



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

To: BLA STN 125587/0

From: Lu Deng, OTAT/DPPT/PDB
Malgorzata Norton, OTAT/DPPT/PDB
Yonggang Wang, OTAT/DPPT/PDB

Through: Michael Kennedy, Team Lead, OTAT/DPPT/PDB
Dorothy Scott, Chief, OTAT/DPPT/PDB

CC: Mark Levi, RPM, OTAT/DRPM

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

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

Subject: Final Review: Response to CR letter dated Feb-10-2016 – CMC

Recommendations

Approval with the following Postmarketing Commitment:

1. Octapharma commits to submitting the final validation report for the ongoing production (b) (4)

Executive Summary

This is a combined review of the Chemistry Manufacturing Control (CMC) portion of a Complete Response (CR) for a Biologics License Application (BLA) for Immune Globulin Intravenous, Human 10%, trade name Panzyga from Octapharma Pharmazeutika Produktionsges m.b.H.. Octapharma submitted their response to the February 10, 2016 CR Letter on January 31, 2018.

Panzyga is prepared from (b) (4) 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. There are three virus inactivation/reduction steps in the Panzyga process: a solvent/detergent (SD) treatment step, a 20 nm nanofiltration, and an ion exchange (b) (4) chromatography step. 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. The manufacturing process until final bulk solution is performed at Lingolsheim, France (OSA). Filling of the bulk solution is performed at Vienna, Austria (OPG). Quality Control is performed at Lingolsheim (OSA) or Vienna (OPG).

One PMC is generated to monitor the proposed (b) (4) (see 125587/0.62). The response to the CR Letter was found to be generally acceptable. However, certain items are requested for follow up during the next GMP inspection, including a follow up of the 483 observations from the May 21-25, 2018 Pre-License Inspection (PLI):

- a. Octapharma has been having nanofilter (b) (4) issues since their 2013 conformance batch campaign. The effectiveness of the following corrective actions should be checked:

(b) (4)

- b. Octapharma requested (b) (4) life cycles for their (b) (4). However, the (b) (4) are allowed to use up to the currently validated (b) (4) cycles with maximum hold times of (b) (4) respectively, given that no small scale studies have been performed and no other supporting data were provided.
- c. Octapharma was reminded that they are only validated for the maximum (b) (4) which were used in the process validation.
- d. Follow up of 483 items such as, no maximum time limit for the (b) (4) and maximum allowable time for nanofiltration duration.

CMC Review Summary

Octapharma submitted the original Biologics License Application (BLA) for Immune Globulin Intravenous, Human 10%, trade name Panzyga in 2015. A CR letter was issued on February 10, 2016. FDA communicated with Octapharma in a type C meeting on January 19, 2017 regarding their approaches on manufacturing process performance qualification lots and stability study plan together with other related issues. Octapharma responded to the CR letter on January 31, 2018. This review covers the sponsor's responses to our CMC CR items # 13, 14, 15, 16, 17 and 18. A separate memo regarding product stability and proposed shelf life was provided separately (see EDR). The following sections were reviewed in the original submission and were found acceptable: Process Development, Control of Intermediates and Bulks, Raw Materials, and Comparability of Clinical Material.

FDA CR item #13

Regarding CAPA 25298 to Deviation 25142, the removal of the upper limit of duration of stirring during (b) (4) is not justified. Please provide a validation which shows no impact on the product from stirring for an unlimited amount of time at this step. Please also review all other process steps and assure that a minimum and maximum time is validated.

Octapharma added the upper limit of (b) (4) for the duration during (b) (4) in the batch record following CC 51096. Octapharma also reviewed the process steps and confirmed they were

validated within PPQ 2017 batches for minimum and maximum time according to PPQ Report 2017 150PPQR1726/00. The response is acceptable.

FDA CR item #14

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.

The maximum process time of (b) (4) for the duration of (b) (4) at Step (b) (4) was challenged for batch (b) (4) in the course of 2017 Process Performance Qualification. Results are presented in section 11.6 of the 2017 process validation report 150PPQR11726/00. The amount of (b) (4) used in both batches were (b) (4). All results of the quality test parameters and process control parameters met the predefined acceptance criteria. No deviations related to this challenged has occurred during the process performance qualification.

FDA CR item #15

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.*

(b) (4)

(b) (4)

(b) (4)

FDA CR item #16

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.

Following the implementation of the corrective actions in relation to FDA's 483 dated Oct 14, 2015, additional qualification batches of Panzyga were produced in 2017, which included the following improvements:

- In-Process Controls for samples (b) (4) : determination of (b) (4) content.
- Maximum batch size of (b) (4) in combination with the maximum process and holding times.
- Minimum batch size of (b) (4) in combination with the minimum process and holding times, where applicable.

Due to summer shut down in 2017, Filling Line (b) (4) at OSA was not operated for the filling of the current PPQ lots.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

FDA CR item #17

Please provide the final production-scale performance validation reports on the column life-cycles of
(b) (4) *respectively.*

(b) (4)

(b) (4)

FDA CR item #18

Please provide the final production-scale performance validation report on the life-cycle of the

(b) (4)

(b) (4)

(b) (4)

Information Requests

The following Information Request questions were sent to Octapharma and the answers were found to be satisfactory.

Sent March 8, 2018; Response received in Seq. 0049 on March 19, 2018.

1. Please submit an updated list of changes related to the Panzyga process since the issuance of the CR Letter.

Sent April 2, 2018; Response received in Seq. 0050 on April 12, 2018.

1. For CC55648,

- a. Why the maximum batch size in (b) (4) needs to be (b) (4) when the Fractionation (b) (4) (CC39087, CC39251, CC43151)?
- b. Was the maximum size of (b) (4) validated? Please submit the validation report.
- c. Was there any Panzyga lot manufactured with maximum batch size of (b) (4)?
2. For *corporate CC 35306, local CC 51090*, how the (b) (4) from the new supplier (b) (4) is qualified? What is the (b) (4)? How the (b) (4) expiration date is determined?
3. Please provide detailed information and rational for the change CC59326 at Step (b) (4).
4. For CC47394 and CC56874,
 - a. Why the new tank (b) (4) was added in addition to (b) (4)?
 - b. Is the configuration of (b) (4) the same as (b) (4)?
 - c. How the (b) (4) were validated for the (b) (4)?
 - d. How the mixing of (b) (4) is compared with (b) (4)?
5. Process Performance Qualification Report 150PPQR1726/00, (b) (4)
6. (b) (4)
7. (b) (4) interim report 750RQP007.00, (b) (4)
8. (b) (4) interim report 750RQP008.00, (b) (4)

(b) (4)

9. In the first paragraph of section 2.2, it states that “the monomer and dimer content is $\geq 90\%$ ”. This is inconsistent with your current drug production specification for monomer and dimer content (b) (4). Please correct it.
10. Please provide information on how the batch numbers are named throughout Panzyga’s manufacturing process. If already provided, please indicate its location in eCTD.

Sent May 1, 2018; Response received in Seq. 0051 on May 15, 2018.

1. Please explain the (b) (4) activity results in the current PPQ batches (report 020STD82x.433/00) compared to the consistency batches manufacture in 2014 (report 020STD821.826.278/00).
2. Please provide a list of Process segments and time limits (ranges)
3. Please provide a table of Step (b) (4) addition and pH readjustment for all the conformance lots and the corresponding impurities measured after this step. Please explain how the (b) (4) amount was determined and why the pH has to be readjusted after this addition.
4. Please provide a table of the manufacturing and expiration dates for all the conformance batches.
5. For the maximum process conditions under which the conformance batches were produced, did you also challenge the maximum mixing speeds? If so, please provide the list of mixing speeds used at each step.
6. Please explain the acceptance criterion and results for final container (b) (4) Table 45 in report 150PPQR1726/00. Your Drug Product specification for (b) (4); however, your acceptance criteria (b) (4) and results (b) (4) are above the Drug Product specification and stability specification ((b) (4)) and results ((b) (4)) in report 17P012.
7. Please justify the specifications for (b) (4), Sodium, (b) (4), and IgA based on PPQ and historical lot results to date.
8. Please provide an update on your ongoing stability studies. Please also update your stability tables to include the proposed revision of the limit for “Fragments”, i.e., “Fragments (b) (4)”.
9. In your response to Question 15b, it stated that the in-process acceptance criteria for (b) (4) concentration of sample (b) (4) and sample (b) (4) were calculated based on “(b) (4)”, however in the corresponding supporting document 150PPQR1726/00 (tables 48 and table 50), it appeared that they had been calculated based on “(b) (4)” instead. In addition, it is unclear how the obtained values were then used to set the “setting limit min” and “setting limit max”. Please explain, and also provide the (b) (4) test results for the additional manufacturing batches, which had been used in rechecking the preliminary limit for (b) (4) content, in the (b) (4).
10. In the (b) (4) validation study, “Influence of Storage Temperature at (b) (4) were studied using batch (b) (4). The test results for (b) (4) samples showed as “trend observed → failed” on both page 97 and page 104, however in the corresponding discussion sections you concluded that “there was no trend observed according to (b) (4) test. Therefore, (b) (4) Panzyga (b) (4) samples can be stored for (b) (4)”. Please clarify these apparent discrepancies.

11. In the file 150ADD1726/00 – Addendum to Process Validation Report – 2017, it stated that both lot (b) (4) will not be marketed in USA (pages 9 and 10). Please indicate if they are manufactured for non-US market originally or subjected to re-allocation. Please provide a copy of SOP that is used for allocation and/or re-allocation of manufactured batches in OSA.
12. Please provide a list of the filters and how many are used per batch. Please provide information on how many of each filter are used per batch, how are they configured (parallel, sequential), and whether they are (b) (4) changed out. Please state how many filters were used in each step during the manufacture of the conformance lots.
13. Please correct the IgG content on the label from (b) (4).
14. Please provide the executed batch record of the maximum process time lot.
15. Please provide the (b) (4) content test results for Samples (b) (4) and final container from the (b) (4) Panzyga lots manufactured post- implementing (b) (4).
16. Please provide the Extractables and Leachables (E/L) studies and risk assessment conducted for using (b) (4) step. Please provide a copy of material specification for the (b) (4), and a copy of SOP for (b) (4).

Sent June 8, 2018; Response received in Seq. 0053 on June 15, 2018.

1. Please include the following information into the eCTD section 3.2.S.2.2 Description of Manufacturing Process and Process Controls:
 - a. A table containing Panzyga manufacturing process control parameters and acceptance limits.
 - b. Process segments and time limits (ranges) (your response to Question 2 of FDA Information Request dated May 01, 2018).
 - c. The table you provided in response to Question 12 of FDA Information Request dated May 01, 2018.
 - d. How the batch numbers are named throughout Panzyga's manufacturing process (your response to Question 10 of FDA Information Request dated April 02, 2018).
2. Based on the filter usage information provided in your response to Question 12 of FDA Information Request dated May 01, 2018, please update your master batch record accordingly. Please remove any language (b) (4)
3. You asked for (b) (4) cycle lifetime for both (b) (4). Please provide small scale studies to support your requests. If already submitted, please indicate their locations in eCTD.
4. Please update your final container drug product specifications according to your response to Question 7 of FDA Information Request dated May 01, 2018.
5. Please insert a footnote in Table 45 of report 150PPQR1726/00, explaining the reference standard unit difference for (b) (4) measured by (b) (4) assay and (b) (4) activity measured by (b) (4) assay.
6. Please define an in-process acceptance criterion for (b) (4)
7. Please provide an update on the column life-cycle studies for (b) (4).

Sent June 20, 2018; Response received in Seq. 0057 on June 25, 2018.

1. Please provide a copy of English summary of the deviation reports for the following deviations: 48900, 58464, 59272, 59818, 60829, 64700, 65035, 65318, 66208, 66304, 66624, 68487, 69766, 69975, 70177, 70333, 72961, 74612, 76966, 76967, 78104, 78554, 79076, 81392, 81935, 81975, 82369, 82370, 82386, 82635, 82961, 85436, 74334, 75270.

Sent July 4, 2018; Response received in Seq. 0060 on July 9, 2018.

1. Regarding the response to Question 5 from the May 1, 2018 IR, please provide the list of actual mixing speeds used at each step for the manufacture of the conformance lots.

Sent July 13, 2018; Response received in Seq. 0064 on July 18, 2018.

1. Please remove “(b) (4) plasma” under “Proportion” in Lot Release Protocol.
2. Please provide life cycle study updates for (b) (4). Please note that the life cycles of (b) (4) usage are based on your validation studies (750RQP007_00_(b) (4) and 750RQP008_00_(b) (4), submitted in response to the June 08, 2018 IR). Given that no small scale studies have been performed and no other supporting data were provided, the (b) (4) are allowed to use up to (b) (4) cycles, respectively.

Sent July 13, 2018; Response received in Seq. 0068 on July 20, 2018.

1. Please note that you are only validated for the following maximum mixing speeds challenged in you process validation as provided in the response to the July 4, 2018 IR. Please amend your batch record and associated documents with these maximums.

(b) (4)

Sent July 17, 2018; Response received in Seq. 0065 on July 18, 2018

1. Octapharma commits to submitting information on the stability study I7PO 12 annually as a "Postmarketing commitment - Status Update". The final stability reports will be submitted as a "Postmarketing Commitment - Final Study Reports" by Oct 30, 2020. Octapharma will also report any confirmed out-of-specification results at the recommended storage conditions from the stability monitoring to the Agency within 45 days of the event(s).
2. Octapharma commits to submitting the final validation reports for the ongoing production (b) (4)
[REDACTED]
3. Octapharma commits to submitting the final validation report for the ongoing production (b) (4)
[REDACTED]

Sent July 19, 2018; Response received in Seq. 0069 on July 20, 2018

1. Given that no small scale studies have been performed and no other supporting data were provided, the requested (b) (4) life cycles for (b) (4) are not acceptable. Based on the life cycle study reports (b) (4) (750RQP007_01) and (b) (4) (750RQP008_01) submitted in Amendment 64 on July 18, 2018, the (b) (4) are only allowed to use up to (b) (4) cycles with maximum hold times of (b) (4), respectively. Please update your mater batch record and other affected documents accordingly.

Sent July 27, 2018; Response received in Seq. 0072 on July 30, 2018

1. Regarding your response to the July 13 Information Request, please note that your mixing studies did not include product impact data (e.g., aggregates, etc.) for the maximum mixing speeds; therefore, please set the maximum mixing speed for those steps according to the maximum mixing speeds used in the Process Validation.