



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

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To: To File (BLA STN 125350/0)

From: Douglas J. Frazier, Biologist, CBER/DH/LPD/HFM-345 By Douglas J. Frazier at 9:25 am, Dec 29, 2009

Through: Dorothy Scott, MD, Chief, CBER/DH/LPD/HFM-345 By Dorothy E. Scott at 4:54 pm, Dec 29, 2009

CC: Pratibha Rana, RPM, HFM-380

Applicant: CSL Behring AG

Product: Immune Globulin Subcutaneous (Human), 20% Liquid
Trade name (proposed): HIZENTRA™

Subject: Midcycle Review

Recommendation

To send the following Information Request:

Please provide the following documentation, plus an English translation, for the process steps CZ1400-1500:

- The master batch record and three consecutive executed batch records for IgPro20;
- A table of in-process tests and acceptance specifications for these steps. Please indicate whether any tests are performed that are not noted in the master batch record.

Background Summary

The pharmaceutical company CSL Behring AG located at Wankdorfstrasse 10, CH-3000 Berne 22, Switzerland (US License 1766) (CSLB) has submitted a Biologics License Application for a new immune globulin product, Immune Globulin Subcutaneous (Human), 20% Liquid. This new IG product is known internally within CSL as "IgPro20" with a proposed trade name of "HIZENTRA™", and is supported by BB-IND [REDACTED]. The pivotal clinical study (Study ZLB04_008CR) is a Phase 3 open-label, prospective multicenter study on efficacy, tolerability, safety, and pharmacokinetics in PID patients. CSLB is also concurrently conducting a Phase 3 clinical trial in Europe.

The proposed indication for IgPro20 is treatment of patients with primary immunodeficiency. IgPro20 is a liquid, sterile, 20% protein solution, with an IgG purity of NLT 98%, a pH of 4.6 – 5.2, and contains 210 – 290 mM L-proline and 10 – 30 µg/mL polysorbate 80, with "trace amounts of sodium" and < 50

µg/mL IgA. No preservative is included. IgGPro20 is to be provided in fills of 5, 10, (b)(4) and 20 mL, in (b)(4) glass vials. The proposed storage condition is 2 – 25 deg C, protected from light, for (b)(4) (b)(4)

IgGPro20 is manufactured by CSL Behring AG in its Bern, Switzerland facility (US Lic. 1766) from (b)(4) made either at the Bern facility (b)(4) or at the (b)(4) (b)(4) IgGPro20 bulk manufacturing will be performed in the Bern (b)(4) facility, with aseptic filling done on Filling Line (b)(4). The manufacturing procedure is the same as is used to make the US-licensed IgPro10 (Privigen) product, except for concentration, formulation, sterile filtration, and filling of final bulk at the higher 20% concentration. CSLB notes that all facilities and equipment used in the manufacture of IgGPro20 have been already inspected and licensed except for the additional equipment used for (b)(4) (b)(4) which is currently under review via STN 103955/5230.

CSL Behring AG is a company of CSL Behring L.L.C., headquartered in King of Prussia, Pennsylvania, USA. CSL Behring L.L.C. is a wholly-owned subsidiary of the biopharmaceutical company, CSL Limited, based in Melbourne, Australia. The US distributor is to be CSL Behring LLC.

Supplement Review Summary

The assigned review task is to assess process validation. Since the process is the same as that previously licensed for IgGPro10* and is to occur exclusively in the US-licensed (b)(4) manufacturing facility and Filling Line (b)(4) only the novel variations in processing are of concern. Such variations include use of:

(b)(4)

CSLB has assessed final product made using these variations, and provides studies (reviewed below).

Other process changes include the final formulation of the bulk solution (b)(4) (b)(4) to IgPro20 final sterile bulk and subsequent filling (b)(4) (b)(4). Of particular interest are: the concentration of the 10% bulk to a final concentration of 20% and final formulation. Stability of bulk and final product has been assessed by DH Reviewer Robert Fisher PhD, and sterile filtration and aseptic filling are under the purview of DMPQ reviewers.

The IgPro20 manufacturing process is performed using the identical procedure as for IgPro10 down to the production of the drug substance, (b)(4) (for process steps, equipment schematic, and identification of (b)(4) apparatuses, see Attachments 1, 2, & 3). The drug substance, (b)(4), is further processed and formulated to yield the IgPro20-Bulk product which is subsequently aseptically filled into the final vials.

CSLB notes that "Neither reprocessing nor reworking procedures are currently foreseen for the manufacture of IgPro20."

* "The IgPro20 manufacturing process is performed using the identical procedure as for IgPro10 down to the production of the drug substance, (b)(4). The drug substance, (b)(4), is further processed and formulated to yield the IgPro20-Bulk product which is subsequently aseptically filled into the final vials. In detail, the manufacturing steps downstream from (b)(4) consist of protein concentration and formulation (CZS1500), (b)(4) bulk filtration and storage (CZS1550), sterile filtration (CZS1600), aseptic filling (CZS1700), visual inspection (CZS1900) and labeling & packaging (CZS2000)."

Process Validation

Process validation studies were performed to evaluate and demonstrate that drug product derived from (b)(4) consistently meet predetermined acceptance criteria with regard to 1) process control parameters, 2) quality attributes (in process / final product specifications), and 3) yield. These studies are summarized and assessed below:

(b)(4)

Pages 4 through 10 redacted for the following reasons:

(b)(4), (b)(4)