



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

Date: January 15, 2016

To: To File (BLA STN 125587/0)

From: Malgorzata G. Norton, Biologist
CBER/DHRR/LPD

Through: Michael Kennedy, Ph.D., Team Leader
CBER/DHRR/LPD

CC: Christopher Hooban, RPM
CBER/DBA/RPMB

Yonggang Wang, Ph.D.
CBER/DHRR/LPD

Lu Deng, Ph.D.
CBER/DHRR/LPD

Applicant: Octapharma Pharmazeutika Produktionsges, m.b.H

Product: Immune Globulin Intravenous (Human) 10% S/D
Trade name: Panzyga (formerly NewGam)

Subject: Final Review: Process Development, Specifications, Control of Intermediates and Bulks,
Raw Materials, Comparability of the Clinical Material (with Yonggang and Lu),
Conformance Lots: batch analysis and impurity profiles (with Yonggang and Lu)

Recommendation

A Complete Response (CR) Letter with the item listed below in addition to those already outlined by Yonggang Wang and Lu Deng.

CR Letter Ready Item

1. 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 product impact of 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.

Background Summary

On April 15, 2015, Octapharma submitted a BLA for Immune Globulin Intravenous (Human), 10%. The starting material for the bulk process is (b) (4) plasma which is further manufactured to (b) (4) according to a cold-ethanol plasma fractionation process. Furthermore, the purification process includes (b) (4) steps. It also contains virus inactivation and reduction steps using solvent/detergent (S/D) treatment, a 20 nm

nanofiltration, and an ion exchange (b) (4) chromatography step. The final product is formulated using glycine as the excipient. The late cycle meeting is September 29, 2015. The submission is due April 14, 2016.

A Pre-BLA meeting was held on December 12, 2013. The following comments were communicated with the Sponsor:

The summary validation report you submitted to support NewGam manufacturing at Lingolsheim and Springe facilities presents several issues:

- 1. Multiple deviations that occurred during the conformance batch campaign, such as excess total viable counts, processing time excursions, nanofiltration pressure outside of specified limits, and nanofilter (b) (4), suggest that the manufacturing process may not be well controlled at these facilities.*
- 2. Your presentation of visual inspection results as "conform" in a summary table, with a footnote indicating that the results did not conform, raise questions about the integrity of the data set.*
- 3. Mixing validation studies for the Lingolsheim and Springe facilities, and stability data for the conformance batches, have not been submitted.*
- 4. Based on these concerns, we recommend that you do not submit the manufacturing validation activities for the Lingolsheim and Springe sites in the BLA. Validation of these sites would be better supported with the submission of a comparability study proposal for review and comment, followed by a conformance batch manufacturing study.*

A comparability protocol was submitted June 2014 as amendment 0031 (0033 in our records) to IND 14121, and was approved Aug 2014.

Supplement Review Summary

Introduction


1. The manufacturing process was developed at Octapharma Pharmazeutika Produktionsges.m.b.H., Oberlaaer Strasse 235, A-1100 Vienna, Austria (OPG, FEI: 3002809097) and pilot scale batches were produced for preclinical and clinical studies at this site.
2. The IVIG 10% process was transferred and scaled up to commercial scale at the Octapharma site at Lingolsheim (OSA), where conformance batches were already produced in 2013 as first verification of the successful transfer.
3. After technical improvements consistency (process validation) batches were produced at Octapharma Lingolsheim in 2014.
4. The starting material for the NewGam bulk process is plasma which is further manufactured to (b) (4) according to the (b) (4) plasma fractionation process.
5. The purification process includes (b) (4) steps. Virus reduction and inactivation is granted by a SD – treatment step, a 20 nm nanofiltration and an ion exchange (b) (4) chromatography. The final product is formulated in glycine.

My review was focuses on the following sections:

1. Process Development
 - a. 020STD82x.258/00 Development Report: Drug Substance – NewGam
 - i. (b) (4) – this is acceptable.
 - b. 020STD821.826.289/00 Development Report: Drug Product Formulation – NewGam

- c. Compared the process parameters ((b) (4)) to that of Section 3.2.S.2.4.2 “Control of critical steps.”
- 2. Specifications
 - a. Octapharma were advised in the October 5, 2015 IR to report the (b) (4) titer, and change the specification to “(b) (4)”, rather than “(b) (4)”
 - b. On inspection, Octapharma was also advised that the measles titer limit should be (b) (4) CBER 176 for a 16.5% solution ((b) (4) CBER 176 for a 10% solution)
 - c. Please see the Lot Release protocol for the updated specifications
- 3. Control of Intermediates and Bulks
 - a. 3.2.S.2.4.1 Control of Intermediates: (b) (4)
 - b. (b) (4) Please refer to 3.2.S.7.1 and 3.2.S.7.3.
 - c. 3.2.S.2.4.2 Control of critical steps
 - d. 3.2.S.2.4.3 In-process Control Results
- 4. Raw Materials
 - a. 3.2.P.3.2 BATCH FORMULA
 - b. Plasma – (b) (4) – please see IR questions below.
 - c. In response to IRs, Octapharma provided:
 - i. SOPs on the testing, rejections and release of Raw material.
 - ii. The procedure if a change is made in the raw material or GMP deficiencies, etc.
- 5. Comparability of the Clinical Material (With Yonggang and Lu)
 - a. Review focused on if the product is biochemically comparable to the clinical material, as well as impurity profiles, etc.
 - b. Comparability Report
(b) (4)

(b) (4)



- a. Conformance batches= batches manufactured in the course of the upscale from pilot scale to commercial scale and simultaneously process transfer from OPG to OSA in 2013
- b. Consistency (Process validation) batches= batches manufactured in the course of process batches at commercial scale at OSA 2014
- c. Impurities seemed low (below spec)

First information request (Sent August 27, 2015; Response received September 28, 2015) (with Yonggang Wang and Lu Deng)

1. Please confirm that you use dedicated (b) (4) ion-exchange columns for lots manufactured for the US market.
2. Please provide the proposed validation study of sample storage time with (b) (4) if it has been performed. If not, please indicate when this study report will be available for review.
3. Please provide a complete list of deviations, which occurred during the process validation, along with the corresponding investigation reports.
4. For the STEP (b) (4) Nanofiltration, what is the process (b) (4) for the step of “the product (b) (4)”? Was the same (b) (4) step performed in the conformance lots manufactured in 2013?
5. Please provide detailed information on the issues/deviations that were encountered during the conformance batch manufacturing, (b) (4) during nanofiltration. Please provide detailed information on how these issues/deviations were fixed.
6. Please provide the reference documents [12] and [13] indicated in page 64/93 of the Comparability Study Report:
(b) (4)
7. Please explain how the acceptance criteria of process control parameters for each processing steps were established.
8. In the Comparability Study Report, please clarify how the pilot scale batches were chosen. Please refer to the following Tables listed in the report: Table 8, Table 11, Table 12, Table 13, Table 16, Table 18, Table 19 and Table 20. Please provide the raw data in an excel spreadsheet for individual lot being used in the comparability study report.
9. At step (b) (4)
10. Please provide a complete list of the technical batches used in the mixing studies, along with the following information (if applicable): batch numbers, filling sizes, production scales, manufacture sites, and manufacture dates.
11. Please provide the validation reports for the following step/testing:
 - a) The integrity tests for the (b) (4) filter (b) (4) at Nanofiltration step
 - b) The integrity tests for the (b) (4)
12. For a mixing study, the worst case scenarios should include both the minimum and maximum batches to ensure that (b) (4) at minimum batch size and (b) (4) at maximum batch size can be assessed. However only the maximum (b) (4) was considered in all the mixing studies except the one for (b) (4). Please provide your justification why the

minimum batch sizes were excluded in your studies and why no worst case scenarios were considered in the mixing study for (b) (4). Please provide your estimate of how the worst case conditions may impact the product stability. Please also indicate which lots under the stability studies were manufactured under the worst case conditions. Please provide your justification if no such lots have been included.

13. Please provide the life cycle validation reports for the (b) (4).

Second information Request (Sent October 7, 2015; Response received October 19, 2015)
(Yonggang Wang, Lu Deng, Malgorzata Norton)

1. Please provide the mixing study report for setting the mixing speed range at (b) (4) for manufacturing step (b) (4).

2. Please provide data to (b) (4)

Please also provide assessment of the impact that this variation may have on the quality and purity of the final product.

3. In deviation 21457, it is described that (b) (4)

Please confirm the recounting of the life cycle for the (b) (4) and its impact on the ongoing life cycle study.

4. Please provide the following documents for review:

a. 080VRE10314.103/00: Validation Report IVIG 10% (NewGam) – Manufacture of Clinical Batches

5. Please clarify that under what circumstances STEP (b) (4) and STEP (b) (4) will be included in the manufacturing process of Newgam. Please provide the Batch Records for the (b) (4) steps or direct us to the BLA section containing this information.

6. Deviations 36254, 36261 and 36596, which affected multiple batches during the manufacturing of the consistency lots, were attributed to the use of US plasma. However, according to your IR response (Question 5 of FDA August 27, 2015 Information Request), such deviations did not occur during the manufacturing of the conformance lots which were also derived from US plasma. Please explain.

7. Please submit (b) (4) data for all available lots. Please include: graphs, input/output parameters (including, but not limited to (b) (4)), instrument used, and software version. Please also submit your SOP for (b) (4) testing.

8. Please provide the plasma pool and minipool testing SOPs.

9. Please submit your plasma inventory hold, lookback, and traceability procedure(s).

10. Please submit the SOP(s) on testing, rejection, and release of Raw Materials.
11. Please submit documentation of agreements with Raw Material suppliers, which specify that Octapharma will be notified of any changes to the material.
12. Please submit four (4) consecutive conformance and four (4) consecutive consistency lots, 2 vials each, for research purposes, to the following address:
FDA/CBER/OBRR
Attn: M. Norton /Nancy Eller/Dr. Dorothy Scott
Building 52/Room 4122
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Telephone: (240) 402-8210
Please notify Dr. Dorothy Scott (dorothy.scott@fda.hhs.gov), Ms. Nancy Eller (nancy.eller@fda.hhs.gov), and Ms. Malgorzata Norton (malgorzata.norton@fda.hhs.gov) when the samples are being shipped, and please include the tracking number in the email.

Third Information Request (Sent November 25, 2015; Response received December 11, 2015 and December 18, 2015) (combined with Lu Deng and Yonggang Wang)

1. In your stability studies, the result for parameter of Clarity ((b) (4)) was shown as either “according” or “not demanded”. Please confirm if these meant “pass” or “not determined.”
2. The mixing duration range after ((b) (4)) in your process validation and/or evaluation report (3.2.S.2.5) as well as in mixing study (753RVP007/00). However, in your batch record, the maximum stirring time of ((b) (4)) is not indicated. Please correct it and add the maximum stirring time to your Master Batch Record (MBR).
3. In your mixing study report (753RVP009/02), the validated stirring speed range is set as the range of ((b) (4)), which is different from the one shown in your MBR ((b) (4)). Please clarify this discrepancy and indicate if the range of ((b) (4)) has been validated. Please provide your supporting document(s) which show(s) how the stirring speed range of ((b) (4)) was initially determined. Please provide the following documents for agency’s review:
 - Mixing study protocol ((b) (4)) 753PVP009/02.
 - 753RVP009/01
 - 753RVP009/00
 - 753RVP009/00
 - 753RVP004/01
 - 753RVP004/00
4. Please provide the batch record of ((b) (4)) from Step ((b) (4)) to Step ((b) (4)) Nanofiltration.
5. In your deviation 37097, as part of the CAPA, the procedure 753MOS016 was updated to enable ((b) (4)) is not acceptable, and it is recommended to keep your previous version of 753MOS016 unchanged and modify Master Batch Record accordingly. Please provide a copy of the final 753MOS016 and MBR for review after modifications. Please commit not to releasing the lots ((b) (4)) lots made from lot ((b) (4)) associated with deviation 37097, to the US market.

6. The investigation report for your deviation 25282 indicated that “according to the process experts on the Vienna site, the disruptions to the (b) (4) stage could be the cause of the (b) (4) nanofiltration stage”. Please provide the justification or evidence for this explanation.

7. For deviation 37429, the root causes were not clearly identified but it stated that it could be a combination of several factors let to (b) (4)

8. For the (b) (4) steps, please provide the information on how the (b) (4)-runs in production scale was determined as the lifetime of the (b) (4).

9. Regarding the (b) (4)

10. Please change the Measles Ab specification in the lot release protocol to (b) (4) NIH 176 as agreed to during the PAI.

11. Please provide the short supply agreement for the (b) (4) plasma, which should include: collection, (b) (4), storage, and shipment conditions for (b) (4) plasma for further manufacture into IGIV.

12. Please provide an update on CAPAs 24404 and 25342. Please provide a list of any deviations which have occurred since the implementation of these CAPAs that are related to the same root cause(s).

13. In Deviation 36930, the (b) (4) was out of the (b) (4) range. You mention that you will update the range to (b) (4) due to the range being set incorrectly after (b) (4) technical runs. Please provide a justification on why the range will be changed after only one lot is out-of-range. The process validation should confirm already determined parameters.

14. Following the review of the October 19, 2015 IR response, it is still unclear if all the issues that were encountered during the conformance batch manufacturing were resolved. Please provide a list of the manufacturing changes between the conformance lots and the consistency lots.