



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

Date: October 16, 2009

To: STN: 125350.0

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Applicant: CSL Behring AG

Product: Immune Globulin Subcutaneous (Human), 20% Liquid, IgPro20
Proposed Trade name: Hizentra™

Subject: Mid-cycle Review (Viral Validation)

Recommendation

The following Information Request needs to be sent to the sponsor:

1. You have claimed log10 reduction factors (LRF) based on -----(b)(4)-----, pH 4 incubation, and -(b)(4)-- depth filtration manufacturing steps independently. However, we understand that the -----(b)(4)----- . Please clarify that each of these 3 steps is mechanistically distinct since -(b)(4)- is present in all 3 steps.
2. -----(b)(4)-----

3. You have provided summaries of study reports for evaluating LRF including PRV, BVDV, EMCV, and MVM. Please submit the raw data that support these summaries.
4. Please provide data from the “untreated bench sample” to demonstrate that the loss of virus infectivity was taken into account during both your robustness studies and viral validation studies for PRV, BVDV, EMCV, and MVM.

5. Please be advised that the agency regards the B19 ---(b)(4)--- assay as experimental and not well established. As such, the B19 validation results should not be claimed in the viral clearance table, but may be included as a footnote to the table. We suggest the following language for the footnote: “In addition, virus clearance of human parvovirus B19 was investigated experimentally at the pH 4 incubation step. The estimated Log Reduction Factor obtained was ≥ 5.3 .”

Summary

This submission by CSL for the product of Immune Globulin Subcutaneous (Human) 20% Liquid (IgPro20) was received by the CBER/FDA on April 30, 2009 as a BLA. In this submission, the firm provided viral safety data to support the approval of the BLA. The viral validation studies are performed based on the procedures for Privigen (IgPro10), which was previously licensed by the FDA. These studies include 1) Plasma screening; 2) Analytical assay validation (serological testing for antibodies and antigen and NAT testing); and 3) Manufacturing procedures that are intended for virus clearance.

All plasma collection centers are licensed by the FDA. All Plasma donations including Source Plasma and Recovered plasma used for manufacturing IgPro20 are collected in the United States. Source Plasma is collected, stored at, and shipped from --(b)(4)---. The starting plasma includes both Source Plasma and recovered plasma which are stored at Berne for fractionation.

In-process controls conducted on plasma pools or cryo-depleted plasma pools at both locations include testing for HBsAg, anti-HCV and anti-HIV-1 and -2 antibodies, and NAT procedures for HIV, -(b)(4)-, HBV, HCV and parvovirus B19. The parvovirus B19 DNA limit for the manufacturing plasma pools is set as less than or equal to 10^4 IU/mL.

There are four manufacturing steps that are specifically claimed by the firm to remove or inactivate viruses: -----(b)(4)-----; 2) pH 4 incubation; 3) -----(b)(4)----- depth filtration -(b)(4)- -----; and 4) Nanofiltration with -----(b)(4)-----.

CMC Review - Viral Safety

The viral log reduction by manufacturing steps obtained from validation studies are identical to that described in the Original BLA and BLA supplement (Privigen, STN 125201/0 and STN 125201/113 - Attachment, previously approved by the FDA, June 2009). However, CSL has included step 1, -(b)(4)- -----.

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

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

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

One (1) Page Determined to be Non-Releasable: (b)(4)

Viral Clearance Steps

	Designation	Process conditions
1	(b)(4)	(b)(4)
2	pH 4 incubation (steps CZ0600 to CZ0700)	
3	(b)(4) depth filtration (b)(4) (steps CZ0800 to CZ1050)	
4	Virus filtration (Nanofiltration) (step CZ1300)	

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

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

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

[--(b)(4)--]

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

3. Log Reduction Table

Summary of claimed Log reduction by manufacturing steps

[
--(b)(4)--
]

Note:

1). The firm claimed above log₁₀ reduction factors (LRF) based on -----(b)(4)----- and --(b)(4)-- depth filtration manufacturing steps independently. -----(b)(4)-----

2). The effects of -(b)(4)- on other viral clearance steps need to be evaluated to support LRF claims.

3). B19 ---(b)(4)-- assay is considered as experimental and not well established. As such, the B19 virus results should not be claimed in the viral clearance table in the PI, but may be included as a footnote to the table.

Reviewer’s Comments

Viral validation studies for -(b)(4)-, Low pH and nanofiltration steps are performed for IgPro20 which are identical to those for Privigen, which have been approved by the FDA (Refer to STN: 125201/0 and see attachment STN: 125201/113).

The firm proposes to claim viral clearance for -----(b)(4)----- step and add to the final reduction factor table. Information requests were sent to the firm for further clarification on virus reduction based on -----(b)(4)----- and virus removal by precipitation/filtration independently so the claim can be separated by filtration mechanism from -(b)(4)-- step. In addition, the impact -----(b)(4)----- on following steps needs to be evaluated to support LRF claims. The final LRF table should be revised accordingly.

One (1) Page Determined to be Non-Releasable: (b)(4)