

**To: Paul Hartmann**  
**CSL Behring AG**  
**Date: November 5, 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.

1. 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.
2. Please supply a table indicating which filters and --(b)(4)-- were used for each bulk lot examined in your stability studies.
3. Please submit a summary of what manufacturing changes were implemented between the production of the bulk lots on stability, other than use of --(b)(4)-- -----.
4. Please clarify what tests are performed on incoming filter materials and excipients by CSL Behring.
5. Your appearance specification calls for a “clear and pale-yellow to light-brown solution -----(b)(4)-----  
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6. Please identify which lots are to be considered as conformance lots.
7. 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. A dating period of 18 months will be considered based on the updated 18 month data contained in STN 125350/0.3.
8. Please provide the following documentation, plus an English translation, for the process step CZS1400 (------(b)(4)-----):
  - a. An executed batch record for this step for a batch of IgPro20;
  - b. Any associated control parameters and/or acceptance specifications that are not included in the above document.

9. You have claimed log<sub>10</sub> reduction factors (LRF) based on -----(b)(4)-----, pH 4 incubation, and -(b)(4)- depth filtration manufacturing steps independently. However, -(b)(4)- is present in all the 3 steps. We understand that the -----(b)(4)----- is effective in inactivating virus -----(b)(4)----- . Please provide data on the level and the duration of -(b)(4)- to demonstrate that the presence of -(b)(4)- does not lead to an overestimation of viral log<sub>10</sub> reduction at the steps of pH 4 incubation and -(b)(4)- depth filtration.

10. -----(b)(4)-----  
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11. 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.

12. 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.

13. 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  $\geq 5.3$ .”

14. The proposed specification for Appearance, “...*light brown solution* ----(b)(4)-----”, represents a reduction in product quality standards compared to the current IgPro10 specification. Please provide an appropriate justification for the lowering of this specification. Also, please provide additional information on the following related items:

a. -----(b)(4)-----  
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b. -----(b)(4)-----  
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- c. -----(b)(4)-----  
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- d. -----(b)(4)-----  
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15. Please set final container specifications for the following physicochemical and biological requirements:

- a. ----(b)(4)-----
- b. -----(b)(4)----- (at release and at end of shelf life)
- c. --- (b)(4)--- (upper and lower limits)
- d. -----(b)(4)-----

In addition, please provide an English translation of the appropriate SOPs and validation reports for each of the test methods used.

16. Please specify the following “other characteristics/batch-related requirements”:

- a. Visual inspection (100% of the bottles are controlled)
- b. Date of manufacture
- c. Transport conditions

17. When using Reference Immune Globulin Lot 176 (a 16.5% IgG solution) for purposes of meeting the minimum potency requirements for anti-measles and anti-polio type 1 in IgPro20 (a 20% IgG solution), the potency ratios should be adjusted to correct for the difference in IgG concentration. Thus, the adjusted minimum ratio for anti-measles for lot release of IgPro20 should be -(b)(4)- if the required ratio for a 16.5% IgG solution is set at -(b)(4)-. Please use the adjusted ratio in the lot release protocol.

18. For diphtheria antitoxin, the specification listed in Table 3 (Batch analysis report, pg 8 of 10) is -----(b)(4)----- . Please use the US Standard Diphtheria Antitoxin for validation and express the specification for lot release as U (units)/mL. The minimum ratio for a 16.5% IgG solution is 2 units (U)/mL and hence the adjusted ratio for IgPro20 is close to -(b)(4)-. Please provide the conversion ratio between IU and U.

19. New WHO Reference Reagents (RR) for testing ----- (b)(4) ----- in immune globulin products were established recently, along with the reference test, ----- (b)(4) ----- . Because FDA CBER is harmonizing with the EDQM to

adopt these new -----(b)(4)----- standards, we recommend that you revise your -----(b)(4)----- testing with the following measures:

- a. Replace your current -----(b)(4)----- test method (----(b)(4)---  
----- test method) with the recommended reference test (--(b)(4)--  
-----). To support this change, please provide your method SOP  
and method validation data.
- b. Use the WHO Reference Reagents, CBER Lots ---(b)(4)---- (also known  
as -----(b)(4)-----, respectively) to standardize your testing.  
(FDA CBER can provide you a few vials of these standards upon request.)
- c. Revise your -----(b)(4)----- specifications to “-(b)(4)-  
-----”

20. In your validation of your -(b)(4)- test method, you were able to demonstrate a linear range of -(b)(4)- IU/mL, which was adequate for testing IgPro10 lots, but not IgPro20 lots. Please re-validate your method's linear range with -(b)(4)- amounts that will adequately cover IgPro20's proposed specification of -(b)(4)-.
21. You submitted method summaries and validation reports for the Parvovirus B19 NAT methods of the -----(b)(4)-----, however, their intended uses were not specified.
  - a. Please clarify which methods will be used to test B19 in:
  - b. ---(b)(4)--- and manufacturing pools
  - c. Source Plasma and recovered plasma
  - d. Please provide additional information regarding the testing sensitivities for --(b)(4)-- NAT screening and cut-off levels in terms of original plasma donations being excluded from manufacturing.
22. There are conflicting reports in your submission regarding your endotoxin test method and specification. In the Biological Requirements section, the method and specification are listed as Q000443D and ----(b)(4)----, respectively. However, in the Characterization of Impurities section, the method and specification are listed as Q000081D and ---(b)(4)--- (if using -(b)(4)- test), respectively. Please clarify which method is used at specific points in manufacture.
23. For your anti-Polio Type 1 method validation, please tabulate the validation results (in IU/mL) side-by-side with the equivalent values in “x Ref 176 CBER” for easier comparison.
24. In study no. -(b)(4)- 01/06, titled “Effects of Sandoglobulin, IgPro10 and IgPro20 on blood pressure in rats” in the conclusions section you state that “...lot number 143109-00001 of IgPro20 caused a similar hypotension ... to Sandoglobulin. Lot 43109-00002 appeared to cause a slightly more pronounced hypotension.” However, according to table 2 (pg 14) the opposite is true. You continue to say that such an effect “...was in the range of the model's variance”. Please clarify.

25. Please include names of the responsible personnel in “Legacy Study Report Bacterial Stress Gene Assay Zen-0995” signature page (pg 2).

Please submit a response to this request as an amendment to the file by November 30, 2009.

Thank you.

Pratibha Rana