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

Chemistry, Manufacturing and Controls (CMC) Review Memorandum

To: File of STN 125659/0

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From: Ze Peng, PhD, HB/DPPT/OTAT

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

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Subject: Final review of Adventitious Agents Safety Information in Prometic's original BLA for Plasminogen (Human)

Cc: Alexey Khrenov, PhD, Committee Chair, HB/DPPT/OTAT

Executive Summary

This memorandum summarizes the review of Adventitious Agents Safety Information in the original Biologics License Application (BLA) under STN 125659/0 submitted by Prometic Biotherapeutics, Inc. (Prometic) for Plasminogen (Human). The proposed proprietary name of this product is RYPLAZIM.

Upon review, three deficiencies were identified during the first review cycle: (1) life-cycle limit of the (b) (4) used in the (b) (4) chromatography step; (2) (b) (4) integrity testing of the nanofilter; and (3) homogeneity of the (b) (4) solvent/detergent (S/D) (b) (4) S/D treatment. These deficiencies were part of the Complete Response (CR) Letter, which was issued to Prometic on 9 April 2018.

Prometic submitted the responses to the CR Letter in Amendment # 18 on 1 September 2020. Based on the updated information, I found the measures taken by Prometic to control adventitious agents in the manufacture of Plasminogen (Human) to be adequate and acceptable, and therefore I recommend approval of the BLA under STN 125659/0.

Evaluation of safety regarding adventitious agents

For non-viral adventitious agents, such as (b) (4), the potential of contamination of these agents is well controlled through the use of validated cleaning/ sanitization procedures, e.g., the use of (b) (4), and in-process (b) (4) (b) (4) (b) (4). The final product of Plasminogen (Human) is further ensured to be free of non-viral adventitious agents by testing for Sterility and Endotoxins. Prometic manufactures Plasminogen (Human) according to GMP regulations.

To minimize the risk of transmissible spongiform encephalopathy (TSE) agents, Prometic uses only Source Plasma collected from FDA-licensed plasma collection centers. The donors who are at risk are excluded from plasma donation, as specified in the current FDA guidance regarding donation collection in the US.

All plasma donations, (b) (4), and manufacturing pools are tested for viral markers in compliance with FDA requirements. No raw materials of human or animal origin are used in the manufacture of Plasminogen (Human) other than Source Plasma. No excipients of human or animal origin are used in the formulation of Plasminogen (Human) drug product (DP). Thus, the potential risk of contamination by adventitious viruses or TSE agents is minimized.

Additionally, the potential of viral contamination of Plasminogen (Human) is mitigated by two dedicated, orthogonal viral clearance steps: S/D treatment (b) (4), and nanofiltration (b) (4). The (b) (4) affinity chromatography step in the manufacturing process also contributes to viral removal. Prometic has evaluated these steps in down-scale studies. The enveloped viruses selected in the studies include human immunodeficiency virus type 1 (HIV-1); pseudorabies virus (PRV, model virus for enveloped DNA viruses including hepatitis B virus (HBV)); and bovine viral diarrhea virus (BVDV, model virus for enveloped RNA viruses). The non-enveloped viruses selected in the studies include hepatitis A virus (HAV); encephalomyocarditis virus (EMCV, model virus for HAV); reovirus type 3 (Reo-3); and porcine parvovirus (PPV, model virus for human parvovirus B19 (B19V)). These viruses resemble viruses which may contaminate the production of Plasminogen (Human) and represent a wide range of physico-chemical properties in the testing of the ability of the manufacturing process to eliminate viruses. Down-scale studies on the relevant steps resulted in the following total log reduction factors, in parenthesis, for these viruses: HIV-1 (≥ 17.2), PRV (≥ 13.$^{(b)(4)}$, BVDV (≥ 11.8), HAV (≥ 10$^{(b)(4)}$), EMCV (≥ 11.2), Reo-3 (≥ 7.1), and PPV (≥ 9.7). These results are sufficient to support the effectiveness of viral clearance in the proposed commercial manufacturing process.

Total virus reduction factors (log_{10}) for inactivation/removal of various viruses achieved by the manufacturing process of Plasminogen (Human)

Manufacturing step	Virus reduction factor (log_{10})						
	Enveloped viruses			Non-enveloped viruses			
	HIV-1	PRV	BVDV	HAV	EMCV	Reo-3	PPV
(b) (4) affinity chromatography	≥ 5.2	ND	ND	3$^{(b)(4)}$	3.6	ND	2$^{(b)(4)}$
Solvent/detergent treatment	≥ 6.1	≥ 6.5	≥ 5.8	NA	NA	NA	NA

Nanofiltration	≥ 5.9	≥ 6.5	≥ 6.0	≥ 7.1	≥ 7.6*	≥ 7.1	≥ 7.0
Total virus reduction factors (log_{10})	≥ 17.2	≥ 13.0	≥ 11.8	≥ 10(b) (4)	≥ 11.2	≥ 7.1	≥ 9.7

ND: not done; NA: not applicable; *: the result generated from the (b) (4)

Background

RYPLAZIM is a human plasma-derived concentrate of Plasminogen. The Plasminogen (Human) DS is manufactured at Prometic BioProduction Inc. located at Laval, Quebec, Canada. The Plasminogen (Human) DP is manufactured at (b) (4)

This product is supplied as a lyophilized powder at 68.8 mg per vial to be reconstituted with 12.5 mL of sterile Water for Injection, for intravenous administration. The excipients are sodium citrate, sodium chloride, glycine, and sucrose. This product has not been marketed in any country.

The manufacturing process of Plasminogen (Human) includes two dedicated, orthogonal viral clearance steps: S/D treatment (b) (4) and nanofiltration (b) (4) affinity chromatography in the manufacturing process also contributes to virus removal. Furthermore, other than Source Plasma, no raw materials or ingredients of animal and human origin are used in the manufacturing process, which further mitigates the potential of viral contamination.

Summary of Review

Flow diagram of the manufacturing processes

Plasminogen (Human) drug substance

(b) (4)

Plasminogen (Human) drug product

- (b) (4)
- (b) (4)
- Aseptic filling (b) (4)
- Lyophilization (b) (4)
- Crimping
- 100% visual inspection
- Labeling and packaging
- DP

Product reviewer's comment: Bolded in the above flow diagram are the two dedicated steps used for either inactivating or removing viruses, thus lowering the potential of viral contamination. As described in the following section of this memo, *Evaluation of process capacity to clear viruses*, the step of (b) (4) affinity chromatography also contributes to viral clearance.

For the proposed commercial manufacturing process, Prometic did not provide the data to show that the (b) (4) S/D reagents is homogeneous (b) (4) S/D treatment. To have this (b) (4) to be homogeneous is important for the effective inactivation of enveloped viruses. Therefore, I asked Prometic to submit these data to support the thoroughness of the S/D treatment step for viral inactivation.

This comment was sent to Prometic in the CR Letter dated 9 April 2018, and they responded in Amendment # 18 on 1 September 2020. The response is summarized below:

Prometic's response: A (b) (4) study *No. MPV-035.01-R* was performed for the S/D treatment step. In the study, (b) (4) runs (Lot No. (b) (4)) were completed under the worst-case scenario (b) (4)). The study showed that the homogeneity of the (b) (4) with S/D reagents was achieved after (b) (4) and maintained (b) (4) S/D treatment. The parameters used in the evaluation include (b) (4) .

Product reviewer's comment: The results from this study support that the proposed commercial manufacturing process can ensure the homogeneity of the (b) (4) with S/D reagents (b) (4) S/D treatment. The response is acceptable.

Evaluation of process capacity to eliminate non-viral adventitious agents

For non-viral adventitious agents, such as (b) (4) , the potential of contamination of these agents is well controlled through the use of validated cleaning/ sanitization procedures, e.g., the use of (b) (4) , and in-process (b) (4) (b) (4) (b) (4) . The final container of Plasminogen (Human) is further ensured to be free of non-viral adventitious agents by the testing for Sterility and Endotoxins. Prometic manufactures Plasminogen (Human) according to GMP regulations.

Product reviewer's comment: The measures taken by Prometic to control non-viral adventitious agents in the manufacture of Plasminogen (Human) are acceptable.

Evaluation of process capacity to control transmissible spongiform encephalopathy agents

To minimize the risk of TSE agents, Prometic uses only Source Plasma collected from FDA-licensed plasma collection centers, which include (b) (4) from the US, and (b) (4) from Canada. The latter is (b) (4) Canada. The donors who are at risk are excluded from plasma donation, as specified in the current FDA guidance regarding donation collection in the US.

No raw materials of human or animal origin are used in the manufacture of Plasminogen (Human) other than Source Plasma. No excipients of human or animal origin are used in the formulation of Plasminogen (Human) DP.

Product reviewer's comment: Based on the information above, the potential risk of contamination by TSE agents is low in the manufacture of Plasminogen (Human).

Evaluation of process capacity to clear viruses

1. Selecting and testing human plasma for the absence of detectable viruses

   Only human Source Plasma (21 CFR 640.60) collected in centers licensed by FDA can be used for the manufacture of Plasminogen (Human) for the US market. A physical examination and suitable answers to an extensive questionnaire are required for all donors before each donation. Each donation is tested and found non-reactive for the presence of hepatitis B surface antigen, antibodies against HIV-1/2, HCV, and syphilis. Thus, donor selection is performed in accordance with the requirements of 21 CFR and respective FDA guidelines.

2. Testing the plasma pools for the absence of contaminating infectious viruses

   The plasma pools in the manufacture of Plasminogen (Human) will be tested by (b) (4) . Each (b) (4) is tested for the absence of viral genome of HAV, HBV, HCV, and HIV-1. None of the B19V test results in (b) (4) . The same tests are performed for the (b) (4) plasma pools.

3. Validation of viral clearance in selected steps of the manufacturing process of Plasminogen (Human)

   (b) (4)

(b) (4)

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

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

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

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Product reviewer's comment: For the nanofiltration step, I noticed that only a (b) (4) integrity test (i.e., the (b) (4)) is performed for the nanofilter. I asked Prometic to describe the (b) (4) integrity test(s) performed for the nanofilter in the proposed commercial manufacturing process.

This comment was sent to Prometic in the CR Letter dated 9 April 2018, and they responded in Amendment # 18 on 1 September 2020. In the response, Prometic stated that the same integrity test (acceptance criterion: (b) (4)) will be performed in the proposed commercial manufacturing process to verify the integrity of the (b) (4) before its use. The response is acceptable.

2) Viral clearance studies

The following viruses were selected in the viral clearance studies:

- Relevant enveloped virus: HIV-1
- Model virus for enveloped DNA viruses including HBV: PRV
- Model virus for enveloped RNA viruses: BVDV
- Relevant non-enveloped RNA virus: HAV
- Relevant non-enveloped RNA virus: Reo-3
- Model virus for HAV: EMCV
- Model virus for non-enveloped DNA virus B19V: PPV

These viruses are relevant or model viruses for human plasma-derived products, which represent a wide range of physico-chemical properties in evaluating the ability of the manufacturing process to clear viruses.

(b) (4) (b) (4) performed these viral clearance studies. The samples (i.e., (b) (4)) used in the virus clearance studies were tested for (b) (4) of the test samples was determined by using either the (b) (4) upper confidence limits. For the study on the inactivation of PRV by S/D treatment (b) (4)), the statistical method was referenced to (b) (4) The viral clearance studies were performed by (b) (4) samples collected at relevant manufacturing steps. At least (b) (4) independent runs were conducted for each virus.

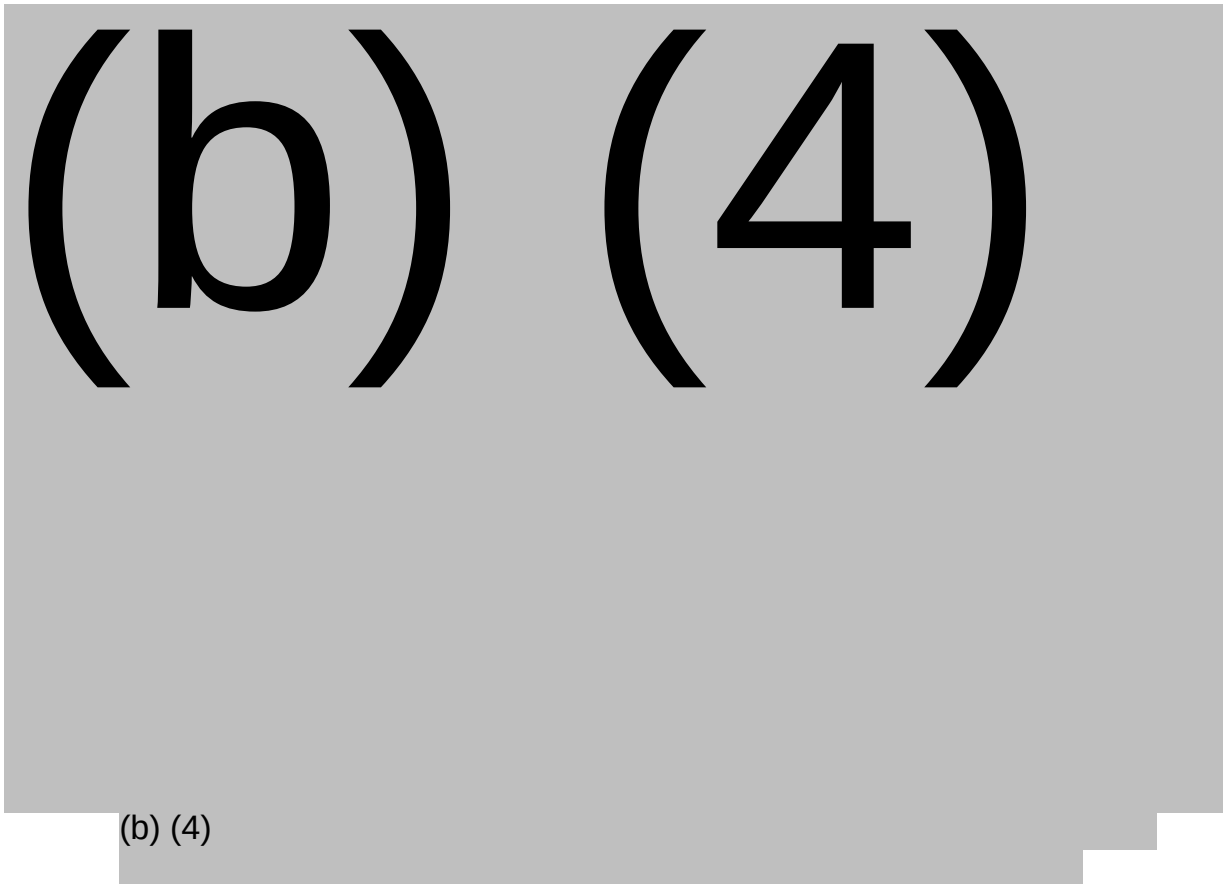
a) Solvent/Detergent treatment

The viral clearance data on S/D treatment for the manufacture of Plasminogen (Human) are included in the following reports:

- GLP robustness studies for the solvent/detergent treatment step for plasminogen purification (*Document No. PDR-5026.060 version 02*)
- Summary of viral clearance data for S/D treatment in the plasminogen purification process (*Document No. PDR-5026-006 version 01*)
- Evaluation of inactivation/removal of HIV-1 from (b) (4) test article (*Study No. AD73XH.022280.BSV* and *AD94FK.022280.BSV*)
- Evaluation of inactivation/removal of BVDV from (b) (4) test article (*Study No. AD73XH.022271.BSV* and *AD94FK.022271.BSV*)

- Evaluation of inactivation/removal of PRV from (b) (4) test article (*Study No. AD73XH.022277.BSV*)
- Evaluation of inactivation/removal of virus from (b) (4) test article (*Study No. AE12HK.022500.BSV*)

Based on these studies, the kinetics for the referenced three enveloped viruses using the test samples from the (b) (4) process are graphed as follows:



As these data showed, (b) (4) was below the LOD for HIV-1, BVDV, and PRV after respective "(b) (4) " (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) log reduction factors, in parenthesis, for these viruses: HIV-1 (b) (4) BVDV (b) (4)), and PRV (b) (4)) from LVP testing.

Additionally, the robustness studies on HIV-1, BVDV, and PRV were performed by (b) (4) used the test samples from the (b) (4) process in the robustness studies. They found that there was no significant impact on the inactivation kinetics even the concentrations of the (b) (4) which showed no significant impact on the inactivation kinetics when the (b) (4) (b) (4)) or

(b) (4) (action limits for commercial-scale: (b) (4) Similarly, no virus was detected in the test samples from the (b) (4) process after (b) (4) of S/D treatment when the concentrations of the (b) (4) (b) (4) (b) (4) .

Product reviewer's comment: (b) (4) performed extensive viral clearance studies on the S/D treatment process, which included those under various conditions, e.g., (b) (4) These data support that the S/D treatment process is a robust step for the inactivation of the referenced enveloped viruses in the manufacturing process of Plasminogen (Human).

b) Nanofiltration

The capacity of removing enveloped and non-enveloped viruses was evaluated in a (b) (4) system for the nanofiltration step. (b) (4) examined the critical process parameter in the robustness studies on nanofiltration for the clearance of HIV-1, BVDV, PRV, EMCV, and PPV. The nanofilter was (b) (4) (b) (4) , (b) (4) (b) (4) (b) (4) .

The viral clearance studies indicated that the nanofiltration step can achieve viral reduction of (b) (4) for HIV-1, (b) (4) for BVDV, (b) (4) for PRV, (b) (4) for HAV, (b) (4) for EMCV (generated from the (b) (4) manufactured in the (b) (4) process), and (b) (4) for Reo-3. The studies using human B19V (b) (4)) are considered experimental in nature. Therefore, viral clearance studies on PPV, a model virus of B19V, were performed. The studies indicated that the nanofiltration step can achieve viral reduction of (b) (4) for PPV. The details on the viral clearance studies are described in the following reports:

- Viral clearance studies for nanofiltration in the commercial plasminogen purification process (*Document No. PDR-5026.069*)
- Summary report of the GLP vial clearance by nanofiltration in the plasminogen purification process (*Document No. PDR-5026.018*)
- Evaluation of inactivation/removal of HIV-1 from (b) (4) test article (*Study No. AD73XH.022280.BSV* and *AD94FK.022280.BSV*)
- Evaluation of inactivation/removal of BVDV from (b) (4) test article (*Study No. AD94FK.022271.BSV* and *AD73XH.022271.BSV*)
- Evaluation of inactivation/removal of PRV from (b) (4) test article (*Study No. AD94FK.022277.BSV* and *AD73XH.022277.BSV*)
- Evaluation of inactivation/removal of EMCV from (b) (4) test article (*Study No. AD94FK.022269.BSV*)
- Evaluation of inactivation/removal of PPV from (b) (4) test article (*Study No. AD94FK.022295.BSV*)
- Evaluation of inactivation /removal of virus from (b) (4) test article (*Study No. AE12HK.022500.BSV*)

Product reviewer's comment: Robustness studies on nanofiltration were performed using the referenced viruses. (b) (4) has no substantial impact on viral removal. Additionally, at least (b) (4) independent runs were conducted for each virus, which are consistent with the requirement of the (b) (4) guideline. All the data provided in these studies support nanofiltration as an effective step for the removal of both enveloped and non-enveloped viruses.

c) (b) (4) affinity chromatography

The (b) (4) affinity chromatography step was also validated for viral clearance. To demonstrate the robustness of this step, (b) (4) tested HIV-1, EMCV, HAV, and PPV under various conditions, e.g., (b) (4) As the data show in the following table, the (b) (4) affinity chromatography step can result in at least (b) (4) reduction of the referenced viruses.

Virus	(b) (4)
HIV-1	
EMCV	
PPV	

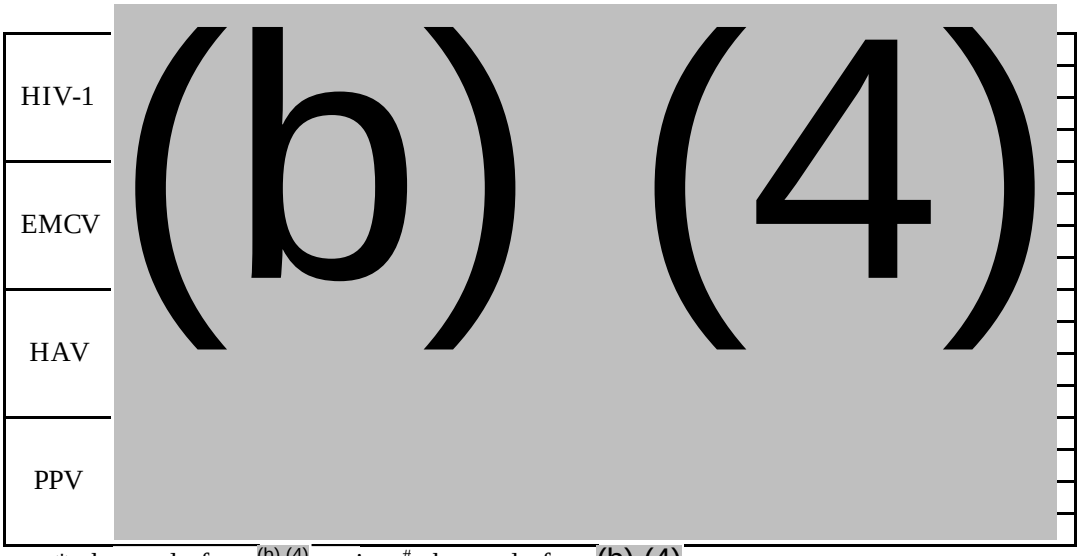
*: the results from (b) (4) testing; #: the results from (b) (4) assays.

Product reviewer's comment: For the (b) (4) affinity chromatography step, the virus reduction data presented in the table support that the (b) (4) at this step can be (b) (4) (b) (4) in the proposed commercial manufacturing process. However, Prometic stated that the (b) (4) (b) (4) (b) (4) in the proposed commercial manufacturing process based on study reports *PDP-018* and *PDR-2002.001*. I asked Prometic to revise the (b) (4) (b) (4) at the (b) (4) affinity chromatography step to (b) (4) because the (b) (4) (b) (4) is also dependent on the viral clearance data.

This comment was sent to Prometic in the CR Letter dated 9 April 2018, and they responded in Amendment #18 on 1 September 2020. The response is summarized below:

Prometic's response: A new viral clearance study No. *PDR-5026.047* was performed by (b) (4) for Prometic. The test samples used in the study were from the (b) (4) process, and the viral clearance data on HAV was also included. Base on the data summarized below, Prometic updated the life-cycle limit of the (b) (4) at the (b) (4) affinity chromatography step for up to (b) (4).

Virus	(b) (4)



*: the results from (b) (4) testing; #: the results from (b) (4) assays.

Additionally, they checked the samples after (b) (4), and evaluated the effectiveness of the cleaning procedure for viruses. The amounts of EMCV, and HAV were significantly reduced after the (b) (4) step, and no infectivity was detected in the same (b) (4) for HIV-1, and PPV. The (b) (4) samples were also tested following the subsequent (b) (4) material. No virus was detected in these samples. These data indicate that the potential of viral contamination from the previous runs at the (b) (4) affinity chromatography step is well controlled.

Product reviewer's comment: The viral clearance data generated from the (b) (4) from the (b) (4) process are consistent with those from the (b) (4) process at the (b) (4) affinity chromatography step. The data presented in the table above support that the (b) (4) at this step can be used for up to (b) (4) without a significant change in its viral clearance capacity in the proposed commercial manufacturing process. The life-cycle limit of the (b) (4) at this step is also updated in Section 3.2.S.2.2 *Description of Manufacturing Process and Process Controls* of the BLA. The response is acceptable.

3) Virus reduction claimed

Based on the viral clearance data provided in the original BLA submission and Amendment # 18 on 1 September 2020, the log reduction factors of the different manufacturing steps for the relevant and model viruses are summarized in the following table.

Total virus reduction factors (log_{10}) for inactivation/removal of various viruses achieved by the manufacturing process of Plasminogen (Human)

Manufacturing step	Virus reduction factor (log_{10})						
	Enveloped viruses			Non-enveloped viruses			
	HIV-1	PRV	BVDV	HAV	EMCV	Reo-3	PPV

(b) (4) affinity chromatography	≥ 5.2	ND	ND	3(b)(4)	3.6	ND	2(b)(4)
Solvent/detergent treatment	≥ 6.1	≥ 6.5	≥ 5.8	NA	NA	NA	NA
Nanofiltration	≥ 5.9	≥ 6.5	≥ 6.0	≥ 7.1	≥ 7.6*	≥ 7.1	≥ 7.0
Total virus reduction factors (log_{10})	≥ 17.2	≥ 13.0	≥ 11.8	≥ 10(b)(4)	≥ 11.2	≥ 7.1	≥ 9.7

*: the result generated from the (b) (4) .

Product reviewer's comment: As described above, product safety related to the potential viral contamination in the manufacturing processes is mainly demonstrated through these viral clearance studies other than the control of the potential viral load in plasma pools. These results are sufficient to support the effectiveness of viral clearance in the proposed commercial manufacturing process of Plasminogen (Human).

Recommendation

The safety of the product with respect to non-viral adventitious agents, including (b) (4) is well controlled by validated cleaning/sanitization procedures, in-process controls, (b) (4) (b) (4) (b) (4) , and implementation of release tests of Sterility and Endotoxins in the final product of Plasminogen (Human). The safety of the product with respect to adventitious viruses is well controlled in the manufacturing process of Plasminogen (Human): S/D treatment proves effective in inactivating the enveloped viruses; nanofiltration is confirmed to be a critical step for the removal of both enveloped and non-enveloped viruses; and the (b) (4) affinity chromatography step in the manufacturing process also contributes to viral removal. The viral safety of the product is mainly ensured through these viral clearance studies other than the control of the potential viral load in plasma pools. The measures taken by Prometic to control adventitious agents in the manufacture of Plasminogen (Human) are acceptable. Therefore, I recommend approval of the BLA.