



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

To: File for STN 125350/0

From: Robert W. Fisher, CMC Reviewer, DH, OBRR, HFM-345

Through: Michael Kennedy, Team Leader, DH, OBRR, HFM-345

CC: Pratibha Rana, RPM, RPMB, DBA, OBRR, HFM-380

Applicant: CSL Behring AG

Product: Immune Globulin Subcutaneous (Human), 20% Liquid (IgPro20)

Subject: Midcycle Review of STN 125350/0, Original BLA for Immune Globulin Subcutaneous (Human), 20% Liquid (IgPro20): Raw materials and stability

Recommendation:

Please forward the following letter-ready comments to the sponsor:

- Please describe the frequency and scope of audits with regard to critical processing materials such as -----(b)(4)----- . In addition, please provide an English translation of the appropriate SOPs.
- Please supply a table indicating which filters and --(b)(4)- were used for each bulk lot examined in your stability studies.
- Please submit a summary of what manufacturing changes were applied between the production of the bulk lots on stability, other than use of -----(b)(4)----- .
- Please clarify what tests are performed on incoming filter materials and excipients by CSL Behring.
- Your appearance specification calls for a “clear and pale-yellow to light-brown solution -----(b)(4)----- .
- Please identify which lots are to be considered as conformance lots.
- Please note the dating period should be based on stability data from lots of IgPro20 manufactured from the relevant starting materials; --- (b)(4) --- stability data from two lots of IgPro20 manufactured from one starting material (US recovered -(b)(4)-) may not be sufficient for the requested --- (b)(4) --- dating period.
- We note that 12 month stability data was provided for lots of IgPro20 manufactured from US source -(b)(4)-, US recovered -(b)(4)-, and US source -(b)(4)-, and that according to 3.2.P.8.2 additional (18 month) data should be available in October 2009. Please submit the updated stability reports prior to 15

Executive Summary:

No critical issues have been identified at midcycle, however CSL may not have adequate stability data to support a ---(b)(4)-- dating period. Details should be provided by CSL with regard to vendor audit procedures and -----(b)(4)----- Review of the specific stability data (11 lots; 3 storage temperatures, up to ---(b)(4)-- is ongoing.

Supplement Review Summary

- 1.** STN 125350/0 is an eCTD formatted BLA, received in DH on 30 April 2009 for Immune Globulin Subcutaneous (Human), 20% Liquid (IgPro20).
- 2.** CMC review for process validation, raw materials, and stability was assigned to Douglas Frazier and myself.
- 3.** This review is limited to raw materials and stability.
- 4.** IgPro20 is manufactured using a process identical to that of Privigen (Immune Globulin Intravenous (Human), 10% liquid (IgPro10, STN 125201) until the formulation stage; i.e. the drug substance is identical.
- 5.** Source plasma is collected at -----(b)(4)----- facilities. Recovered plasma is collected from -----(b)(4)----- facilities.
- i. Collection facilities are FDA licensed and inspected.
 - ii. Source plasma suppliers are audited --(b)(4)--. The audit schedule for recovered plasma suppliers is not clear.
 - iii. All donations are serologically tested for HBsAg, antibodies against HIV-1/2, and HCV.
 - iv. --(b)(4)--- are NAT tested for HCV, HIV-1, and B19.
 - v. Manufacturing pools are serologically tested for anti HIV-1/2 and HBsAg, and are NAT tested for HCV, HIV-1, HBV, and B19.
 - 1. The limit for B19 DNA is “not to exceed” 10^4 IU/mL in the manufacturing pool.
 - 2. NAT testing is performed by CSL Behring (HCV, HIV-1, HBV), -(b)(4)- (B19), -(b)(4)- (HCV, HIV-1, HBV, B19), or -(b)(4)- (HCV, HIV-1, HBV, B19).
 - 3. Validation reports are provided for each test at each vendor site.
- 6.** Excipients used in the manufacture of IgPro20 are L-proline, polysorbate-80, and WFI.
- i. L-proline, polysorbate-80, and WFI correspond to -----(b)(4)----- monographs.
 - ii. L-proline and polysorbate-80 are of plant origin.
 - iii. The eCTD states that “suppliers certify that [L-proline, polysorbate-80] complies with the respective monographs”, and that the excipients are tested for “identity, physico-chemical characteristics and microbial contamination”.
 - iv. It is not clear what testing is performed by CSL upon receipt of the excipient material.
- 7.** CSL Behring is requesting a dating period of --(b)(4)--- from date of manufacture when stored at “up to 25°C”.
- 8.** To support this dating period CSL has placed 11 bulk lots on stability.
- 9.** Stability parameters include:
- i. Appearance (pass; clear and pale-yellow to light-brown solution -----(b)(4)-----

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 - ii. -----(b)(4)-----
 - iii. L-proline (210-290 mM)

- iv. Polysorbate-80 (10-30 µg/mL)
- v. Purity (≥ 98.0%)
- vi. -----(b)(4)-----
- vii. pH (4.6-5.2)
- viii. -----(b)(4)-----
- ix. General safety test (pass)
- x. Sterility (pass)
- xi. -----(b)(4)-----
- xii. Anti-polio type I (-(b)(4)- x Ref; CBER lot 176)
- xiii. Anti-Measles (-(b)(4)- x Ref; CBER lot 176)
- xiv. -----(b)(4)-----
- xv. Diphtheria antitoxin ----(b)(4)-----
- xvi. -----(b)(4)-----
- xvii. -----(b)(4)-----
- xviii. -----(b)(4)-----
- xix. Fc Function -(b)(4)-
- xx. -----(b)(4)-----

10. The 11 bulk lots on stability were filled into 5mL or 20 mL ----(b)(4)----- containers.

- i. Two lots were manufactured in -(b)(4)- from US recovered -(b)(4)-, filled on FL -(b)(4)- without a -(b)(4)-, and stored at 5°C, 25°C, or ----(b)(4)--- data was supplied for the fills from 1 bulk lot and 18 month data for the other. The fills from both bulk lots were also stored at -----(b)(4)----- (both lots) and the fills from one bulk lot were stored at 5°C in the presence of light for 6 months. The data was reported in RSTAB0055; see Figure 1.
- ii. One lot was manufactured in -(b)(4)- from US recovered -(b)(4)-, one lot from US source -(b)(4)-, and one lot from source --- (b)(4) --. These three bulks were filled on FL -(b)(4)- with a -(b)(4)- and placed on stability. Data was provided for 6 month storage at -(b)(4)- (report PSTAB0158) and 12 month storage at 5°C or 25°C (reports PSTAB0156 and PSTAB0157). See Figure 2.
- iii. Three bulk lots were manufactured from -----(b)(4)----- . Data was provided after 3 months storage at 5°C, 25°C, -(b)(4)-. See Figure 3.
- iv. One lot was manufactured from -----(b)(4)-----, one lot from US source -(b)(4)-, and one lot from US source -(b)(4)-. 3 months of stability data was provided from samples stored at 5°C, 25 °C, -(b)(4)-. See Figure 4.

11. In summary, no critical items have been identified at midcycle. The information request (above) should be forwarded to the sponsor.

Figures

Two (2) Pages Determined to be Non-Releasable: (b)(4)