



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Administrative File: STN BL 125587/0, Panzyga (Immune Globulin Intravenous, Human 10%)

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Subject: **BLA** Review Memorandum – Response to the CR Letter – Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma): to provide information for U.S. market approval of Panzyga, an immune globulin intravenous (human) 10% liquid preparation indicated for the treatment of primary humoral immunodeficiency and chronic immune thrombocytopenic purpura in adults.

Due Date: August 2, 2018

REVIEW RECOMMENDATION

I reviewed Octapharma's responses to the Complete Response (CR) Letter items associated with the Quality System (QS) in Question No. 1 and found them to be acceptable. Outstanding facilities and equipment issues from the CR Letter were evaluated in a separate memo by Randa Melhem and in the Establishment Inspection Report (EIR) from the second Pre-License Inspection (PLI) of the firm's Lingolsheim (OSA), France, facility (conducted from May 21 – 25, 2018) and found to be acceptable.

I recommend approval of this BLA submission with Product Office concurrence.

NARRATIVE REVIEW

Items Reviewed

- Amendment STN 125587/0.45 (received on January 31, 2018) – Complete response to the CR Letter

Background

CBER received this electronic submission on April 15, 2015. Octapharma submitted this original BLA to provide information to support U.S. market authorization of Panzyga (working title “NewGam”), an immune globulin intravenous (human) 10% liquid preparation indicated for the treatment of primary humoral immunodeficiency (PI) and chronic immune thrombocytopenic purpura (ITP) in adults. This product is a liquid formulation intended for intravenous injection. Panzyga will be formulated in the following presentations: 10 mL, 25 mL, 50 mL, 100mL, 200 mL, and 300 mL.

CBER performed a PLI of the OSA Lingolsheim facility from October 5 – 14, 2015, in support of the review of original BLA 125587/0. The PLI was the first FDA inspection of the OSA facility and resulted in issuance of a nine-item Form FDA 483, Inspectional Observations. Deficiencies included the following:

- Aseptic areas are deficient with regard to air supply that is filtered through HEPA filters under positive pressure
- Equipment and rooms utilized in the manufacture of Panzyga are not always maintained in a qualified state for manufacturing operations
- The environmental monitoring program is deficient
- Equipment cleaning validations are deficient
- CAPA effectiveness checks are not always performed in a timely manner
- The deviation/investigation system is deficient
- Change controls are not always closed in a timely manner
- Written procedures for cleaning, disinfection, and sporicidal treatment of classified areas do not include surface contact times for sporicidal/fungicidal disinfectant (b) (4) or bacterial/fungicidal disinfectants (b) (4)
- Written procedures have not been established for processing and monitoring of requalification tasks within the Maintenance Management Software (MMS) database.

The firm’s response to the Form FDA 483 was received on November 4, 2015, in Amendment STN 125587/0.26. Following review of the 483 responses, a CR Letter was issued to the firm (dated February 10, 2016) for unresolved inspectional, review, and clinical pharmacology issues. Regarding the inspectional issues, it was noted that the firm’s corrective actions to the 483 Observations did not appear to be comprehensive or address the underlying issues. Specific examples listed in the CR Letter are as follows:

- The Panzyga process validation lots were manufactured prior to implementation of corrective actions associated with Performance Qualification (PQ) non-conformances.
- Inadequate oversight of the non-conformances associated with the HVAC system for the aseptic core and the autoclaves used to sterilize items in the aseptic core.
- Equipment cleaning and maintenance deficiencies were noted, and there has been a failure to investigate and/or correct some of the non-conformances. Cleaning failures occurred, yet the equipment continued to be used in manufacturing without completing corrective actions.

The firm requested a Type C meeting (January 19, 2017) to discuss their response to the CR Letter; however, as they were satisfied with FDA preliminary responses (dated January 17, 2017), the meeting was cancelled. The firm's complete response to the CR Letter was received on January 31, 2018, in Amendment STN 125587/0.45.

Introduction

The firm's complete response indicated that Filling Line (b) (4) from the initial PLI was dismantled during the 2017 summer shutdown per change control (CC) 62017. The firm also reported that a new a filling line, capping machine, and inkjet printer had been installed in Rooms (b) (4) (Room (b) (4) was modified accordingly); however, the new filling/capping machine was *not* submitted as part of the complete response. **Consequently, production activities for U.S. Panzyga batches (at OSA Lingolsheim) are now limited to bulk drug substance (DS) operations [plasma to bulk solution (b) (4)]**. Furthermore, filling of U.S. Panzyga batches will now be performed exclusively at the firm's Vienna, Austria, location (OPG). It should be noted that the new Panzyga process conformance lots produced to address the CR Letter comments were manufactured in the OSA Lingolsheim facility and shipped to the OPG Vienna facility for aseptic filling operations (Q2 2017).

During a teleconference on February 28, 2018, the firm clarified that new Filling Line (b) (4) is currently qualified and used for filling of non-US licensed products (including Panzyga for the EU and Canadian markets – both of which were approved in 2016). The firm also clarified that a (b) (4). (b) (4) FDA recommended that the firm submit an amendment to request that all information related to filling/aseptic operations (including corrective actions) be removed from the complete response to the CR Letter. The firm submitted its revised complete response to the CR Letter on March 16, 2018, in Amendment STN 125587/0.46. The following eCTD sections were updated to reflect the removal of information regarding aseptic/filling operations:

- Module 1.2
- Module 3.2.P.3.5
- Module 3.2.A.1 (Lingolsheim facility)

Manufacturing Process

For ease of review, an overview of the manufacturing process is provided below.

The manufacturing process for Panzyga is a continuous process that is initiated at the OSA Lingolsheim facility with manufacture of drug substance [plasma to final bulk (b) (4)] from U.S. (b) (4) plasma according to the (b) (4) plasma fractionation process. The purification process includes (b) (4) steps. Virus reduction and inactivation is achieved by an SD-treatment step, a 20 nm nanofiltration, and IEC (b) (4) chromatography. The final bulk product is formulated in glycine. Final drug product is filled at the OPG Vienna facility. Visual inspection, labeling and packaging are performed at OPG and Octapharma GmbH Dessau facility (ODE) located at Otto-Reuter-Str. 3, D-06847 Dessau, Germany.

The proposed shelf life of Panzyga is 24 months at +2°C to +8°C (36°F to 46°F). Within its shelf life, the product may be stored at $\leq +25^{\circ}\text{C}$ (77°F) for up to 9 months.

Manufacturing Steps

(b) (4)

Review of the CR Responses

Note: The firm's complete response to the CR Letter included information regarding modifications to the HVAC system in the aseptic core; however, as this information was removed (per Amendment 125587/0.46), my review is limited to the QS improvements outlined in the response to Question No. 1. As noted above, all remaining facilities and equipment issues were

addressed in a separate memo by Randa Melhem and in the EIR from the second PLI of the firm's Lingolsheim, France, facility (conducted from May 21 – 25, 2018).

Inspectional CR Issues – Comment/Question 1

CBER conducted a Pre-License Inspection (PLI) of the Octapharma S.A.S. facility from October 5 through 14, 2015, and noted serious deviations at the end of the inspection. We received the response to the FDA 483 on November 4, 2015, and find that it does not sufficiently address the concerns noted during this inspection. Your corrective actions do not appear to be comprehensive and address some of the underlying issues. Examples include:

- i. The Panzyga® process validation lots were manufactured prior to implementation of corrective actions associated with Performance Qualification (PQ) non-conformances.***
- ii. There is inadequate oversight of the non-conformances associated with the HVAC system for the aseptic core and the autoclaves used to sterilize items for use in the aseptic core.***
- iii. Equipment cleaning and maintenance deficiencies were noted, and there has been a failure to investigate and/or correct some of the non-conformances. Cleaning failures occurred, yet the equipment continued to be used in the manufacturing without completing corrective actions.***

The deficiencies described in the Form FDA 483 issued at the close of the inspection referenced above are an indication of your Quality Control unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of Panzyga®. Approval of a biologics license application or issuance of a biologics license constitutes a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products. Applicable requirements for the maintenance of establishments for the manufacture of a product include, but are not limited to, the good manufacturing practice requirements.

- a. Your corrective actions need to be more comprehensive with respect to addressing the underlying quality oversight issues, and,***
- b. A second PLI will be necessary to verify the corrective actions once they have been fully implemented.***

The firm's response included a Quality Review Board (QRB) summary report (dated January 2018). This report presented an overview of the improvements implemented since the initial PLI for Quality oversight and CAPAs specific to the following:

- Qualification, requalification, and cleaning validation activities (see memo by Randa Melhem)
- The deviation management system (including CAPAs)
- PQ non-conformances including CAPAs
- Equipment cleaning and maintenance (see memo by Randa Melhem)

Section 3.5 – Deviation management system including CAPAs

The deviation management system is governed by corporate policy 011POL010, Corporate Deviation Handling Policy, and local procedure 713SOP002, Handling of Discrepancies: Deviations and Events. The following aspects of the deviation management system were addressed:

- Escalation of non-conformances during PQs and requalifications (including cleaning validations)
 - The systematic escalation of non-conformances during qualifications and requalifications (including cleaning validations) as deviations in the (b) (4) system became effective on December 10, 2015. An investigation team is appointed with the necessary expertise and any impact on other batches is thoroughly investigated and assessed.
- CAPAs relevant to PQ related deviations
 - The role of the QRB in the review of CAPAs relevant to PQ related deviations has been emphasized as all CAPAs defined in the frame of such deviations are presented weekly to the QRB for their review (including the implementation due date). The corporate and site procedures noted above were both updated to include this requirement (effective November 30, 2015).
- CAPA timeliness and effectiveness
 - In accordance with the corporate and site procedures note above, lead times within the deviation management system are as follows:
 - Deviations are opened within one working day
 - Deviations are approved within 60 days
 - CAPAs are completed within 45 days

Several enhancements were also implemented regarding CAPA timeliness, effectiveness check rules, and monitoring of effectiveness checkss (by QRB). Specifically:

- Any extension of a CAPA due date must be justified and approved by the Quality Unit and escalated to the QRB.
- Any CAPA resulting from a major/critical deviation must have an effectiveness check defined by the responsible Quality function. If no effectiveness check is defined, justification must be provided in the (b) (4) system.
- An effectiveness check shall cover the next 12 – 20 batches produced after implementation of a CAPA and be performed no later than three months after implementation of the CAPA. If a different number of batches or a different observation period is defined, justification must be recorded in (b) (4) and approved by the Quality Unit.
- CAPA effectiveness checks must be reviewed by the QRB on a quarterly basis. The relevant data are compiled by the respective Quality function responsible for the CAPA(s).

Section 3.6 – Product Lifecycle Policy

A new corporate product lifecycle policy (019POL201 – Product Lifecycle Policy) was implemented on May 31, 2016, to describe the product lifecycle and product lifecycle management based on ICH Q8, Q9, and Q10 principles and FDA process validation guidelines. The objective of this policy is to define a common understanding and approach for product realization and proactive management of products throughout their lifetime by application of appropriate resources (including the quality processes and supporting processes in the firm's QS) to ensure product quality and reliable supply to patients. According to the firm, the objective of the product life cycle policy is achieved with an established/effective QS, integration of product and process understanding, and appropriate utilization of quality risk management principles.

Section 3.7 – Systemic Improvements

Octapharma's senior management also implemented the following systemic improvements to address the 483 Observations and CR Letter issues:

- 3.7.1 – Organizational improvements – the Head of QiO was replaced by the Head of QA (Muriel Le Henaff). As Head of QA and QiO, Ms. Le Henaff is now responsible for all QA matters (including sterility assurance) at OSA Lingolsheim. The firm believes this step, which allows them to capitalize on Ms. Le Henaff's professional experience and bring the QA and QiO departments (and sterility assurance) under one manager, has resulted in significant improvement with regard to management of the Lingolsheim QS.
- 3.7.2 – Update of Quality processes – several corporate and local Quality procedures were updated. These include the following:
 - 019POL200 – Qualification and Validation – new corporate policy implemented in April 2016 to outline the overall qualification and validation strategy for all Octapharma sites. The validation concept is built upon a lifecycle approach with integrated science based risk management to include overall quality objectives such as focus on patient safety, product quality (safety, purity, efficacy, and identity), and compliance with regulatory requirements.
 - 150SOP015 – Cleaning Validation Strategy – revised corporate procedure implemented in January 2017 to include a number changes and clarifications. Specific to the 2015 PAI, a new acceptance criterion for (b) (4) was implemented based on a (b) (4).
 - 019POL201 – Product Lifecycle Policy – as described above, this new corporate policy was implemented in May 2016 to outline the product lifecycle and product lifecycle management for the firm's medicinal products based on ICH Q8, Q9, and Q10 principles and FDA Process Validation Guidelines.
 - 780SOP023 – Periodic Qualification Handling Using the Maintenance Management Software (MMS) – new local procedure implemented in November 2015 in response to Observation No. 9 from the initial PLI for STN 125587. The purpose of this document is to describe the management of periodic equipment qualification scheduling with the Computerized Maintenance Management System (CMMS).
 - 780SOP018 – Deviation Handling during Qualification – local procedure revised in December 2015 in response to Observation No. 6 from the initial PLI for STN 125587. Revisions included an updated flow chart (paragraph 6.2) and

- implementation of a requirement that all deviations detected during execution of a PQ be documented and investigated with a deviation in the (b) (4) system.
- 713SOP002 – Handling of Discrepancies: Deviations and Events – local procedure revised in July 2017 to include a number of changes relevant to the 483 Observations from the initial PLI of the OSA Lingolsheim facility. Specific changes to this SOP were reviewed during the 2nd PLI in May 2018 and summarized in the EIR.
 - 011POL010 – Corporate Deviation Handling Policy – revised corporate policy implemented in September 2017 to include an updated (b) (4) workflow and a checklist and guidance for root cause investigations.
 - 780SOP024 – Visual Inspection of Production Equipment after Cleaning – local procedure revised (effective in November 2017) to include a visual check of equipment cleanliness prior to use (“commitment to product”).
 - 770SOP028 – Maintenance of Production Tanks – new local procedure implemented in October 2017 to describe the operations defined for maintenance of production tanks (specifically damage to the tanks in the form coloration and/or scratches and leaks tests to evaluate the integrity of each vessel).
- 3.7.3 – Increase of Quality awareness – MyQuality Initiative – in January 2017, the firm initiated the MyQuality Initiative to enhance its overall quality culture. The MyQuality Initiative is a two-year project aimed at providing a global and supporting vision for ensuring continuous and systemic improvement of the QS. The objective of this project is to develop stronger ownership and increased awareness of quality matters by each member of the Octapharma organization.
 - 3.7.4 – Compliance Task Force – the firm implemented a cGMP Compliance Improvement Plan that is managed by a team within the Quality Unit under the Head of QA/QiO (Muriel Le Henaff). This plan is continuously updated based on signals from the following:
 - Regular GMP inspections conducted by regulatory health authorities at the Lingolsheim facility
 - Regular corporate QA inspections ((b) (4))
 - Internal inspections performed Lingolsheim QA ((b) (4))
 - GMP inspection reports from other Octapharma manufacturing sites
 - Customer GMP audits
 - cGMP audits by external professionals (see below)
 - 3.7.5 – cGMP Auditing Frequency (internal, external) – in addition to the (b) (4) internal inspection program and (b) (4) corporate QA inspections of OSA Lingolsheim, the firm has committed to a program of regular inspections performed by an external professional (a former FDA field investigator). This program encompasses all Octapharma sites and provides a compliance check and important training regarding U.S. cGMP expectations. The firm reported that OSA Lingolsheim was inspected twice in 2017 and a follow-up inspection is planned for 1Q 2018.

- 3.7.6 – Corporate Improvement Projects – in August 2017, Octapharma conducted a workshop where participants reviewed all inspection and audit findings across all manufacturing sites. According to the firm, this project revealed that corporate and local site procedures complied with all relevant requirements; however, interpretation and implementation of these procedures varied across sites. Consequently, the firm defined the best practice site or department and subsequently nominated a corporate process owner from each site or department. The nominated corporate process owner is responsible for providing practical training activities at all relevant manufacturing sites. Octapharma follows these trainings with regular process audits/workshops. Octapharma believes that the provision of direct feedback by the corporate process owners to specific manufacturing sites through training, audits, and workshops leads to increased knowledge and implementation of best practices across all sites. Octapharma also utilizes this project to harmonize implementation, knowledge, and local ownership of new corporate processes.

Reviewer's Comments: *At the time of firm's complete response (received by CBER on January 31, 2018), the changes outlined in their submission appeared to be appropriate responses to the concerns outlined in the CR Letter. However, during the 2nd PLI of OSA Lingolsheim in May 2018, it was noted that a number of additional changes (to include selection of Panzyga deviation specialists, implementation of a dedicated Panzyga deviation committee, implementation of additional investigation tools, etc.) had been implemented to further enhance the QS and improve the overall quality culture. While the additional changes reviewed during the 2nd PLI (and summarized in the EIR) also appeared to be appropriate responses to the concerns outlined in the CR Letter, their implementation suggests that the firm's response to their QS deficiencies is still evolving. As I noted during the 2nd PLI, the number and recent implementation of many of the changes (1Q/2Q 2018) dictates that more time is needed before an accurate assessment can be made regarding their effectiveness. Given the depth and scope of the changes, it is reasonable to assume that proper implementation and compliance with these initiatives could result in a more mature QS capable of providing effective oversight of DS operations; however, the first surveillance inspection will be critical in determining the actual effectiveness of these initiatives and the status of the QS.*