

To: Paul Hartmann
CSL Behring AG
Date: December 23, 2009

This is regarding your BLA submission STN 125350/0 for Immune Globulin Subcutaneous (Human), 20% Liquid, submitted to the Agency on April 30, 2009. FDA continues with the review of the referenced submission and requests CSL Behring AG to provide the following information.

This is regarding CSL Berning's amendment dated November 30, 2009 to FDA information request dated November 5, 2009.

Review of Response to Question 7:

Submission of --(b)(4)--- stability data in January 2010 would be considered a major amendment and would extend the review clock. As previously discussed, a dating period of 18 months is being considered, however, it should be realized that this may be influenced by the -----(b)(4)-----
-----.

Review of Responses to Questions 5, 14, 14b:

For the FDA-licensed subcutaneous immune globulin product, Vivaglobin, the specification for Appearance is listed as: "Clear solution. Color can vary from colorless to pale yellow". -----(b)(4)-----

-----; therefore, we recommend
that you adopt an Appearance specification for IgPro20 (at lot release) that is
similar to that of Vivaglobin.

Review of Response to Question 14a:

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

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

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

Review of Response to Question 14c:

1. Please provide the visual inspection results for the following US clinical trial lots after aseptic filling: lot numbers 43109-00001, 43109-00002, 43109-00003, 43109-00004, 43109-00005, and 43109-00006.
2. Have these lots been placed on stability monitoring as well? If so, please provide the stability results to date. We also request that you provide a more detailed description of the stability results beyond the usual “pass/fail” for these lots, i.e., for quantitative assays, the numerical value of the test result.
3. Please provide the Date of Manufacture for the following US clinical trial lots: lot numbers 43109-00001, 43109-00002, 43109-00003, 43109-00004, 43109-00005, and 43109-00006.

Review of Response to Question no. 15a:

You may submit the validation report and the analytical method SOP for the testing of ----- (b)(4) ----- on IgPro20 final product before the end of January 2010.

Review of Response to Question no. 18:

You may submit data to support the conversion ratio between international units (IU) and the U.S. units (U) as well as the method validation results expressed in U/mL for diphtheria antitoxin testing on IgPro20 final product before the end of January 2010.

Review of Response to Question 21:

1. Please submit the following information regarding the B19 NAT --(b)(4)-- testing of recovered plasma at --- (b)(4) ----:
 - a. --- (b)(4) --- size
 - b. Resolution algorithm (from --- (b)(4) --- to individual positive donations)
 - c. Clarification of the cut-off level of ----- (b)(4) ----- B19 DNA for the single donation versus the testing sensitivity of ----- (b)(4) ----- for the single donation listed in Table 9 (CSLB response letter dated 5-NOV-09). Please provide the procedure, e.g., ----- (b)(4) -----, for approaching such a cut-off level when a qualitative NAT procedure is used.

- d. The resolution time between Whole Blood collection and identification of single B19 DNA-positive donation(s). Please shorten such resolution time so that a meaningful notification or retrieval is feasible within the dating period of any cellular blood component associated with high-titer donations that will be excluded from manufacturing.
 - e. A summary description of ----(b)(4)---- B19 NAT method with details on the sample preparation, sample input volume, sequences and map locations of the primers and probes used, and cycling conditions. Please also provide a copy of ---(b)(4)---- SOP for B19 NAT.
 - f. -(b)(4)- analysis of all their B19-specific primers and probes to demonstrate that all three known genotypes can be efficiently detected.
 - g. Validation of ----(b)(4)---- B19 NAT method done according to the ICH and OMCL guidelines. Please provide copies of the method validation protocol and the validation study report.
 - h. Prevalence of high-titer, B19 DNA-positive recovered plasma donations since the implementation of such --(b)(4)-- screening.
2. Since -----(b)(4)----- NAT procedure is a qualitative test, please also clarify how you approach the cut-off level of -----(b)(4)----- for the single donation when the testing sensitivity for the single donation is -----(b)(4)----- of B19 DNA (listed in Table 9).
 3. Please provide a description and the relevant SOPs for the receipt, tracking, and management of B19 --(b)(4)-- NAT results received from ----(b)(4)---. Please also provide the procedures for the quarantine and disposal of high-titer B19-positive recovered plasma donations.

Samples Needed for Conformance Lot Testing:

Please contact CBER Product Release Branch and provide the following samples for conformance lot testing as soon as possible:

6 vials of each 5 mL fill lot (lots -----(b)(4)-----);
 3 vials of each 20 mL fill lot (lots -----(b)(4)-----).

Please identify that the shipment and vials are in support of STN 125350, and contact Ms. Rana (RPM) when you have shipped these vials.

Samples Required for Routine Lot Release:

Please contact CBER Product Release Branch and provide 6 vials of 5 mL fill lots, 4 vials of 10 mL fill lots, 3 vials of -(b)(4)- fill lots, and 2 vials of 20 mL fill lots for CBER lot release testing. Please identify that the shipment and vials are in

support of STN 125350. Please contact Ms. Rana (RPM) when you have shipped the requested vials.

Pyrogen Test:

Please note that the testing of all lots of final drug product must include a test done in rabbits for pyrogenic substances, as required by the United States Code of Federal Regulations, Title 21, Part 610.13(b). This requirement is mandatory, and may not be waived. However, under 21 CFR 610.9, an application may be made for the use of an equivalent method that provides equal or greater assurance of safety and purity of the product. Such an application should include rabbit pyrogen test results, compared to test results by the proposed equivalent method, for a number of final product lots sufficient to robustly demonstrate 1) equivalent or better test accuracy and precision; and 2) ongoing consistency and adequate control of facility environment and production bioburden levels.

Identity Test:

Please note that you may eliminate the reporting of the Identity Test result from the Lot Release Protocol of IgPro20; i.e., remove item no. 4: "Identity: Performed after packing".

Additional Information Request: Review of ---(b)(4)---

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Please submit a response to this request as an amendment to the file by January 15, 2010.

Thank you.

Pratibha Rana