



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

To: BLA STN 125587/0

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CC: Christopher Hooban, RPM, OBRR/RPMS

Applicant: OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.

Product: Immune Globulin Intravenous, Human 10%
Trade name: Panzyga®

Subject: Final Review: Original Biological license application – Process Validation

Recommendation

The process validation studies in support of the manufacturing of Panzyga are inadequate and incomplete. Please communicate the following complete response to the sponsor:

1. The maximum process time of (b) (4) for “Duration of (b) (4)” at the STEP (b) (4), is not completely validated. Please provide the validation data of manufacturing close to the upper limit of (b) (4) challenged with the maximum process time of (b) (4), using the updated MOP 751SOP026.
2. Regarding the (b) (4) concentration measurement at STEP (b) (4):
 - i. Please provide the SOP and assay validation report regarding the (b) (4) concentration measurement.
 - ii. Please set the in-process acceptance criteria for (b) (4) concentration. Please add a routine measurement of (b) (4) in the product (b) (4) steps.
3. Three additional consecutive lots should be manufactured after resolving the issues associated with Steps (b) (4), and the implementation of the more comprehensive corrective actions to ensure that they are manufactured under cGMP conditions. These three lots should be placed on real-time and accelerated stability studies. The corresponding validation report should be provided along with stability data.
4. Please provide the final production-scale performance validation reports on the column life-cycles of (b) (4) respectively.
5. Please provide the final production-scale performance validation report on the life-cycle of the (b) (4).

Executive Summary

This review focuses on the process validation section (excluding virus clearance validation) of Panzyga manufacturing. Data submitted by Octapharma support the comparability among the process validation batches manufactured in 2014, the conformance batches manufactured in 2013 and the clinical batches manufactured during 2007-2011. However, a number of deviations occurred in 2013 and 2014 suggest inconsistency of the current manufacturing process. The process validation studies

of Panzyga are also found inadequate and incomplete. We recommend a Complete Response shown in the Complete Response Letter-Ready Comments.

Background Summary

This submission was received from Octapharma Pharmazeutika Produktionsges.m.b.H. as an original Biological License Application (BLA) on April 15, 2015. It is for Panzyga, a liquid 10% (100 mg/mL) human immune globulin intravenous (IGIV) product. Panzyga is indicated for the treatment of primary humoral immunodeficiency (PI) and chronic immune thrombocytopenic purpura (ITP) in adults.

Panzyga is prepared from plasma donated by healthy qualified plasma donors. The plasma is processed to (b) (4) according to the (b) (4) fractionation process. The purification process includes (b) (4) steps. Virus inactivation and reduction is ensured by a solvent/detergent (SD) treatment step, a 20 nm nanofiltration and an ion exchange (b) (4) chromatography step. Figure 1 shows the flow chart of Panzyga manufacturing process.

The final product is formulated using glycine as the excipient and will be filled in configurations of 10 mL, 25 mL, 50 mL, 100 mL, 200 mL and 300 mL solution. The product is supplied in (b) (4) glass vials with bromobutyl rubber stoppers and aluminum flip off cap. Octapharma proposes a shelf life of 2 years at 2-8 °C, and within its shelf-life, the product may be stored at 25 °C for up to 6 months.

The manufacturing process of Panzyga was developed at Octapharma Pharmazeutika Produktionsges. m. b. H (OPG) in Vienna, Austria; pilot scale batches were produced for preclinical and clinical studies at this site. The process was transferred to and scaled up to commercial scale at the Octapharma site at 72 rue du Marechal Foch, 67380 Lingolsheim, France (OSA) where the commercial batches were produced. OSA is not FDA licensed yet. In 2013, a total of (b) (4) bulk batches were manufactured in OSA which resulted in (b) (4) final container batches. These batches are referenced as “conformance batches”. Due to the issues encountered during the production of the conformance batches, Octapharma decided to produce new “consistency batches” which were the batches used in the process validation for this BLA. After some technical improvements, a total of (b) (4) bulk batches were produced at OSA in 2014; there were total of (b) (4) final container batches.

The manufacturing of Panzyga consistency batches involves different sites summarized in the table below:



