



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

Recommendation:

Approval.

Executive Summary:

No critical issues were identified for this subcutaneously injected product. Procedures for control of critical processing materials including plasma appear adequate. Data supplied supports a dating period of 18 months for product stored at 5-25°C protected from light.

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. Sections reviewed include 3.2.S.2.3 (Control of Materials), 3.2.P.4 (Control of Excipient), 3.2.P.5.2 (Analytical Procedures), 3.2.P.5.3 (Validation of Analytical Procedures), and 3.2.P.8 (Stability). Additional plasma handling information was reviewed in 3.2.A.1.
4. An information request was submitted to CSL on 05 November 2009. The response (STN 125350/0.5) was received on 30 November 2009.
5. 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.
6. Source plasma is collected at -----(b)(4)----- facilities. Recovered plasma is collected from -----(b)(4)----- facilities.
 - a. Collection facilities are FDA licensed and inspected.

- b. Suppliers are considered a Category 1 and as such are requalified -----(b)(4)-----
----- A quality agreement is required, as is a site audit. -----(b)(4)-----
-----.
 - c. Donor suitability is based on a physical examination, answers to a predefined questionnaire, and a deferral policy.
 - d. All donations are serologically tested for HBsAg, antibodies against HIV-1/2, and HCV.
 - e. An electronic inventory system (----- (b)(4) -----) checks plasma unit identification codes and checks the units received against the electronic invoice. The system creates a log of all single plasma units in a specific plasma pool. The scanned units are placed in bins that are assigned a unique ID number; prior to pooling the bin ID is used to determine if any of the individual plasma units are subject to quarantine based on post donation information.
 - f. --- (b)(4) -- are NAT tested for HCV, HIV-1, and B19.
 - g. Manufacturing pools are serologically tested for anti HIV-1/2 and HBsAg, and are NAT tested for HCV, HIV-1, HBV, and B19.
 - i. The limit for B19 DNA is “not to exceed” 10^4 IU/mL in the manufacturing pool.
 - ii. 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).
 - iii. Validation reports are provided for each test at each vendor site.
7. Excipients used in the manufacture of IgPro20 are L-proline, polysorbate-80, and WFI.
- a. L-proline, polysorbate-80, and WFI correspond to Ph. Eur. and USP monographs. Each container of L-proline and polysorbate-80 is tested for ----- (b)(4) -----
----- Full scale testing based on the corresponding pharmacopoeia monographs is performed ----- (b)(4) -----, whichever comes first.
 - i. L-proline is of plant origin. Certificates of analysis were provided for two lots of L-proline. One lot (--- (b)(4) ---) was from ----- (b)(4) -----, and the other (lot ---- (b)(4) ----) was from -- (b)(4) --. Both lots met USP and EP specifications.
 - ii. Polysorbate 80 is also of plant origin. A certificate of analysis was provided for one lot of polysorbate 80; this lot met all USP and EP specifications.
8. Stability parameters (with the final specifications) include:
- a. Appearance (pass; at release, clear and pale-yellow to light brown solution. At end of shelf life, (----- (b)(4) -----
-----).
 - i. ----- (b)(4) -----
-----.
 - ii. CSL also pointed out that two visual controls are applicable to IgPro20: visual inspection of all vials at step CZS1900 and the “appearance” specification for lot release and stability studies.
 - iii. In their response (STN 125350/0.14, received 10 February 2010) to an information request dated 03 February 3010, CSL ----- (b)(4) -----
and updated release specifications for IgPro20.
 - iv. ----- (b)(4) -----

 - b. ----- (b)(4) -----
 - c. L-proline (210-290 mM)
 - d. Polysorbate-80 (10-30 µg/mL)

- e. Purity ($\geq 98.0\%$)
 - f. -----(b)(4)-----
 - g. pH, 1% protein in NaCl 0.9% (4.6-5.2)
 - h. -----(b)(4)-----
 - i. General safety test (pass)
 - j. Sterility (no microbial growth detectable)
 - k. -----(b)(4)-----
 - l. Anti-polio type I (-(b)(4)- x Ref; CBER lot 176)
 - m. Anti-Measles (-(b)(4)- x Ref; CBER lot 176)
 - n. -----(b)(4)-----
 - o. Diphtheria antitoxin (-(b)(4)-)
 - p. -----(b)(4)-----
 - q. -----(b)(4)-----
 - r. -----(b)(4)-----
 - s. Fc Function (-(b)(4)-)
 - t. -----(b)(4)-----
9. Note that (b)(4)- testing was not performed. CSL has committed to -----(b)(4)-----
10. The SOPs and validation reports for analytical procedures relevant to the stability program were reviewed.
- a. The Appearance procedure is specified in SOP Q000228D_12. -----(b)(4)-----

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

 - c. The L-proline procedure is specified in SOP Q000417D_09. It is a (b)(4)- method based on -----(b)(4)----- Briefly, -----(b)(4)----- CSL successfully validated the procedure from -----(b)(4)-----.
 - d. The polysorbate 80 procedure is specified in SOP Q000480D_01. Proteins in IgPro20 are precipitated out of solution using -----(b)(4)-----

with a -----(b)(4)----- The validated range was linear from -----(b)(4)----- polysorbate 80 in IgPro20.
 - e. The purity procedure is specified in SOP Q000033D_14. It is performed according to -----(b)(4)----- and is an -----(b)(4)----- procedure. It was validated for use with IgPro20 over a range of -----(b)(4)-----.
 - f. -----(b)(4)-----

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

- g. pH is measured in accordance with Q000008D_06. Samples are diluted with 0.9% NaCl to 1% protein, and the pH measured using a ----- (b)(4) ----- determination corresponding to ----- (b)(4) ----- . The method was validated for IgPro20 over the range of 4.18-6.85.
- h. ----- (b)(4) -----

- i. The general safety test is described in Q000032D_10 and is based on ----- (b)(4) ----- . No IgPro20-specific validation was performed.
- j. Sterility is examined using a membrane-filtration method specified in SOP Q000027D_12 and in accordance with ----- (b)(4) ----- . Three lots of IgPro20 were examined for bacteriostatic or fungistatic properties using ----- (b)(4) ----- in Fluid Thioglycollate Medium and ----- (b)(4) ----- in Trypticase Soy Broth. Growth was observed within 5 days for all lots examined.
- k. ----- (b)(4) -----

- l. Anti-polio titers are determined using a ----- (b)(4) ----- assay described in SOP Q000025D_17. Units are assigned based on comparison to a reference standard. The assay was validated using three lots of IgPro20 for a range of ----- (b)(4) ----- . Significant variability was noted in the intermediate precision results (up to 48.9%), however this is not unusual for this type of --- (b)(4) --- assay.
- m. Anti-measles titers are also determined using a ----- (b)(4) ----- test. The assay is described in SOP Q000452D_02 and assigns units by ----- (b)(4) ----- . The assay was validated with a single lot of IgPro20 for a range of --- (b)(4) -- x CBER reference lot 176.
- n. ----- (b)(4) -----

- o. Diphtheria antitoxin levels are determined according to SOP Q0001157D_13. This procedure is a ----- (b)(4) ----- assay and assigns units based on a comparison with reference preparations. The assay was validated with three lots of IgPro20 and was linear over a range of --- (b)(4) ---.
- p. ----- (b)(4) -----

- q. ----- (b)(4) -----

c. One lot was manufactured with -----(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 at 5°C, 25°C, -(b)(4)-. 6 months of data was available for review, including the information in STN 125350/0.3 received 30 October 2009. Bulk lot ---(b)(4)--- (from US recovered -(b)(4)-) was split into filling lot ----(b)(4)---- (5mL) and -----(b)(4)----- (20mL). Bulk lot -----(b)(4)----- (from US source -(b)(4)-) was split into filling lot ----(b)(4)---- (5mL) and ----(b)(4)---- (20mL). Bulk lot ----(b)(4)---- (from US recovered -(b)(4)-) was split into filling lot ----(b)(4)---- (5mL) and -----(b)(4)---- (20mL). See Figure 4.

- i. Data for 5°C storage was provided in PSTAB0181, see attachment 3. All stability parameters remained within specification over the 9 months of data provided, with the exception of polysorbate 80 at 6 months for lot -----(b)(4)---- as described in QI20090453. Trends were noted for anti-measles and -----(b)(4)----- titers; anti-measles titers demonstrated a slight increase in one 5mL lot (----- (b)(4)----, from --- (b)(4)----) and -----(b)(4)----- demonstrated a decrease in one 20mL lot (-(b)(4)-----, also from ----(b)(4)----).
- ii. Data for 25°C storage was provided in PSTAB0184, see attachment 4. All stability parameters remained within specification over the 9 months of data provided.
- iii. -----(b)(4)-----

~~(b)(4)~~

[illegible]

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