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

Chemistry, Manufacturing and Controls (CMC) Review Memorandum

To: File of STN 125659/0
Rana Pratibha, Regulatory Project Manager, RPMB II/DRPM/OTAT

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

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

Basil Golding, MD, Director, DPPT/OTAT

Subject: 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 for this product is RYPLAZIM. As described below, the information provided by Prometic to control adventitious agents in the manufacture of Plasminogen (Human) is insufficient. I recommend the issuance of a complete response (CR) letter to Prometic, to convey the identified deficiencies, as they are listed at the end of this document.

Background

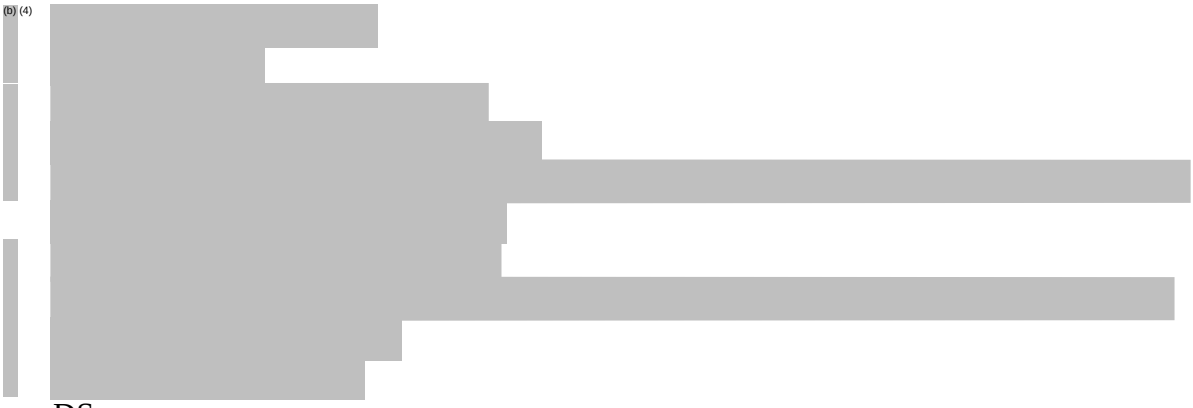
RYPLAZIM is a human plasma-derived concentrate of Plasminogen. The drug substance (DS) is manufactured at Prometic BioProduction Inc. in Laval, Quebec, Canada. The final drug product (FDP) is manufactured at (b) (4) .

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 injection. The excipients are sodium citrate, sodium chloride, glycine, and sucrose. This product has not been marketed in any country.

Summary of Review

Flow diagram of the manufacturing processes

Plasminogen drug substance



- DS

Plasminogen final drug product

- Aseptic filling (b) (4)
- Lyophilization
- Capping and oversealing
- Visual inspection
- Labeling and packaging
- Over inspection
- FDP

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, *Evaluation of viral elimination capacity*, the step of (b) (4) affinity chromatography also contributes to viral clearance.

For the proposed manufacturing process, Prometic did not provide the data to show that the (b) (4) To keep the (b) (4) homogeneous is important for the effective inactivation of enveloped viruses. Therefore, we will ask Prometic to submit these data to support the S/D treatment step for viral inactivation.

Evaluation of process capacity to eliminate non-viral adventitious agents

Prometic manufactures Plasminogen (Human) according to GMP regulations. 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) The final container of Plasminogen (Human) is also guaranteed to be free of non-viral adventitious agents by the testing for Sterility and Endotoxins.

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 transmissible spongiform encephalopathy (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 donations collection in the US.

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

Product reviewer's comment: Based on the information above, the potential risk of contaminating 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 the 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 Human Immunodeficiency Virus (HIV)-1/2, Hepatitis C Virus (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) using (b) (4) . Each (b) (4) is tested for the absence of viral genome of Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), HCV, and HIV-1. For human parvovirus B19 (B19V), none of the B19V test results in each (b) (4) Similar tests will be performed by (b) (4)

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

(b) (4)

Product reviewer's comment: For the nanofiltration step, we noticed that only a (b) (4) integrity test of the filters (b) (4)) is performed. We will ask Prometic to confirm if they also perform a (b) (4) integrity test of the nanofilter in the commercial process.

2) Viral clearance studies

The following viruses were selected to be used in the viral clearance studies:

- Relevant enveloped virus: HIV-1
- Model virus for enveloped DNA viruses including HBV: Pseudorabies virus (PRV)
- Model virus for enveloped RNA viruses: Bovine viral diarrhea virus (BVDV)
- Model virus for HAV: Encephalomyocarditis virus (EMCV)
- Model virus for B19V: Porcine parvovirus (PPV)

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

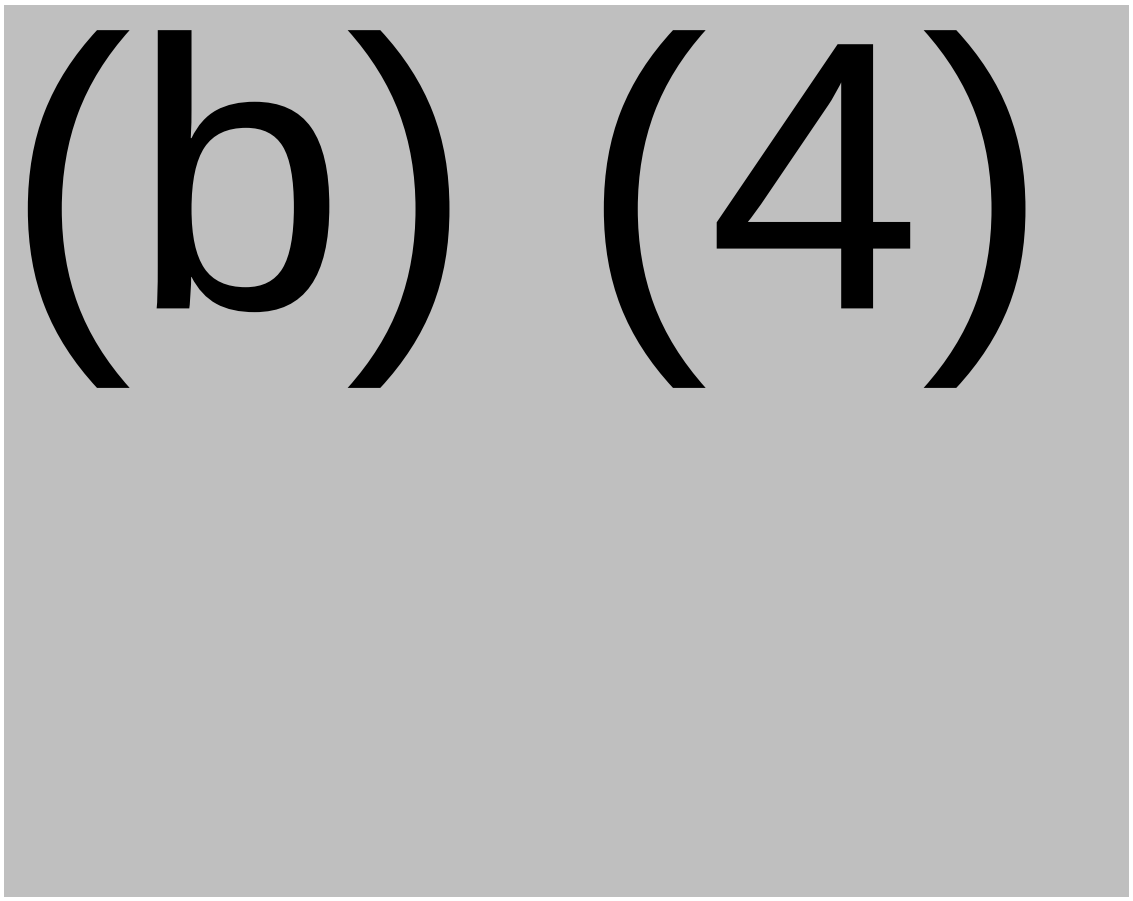
(b) (4) performed all viral clearance studies. The materials used for the virus clearance studies were tested for (b) (4) . The (b) (4) of each sample was determined by using either the (b) (4) upper confidence limits. The viral clearance studies were performed by (b) (4) samples collected at relevant 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:

- 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 the studies above, the kinetics for the referenced three enveloped viruses are graphed as follows:



As the data above show, (b) (4) was below the LOD for HIV-1, BVDV, and PRV after (b) (4) Additionally, studies of robustness on HIV-1, BVDV, and PRV were performed. They found that there was no effect on the inactivation kinetics when the (b) (4) Moreover, these studies indicated that no virus was detected after (b) (4) prolonged the time of inactivation of these viruses.

Product reviewer's comment: (b) (4) performed extensive viral clearance studies on S/D treatment of the manufacturing process of Plasminogen (Human), which include those for robustness under various conditions, e.g., (b) (4) Based on the information provided, we consider the S/D treatment a robust step for the inactivation of the referenced enveloped viruses.

b) Nanofiltration

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

The viral clearance studies indicated that the nanofiltration step can achieve viral reduction of (b) (4) The studies using human B19V (b) (4) are considered experimental in nature. Therefore, viral clearance studies (b) (4) on PPV, a model virus of B19V, were performed. These 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:

- 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 examining the nanofiltration step were performed using the referenced viruses. (b) (4) has no substantial impact on the 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 the nanofiltration step (b) (4)) as an effective method 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, and PPV under a wide range of different 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	(b) (4)			
EMCV	(b) (4)			
PPV	(b) (4)			

*: Based on the results from (b) (4) assay; #: based on the results from (b) (4) assay. (b) (4)

Additionally, they checked the samples after sanitization, and evaluated the effectiveness of the cleaning procedure for viruses. No (b) (4) was detected in the samples collected during (b) (4) sanitization. The (b) (4) samples were also tested following the subsequent (b) (4) No virus was detected in these samples. Taken together, these data indicate that the potential of viral contamination from previous runs at the (b) (4) affinity chromatography step is well controlled.

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

Recommendation

I reviewed all the information provided in this original BLA, and find it insufficient to support approval in this review cycle from a CMC (Product) perspective. I recommend issuing Prometic a CR letter listing the following deficiencies:

1. For the (b) (4) affinity chromatography step, the (b) (4) viral clearance studies were performed with (b) (4) that had been (b) (4) . However, Prometic stated that the (b) (4) based on study reports PDR-018 and PDR-2002.001. Please revise the (b) (4)

(b) (4) Affinity chromatography step to (b) (4) is also dependent on the available viral clearance data.

2. For the nanofiltration step, Prometic stated that a (b) (4) integrity test of the filters (b) (4) will be performed. Please describe the (b) (4) integrity test(s) performed for the nanofilter - (b) (4) .

3. Please provide data to demonstrate that the (b) (4) is (b) (4) during the S/D treatment period (b) (4)