

DEPARTMENT OF HEALTH & HUMAN SERVICES



U.S. 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 125587/0 for Immune Globulin Intravenous (Human) 10%

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Subject: **Review Memo BLA – Response to CR letter:** [Octapharma Pharmazeutika Produktionsges.m.b.H, License # 1646] Approval for Immune Globulin Intravenous (Human) 10% liquid preparation supplied in six doses and indicated for the treatment of primary humoral immunodeficiency (PI) and chronic immune thrombocytopenic purpura (ITP) in adults. The drug substance is manufactured at Octapharma facility in Lingolsheim, France (OSA); the final drug product is filled at Octapharma facility in Vienna, Austria (OPG); visual inspection, packaging and labeling of the final drug product are performed at OPG Vienna facility and Octapharma facility in Dessau, Germany (ODE).

Action Due: August 2, 2018

Recommendation:

I reviewed Octapharma's responses to the CR letter items applicable to DMPQ: Outstanding inspectional issues (cleaning and sterilization) from the Pre-License Inspection (PLI) performed October 5-14, 2015, and found them to be acceptable.

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

Background

CBER received this electronic submission on April 15, 2015. Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma) submitted this BLA to provide information to support US market authorization of Panzyga (IND name 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. The product is a liquid formulation and intended for intravenous injection. Panzyga is available in different doses (fill volumes and weights): 10mL, 25mL, 50mL, 100mL, 200mL and 300mL which are presented in the following vial sizes: 20mL, 30mL, 70mL, 100mL, 250mL and 300mL respectively.

CBER performed a Pre-License Inspection (PLI) at Octapharma OSA facility in Lingolsheim [FEI # 3010600159] from October 5-14, 2015 to support the review of the original BLA 125587/0. This was the first FDA inspection of the OSA facility and resulted in nine 483 observations. The deficiencies described in the Form FDA 483 issued at the close of the inspection is an indication that the quality control unit has not been fulfilling its responsibility to assure the identity, strength, quality, and purity of Panzyga. On November 4, 2015, CBER received the response to the FDA 483 observations. Upon review, it was determined that the responses do not sufficiently address the concerns noted during the inspection. The corrective actions do not appear to be comprehensive and they do not address some of the underlying quality issues. Examples include:

- The Panzyga process validation lots were manufactured prior to the implementation of corrective actions associated with Performance Qualification (PQ) non-conformances.
- There is inadequate oversight of the non-conformances associated with the HVAC system for the aseptic core and autoclaves used to sterilize items for use in the aseptic core.
- Equipment cleaning and maintenance deficiencies have been 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.

On February 10, 2016, a Complete Response (CR) letter was issued to Octapharma. In the CR Letter, CBER outlined the deficiencies, and requested implementation of comprehensive corrective actions, to address the inspectional deficiencies and underlying quality oversight issues. CBER also requested the manufacturing of new conformance lots. CBER confirmed that a second pre-license inspection will be necessary to verify the corrective actions once they have been fully implemented.

In addition, information request questions were submitted regarding visual inspection, sterile filtration, container closure integrity testing, and qualification of equipment, as well as product related issues (clinical pharmacology and labeling).

Octapharma requested a Type C meeting (January 19, 2017) to discuss their responses to the CR. Octapharma was satisfied with FDA preliminary responses (January 17, 2017) and cancelled the meeting.

Octapharma submitted the complete responses on January 31, 2018.

INTRODUCTION

Octapharma submitted in their response to the CR letter, the actions taken to address the inspectional deficiencies. They also listed all the regulatory changes implemented since the submission of the BLA at OSA Lingolsheim, OPG Vienna and ODE Dessau facilities.

Octapharma reported that the OSA Line (b) (4) (used for filling of Panzyga in the initial BLA submission, 2015) was dismantled during the 2017 summer shut down, and is currently not used for filling of Panzyga to support the approval of this BLA. They stated that the bulk drug substance (from plasma to (b) (4)) for the new conformance lots produced to address the CR comments, were manufactured in OSA Lingolsheim facility, and shipped to OPG Vienna facility for filling (Q2 2017). They clarified during February 28, 2018 telecon, that OSA Line (b) (4) is currently qualified and is used for filling of non-US licensed products (including Panzyga for the EU and Canadian market).

Octapharma stated that the qualification of the filling line and the validation of the filling operation is not part of the CR letter response, (b) (4). As such, CBER requested during the telecon that all information and/or documentation associated with filling/aseptic operations in OSA to be removed from their submitted response to CR letter in amendment 125587/0.45.

Octapharma submitted the revised response on March 16, 2018 in amendment 125587/0.46, where the following eCTD sections were updated to reflect the removal of information regarding the aseptic/filling operations.

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

Octapharma also confirmed during the February 28 telecon that Panzyga was approved in 2016 for the Canadian/EU market. They clarified that Panzyga is produced using US (b) (4) plasma for both the US and the non-US markets, and as such no manufacturing campaigns (US vs. non-US Panzyga) is required.

The memo includes four sections:

- In the first section of this memo, I reviewed the actions taken and the reports submitted to support the cleaning of the equipment at the OSA Lingolsheim facility CR comment 1.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.
Other information (under DMPQ purview) provided in response to the CR comment 1 regarding inspectional issues of the OSA Lingolsheim facility during the manufacturing of the drug substance is reviewed by Christian Lynch in a separate memo.
- In the second section of this memo, I reviewed Octapharma's responses to CBER comments regarding the operations for OPG Vienna and ODE Dessau facilities (comments 2-12).
- The third section includes facility changes to the OPG Vienna Facility
- The fourth section includes Filling and Visual Inspection of the new PPQ lots.

The inspections were waived for OPG and ODE facilities based on compliance history, as documented in the respective Inspection Waiver memos.

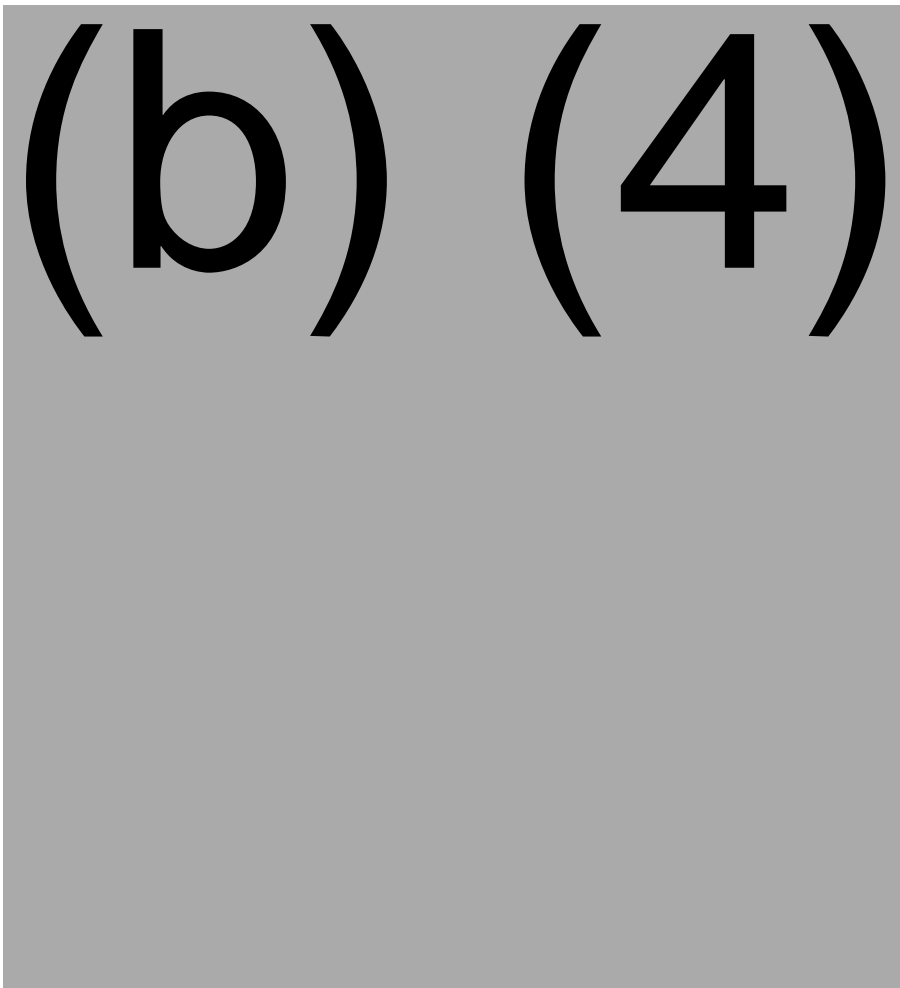
BACKGROUND

- **Manufacturing Process**

The manufacturing process of Panzyga is a continuous process and the drug substance (plasma to final bulk) is manufactured at the OSA Lingolsheim facility from US (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 SD – treatment step, a 20 nm nanofiltration and an ion exchange (b) (4) chromatography. The final product is formulated in glycine. The drug product is filled at OPG Vienna facility. Visual inspection, labeling and packaging are performed at OPG and Octapharma GmbH Dessau facility 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 ≤ 25°C (77°F) for up to 9 months.

- **Manufacturing Steps**



REVIEW OF THE CR RESPONSES

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.*

Octapharma responded to the inspectional issues including the HVAC system supporting the aseptic core. However, Octapharma indicated that the OSA Lingolsheim facility is going to be used only for drug substance manufacturing, and thus they withdrew in amendment 125587/0/46 all submitted information related to the drug product manufacturing operations at OSA including the HVAC of the aseptic core.

The information regarding the cleaning of the equipment used for the drug substance manufacturing operations is reviewed below. All other information submitted in response to Q1 will be reviewed by Christian Lynch and Michael Kennedy in separate memos.

CLEANING OF EQUIPMENT AT OSA LINGOLSHEIM FACILITY

In response to FDA 483 observation regarding the inadequate cleaning validation of equipment, and the use of equipment that is “not visibly clean” for the manufacture of Panzyga drug substance and drug product, Octapharma reported that they performed a comprehensive review of the last periodic re-qualification reports including cleaning validation of all rooms and

equipment related to Panzyga. The review, completed in November 2015 resulted in the following recommendations:

- All equipment/ tanks which were observed with questionable visual inspection results during the initial cleaning validation were re-evaluated by a cross-functional team (Production, Operation Support, Maintenance and Quality)
 - If the outcome of the visual re-inspection by the cross-functional team concluded that the equipment is visibly clean, no re-validation was considered necessary and the equipment will be re-qualified according to corporate cleaning validation procedure *150SOP015 – Cleaning Validation Strategy*, by the next requalification due date.
 - If the equipment was rated as not visibly clean during re-inspection by the cross-functional team, the following steps were followed according to local SOP *780SOP024*
 - A deviation was opened,
 - A systematic scientific assessment of the root cause for the visually unclean observation was performed,
 - Corrective and preventive actions were defined and implemented,
 - Re-validation of the cleaning was performed.

Octapharma reported that the following corrective actions were considered for the equipment deemed not visibly clean:

(b) (4)

Subsequent to the corrective actions, revalidation of the cleaning was executed per corporate procedure *150SOP015, Cleaning Validation Strategy* to include (b) (4) placebo runs and one product-run.

Octapharma submitted the following SOPs related to cleaning and maintenance of equipment:

- *780SOP024/02, Visual Inspection of Production Equipment after Cleaning* (effective 26 Oct 2017)
- *150SOP015/01, Cleaning Validation Strategy, General definition of Cleaning Validation Activities for Production Equipment* (effective 30 Jan 2017)
- *770SOP028/00, Maintenance of Production Tanks* (effective 30 Oct 2017)

SOP *780SOP024/02* defines Octapharma's criteria for visibly clean: (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Review of Cleaning/Sterilization of equipment

In this section, I review the validation studies performed after corrective actions were implemented on equipment that was deemed “*Not Conform*” during the QRB review.

(b) (4)

(b) (4)

(b) (4)

[REDACTED]

(b) (4)

Octapharma provided the results for the cleaning validation including the dirty hold time and clean hold time for the equipment, and the results met the acceptance criteria as summarized in the following Table:

(b) (4)

(b) (4)

Manual Cleaning of Equipment

- 751RQP128/01, *Requalification Report for the Manual Cleaning of Mobile Equipment in the Fractionation and (b) (4) Purification Areas, (b) (4) Process* (approved 10 Oct 2017)

(b) (4) was performed on the following equipment used in the Fractionation and (b) (4) Purification Areas: (b) (4)

(b) (4)

(b) (4)

RESPONSE TO REVIEW ISSUES

Background

The following Table lists the addresses of the OPG Vienna and the ODE Dessau facilities, and the and activities performed at both facilities. OPG and ODE are US licensed facilities, and the Panzyga operations performed at these facilities are similar to those of other US licensed products. The inspections were waived for these facilities as documented in the respective Inspection Waiver memos.

Manufacturing site	Responsibility
Octapharma OPG Oberlaaer Strasse 235, Vienna, A-1100, AUSTRIA FEI: 3002809097 Duns: 301119178	<ul style="list-style-type: none">• Aseptic Filling of the drug product in 10mL, 25mL, 50mL, 100mL, 200mL, 300mL• Quality Control• Visual Inspection• Labeling and packaging• Batch release

Manufacturing site	Responsibility
Octapharma ODE Otto-Reuter-Straße 3, Dessau-Roßlau, 06847 GERMANY FEI: 3008923644 Duns: 312916852	<ul style="list-style-type: none"> • Visual Inspection • Labeling and packaging

Question 2

Please clarify whether the qualifications of the visual inspection/packaging and labeling for the smaller liquid presentations (20 mL and 30 mL) have been submitted and reviewed by the FDA in association with other U.S. licensed products. If they have, please provide the respective STN numbers and explain why you consider the approved procedures to be applicable to NewGam (solution color/clarity). Otherwise, please provide the studies performed to demonstrate that the current packaging lines at OPG Vienna and ODE Dessau facilities can accommodate the visual inspection, labeling, placing in cartons and carton labeling of these presentations.

Octapharma reported that the visual inspection, packaging and labeling of the 20mL and 30mL presentations were previously reviewed in association with Octagam 5%, Octagam 10% and Wilate as shown in the following Table:

Facility	Vial size	Visual Inspection	Packaging and Labeling
OPG	20mL	Qualification performed in 2015 (see report 041VFK054)	Wilate: STN BL 125251/0
	30mL	Octagam 5%: STN 125062/414 Octagam 10%: STN 125062/440	Octagam 5%: STN 125062/296 Octagam 10%: STN 125062/234
ODE	20mL	Wilate: STN BL 125251/50 (visual inspection for transport damages only)	Wilate: STN BL 125251/50
	30mL	Octagam 5%: STN 125062/414 Octagam 10%: STN 125062/440	Octagam 5%: STN 125062/296 Octagam 10%: STN 125062/234 STN 125062/418

Octapharma explained that Octagam, is an IgG-solution with comparable color and clarity to Panzyga, and so no additional qualifications were performed for the 30mL presentation.

For the 20mL presentation (similar to Wilate), Octapharma explained that the visual inspectors are trained on (b) (4) (IgG-solution with comparable color and clarity to Panzyga), and are thus qualified to inspect Panzyga. They added that the semi-automatic visual inspection equipment required new format parts to accommodate the 20mL vials. Additional qualification with the new format parts was performed and the information provided in the following report,

- Report 041VFK054, Adaption of (b) (4) for 10 ml, 20 ml & 125 ml vial format (approved 27 Feb 2015)

The report describes the adaptation of both (b) (4) inspection equipment ((b) (4)) with format parts to accommodate the 20mL vials.

Octapharma added that the existing labelers and cartoning machines, and printing machines for labels and cartons have been qualified for the 20mL and 30mL vials.

Octapharma added that the Visual Inspection at ODE includes the semi-automatic inspection machine (b) (4) which was initially qualified for the 20mL vial size (VAL2015) and is already in use for visual inspection for transport damages of Wilate (STN BL 125251/50). They added that the machine is in use routinely for 100% visual inspection of other (non-US licensed) IgG products in 20 mL vials.

Reviewer comment: Additional clarification was requested about the visual inspection of the smaller presentations as there were contradictory information in the submitted response (Table vs. narrative). Octapharma revised the information provided in amendment 125587/0.50 and the information above was revised accordingly.

Response is acceptable

Question 3

You provided the validation of sterile filtration at the OSA Lingolsheim facility (performed by (b) (4)), and the sterile filtration at the OPG Vienna facility performed by (b) (4). There seems to be a discrepancy between the two validation reports:

(b) (4)

Octapharma stated that the validation of (b) (4) is performed by the filter vendors for their specific filter. Prior to defining the validation approach of the (b) (4) validation, each vendor performed a (b) (4) study to evaluate if the (b) (4) in the product solution and to define the validation approach accordingly.

(b) (4)

(b) (4)

Response is acceptable

Question 4

Please confirm which product filters are utilized for sterile filtration of Panzyga® on Line (b) (4) at the OSA Lingolsheim facility. Additionally, please provide a copy of 764MOS001, Operating Procedure – (b) (4).

Octapharma reported that OSA Lingolsheim Filling Line (b) (4) has been dismantled during summer shut down 2017 according to change control CC 62017.

During a February 28, 2018 telecon, CBER/DMPQ review team requested that Octapharma submit an amendment to withdraw all the information submitted regarding the aseptic core at OSA Lingolsheim including filling Line (b) (4).

Octapharma submitted amendment 125587/0/46 where they stated that the OSA Lingolsheim facility “will only perform manufacturing from plasma to bulk solution (b) (4). Lingolsheim (OSA) manufacturing facility is withdrawn as filling site for Panzyga bulk solution.”

The information provided in response to this question was not reviewed.

Question 5

You provided the interim report 087RPQ13210.000 for the qualification of the vial washer at the OPG Vienna facility. Please submit the final report.

Octapharma reported that Interim report 087RPQ13210.000 covers qualification of 20mL, 30mL, 50mL, 70mL and 100mL vials for several products filled on Filling Line (b) (4) at OPG Vienna.

Reviewer comment: In the initial submission and amendments, Octapharma reported that the validation protocol requires three validation runs for each vial size. However, due to production planning, cleaning validation of the 20mL ((b) (4) completed), 50mL ((b) (4) completed) and 100mL ((b) (4) completed) infusion bottles was still ongoing when this report (087RPQ13210.000) was issued. Thus, additional studies to qualify the cleaning of the 20mL, 50mL and 100mL vials/infusion bottles are needed.

Octapharma stated that only 20mL and 30mL vials were used for filling the Panzyga Process Performance Qualification (PPQ) Batches in 2017 on Filling Line (b) (4) at OPG Vienna facility. They submitted the following reports (reviewed below) for the 20mL and 30mL presentations. For each of these vial sizes a final report was issued:

- 087RPQ15342.000, Report Performance Qualification, Cleaning Validation Bottle Washing Machine (b) (4) – Filling Line (b) (4), 20mL Injection Vials Production (b) (4) (approved 15 Dec 2015)

During the initial qualification in 2013 (087RPQ13210.000), a sampling error for the evaluation of the level of particles occurred for the (b) (4) validation run of the 20mL vials, and thus an additional validation run (b) (4) was performed in 2014. Octapharma provided the results for the different runs in report 087RPQ15342.000.

Following cleaning, the vials were visually inspected and (b) (4) samples were collected. In addition, the (b) (4) was also tested. The results are presented below:

(b) (4)

(b) (4)

- 087RPQ15343.000, *Report Performance Qualification, Cleaning Validation Bottle Washing Machine (b) (4) – Filling Line (b) (4), 30mL Injection Vials Production (b) (4)* (approved 10 Dec 2015)

In report 087RPQ15343.000, Octapharma provided the results already presented in the interim report 087RPQ13210.000 including the results for the three validation runs to support the cleaning of the 30mL vials. Interim report 087RPQ13210.000 was reviewed in the DMPQ review memo dated 17 November 2015. The results met the acceptance criteria.

Response is acceptable

Question 6

You reported that the cleaning validation strategy will be updated (by January 2016) to cover three runs with maximum dirty hold time at the OPG Vienna facility. You also reported that the dirty hold time of vessels (b) (4) as well as (b) (4) vessel (b) (4), will be re-evaluated by January 2016. Please provide the revised cleaning validation strategy and the protocols/reports for the cleaning validation, including the dirty hold times of the (b) (4) vessels.

Octapharma provided the revised cleaning validation strategy 087SOP004/09 which was implemented in January 2016.

- 087SOP004.09, *Cleaning Validation Strategy* (effective 29 Jan 2016)

The revised SOP includes the following updates:

- (b) (4)
-
-
-

Octapharma provided the following reports to document the additional cleaning validation studies performed to comply with the new cleaning validation strategy (i.e. additional runs to validate the dirty hold time). The Table below lists the new validation studies, the validated dirty

(b) (4)

Response is acceptable

Question 7

As discussed during the October 29, 2015 telecon, the (b) (4) method used for CCIT is not adequate as it does not test the exposure of the vials to contamination ((b) (4) to simulate shipping conditions) or identify any critical leaks detected. It was agreed that new container closure validation studies will be performed to address the deficiencies. However, in your written responses (amendment BL 125587/0/28), you stated that you do not plan to revalidate the (b) (4) CCIT (b) (4) using an appropriate positive control. If you plan to use the (b) (4) method for verifying the container closure integrity for NewGam under routine conditions at Octapharma manufacturing facilities, the method should be properly validated.

Octapharma clarified that they no longer use the (b) (4) method to verify container closure integrity, and thus the method will not be revalidated.

They stated that they validated the (b) (4), and it has been in use for all container closure integrity studies.

The (b) (4) system was used for CCIT during stability studies as documented in the following reports. For each study, Octapharma listed the number of samples tested, and the storage conditions (temperature/humidity) for the different lots. The CCIT results were compliant, in that the (b) (4) for the stability samples were less than the positive controls ((b) (4)).

- 000SSR82x.13P003.02/xx CCIT, CCIT of Panzyga, OSA, OPG Intravenous Immunoglobulin Human 10 % SD Study 13P003 (b) (4) months' and (b) (4) months' data (approved 12 Oct 2017)

The CCIT covers different vial sizes and different storage conditions (temperature, humidity and time) during stability studies.

(b) (4) Panzyga batches manufactured at OSA Lingolsheim ((b) (4) 50mL and (b) (4) 300mL filling size), and (b) (4) batches filled at OPG Vienna ((b) (4) 10mL, (b) (4) 25mL, (b) (4) 50mL and (b) (4) 200mL filling size) were put on stability and are tested for container and closure integrity using (b) (4) at selected time points throughout the studies.

The schedule for the stability testing is presented in the following Table:

Storage Conditions: Sealed, (b) (4)	Duration	Testing	Interim Results	Results
Long-term at 5°C	(b) (4) months	0*, (b) (4) months	0, (b) (4) months	Pass
Long-term at 25°C/ (b) (4)	(b) (4) months	0*, (b) (4) months	0, (b) (4) months	Pass
Intermediate at (b) (4)	(b) (4) months	(b) (4) months	(b) (4) months	Pass
Excursion studies (b) (4)	(b) (4)	(b) (4)	(b) (4)	Pass

Storage Conditions: Sealed, (b) (4)	Duration	Testing	Interim Results	Results
	(b) (4)			
Accelerated studies (b) (4)	(b) (4)	(b) (4)	(b) (4)	Pass
*Samples are tested from each configuration at Time 0, which applies to all conditions. Tolerances: temperature (b) (4), relative humidity (b) (4) ** Protocols specified (b) (4) months, but testing performed after (b) (4) months storage				

Octapharma reported that the CCIT (b) (4) testing was performed at the OPG Vienna facility up to the 24 months' time point for all batches. However, CCIT performed after (b) (4) months and (b) (4) months storage for the batches manufactured at OPG Vienna were performed at OPG facility, and the batches manufactured at OSA Lingolsheim were performed at OSA facility.

The current study report comprises (b) (4) months' data of the long-term studies at 5°C and 25°C (b) (4), (b) (4) months' final data of the intermediate condition studies at (b) (4), and (b) (4) months' final data of the accelerated condition studies at (b) (4) of the container closure integrity testing of Panzyga. Octapharma reported that the accelerated data stability studies should have been completed by (b) (4) months, but the final testing was performed after (b) (4) months, and the results were acceptable. The accelerated stability data were reported and reviewed in the initial BLA submission.

Furthermore (b) (4) months' final data of the temperature excursion studies ((b) (4)) were also presented.

Octapharma reported that the studies are completed for all storage conditions, except for the 5°C long term storage where additional sampling will be performed after (b) (4) months' storage.

Octapharma reported the results for all studies, and CCIT results met the acceptance criteria, in that the (b) (4) for the stability samples were less than the positive controls ((b) (4))

- 000SSR82x.14P022.01/xx CCIT, CCIT of Panzyga, OSA, OPG Intravenous Immunoglobulin Human 10 % SD Study 14P022, (b) (4) months' data (approved 12 Oct 2017)

The CCIT covers different vial sizes and different storage conditions (temperature, humidity and time) during stability studies.

(b) (4) Panzyga batches manufactured at OSA Lingolsheim ((b) (4) 50mL and (b) (4) 300mL filling size), and (b) (4) batches filled at OPG Vienna ((b) (4) 10mL, (b) (4) 25mL, (b) (4) 50mL and (b) (4) 300mL filling size) were put on stability and are tested for container and closure integrity using (b) (4) at selected time points throughout the studies.

The schedule for the stability testing is presented in the following Table,

Storage Conditions: Sealed, (b) (4)	Duration	Testing	Results	Results
Long-term at 5°C	(b) (4) months	0*, 24 and (b) (4) months	0 and 24 months	Pass
Long-term at 25°C (b) (4)	(b) (4) months	0* and (b) (4) months	0 and (b) (4) months	Pass
Excursion studies (b) (4)	(b) (4)	(b) (4)	(b) (4)	
Excursion studies (b) (4)	(b) (4)	(b) (4)	(b) (4)	Pass
*Samples are tested from each configuration at Time 0, which applies to all conditions. Tolerances: temperature (b) (4), relative humidity (b) (4)				

Octapharma reported the results for up to (b) (4) months, and all CCIT results were compliant. The (b) (4) months was not completed during the writing of this report.

Reviewer comment: Octapharma reported that OSA Lingolsheim Filling Line (b) (4) has been dismantled during summer shut down 2017 according to change control CC 62017, and that the filling of Panzyga on filling Line (b) (4). As such, Octapharma withdrew the validation of the (b) (4) CCIT performed at OSA Lingolsheim (amendment 125587/0.56).

- 000SSR82x.17P012.00/US, Panzyga, OSA and OPG US Conformance Batches Study 17P012, 3 months' data (approved 22 Nov 2017)

This stability study was initiated following the manufacture of conformance lots in 2017 (10mL, (b) (4) 100mL, and (b) (4) 300mL filling size). One of the batches was manufactured from (b) (4).

This report includes the 3 months' data of the long-term studies at 5°C and 25°C/(b) (4), the intermediate condition studies at (b) (4) and the accelerated condition studies at (b) (4) for (b) (4) batches of Panzyga manufactured at OSA Lingolsheim, France and filled at OPG Vienna, Austria. The results for excursion studies are not reported as the first sampling point is (b) (4) months.

The schedule for the stability testing is presented in the following Table. Octapharma reported that the CCIT results for the first two time-points (0 and 3 months) met the acceptance criteria.

Storage Conditions: Sealed, (b) (4)	Duration	Testing	Interim Results	Results
Long-term at 5°C	(b) (4) months	0*, 3, 6, 9, 12, 18, 24 (b) (4) months	0 and 3 months	Pass
Long-term at	(b) (4) months	0*, 3, 6, 9, (b) (4)	0 and 3	Pass

Storage Conditions: Sealed, (b) (4)	Duration	Testing	Interim Results	Results
25°C/(b) (4)		(b) (4) months	months	
Intermediate at (b) (4)	(b) (4)	(b) (4)	(b) (4)	Pass
Excursion studies (b) (4)	(b) (4)	(b) (4)	(b) (4)	Pass
Accelerated studies (b) (4)	(b) (4)	(b) (4)	(b) (4)	Pass
*Samples are tested from each configuration at Time 0, which applies to all conditions. Tolerances: temperature (b) (4), relative humidity (b) (4)				

Octapharma also provided the following validation report for the CCIT using (b) (4) at the OPG Vienna facility, and it is reviewed below:

- 009VAL193 CCIT (b) (4), *Container and Closure Integrity Testing of Glass Vials with Rubber Stoppers* by (b) (4) with the (b) (4) (approved 22 Aug 2016)

The method was validated using samples from each vial size: 10mL, 20mL, 30mL, 70mL, 100mL, 250mL, and 300mL. The CCIT was performed on vials during media fills where (b) (4) vials and controls (for a total of (b) (4) vials) were evaluated for each size as summarized below. Container closure integrity is demonstrated if there is a significant difference ((b) (4) measurement) between test samples (integral container closure system) and samples with a (b) (4).

In addition, the samples were tested by (b) (4) (with necessary positive/negative controls) to compare the two methods.

(b) (4)

(b) (4)

- 705VAL193 CCIT (b) (4), *Container and Closure Integrity Testing* by (b) (4) with the (b) (4) (approved 13 Dec 2017)

In response to information request, Octapharma submitted amendment 125587/0.46 where they stated that the OSA Lingolsheim facility “*will only perform manufacturing from plasma to bulk solution (b) (4)*”. *Lingolsheim (OSA) manufacturing facility is withdrawn as filling site for Panzyga bulk solution.*”. Thus, the filling operations and container closure integrity testing of the final drug product will be performed at OPG Vienna. Octapharma withdrew the validation of the (b) (4) CCIT performed at OSA Lingolsheim (amendment 125587/0.56).

The CCIT using (b) (4) at OSA was not reviewed

Question 8

The CCIT performed following the transport validation study covers only the 20mL vial presentation. Please provide justification and/or data to demonstrate that the current transport validation study is applicable to all vial presentations during transport with respect to container closure integrity.

Octapharma explained that they considered the 20mL vials as worst case for the following reasons;

(b) (4)

Response is acceptable

Question 9

You provided in amendment BL 125587/0/28 (response to October 30, 2015 information request) the CCIT data collected following transport to verify container closure integrity using the (b) (4)

, and you concluded that the acceptance criteria were met.

You also provided in amendment BL 125587/0/08 (response to June 23, 2015 information request) report 009VAL193 CCIT (b) (4), Container and Closure Integrity Testing of Glass Vials with Rubber Stoppers by (b) (4)

Please provide the acceptance criteria with justification for a successful container closure integrity testing using the (b) (4), as the data presented for the transport studies in amendment BL 125587/0/28 are different from those presented for the validation of the (b) (4) method (report 009VAL193 CCIT (b) (4)).

(b) (4)

(b) (4)

Response is acceptable

Question 10

In your description of the procedures to prevent cross-contamination, it was noted that the clean room concept was amended by additional control measures in order to meet both U.S. and EU requirements. Please provide a detailed summary of these measures and how they were applied to this concept.

Octapharma explained that to meet both EU and US standards, they created a Grade (b) (4) area which is Grade (b) (4) (to satisfy US requirements) as shown in the following Table:

(b) (4)

Response is acceptable

Question 11

With regard to automated equipment cleaning, the acceptance criterion for (b) (4) testing ((b) (4) sampling) was referenced to (b) (4). Please provide a description of the (b) (4) as well as the actual acceptance criterion associated with each applicable piece of equipment. Additionally, please provide the limits for the in-house requirements referenced to the (b) (4) for the equipment washing machines and the (b) (4) concentration for the vial washing machine. Please also describe how these in-house requirements are determined.

(b) (4) sampling

(b) (4)

Question 12

It was reported that CAPA-40299 was opened to implement a controlled procedure for vial integrity (b) (4). Please provide a description/copy of this procedure and a summary of its effectiveness to date.

Octapharma reported that OSA Lingolsheim Filling Line (b) (4) has been dismantled during summer shut down 2017 according to change control CC 62017.

During the February 28, 2018 telecon, CBER/DMPQ review team requested that Octapharma submit an amendment to withdraw all the information submitted regarding the aseptic core at Lingolsheim including Filling Line (b) (4). Octapharma agreed.

Octapharma submitted amendment 125587/0.46 where they stated that the OSA Lingolsheim facility “will only perform manufacturing from plasma to bulk solution (b) (4). Lingolsheim (OSA) manufacturing facility is withdrawn as filling site for Panzyga bulk solution.”

The information provided in response to this question was not reviewed.

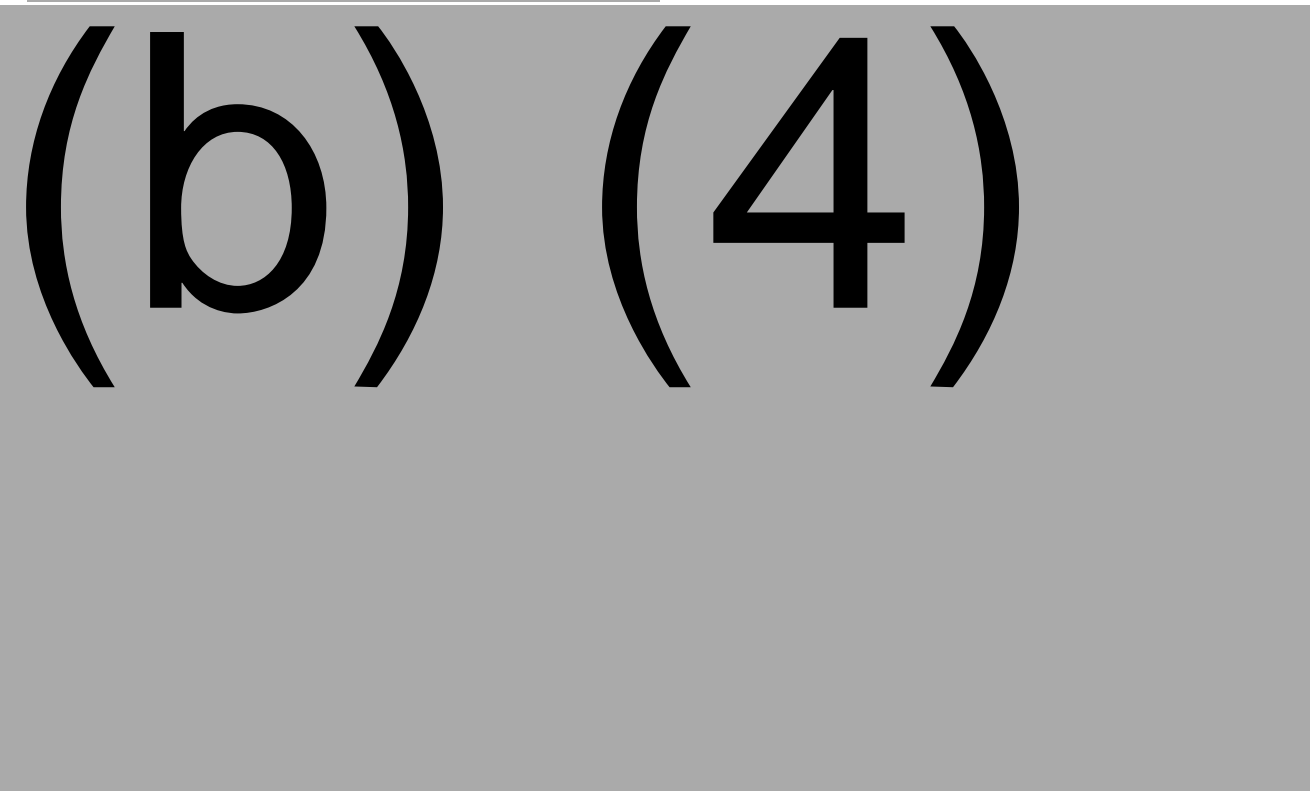


ADDITIONAL CHANGES REPORTED

Octapharma also reported that the following changes were implemented to OPG Vienna facility since the submission of original BLA 125587/0 in 2015.

(b) (4)



(b) (4)



(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

- **Procedures to Prevent Cross-Contamination**

Octapharma added more details to their description of the processes in place to prevent cross contaminations. This includes using a risk based approach for the monitoring in the clean rooms to include “a careful balance between a comprehensive microbiological monitoring program with a high significance and no negative effect on the product. All samples are evaluated with respect to position, activities and criticality in relation to potential negative product impact”.

They also added more details to their Aseptic Process simulation, and frequency of performing media fills in Line (b) (4) and Line (b) (4).

PROCESS VALIDATION

New PPQ batches were manufactured in 2017 following the implementation of the corrective actions in response to form FDA 483 dated October 14, 2015, and subsequent CR letter (February 10, 2016). The PPQ includes the following improvements:

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

Octapharma provided the following PPQ report which included drug substance (bulk manufacturing at OSA), final product filling (at OPG) and visual inspection, packaging and labeling (OPG and ODE)

- 150PPQR1726/00, *Process Performance Qualification: Panzyga at Octapharma Lingolsheim (OSA), Octapharma Vienna (OPG) and Octapharma Dessau (ODE)* (approved 08 Jan 2018)
- 150ADD1726/00, *Process Performance Qualification: Panzyga at Octapharma Lingolsheim (OSA), Octapharma Vienna (OPG) and Octapharma Dessau (ODE)* (approved 16 Jan 2018)

In this review memo, I will cover the drug product filling operations and the visual inspection and packaging operation of Panzyga. The review of the drug substance manufacturing at the Lingolsheim facility will be covered in the Product Office memos.

(b) (4)

(b) (4)

