampling Method Recovery, Neutralization Efficacy and Facility Disinfection Efficacy Challenge Tests,*" approved on September 28, 2020. The firm explained that this report describes the results and acceptance criteria in support of the disinfectant effectiveness studies for (b) (4) as sporicidal agent; in addition, to (b) (4) as disinfectant agents. They explained that this Study was conducted using (b) (4) representative from surfaces of manufacturing areas and equipment. Prometic stated that these (b) (4) were (b) (4) The firm indicated that the following (b) (4) organisms and environmental isolates were used in this study:

**Table 79: Organisms Used for Disinfectant Effectiveness Study**

(b) (4)

Prometic stated that this study was conducted in two external laboratories. They indicated that this study was conducted in two phases as follows:

- Phase 1 - Sampling method qualification to demonstrate the efficacy of (b) (4) as sampling materials to neutralize the residues from the disinfectants and to verify the recovery performance of the selected microorganism exposed in the (b) (4) . The firm indicated that Phase 1 was conducted using method recovery and neutralizer efficacy testing as follow:

**Table 80: Sampling Method Testing Description**

| | |
|---|---|
| **Method Recovery** (b) (4) **Materials** | (b) (4) |
| **Description of Study** | |
| **Acceptance Criteria** | |

No disinfectant was used in the method recovery testing.

**Table 81: Neutralizer Efficacy Testing Description**

| | |
|---|---|
| **Neutralizer Efficacy** (b) (4) **Materials** | (b) (4) |
| **Disinfectant Used** | |
| **Description of Study** | |
| **Acceptance Criteria** | |

Prometic provided the results from the method recovery and neutralizer efficacy testing. They indicated that these testing with the following criteria:

**Table 82: Method Recovery and Neutralizer Efficacy Testing Criteria**

| Testing | Sampling Method | Acceptance Criteria |
|---|---|---|
| Method Recovery | (b) (4) | |
| Method Recovery – (b) (4) Part 1 | | |

| Testing | Sampling Method | Acceptance Criteria |
|---|---|---|
| Method Recovery– (b) (4) Part 2 | (b) (4) | |
| Neutralizer Efficacy | | |

The firm provided the results from the neutralizer efficacy testing in (b) (4) and using (b) (4) as follows:

**Table 83: Neutralizer Efficacy Testing in (b) (4)**

(b) (4)

Prometic stated that the Neutralizer efficacy testing in (b) (4) and using (b) (4) was repeated to (b) (4) They stated that the above testing complied with the criterion of (b) (4) of recovery.

- Phase 2 - Disinfectant efficacy testing on (b) (4) representative from surfaces of manufacturing areas and equipment (b) (4) of the challenge microorganism. Then the disinfectant was applied for defined contact time and the the surfaces were (b) (4) . The content of the (b) (4) was (b) (4)

and (b) (4) and then at (b) (4) for (b) (4). At the end of the (b) (4) period the microbial population in the (b) (4) are counted. The acceptance criteria are (b) (4) for spores and molds and (b) (4) for vegetative bacteria.

Prometic provided a summary of the results from the disinfectant efficacy testing as follows:

**Table 84: Disinfectant Efficacy Testing Results**

(b) (4)

Prometic explained that (b) (4) are not effective against yeast (b) (4) at a contact time of (b) (4). They claimed that this contact time is considered acceptable since yeast is not prevalent in the environment.

The firm indicated that the validated contact times for (b) (4) are the following:

**Table 85: Validated Contact Times for (b) (4)**

(b) (4)

- CVP-050.01-R, "CVP Interim Report for the (b) (4) Cleaning of the GMP Manufacturing Areas," approved on April 25, 2019. This interim report describes the

results from the (b) (4) cleaning conducted according to M-006.A8.V1, (b) (4) *Cleaning Work Instructions*," using (b) (4) in the following manufacturing areas:

**Table 86: (b) (4) Cleaning Using (b) (4)**

| Room Number | Room Classification |
|---|---|
| (b) (4) | |

This report also describes the implementation of the (b) (4) for the (b) (4) cleaning in the floors of Gowning (Room (b) (4)), Clean Corridor (Room (b) (4)), Material Airlock (Room (b) (4)) and (b) (4) Area (Room (b) (4)), which are considered as areas of high traffic of personnel.

Prometic indicated that (b) (4) cleaning runs were conducted between April and June 2018. They explained that (b) (4) and (b) (4) samples were collected from the manufacturing areas prior and post cleaning to detect microbial contamination. The firm stated that the sampling pre-cleaning was conducted in (b) (4) conditions and the sampling post-cleaning was conducted in (b) (4) conditions.

The firm explained that the floors are (b) (4) then they are (b) (4) prior to be (b) (4) . They stated that there is no contact time for the application of (b) (4) Prometic stated that (b) (4) were applied to the surfaces of the manufacturing areas and equipment at the contact times as determined in QAR-017.03.

The firm indicated that visual inspection was conducted after cleaning to verify that residues of the disinfectant was not visible at the end of the contact time.

Prometic stated that the Clean Hold Time (CHT) of the manufacturing rooms is not under the scope of this Study.

The firm stated that the acceptance criteria of this Study are the following:

**Table 87: Viable Particulate Count Criteria in Support for the (b) (4) Cleaning Using (b) (4)**

| Room Classification | (b) (4) Conditions | (b) (4) Conditions |
|---|---|---|
| (b) (4) | | |

The firm indicated that all manufacturing areas complied with the visual inspection criterion of no visible residue of the disinfectant. They explained that most of the manufacturing areas complied with the above sampling criteria in (b) (4)

conditions and all the manufacturing areas complied with the above sampling criteria in (b) (4) conditions. Prometic stated that Zone (b) (4) did not complied with the sampling criteria in (b) (4) conditions, since a microbial excursion was detected in the sample collected from the phone handle prior to be cleaned on Run (b) (4) They considered this situation as an isolated one and Deviation 3 was initiated to address this issue. The firm explained that the sampling in (b) (4) conditions in Zones (b) (4) was conducted prior to complete the disinfectant contact time. Prometic stated that Deviation 2 was initiated to address this issue and they decided to conduct an additional (b) (4) cleaning run in Zones (b) (4) in July 2018. The firm indicated that Zones (b) (4) complied with the above sampling criteria in (b) (4) conditions.

Prometic indicated that 14 deviations were initiated in this Study. They explained that these deviations are associated to missing samples collected, samples collected prior to complete the disinfectant contact time, microbial excursion, protocol generation errors, change in the number of the "(b) (4) *Cleaning Work Instructions*" and personnel not trained prior to initiated this Study. They indicated that these deviations were resolved and closed.

- CVP-059.01-R, "*Cleaning Validation Final Report for the* (b) (4) *Cleaning of the GMP Manufacturing Areas*," approved on December 20, 2019. This summary report describes the results from the (b) (4) cleaning according to CVP-059.01, "*Cleaning Instructions for the* (b) (4) *Cleaning for GMP Manufacturing Areas*," using (b) (4) in the same manufacturing areas as listed in CVP-050.01-R.

  Prometic clarified that cleaning runs (b) (4) were reported in the Interim Report CVP-059.01-INT01. They explained that the results from these runs were inconclusive since the duration of the (b) (4) cleaning was interrupted by unplanned maintenance work in the manufacturing area. They decided to conduct (b) (4) additional cleaning runs in support for the CVP-059.01.

  The firm indicated that (b) (4) cleaning runs (b) (4) were conducted in June, October and November 2019, which are from 40 days to 48 days between each (b) (4) cleaning. They explained that this study was conducted in the same rooms, following the same procedure and acceptance criteria as stated in CVP-050.01-R.

  Prometic explained that the floors are (b) (4) then they are (b) (4) to be (b) (4) . They stated that (b) (4) was applied to the surfaces of the manufacturing areas and equipment at the contact times as determined in QAR-017.03.

  Prometic provided the results from this Study in the summary report. The firm indicated that all samples collected in Run (b) (4) (b) (4) cleaning; in addition to, most of the samples collected (b) (4) cleaning and all samples collected (b) (4) cleaning and in Runs (b) (4) with the acceptance criteria stated in CVP-050.01-R. The indicated that microbial excursions were detected in the following rooms (b) (4) to be clean in Runs (b) (4)

**Table 88: Microbial Excursions in Runs** (b) (4)

| Run # | Room No. | Microbial Excursion |
|---|---|---|
| (b) (4) | | |

The firm indicated that Deviation 7 was initiated to address the above microbial excursions. They stated that (b) (4) is the organism identified in the (b) (4) Room and Airlocks (b) (4). These airlocks are adjacent to the (b) (4) Room. Prometic stated that the root cause for the microbial excursion in the above rooms is the high traffic of manufacturing personnel. They explained that the corrective action implemented for the resolution of this Deviation is to conduct the cleaning of the manufacturing areas between (b) (4) to avoid microbial excursions. They stated that no additional cleaning run was conducted in these rooms.

Prometic stated that all manufacturing areas complied with the visual inspection criterion of no visible residue of the disinfectant at the end of the contact time.

The firm stated that seven deviations were initiated in this Study. They explained that these deviations were associated to the HVAC system was turned off during Christmas vacation, leakage in the roof of several manufacturing rooms, change in the number for the cleaning SOP, protocol generation error, personnel not trained prior to initiated this Study, microbial excursions in gowning, airlocks, (b) (4) preparation and (b) (4) rooms. Prometic stated that these deviations were resolved and closed.

- CVP-061.01-R, (b) (4) *Cleaning of the GMP Manufacturing Area and CHT Determination Under* (b) (4) *Conditions,"* approved on June 19, 2020. This summary report describes the results from the (b) (4) cleaning conducted according to M-006.A8.V2, (b) (4) *Cleaning Work Instructions,*" using (b) (4) in the following manufacturing rooms:

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

(b) (4)

This report also provides the results from the Clean Hold Time (CHT) of (b) (4) conducted in support for the (b) (4) cleaning. Prometic stated that the Dirty Hold Time (DHT) of the manufacturing rooms is not under the scope of this Study.

The firm indicated that (b) (4) runs were conducted between June 2019 to February 2020 following the same procedure as stated in CVP-050.01-R.

Prometic explained that the floors are (b) (4) with (b) (4) then they are (b) (4) to be (b) (4). They indicated that (b) (4) were applied to the surfaces of the manufacturing areas and equipment at the contact times as determined in QAR-017.03.

The firm stated that additional sampling was conducted after a CHT of (b) (4) under (b) (4) conditions. They indicated that the acceptance criteria for the sampling conducted (b) (4) cleaning; in addition, at the end of the CHT are the following:

**Table 90: Viable Particulate Count Criteria in Support for the (b) (4) Cleaning Using (b) (4)**

| Room Classification | (b) (4) Conditions | (b) (4) Conditions |
|---|---|---|
| (b) (4) | | |

Prometic stated that visual inspection was conducted after cleaning to verify that residues of the disinfectant was not visible at the end of the contact time.

The firm indicated that the following activities were conducted in the manufacturing rooms at the time that this Study was conducted:

**Table 91: Batches Manufactured in Support for the (b) (4) Cleaning Study Using (b) (4)**

| (b) (4) |
|---|

Prometic indicated that the sampling results from the (b) (4) cleaning the rooms used for the manufacture of the above lots are considered valid in support for

this Study. These results were documented as “Pass” or “Fail” if they comply or not with the acceptance criteria as discussed earlier in this Study. Also, these rooms were sampled at the end of the CHT.

The sampling results from the CHT were also were documented as “Pass” or “Fail.”

The firm stated the results from the (b) (4) and (b) (4) sampling prior and after cleaning as follows:

**Table 92: Viable Particulate Count Results in Support for the (b) (4) Cleaning Study Using (b) (4)**

(b) (4)

Prometic explained that Deviation 2 was initiated to consider “Invalid/Pass” the sampling results from the (b) (4) cleaning in the following rooms where no manufacturing activity was conducted and were not “soiled”:

**Table 93: “Not Soiled” Rooms**

(b) (4)

The firm indicated that no (b) (4) and (b) (4) sampling were conducted in Zone (b) ( (Room (b) (4)), Clean Corridor (Room (b) (4)), (b) (4) (Room (b) (4)) and Gowning (Room (b) (4)) during Run (b) (4)

Prometic stated that all manufacturing areas complied with the visual inspection criterion of no visible residue of the disinfectant at the end of the contact time.

The firm explained that CHT was conducted to the rooms, in which sampling was conducted (b) (4) cleaning in Runs (b) (4) They indicated that the duration of the CHT from Runs (b) (4) are the following:

**Table 94: CHT in Support of Runs (b) (4)**

(b) (4)

(b) (4)

Prometic stated that the CHT complied with the criterion of CHT of (b) (4). They indicated that most of the runs conducted in the above rooms complied with the "Pass" criterion for the sampling except (b) (4) (Room (b) (4)) in Run (b) (4).

Prometic explained that microbial excursions detected in the (b) (4) samples from the floor of the (b) (4) Room during Runs (b) (4) in addition, to the CHT Run (b) (4). They indicated that these samples exceed the criterion of (b) (4) for (b) (4) in Class ISO (b) (4) (Grade (b) (4) in (b) (4) conditions. The firm stated that Deviation 3 was initiated to address this issue. They stated that the root cause is the high traffic of personnel in this room. The firm indicated that (b) (4) was the organism identified in these excursions. They explained that the corrective action taken was the use of (b) (4) in the (b) (4) cleaning of the floors for this room. Prometic stated that cleaning validation CVP-070.01 will be conducted in support for the implementation of the above corrective action.

The firm indicated that all the rooms complied with the visual inspection criterion of no visible residue of disinfectant agent at the end of the contact time.

Prometic stated that five deviations were initiated in this Study. They explained that these deviations were associated to the addition of the Gowning (Room (b) (4)) in this Study, use of wrong sponges for cleaning, disinfectant contact time not documented, microbial excursions in the (b) (4) Room and to to consider "Invalid/Pass" the sampling results from the (b) (4) cleaning in the following rooms where no manufacturing activity was conducted and were not "soiled." The firm indicated that these deviations were resolved and closed.

- CVP-070.01- R, (b) (4) *Cleaning of the* (b) (4) *Area of the GMP Manufacturing Areas*," approved on June 29, 2020. This Summary Report describes the results from the (b) (4) cleaning of the (b) (4) (Room (b) (4)) and Airlocks (Rooms (b) (4)) using (b) (4) according to Protocol CVP-070.01-P. Prometic stated that Airlocks (Rooms (b) (4) and (b) (4) are adjacent to the (b) (4) Area. They indicated that the following cleaning runs were conducted in this Study:
  - (b) (4) cleaning run conducted when the room and airlocks were not used for (b) (4) process and (b) (4) CHT run of (b) (4) to be consider as a confirmation run;
  - (b) (4) cleaning runs conducted prior and after (b) (4) process and (b) (4) CHT runs of (b) (4).

The firm stated that these runs were conducted from February to May 2020. They explained that (b) (4) were collected (b) (4) cleaning, following the same procedure as stated in CVP-050.01-R.

Prometic explained that the floors are (b) (4) with (b) (4) then they are (b) (4) with (b) (4) to be (b) (4) (cleaning runs (b) (4) (b) (4) process) or (b) (4) (cleaning run when the room and airlocks were not used for (b) (4) process). They indicated that (b) (4) were applied to the surfaces of the manufacturing areas and equipment at the contact times as determined in QAR-017.03.

The firm indicated that additional sampling was conducted after a CHT of (b) (4) under (b) (4) conditions.

Prometic stated that visual inspection after cleaning to verify that there is no residue of disinfectant agent at the end of the contact time.

The firm stated that the runs conducted in this Study complied with the following criteria:

**Table 95: (b) (4) Cleaning of the (b) (4) Area with Viable Particulate Count Criteria**

| Rooms | Room Classification | (b) (4) Conditions | (b) (4) Conditions |
|---|---|---|---|
| (b) (4) | | | |

Prometic stated that the (b) (4) (Room (b) (4)) and Airlocks (Rooms (b) (4)) complied with the visual inspection criterion of no residue of disinfectant agent at the end of the contact time. They indicated that the CHT of the (b) (4) (Room (b) (4)) and Airlocks (Rooms (b) (4)) were the following:

**Table 96: CHT in the (b) (4) Area with No Manufacturing Activities (b) (4) Conditions)**

| Room | Run (b) (4) |
|---|---|
| (b) (4) | |

**Table 97: CHT in the (b) (4) Area with Manufacturing Activities (b) (4) Conditions)**

| (b) (4) |
|---|

The firm indicated that the CHT complied with the criterion of CHT of (b) (4).

Prometic stated that no deviation was initiated in this Study.

- CVOP-063.01-INT01, "*Cleaning Validation Interim Report: Cleaning After Mechanical Shutdown of the GMP Manufacturing Areas,"* approved on December 20, 2019. This Interim Report describes the results of (b) (4) cleaning run conducted in the manufacturing area using (b) (4) according to CVP-063.01-P. Prometic explained that this Study was conducted (b) (4) the completion of the mechanical shutdown in the manufacturing areas on the summer of 2019. They indicated that (b) (4) were collected (b) (4) cleaning in the same rooms and following the same procedure as stated in CVP-050.01-R.

  Prometic explained that the floors are (b) (4) with (b) (4) then they are (b) (4) with (b) (4) to be (b) (4) with (b) (4) . They indicated that (b) (4) were applied to the surfaces of the manufacturing areas and equipment at the contact times as determined in QAR-017.03.

  The firm stated that visual inspection after cleaning to verify that there is no residue of disinfectant agent at the end of the contact time.

  Prometic stated that the run conducted in this Study complied with the following criteria:

**Table 98: Viable Particulate Count Criteria in Support of the (b) (4) Cleaning in the (b) (4) Area**

| Room Classification | (b) (4) Conditions | (b) (4) Conditions |
|---|---|---|
| (b) (4) | | |

  The firm indicated that the manufacturing area complied with the visual inspection criterion of no residue of disinfectant agent at the end of the contact time.

  Prometic stated that no deviation was initiated in this Study.

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

**Firm Responses:** Prometic indicated that (b) (4) used as disinfectant agents for the cleaning of the cleanrooms during the initial PPQ batch manufacture are no longer in use. They explained that (b) (4) are the current disinfectant agents used for the cleaning of the cleanrooms. Disinfectant effectiveness studies were conducted to (b) (4) as part of the response to the Observations #4.a.i, #4.a.ii and #4.a.iii.

- **Observation #4.c.:** (b) (4) used to clean the cleanrooms has not been validated.

**Firm Responses:** Prometic clarified that disinfectant effectiveness study was not conducted to the (b) (4) They claimed that the (b) (4) is not considered as disinfectant agent. The firm explained that the (b) (4) is used to wipe the equipment and surfaces to eliminate any spot left upon the drying of the disinfectant.

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

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #5.a. consisted in the implementation of the following CAPAs:

- CAPA-17-204 and CAPA-17-205 for the review and update the Batch Production Records BPR100 and BPR101 in support the manufacture of Pg Intermediate and BDS. These Batch Production Records were reviewed to include a description of each manufacturing with instruction of each step to be conducted and referring to the respective SOPs and forms. The firm provided copies from these Batch Production Records in support for the response of this observation. These CAPAs were closed on October 26, 2018. These CAPAs are applicable to Observation #10.a.
- CAPA-17-209 to ensure that SOPs are available in the manufacturing area and the verification of the instruction stated in the SOPs used for manufacturing process is clear, accurate and detailed. This CAPA was closed on March 28, 2018. This CAPA is also applicable to Observation #5.c.

Prometic stated that the manufacturing and QA personnel were trained in the updated Batch Production Records and the actions implemented for the resolution of CAPA-17-209.

- **Observation #5.b.:** Batch record has no instructions on how (b) (4) should be attached to the (b) (4). Inconsistency was observed in using (b) (4) in production Zone (b) (4).

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #5.b. consisted in the implementation of the following CAPAs:

- CAPA-17-204 and CAPA-17-205 for the review and update the Batch Production Records in support the manufacture of Pg Intermediate and BDS to describe the instructions for the handling of (b) (4) attached to the Zone (b) (4). These CAPAs are also implemented for the corrective action for the closure and resolution of Observation #5.a;
- CAPA-17-206 was implemented to include instruction for the handling of (b) (4) (b) (4) in SOP M-020 (SOP-0168), "(b) (4) *Management in Production.*" They explained that SOP-0194 and Work Instruction WIN-0162, "*Sterile Connection Setup*" were reviewed and updated as part of CAPA-17-206 to include a description of the (b) (4) to be conducted during the Pg Intermediate and Pg Drug Substance manufacturing steps.

The firm indicated that the manufacturing personnel were trained in the above SOPs and the above CAPAs were closed on February 2018.

- **Observation #5.c.:** Per SOP QC-02003, (b) (4) and Water for Injection," a (b) (4) of (b) (4) is needed for point of use in production areas. However, this requirement is not specific in the (b) (4) preparation batch records.

**Firm Responses:** Prometic stated that the corrective action implemented for the resolution of Observation #5.c. consisted in the implementation of the following CAPAs:

- CAPA-17-207 to include an instruction for the (b) (4) in the WFI points of use in the (b) (4) Preparation Batch Records. Also, this CAPA includes an instruction for (b) (4) in the WFI points of use on SOP M-014 (SOP-163), "*Use and Maintenance of* (b) (4) *and WFI Point of Use in Manufacturing Area."* This CAPA was closed on February 28, 2018;
- CAPA-17-208 to include an instruction for writing clear and detailed batch records in SOP M-034 (SOP-0178), "*Master Batch Production Record – Creation and Control*." This CAPA was closed on March 09, 2018;
- CAPA-17-209 to ensure that SOPs are available in the manufacturing area and the verification of the instruction stated in the SOPs used for manufacturing process is clear, accurate and detailed. This CAPA is also applicable to Observation #5.a. This CAPA was closed on March 28, 2018.

- **Observation #6:** The (b) (4) ) and (b) (4) have not been adequately qualified because no performance qualification was performed on either (b) (4) to demonstrate adequate and consistent performance (e.g., (b) (4) (b) (4) , batch size capacity, etc.) under conditions to simulate those used during actual manufacturing.

**Firm Responses:** Prometic indicated that the corrective action implemented for the resolution of Observation #6 includes the implementation of the following CAPAs:

- CAPA-17-210 and CAPA-17-211 for the Performance Qualification (PQ) studies of the (b) (4) and (b) (4) They provided copies from the summary reports associated to these PQ studies in support for the response to this Observation. These summary reports are discussed below.
  - PQ-1010.01-R, "*PQ Report of* (b) (4) approved on October 11, 2018. This PQ reports describes the results from the (b) (4) verification during (b) (4) performance verification and (b) (4) verification during cleaning process conducted to (b) (4) batches of (b) (4) in the (b) (4) under routine manufacturing conditions as follows:

(b) (4)

(b) (4)

The firm indicated that the above testing complied with the following criteria:

(b) (4)

(b) (4)

(b) (4)

The firm indicated that no deviation was initiated in this PQ Study.

- PQ-261.01-R, "*PQ Report of* (b) (4) , (b) (4) " approved on December 11, 2018. This PQ reports describes the results from the (b) (4) performance during (b) (4) (b) (4) process, including the (b) (4) and nanofilter (b) (4) tests; (b) (4) performance during nanofiltration test and cleaning process conducted to (b) (4) batches of Pg BDS in the (b) (4) during nanofiltration step and under routine manufacturing conditions as follows:

**Table 101: BDS Batches Processed in the** (b) (4)

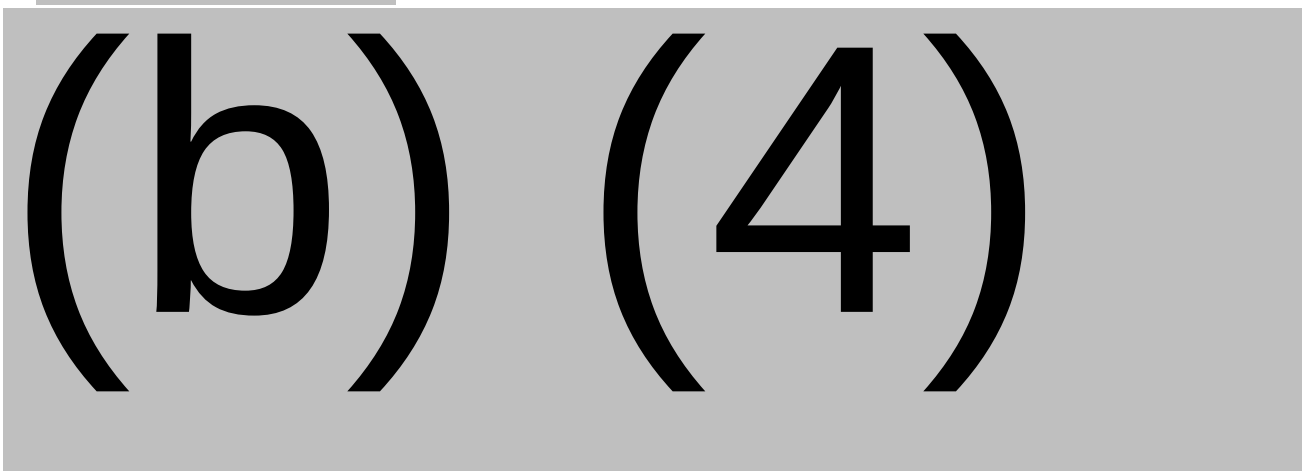
| Run No. | BDS Batch No. | Date |
|---|---|---|
| (b) (4) | | |

Prometic explained that the (b) (4) performance during (b) (4) process was conducted in (b) (4) parts, in which (b) (4)

(b) (4)

Prometic stated that the above testing complied with the following criteria:

(b) (4)




Prometic stated that no deviation was initiated in this PQ Study.

The firm indicated that CAPA-17-210 was closed on November 30, 2018 and CAPA-17-211 was closed on December 14, 2018.

- CAPA-17-212 for the review and update SOP VAL-017 (SOP-264), "*Requirements, Determination for Equipment Systems and Facilities*" to include an instruction that PQ studies are required for the equipment that have direct impact on the product

Critical Quality Attributes (CQAs.) The manufacturing and validation personnel were trained in this SOP and this CAPA was closed on February 12, 2018.

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

**Firm Responses:** Prometic explained that the action taken for the correction and resolution of Observation #7 includes the initiation of CAPA-17-213 to review SOP-241(SOP-MM-005), "*Warehouse Management*" to implement additional controls to ensure proper material management and inventory as follows:

- Implementation of instruction on the gathering and returns of materials with the use of (b) (4) to allow real time inventory status;
- Implementation of instructions to conduct physical inventory when the material is collected;
- Update and review the documentation to be used material inventory verification to identify in advance the further expiration date of the material and to notify QC department for the retesting of material as needed;
- Addition of a quarantine section to segregate material with expired retesting date and require to be retested;

The firm stated that manufacturing and material management personnel was trained in the updated and reviewed SOP-241(SOP-MM-005) and CAPA-17-213 was closed on March 22, 2019.

- **Observation #8:** The preventive maintenance plan is inadequate in that Quality Assurance does not always provide oversight and/or there is no responsible person assigned to perform a specific task. Specifically,
- **Observation #8.a.:** The 2016 (b) (4) preventive maintenance plan for the WFI system was not executed. There was no QA evaluation of the missing preventive maintenance.

**Firm Responses:** Prometic clarified that the preventive maintenance and calibration tasks for the WFI system in 2016 were done and documented. They indicated that the 2016 (b) (4) preventive maintenance plan for the WFI system was not outlined in the SOP F-026, "*Work Order Management*" in support for the preventive maintenance and calibration, when occurred the PLI in Prometic Bioproduction Inc. at Laval, Quebec on November 2017.

The firm explained that the corrective action implemented for the resolution of Observation #8.a. includes the implementation of CAPA 17-214 to outline the maintenance plan for all utilities and equipment in Prometic Bioproduction Inc. in SOP F-026 and the QA review and approval of the maintenance plans and calibrations. Prometic indicated that maintenance personnel were trained in the updated SOP-F-026 and CAPA-17-214 was closed on February 05, 2018.

- **Observation #8.b.:** There is no preventive maintenance plan for the (b) (4) (b) (4) No deviation was initiated, and no product impact was evaluated by the Quality Unit.

**Firm Responses:** Prometic indicated that the (b) (4) have an inactive status in (b) (4). They stated that these (b) (4) were stored in an off-site storage facility. The firm explained that the (b) (4) has an active status in (b) (4) and its (b) (4) was replaced on February 2019 according to the maintenance event 4Y-PM-TK09.

- **Observation #8.c.:** Preventive maintenance plans for (b) (4) do not include all components of the equipment (e.g., (b) (4).)

**Firm Responses:** Prometic indicated that the following documents describe the verification and replacement of (b) (4) for the (b) (4):

**Table 103: Documentation in Support for the Verification and Replacement of (b) (4) in the (b) (4)**

| Equipment | Document |
|---|---|
| (b) (4) | |

The firm explained that the corrective action implemented for the resolution of Observation #8.c. includes the implementation of CAPA 17-215 for the creation and update the preventive maintenance plans as needed, and to include equipment interfaces such as (b) (4). They indicated that the maintenance personnel were trained in the creation and update the preventive maintenance plans. This CAPA was closed on February 04, 2018.

- **Observation #8.d.:** Temperature alarms and abnormal patterns in the (b) (4) are not always evaluated by the Quality Unit for impact to the contents inside the (b) (4)r, which include plasma, drug substance intermediate and drug substance. Similarly, temperature alarms in (b) (4) which was used for the storage of drug substance intermediates until June 2016, were not always evaluated by the Quality Unit for the impact to the contents of the (b) (4).

**Firm Responses:** Prometic explained that the action taken for the correction and resolution of Observation #8.d. consists in the implementation of the following CAPAs:

- CAPA 17-216 and Change Control CCR-18-024.01 to implement guidelines for the evaluation of temperature trends for (b) (4) in the following documents:
  - MWI-Facility-02, "(b) (4) *Inspection Storage;"*
  - SOP-0214 (SOP F-009), "*Use and Maintenance of* (b) (4)
  - SOP-0215 (SOP F-010), "*Use and Maintenance of* (b) (4) ;"

- SOP-0225 (SOP F-023), "*Operation and Maintenance of* (b) (4)
- SOP-0226 (SOP F-024), "Operation and Maintenance of (b) (4)

CAPA 17-216 and Change Control CCR-18-024.01 were closed on February 21, 2018.

- CAPA-17-217 and Change Control CCR-18-054.01 to updated SOP M039.02 (SOP-0181), "Use of (b) (4) to eliminate the use of (b) (4) for temporary storage of Pg Intermediate and Pg Drug Substance. CAPA 17-217 and Change Control CCR-18-054.01 were closed on February 16, 2018.

  The firm indicated that the manufacturing personnel were trained in the updated SOPs prior the closure of the above CAPAs.

o **Observation #8.e.:** (b) (4) of (b) (4), in Building Room (b) (4) was observed to be worn out and partially disassembled. In 2017, there were 2 incidents of spillage of chemicals during (b) (4) preparation due to inadequate sealing of the (b) (4). No evidence of PM of this equipment is provided.

**Firm Responses:** Prometic explained that the action taken for the correction and resolution of Observation #8.e. consists in the implementation of CAPA-17-220 for the removal of the (b) (4) from Building Room (b) (4). They indicated that Change Control CCR-18-043.01 was implemented for the creation of work instruction WIN-019.01, (b) (4) " that describes the (b) (4) of raw materials using (b) (4) and the closing of these (b) (4) using (b) (4) instead of using the (b) (4). Manufacturing personnel was trained in this work instruction, and CAPA-17-220 and Change Control CCR-18-043.01 were closed on February 01, 2018.

o **Observation #8.f.:** (b) (4) was repaired twice (March 2015 and November 2017). No evidence of PM of this equipment is provided.

**Firm Responses:** Prometic explained that the action taken for the correction and resolution of Observation #8.f. consists in the implementation of CAPA 17-215 for the creation and update the preventive maintenance plans as needed, which is also the same corrective action for the closure and resolution of Observation #8.c. They stated that a preventive maintenance plan WO MNT-001934 and calibration event CE-000053, 1Y-CAL-PP was created for the preventive maintenance and calibration of the (b) (4). The firm stated that preventive maintenance plan WO MNT-001934 was executed on September 2017. They explained that the maintenance personnel were trained in the creation and update preventive maintenance plans. This CAPA was closed on February 04, 2018.

o **Observation #8.g.:** During the observation of the SBDS (b) (4) procedure, the battery in the (b) (4) used to measure the (b) (4) of (b) (4) was dead and the (b) (4) was not functional. No spare batteries were available in Zone (b) (4) which caused delay in the process.

**Firm Responses:** Prometic explained that the action taken for the correction and resolution of Observation #8.g. consists in the implementation of CAPA-17-218 and Change Control CCR-18-050.01 to create a battery inventory for the production equipment with the implementation of an internal product code for the batteries in the Controlled Consumable (CCM) at the firm's (b) (4) system. The manufacturing and material management personnel were trained in the handling of the battery inventory in (b) (4). CAPA-17-218 and Change Control CCR-18-050.01 were closed on February 06, 2018.

- **Observation #8.h.:** The use (b) (4) listed (b) (4) between March 6 – April 2017. The logbook stated that in one instance the (b) (4) was "broken" and in another instance "damaged lower lid." Despite multiple requests to provide the history of the (b) (4) for the (b) (4) used, this was not done, and this information is not readily available.

**Firm Responses:** Prometic explained that the action taken for the correction and resolution of Observation #8.h. consists in the implementation of CAPA-17-219 and Change Control CCR-18-040.01 to include FOR-0252, "(b) (4) *Logbook*," FOR-0253, "*Pg* (b) (4) *Logbook"* and FOR-0254, "(b) (4) *Logbook*" in SOP-0165 (SOP M-016), "(b) (4) The purpose of these logbooks is to document (b) (4) activities; in addition, batches processed in these (b) (4). The manufacturing personnel were trained in the updated SOP-0165 and columns logbooks. CAPA-17-219 and Change Control CCR-18-040.01 were closed on February 02, 2018.

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

**Firm Responses:** Prometic explained that the action taken for the correction and resolution of Observation #10.a. includes the implementation of the following CAPAs:

- CAPA-17-204 and CAPA-17-205 for the review and update of BPR100 and BPR101, which are the Batch Production Records in support the manufacture of Pg Intermediate and BDS, to include an instruction to attach a label with the lot number in the equipment used for their respective manufacturing step. Also, SOP-0193, "*Cleanroom Management*" was reviewed and updated to include an instruction to indicated that specific production areas within the clean room are identified with the manufacturing step in process. Both CAPAs were closed on October 26, 2018. These CAPAs are applicable to Observation #5.a.

- **Observation #10.b:** The SBDS (b) (4) is still labeled as (b) (4) (b) (4) " and is labeled for (b) (4) " zone. The (b) (4) is used in Zone (b) (4) since December 2016 and was not re-labeled for use in Zone (b) (4).

**Firm Responses:** Prometic indicated that the action taken for the correction and resolution of Observation #10.b. consists the implementation of CAPA-17-222 and Change Control Request CCR-18-038.01 to conduct physical verification of all the equipment in the manufacturing area. They explained that the information of the

equipment located in the manufacturing area was updated in the (b) (4) software to reflect their current name, status and location. The firm stated that SOP WIN-014 (SOP M-005) "*Manufacturing Equipment List per Zone"* was updated to include a complete inventory of the equipment in the manufacturing area. Prometic indicated that manufacturing and maintenance personnel were trained in the updated SOP WIN-014 (SOP M-005). CAPA-17-222 and CCR-18-038.01 were closed on February 05, 2018.

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

**Firm Responses:** Prometic explained that the action taken for correction and resolution Observation #11 includes the implementation of the following CAPAs:

- CAPA-17-223 for the evaluation of open processes conducted in the (b) (4) units during the manufacture of Pg BDS, Environmental Monitoring (EM) excursions in these units and corrective actions to improve or change these open processes. They stated that RAR-037.01, "Risk Assessment Report for the Usage of (b) (4) Throughout the Manufacturing Process of Pg Bulk Drug Substance," reports the above items in support of CAPA-17-223. This CAPA was closed on March 02, 2018;
- CAPA-17-224 to include instructions in SOP-M-012 (SOP-0161), "*Local Protection Unit-LPU Operation*" for the frequent change of gloves or sanitization of gloves using (b) (4) ) prior to conduct any open process in the (b) (4) units and to conduct open processes inside of the (b) (4) units using aseptic techniques. This CAPA was closed on April 03, 2018;
- CAPA-17-225 to include instructions in SOP QA-011 (SOP-0010) "*Internal Audit Program,*" for department self-audit to increase intra-department oversight and correct inappropriate working behaviors during GMP activities. This CAPA was closed on January 31, 2018.

  The firm indicated that the manufacturing personnel were trained in the updated SOPs prior the closure of the above CAPAs.

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

**Firm Responses:** Prometic indicated that the action taken for correction and resolution Observation #12 includes the implementation of the following CAPAs:

- CAPA-17-226 to include an instruction in BPR101 (Batch Production Record in support for the manufacture of Pg BDS) for the installation and use of a (b) (4) with aseptic connections in the (b) (4) to the (b) (4) used for nanofiltration process. This CAPA was closed October 26, 2018;
- CAPA-17-227 to develop and validate the (b) (4) test method for (b) (4) The results from the development and validation of the (b) (4) test method for (b) (4) was described in QAR-016.01-R, "(b) (4) *Control of* (b) (4) *Used in Plasminogen Manufacturing Process*," approved on April 24, 2018. The

specification for the (b) (4) (SPC-MAT-032.02) was reviewed and updated to include a (b) (4) specification of (b) (4) according to (b) (4) This CAPA was closed on May 09, 2018.

The firm indicated that the manufacturing and QC laboratory personnel were trained in the updated BPR101 and SPC-MAT-032.02 prior the closure of both CAPAs.

✓ ***Reviewer Comments*****:** *Prometic's information provided in amendment STN BL125659/0.19 in support for the corrective action implemented for the resolution and closure of Observations #1.a., #1.b., #1.c., #1.d., #1.e., #1.f., #1.g., #1.h., #2.a., #2.b., #2.c., #2.d., #3.a., #3.b., #3.c., #4.c., #5.a., #5.b., #5.c., #6, #7, #8.a., #8.b., #8.c., #8.d., #8.e., #8.f., #8.g., #8.h., #10.a., #10.b., #11 and #12 were reviewed and found acceptable. These observations can be considered as closed. These corrective actions for the resolution and closure of the above observations,* (b) (5), (b) (7)(E) *Prometic Bioproduction Inc. at Laval, Quebec.*

*The information provided as corrective action for the resolution and closure of Observations #4.a. and #4.b. was reviewed and consider inadequate and inefficient for the following reasons:*

- *In Summary Report QAR-017.03*, "*Surface Sampling Method Recovery, Neutralization Efficacy and Facility Disinfection Efficacy Challenge Tests,*" *the firm did not conduct disinfectant effectiveness study to and* (b) (4) *to evaluate their effectiveness in the cleaning of surfaces in the manufacturing area and to prevent microbial contamination;*
- *In this Summary Report, Prometic did not report the results of the method recovery, neutralizer efficacy and disinfectant efficacy in* (b) (4) *exposed to the following environmental isolates:* (b) (4)
- *Prometic did not provide the Summary Reports SGS-STU-06-041R.00, approved on April 24, 2020 and SGS-STU-06-045R.00 approved on July 22, 2020, in support for the method recovery and neutralizer efficacy for* (b) (4)
- *The supporting data associated to CVP-061.01-R,* (b) (4) *Cleaning of the GMP Manufacturing Area and CHT Determination Under* (b) (4) *Conditions," was found inadequate and is not representative of the* (b) (4) *cleaning after manufacturing operations in all the manufacturing rooms;*

***See IR Questions #4.a, #4.b., #4.c., and #5 – 03/26/2021 (Below.)***

4. *Regarding the Summary Report QAR-017.03*, "*Surface Sampling Method Recovery, Neutralization Efficacy and Facility Disinfection Efficacy Challenge Tests,*" *in support for the response to the Observation #4.a. submitted in the Amendment STN BL125659/0.19* on October 26, 2020;

a. *It was noted in this report that you did not conduct the disinfectant effectiveness study for* (b) (4) *to evaluate its effectiveness in the cleaning of surfaces in the manufacturing area and equipment; in addition, to prevent microbial contamination. Please clarify if you conducted a separate disinfectant effectiveness study to this cleaning agent. If it is so, please provide a summary report of this study, in which includes a description of the testing conducted using* (b) (4) *organisms and environmental isolates, with the surfaces evaluated. Also, ensure to provide a summary of the deviations initiated with a description of the root cause and action taken for correction and resolution. In the case that you did not conduct disinfectant effectiveness study for* (b) (4) *, please provide a justification to not conduct this Study.*

**Firm Responses:** Prometic clarified that (b) (4) is used as a detergent for the cleaning of non-product contact surfaces. They stated that (b) (4) is not used as a disinfectant agent and no disinfectant effectiveness study has been conducted since there is no claim for any microbial log reduction efficacy. The firm indicated that a validated disinfectant is always used after the application of (b) (4) . Prometic explained that disinfectant effectiveness study has been conducted to (b) (4) , (b) (4) , which are the disinfectant agents used after the application of (b) (4)

- ✓ ***Reviewer Comments*****:** *The firm's response is acceptable.*

b. *It was noted in this report that you did not provide the results from the method recovery, neutralizer efficacy and disinfectant efficacy in* (b) (4) *exposed to the following environmental isolates:* (b) (4) *Please provide a summary that describes the results from the above testing for these* (b) (4) *exposed to these environmental isolates and using the above cleaning agents. If you did not conduct these testing, please provide a justification for not conducting these testing.*

**Firm Responses:** Prometic clarified that disinfectant effectiveness study for the (b) (4) exposed to (b) (4) was not conducted in 2020. They explained that this study was conducted in 2019 to the (b) (4) exposed to (b) (4) and using the above cleaning agents. The firm indicated that the environmental isolates used in the 2020 and 2019 disinfectant effectiveness studies are non-spore former, gram positive spore former and mold.

- ✓ ***Reviewer Comments*****:** *The firm's response is acceptable.*

c. *You stated in this report that results from the method recovery and neutralizer efficacy for* (b) (4) *were reported in the Summary Reports SGS-STU-06-041R.00, approved on April 24, 2020 and SGS-*

*STU-06-045R.00 approved on July 22, 2020. However, you did not provide these results. Please provide the above results.*

**Firm Responses:** Prometic provided the results from the method recovery and neutralizer efficacy testing for (b) (4) reported in the Summary Reports SGS-STU-06-041R.00and SGS-STU-06-045R.00. They indicated that the method recovery testing using (b) (4) complied with a criterion of (b) (4) of recovery. The firm stated that the neutralizer efficacy testing complied with a criterion of (b) (4) of recovery.

- ✓ ***Reviewer Comments*:** *The results from the method recovery and neutralizer efficacy testing for (b) (4) reported in the Summary Reports SGS-STU-06-041R.00and SGS-STU-06-045R.00 were reviewed and found acceptable. These results complied with the above criteria as discussed.*

5. *Regarding the Summary Report CVP-061.01-R, (b) (4) Cleaning of the GMP Manufacturing Area and CHT Determination Under (b) (4) Conditions," in support for the response to the Observation #4.a. submitted in the Amendment STN BL125659/0.19* on October 26, 2020;

   *The supporting data from this report is not representative of the (b) (4) cleaning after manufacturing operations in all the manufacturing rooms. It was noted in this Study, that manufacturing activities did not occur in several rooms; however, viable particulate count sampling was conducted in these rooms. Then you indicated that the results from this sampling is consider as "Invalid/Pass." Please provide a justification to consider the viable particulate count sampling conducted to the rooms where manufacturing activities did not occur as acceptable in support for this Study.*

**Firm Responses:** Prometic explained that the results from the viable particulate count sampling conducted in the (b) (4) (Room (b) (4)), Zone (b) (4) (Room (b) (4)), Zone (b) (4) (Room (b) (4)), Clean Corridor (Room (b) (4)), (b) (4) (Room (b) (4)) and Gowning (Room (b) (4)) were considered as "Invalid/Pass" since no manufacturing activity was conducted prior to clean these rooms. They indicated these "Invalid/Pass" were not considered as acceptable in support for the Cleaning Validation Study as in the Summary Report CVP-061.01-R. The firm stated that (b) (4) additional cleaning validation runs were conducted in these rooms and their results described in the Summary Report CVP-070.01-R, "*Cleaning Validation Report for the (b) (4) Cleaning of the (b) (4) Area of the* GMP Manufacturing Areas," approved on June 29, 2020. This report was discussed in the response to the Observation #4.a. submitted in the Amendment STN BL125659/0.19 on October 26, 2020.

- ✓ ***Reviewer Comments*:** *The firm's response is acceptable.*