

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%

From: Randa Melhem, PhD, OCBQ/DMPQ/MRBII

Through: Qiao Bobo, PHD, Acting Branch Chief, OCBQ/DMPQ/MRBII
John Eltermann, Jr., R.Ph., M.S., Director, OCBQ/DMPQ

Cc: Michael Kennedy, PhD, OBRR/DHCR
Christian Lynch, OCBQ/DMPQ/MRBII
Christopher Hooban, OBRR/RPMS

Subject: **Addendum Review Memo BLA:** [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 Linglosheim, France (OSA); the final drug product is filled at the OSA facility and at Octapharma facility in Vienna, Austria (OPG); visual inspection, packaging and labeling of the final drug product are performed at OPG and Octapharma facility in Dessau, Germany (ODE).

Action Due: April 14, 2016

ACTION RECOMMENDED:

A Complete Response (CR) Letter should be sent to Octapharma Pharmazeutika Produktionsges.m.b.H

CR Letter Ready Comments:

Inspectional Issues

1. CBER conducted a pre-license inspection 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 the inspection. Your corrective actions do not appear to be comprehensive and address some of the underlying issues. Examples include:

Octapharma BLA 125587/0 Review (RM)

- 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.

The deficiencies described in the Form FDA 483 issued at the close of the inspection referenced above is 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 pre-license inspection will be necessary to verify the corrective actions once they have been fully implemented.

Review issues

2. Please clarify whether the qualifications of the visual inspection/ packaging and labeling for the smaller liquid presentations (20mL and 30mL vials) have been submitted and reviewed by the FDA in association with other US 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 provide the studies performed to demonstrate that the current packaging lines at OPG Vienna and ODE Dessau facilities can accommodate the visual inspection, labeling, cartooning and carton labeling of these presentations.
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)

■

(b) (4)

4. You provided the interim report *087RPQ13210.000* for the qualification of the vial washer at the OPG Vienna facility. Please submit the final report.
5. 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-validated 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.
6. As discussed during the 29 Oct 2015 telecon, the (b) (4) method used for CCIT is not adequate as the method does not test the exposure of the vials to contamination (b) (4) to simulate shipping conditions, and does not identify the critical leak detected. It was agreed that new container closure validation studies will be performed to address the deficiencies. However, in your written responses (amendment 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.
7. The CCIT performed following the transport validation study covers only the 20mL vial presentation. Please provide justifications and/or data to demonstrate that the current transport validation study is applicable to all the vial presentations during transport with respect to container closure integrity.
8. You provided in amendment 125587/0/28 (response to 30 Oct 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 125587/0/08 (response to 23 Jun 2015 information request) report *009VAL193 CCIT (b) (4), Container and Closure Integrity Testing of Glass Vials with Rubber Stoppers by (b) (4)*

(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 125587/0/28 are different than those presented for the validation of the (b) (4) method (report 009VAL193 CCIT (b) (4)).

SUMMARY

CBER received this electronic submission on 15 April 2015. Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma) submitted this BLA to provide information to support US market authorization of NewGam (Panzyga), 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. NewGam 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.

The manufacturing process was developed at Octapharma facility in Oberlaaer Strasse 235, A-1100 Vienna, Austria (OPG), and pilot scale batches were produced for preclinical and clinical studies at the OPG site. The process was then transferred and scaled up to commercial scale at the Octapharma SAS facility located at 72 rue du Maréchal Foch, 67380 Lingolsheim, France (OSA); and the transfer was validated by manufacture of conformance batches in 2013. Following the transfer, the process was further optimized and consistency batches were produced at OSA facility in 2014.

The manufacturing process of NewGam is a continuous process and the drug substance (plasma to final bulk) is manufactured at the OSA 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 both OSA and OPG facilities. Visual inspection, labeling and packaging are performed at OPG and Octapharma GmbH Dessau facility located at Otto-Reuter-Str. 3, D-06847 Dessau, Germany (ODE).

CBER performed a Pre-License Inspection (PLI) at Octapharma OSA facility in Lingolsheim (FEI # 3010600159) from 05-14 October 2015 to support the review of the original BLA 125587/0. This was the first FDA inspection of this facility. Nine deficiencies were identified during the inspection, and cited as 483 observations. The findings of the inspection are documented in the Establishment Inspection Report (EIR). On 4 Nov 2015, Octapharma submitted in amendment 125587/0/26 a written response that outlined the implemented and proposed corrective actions to address each inspectional observation. ***Review of this response revealed that these corrective actions were inadequate in that they did not fully address the lack of QA oversight with regard to equipment and room qualifications, equipment cleaning validations, deviations, CAPAs, and change controls.***

Octapharma OPG facility in Vienna (Austria) and ODE facility in Dessau (Germany) are US licensed facilities, and the inspections were waived for these facilities as documented in the respective Inspection Waiver memos.

The information provided in the original BLA submission was brief, and lacked details about the qualification of the facility, equipment and the validation of the manufacturing processes. Two telecons (10 June 2015 and 29 October 2015) and four information requests were submitted to request missing/insufficient information: 11 June 2015, 23 June 2015, 23 September 2015 and 30 October 2015, and Octapharma provided additional information in amendments 125587/0/9, 12587/0/8, and 125587/0/17, and 125587/0/28.

The information about OPG Vienna and ODE Dessau facilities and manufacturing operations were mostly covered in the 17 Nov 2015 review memo. Pending issues, not covered in the previous memo, are reviewed in this addendum memo.

The review of OSA facility and equipment, and the production of the drug substance and filling operations of NewGam at OSA Lingolsheim facility are reviewed by Christian Lynch in a separate memo.

INTRODUCTION

In this addendum memo I review the pending items regarding the equipment, container closure, and manufacturing operations for NewGam at the licensed OPG Vienna and ODE Dessau facilities, that were not discussed and reviewed in the 17 Nov 2015 review memo of this BLA. The review will be organized by Topic.

REVIEW OF SUBMITTED INFORMATION

Visual Inspection (VI) and Packaging for the new presentations (300mL and 10mL and 20mL fill volumes for NewGam.

Octapharma provided a very brief description of the equipment and their qualification because the information has been submitted in association with other US licensed products. However, as NewGam is presented in different size bottles (300mL), and vials (20mL and 30mL) than those of the already licensed products, additional information was requested for studies and results performed to demonstrate that the equipment can accommodate the new presentations and the results of the studies (packaging, labeling and VI) to demonstrate that the operations at Dessau and Vienna can handle the different presentations of NewGam. *The information requested is documented in 23 September 2015 and 30 October 2015 information requests.*

• Visual Inspection and packaging operations at ODE Dessau Facility

Octapharma provided in amendment 125587/0/17 the most recent (October 2015) qualifications of (b) (4) packaging lines ((b) (4)). In these reports Octapharma listed the visual inspection equipment, labeler and cartoner used on each line, and the vial/bottle sizes that can be accommodated. Packaging Line (b) (4) is used for lyophilized products, and its labeler is used for labeling the small presentations for NewGam. Packaging Lines (b) (4) are already approved (by FDA) for packaging and labeling for Octagam (STN 125062), Albumin (STN

1251540) and Wilate (STN 125251); and Line (b) (4) is approved for packaging and labeling for Wilate (STN 125251).

The following table provides a summary of the equipment used on each packaging line and their uses for NewGam operations.

(b) (4)

(b) (4)

(b) (4)

- **Visual Inspection and packaging operations at OPG Vienna Facility**

Additional information about the visual inspection, packaging and labeling of the 300mL presentation was requested in the 30 Oct 2015 information request. Octapharma explained in amendment 125587/0/28 that the visual inspection of the 300mL bottles is performed using the existing qualified (b) (4) inspection machines from (b) (4) for lines (b) (4). They explained that the 250mL format part (as already licensed for STN 125062) can be used for the visual inspection of the 300mL bottles as they have the same diameter. So no additional qualification studies were performed.

Octapharma added that the existing qualified labeling machines ((b) (4)) can be used for vial/bottle sizes from 8mL - 500mL. As the 250mL format parts can be used for the 300mL

bottles, no additional studies were performed. However, the cartoning is manually performed for the 300mL bottles.

For the printing on the folding carton, the existing qualified machine ((b) (4)) is used. Cartons used for packaging small vials up to the 500mL bottles can be printed on the ((b) (4)) and therefore, no adjustments or qualifications were needed/performed.

Reviewer's comment: Please clarify whether the qualifications of the visual inspection/ packaging and labeling for the smaller liquid presentations (20mL and 30mL vials) have been submitted and reviewed by FDA in association with other US 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 provide the studies performed to demonstrate that the current packaging lines at OPG Vienna and ODE Dessau facilities can accommodate the visual inspection, labeling, cartooning and carton labeling of these presentations.

Filling Operations at the OPG Vienna Facility

(b) (4)



(b) (4)

[Redacted text block containing multiple paragraphs of information, all obscured by grey boxes.]

They summarized their acceptance criteria for media fills as follows:

Lot size (# of vials filled)	Acceptance criteria/corrective aaActions
< 5000 units	(b) (4)
5000 - 10000 units	
> 10000 units	

(b) (4)

Container Closure Integrity Testing

- The response to Q-19 of 23 Sep 2015 information request is not clear. You reported that the “(b) (4) measurement with the (b) (4) was implemented on 21 Dec. 2012 for non-routine testing of final containers” at the OPG Vienna facility. It is not clear which CCIT method is currently used for routine testing of container closure integrity for NewGam final container at both OPG Vienna and OSA Lingolsheim facilities.

Octapharma clarified in amendment 125587/0/28 that the container closure integrity testing for NewGam final container is performed using the (b) (4) measurement with the (b) (4). The test is performed at OPG Vienna for NewGam manufactured at both sites, OPG Vienna and OSA Lingolsheim facilities.

The (b) (4) test has been used to test the integrity of various vial presentations (20mL, 30mL, 70mL, 250mL and 300mL) during the two stability studies (13P003 and 2014) already reviewed in the Primary review memo (17 Nov 2015).

Octapharma explained that the 100mL container closure is not part of the study; however, the presentation is covered by the other vial/bottle sizes and stoppers as the 70mL, 100mL, 250mL, and 300mL vials are made of the same glass quality, have identical standardized bottle mouth, and use the same stoppers. They added that (b) (4) CCIT studies were performed on the 100mL vials during media fills, and the results were compliant.



Reviewer’s comment: As discussed during the 29 Oct 2015 telecon, the (b) (4) method used for CCIT is not adequate as the method does not test the exposure of the vials to contamination (b) (4) to simulate shipping conditions, and does not identify the critical leak detected. It was agreed that new container closure validation studies will be performed to address the deficiencies. However, in your written responses (amendment 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.

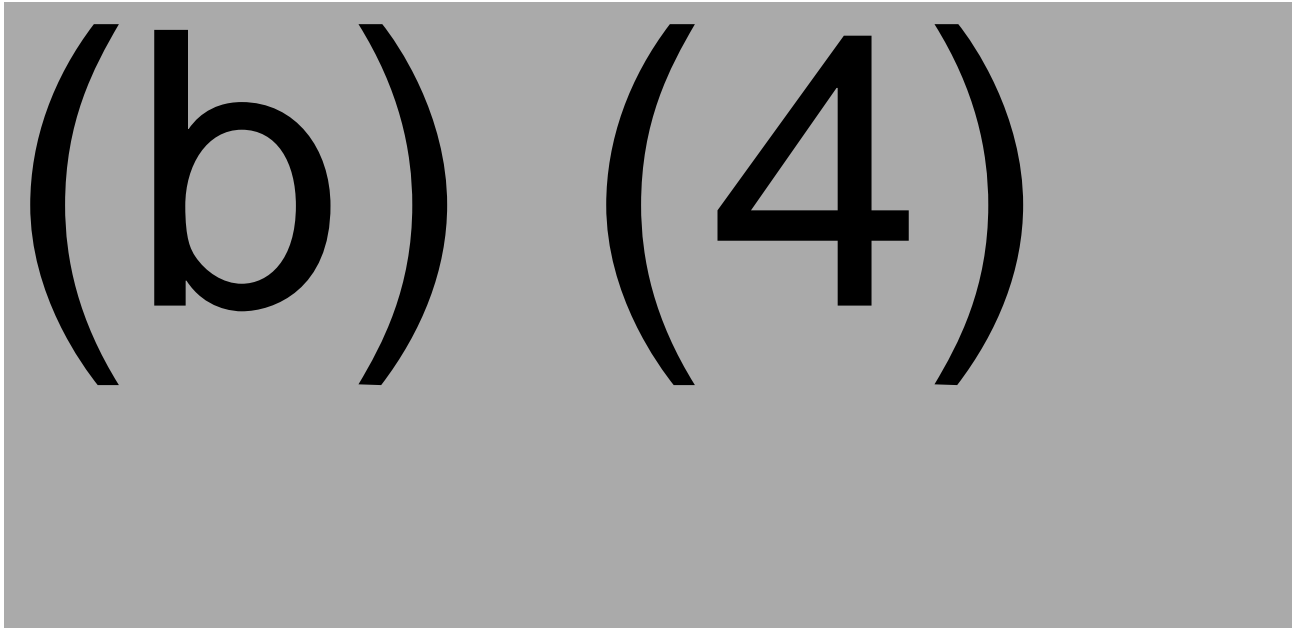
- In response to Q-17 of 23 Sep 2015 information request you provided report 150VRE1529/00 which to describe the CCIT following transport. The information provided about the CCIT was minimal. Please provide the protocol and report for the CCIT to include the positive controls and the critical leak detected. The transport was

performed using 20mL vials; please provide the studies performed to demonstrate container closure integrity for all NewGam vial/stopper presentations.


Octapharma clarified in amendment 125587/0/28 that the CCIT following the transport validation studies was performed using (b) (4)



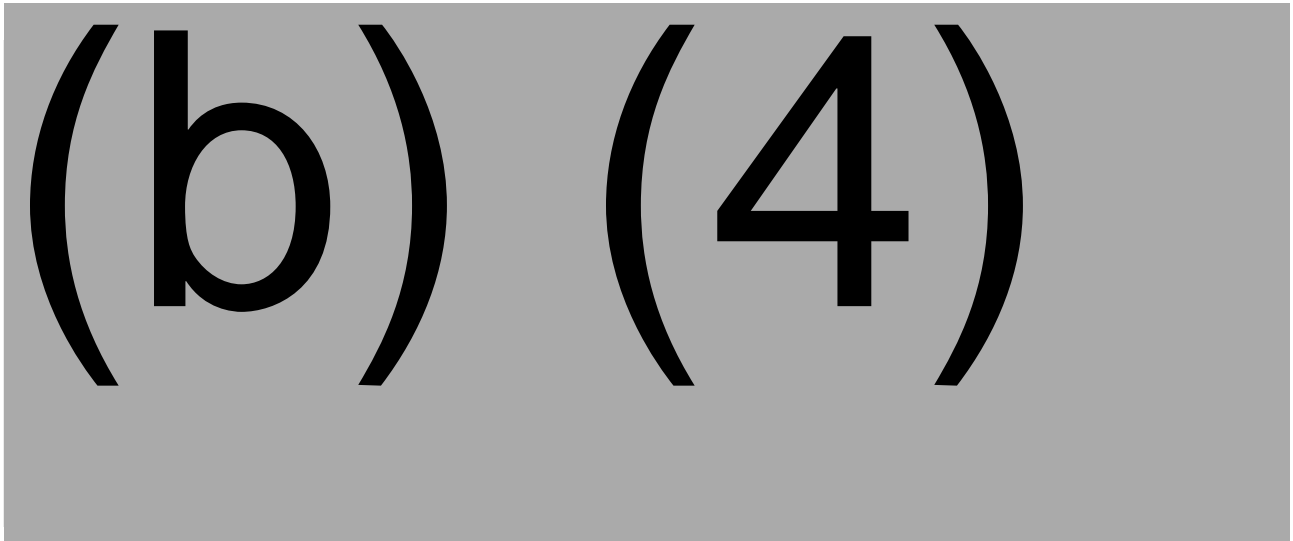
(b) (4)




(b) (4)



(b) (4)



(b) (4)



HVAC System at the OPG Vienna Facility

- **Differential Pressure**

In response to Q-11c of 23 June 2015 information request, Octapharma provided report 080RPQ13217.000 “*Report Performance Qualification according to Qualification Protocol 080VPQ13217.000 Clean Room "in operation" Filling ^{(b) (4)} Change Control CC 7012*”. The PQ was performed during two campaigns which covered the filling of three consecutive batches. Maximum number of operators was in room (b) (4), room (b) (4) and room (b) (4) to simulate worst case conditions.

