

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: Marion Michaelis, 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: **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

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 Pharmazeutika Produktionsges.m.b.H., 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 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).

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, 125587/0/8, and 125587/0/13. *The responses to the last information request are currently under review and will be documented in the addendum memo.*

INTRODUCTION

In this memo I review the facilities, equipment, container closure, and manufacturing operations for NewGam at the licensed OPG Vienna and ODE Dessau facilities. The following Table Lists the address and activities performed at both facilities.

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

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
--	---

This review memo is organized by topic which includes the information provided in the initial submission and subsequent amendments submitted in response to information requests.

The OPG Vienna facility is a US licensed facility, and Octapharma confirmed during the 10 June 2015 telecon, that the filling operations and visual inspection for NewGam are similar to those of other US licensed products. However, they added that NewGam is filled in a new presentation (300mL vial) on the licensed filling Line-(b) (4); and that filling Line-(b) (4) (used for filling of (b) (4) small volume parenterals (SVP) presentations) is not yet approved for filling US licensed products. The description of the facility and utilities and processes that are shared with other US licensed products and already submitted and reviewed in association with other licensed products will be briefly covered in this memo. Equipment and processes specific to NewGam production will be reviewed in detail. This includes the review of the qualification of filling Line-(b) (4) to accommodate the 300mL new presentation; and the qualification of filling Line-(b) (4) and associated equipment and processes.

The ODE Dessau facility is a US licensed facility, and is used for visual inspection (VI), packaging and labeling of US licensed products. The description of the facility and utilities and processes that are shared with other US licensed products and already submitted and reviewed in association with other licensed products will be briefly covered in this memo. The VI, packaging and labeling to accommodate the 300mL new presentation will be reviewed in detail.

The description of the unlicensed 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.

INFORMATION REQUESTS

The following information requests regarding the manufacturing operations at Vienna OPG and Dessau ODE facilities were sent to Octapharma, and the responses are reviewed along with the initial submitted information in the sections below.

10 June 2015 telecon followed by 23 June 2015 information request

Cleaning and Sterilization/sanitization

1. In the BLA submission you presented a summary report of the cleaning validation of the equipment and the acceptance criteria. As we discussed during the June 10 telecon, it was not clear whether (b) (4) sampling was performed and what were the acceptance criteria. Moreover, please describe the (b) (4) sampling and justify the acceptance criteria.
2. Please provide in a Table format the equipment used for Line-(b) (4) and Line-(b) (4) filling (and both lines), the cleaning process ((b) (4), washing machine, manual), and sampling

performed (b) (4). Also include the sanitization/sterilization process used (b) (4), autoclave) for the relevant equipment.

3. In the BLA submission you listed (b) (4) autoclaves used for the sterilization/sanitization associated with Filling Line (b) (4) and Filling Line (b) (4). Please provide a description of the autoclaves, and list the different validated loads and the cycle parameters for the different sterilization/sanitization cycles associated with NewGam production. Clarify if the qualification of the autoclaves and the validation of the sanitization/sterilization of the different loads used in NewGam production has been submitted, reviewed and approved in association with other licensed products (provide STN and approval date). Please state the revalidation program for the autoclaves and provide the latest revalidation report for both autoclaves.
4. You stated that (b) (4) sterilizers (b) (4) are used for stoppers and caps. Please describe the sterilizers, provide the qualification including empty chamber mapping, and the validation of the different loads associated with Line (b) (4) (300mL presentation) and Line (b) (4) (both presentations). Please describe the loads and clarify whether they are defined, or variable.
5. Please list the validated dirty, clean and sterile hold times for the equipment associated with the production of NewGam, and provide supportive data.

Container Closure:

6. There are several vial presentations and stoppers used for the filling of NewGam. As we discussed during the June 10 telecon, there were inconsistencies whether the stoppers were cleaned /sterilized or just sterilized and whether the bottles were (b) (4) or not. Please provide in a Table format the vials used ((b) (4) or not and whether that is performed in house), and stoppers (cleaned, sterilized – in house or by the supplier).
7. You clarified during the June 10 telecon that container closure integrity was tested using the (b) (4) method on several lots filled at OPG and OSA during the stability studies. Please describe the CCIT method used, the number of vials/bottles used and how it was validated (include conditions of testing and positive and negative controls), and provide the results.

Filling Line (b) (4)

8. Line (b) (4) has been approved for the filling of Albumin and Octagam. You stated during the June 10 telecon that the containers/closures used for NewGam are the same as those used for the licensed products with the exception of the 300mL vials – only used for NewGam. Please provide the validation of the vial washing cycle, depyrogenation, filling, stoppering, and capping for the new 300mL presentation.

Filling Line-^{(b) (4)}

9. You confirmed during the June 10 telecon that Line-^{(b) (4)} ((b) (4) product contact equipment: tubing and needles) is not licensed for filling US products; and you added that it is used for filling non-US products. You stated that filling/stoppering is performed using (b) (4) technology (Grade ^{(b) (4)}) and capping is performed using (b) (4) under Grade ^{(b) (4)} air supply. You also stated that the qualification, cleaning and sterilization of stainless steel vessels used to support filling on Line-^{(b) (4)} have not been reviewed/approved by FDA.
10. Please provide the protocols and summary report(s) for the validation of cleaning and sterilization of the vessels and state how that compares to routine operations.
11. As we discussed during the telecon, the following information is necessary for us to review and evaluate the new filling Line-^{(b) (4)}:
 - a. Schematic diagram of the filling./stoppering/capping within the (b) (4) with the locations of the (b) (4)
 - b. Qualification of the equipment and validation of the processes (cleaning, sterilization/ sanitization, depyrogenation, (b) (4), etc...), associated with Filling Line-^{(b) (4)}:
 - i. Vial washer, depyrogenation tunnel, filling/stoppering/capping, (b) (4), and tanks. Please provide protocols and summary reports.
 - ii. For the cleaning and (b) (4) of the (b) (4), please provide validation of the (b) (4) cycle and (b) (4) cycle. Please include schematic diagram/photos showing the locations of the BIs (biological indicators) in the loaded (b) (4) during the validation cycle, and why these are considered worst case.
 1. Are the (b) (4) placed (b) (4) prior to (b) (4)? Please clarify whether (b) (4) testing is performed on (b) (4) after the (b) (4) and provide results of the studies performed.
 - c. Please describe the studies performed and the summary reports for the classification of the (b) (4) and background area under static and dynamic conditions. Please describe EMPQ (environmental monitoring performance qualification) to support the filling of NewGam using Line-^{(b) (4)}, and provide the summary report.
 - d. For routine operations:
 - i. State whether the (b) (4) is monitored and describe the procedure? Please justify your response.
 - ii. Describe the environmental monitoring with justification for viable and non-viable, sampling locations, frequency and duration of sampling.
12. You provided the results of media fill simulation for Line-^{(b) (4)} in the BLA submission. As this is a new filling line, please provide the protocol and results for the aseptic media simulations to include interventions, duration, personnel, etc...

13. You clarified during the June 10 telecon that the (b) (4) is validated for (b) (4) (to include several filling operations) between (b) (4). You added that the (b) (4) hold time was validated by at least (b) (4) media simulation runs – (b) (4). Please state the number of filling operations that can be performed during the (b) (4) and provide the studies performed to demonstrate that you have validated status support filling that number of lots. Please justify your response

23 September 2015 information request

Dessau Facility

1. The Dessau facility is approved for the visual inspection, packaging and labeling of several US FDA licensed products. However as NewGam is presented in different size vials than those of the already licensed products, please provide the qualification studies performed and the results of the studies (visual inspection, packaging and labeling) to demonstrate that the operations at Dessau can handle the different presentation for NewGam final drug product.

Vienna Facility – Filling Line

2. Report 089VRE15018.000_US - IVIG 10% (NewGam): Consistency of Filling on Filling Line (b) (4)
- a. In report 089VRE15018.000 there seems to be a discrepancy in the labeling of the conformance lots. On p. 6 of the document, it is stated that “Batches (b) (4), respectively were filled with filling size 5.0 g and batches (b) (4), respectively were filled with filling size 30.0 g”. However, when summarizing the results (p.15): Batches (b) (4) were filled with 5.0g while batches (b) (4) were filled with 30g. Please explain and justify your response. Please send the correct version.
- b. (b) (4)
- c. (b) (4)
- d. (b) (4)

(b) (4)

- e. You provided the number of vials rejected during the visual inspection for the different lots. Please provide the number of vials rejected during the filling/stoppering/capping/printing operations and the reason(s) for the rejection.

Vienna Facility – Filling Line- (b) (4)

3. You reported that for filling Line- (b) (4), the bulk solution is sterile filtered and transferred via (b) (4).
- Please provide the description and validation of the sterile filtration for the bulk that will be filled on filling Line- (b) (4), as well the (b) (4) filter integrity testing.
 - (b) (4) were used for the bulk associated with the conformance lots manufactured to support qualification of filling Line- (b) (4). Please describe the (b) (4) and provide studies performed and data to support the use of the (b) (4) in the manufacturing process.
 - Please provide media fill studies and results to demonstrate that the (b) (4) can maintain and support aseptic manufacturing.
4. In your response to Q11bi (p. 55/7) of amendment 125587/0/8 regarding the aseptic validation of Line- (b) (4) at the Vienna facility, you stated that “*The performance qualification (covering process, filling line, and personnel) demonstrated a sterility assurance level (SAL) of (b) (4) recommended by (b) (4) for aseptic processing*”. Please explain.
5. Please describe the filling operation to include (b) (4) of the vials, and use of camera(s) for monitoring the filling, stoppering /capping operation. Is there one or more reject stations? Please describe the validated process and specifications. Please describe the frequency of calibration of the (b) (4) stations, counting station and the cameras that monitor the operation.
6. In report OPG_VFVM7031_IQOQ, you reported that the OQ included verification of machinability of the filling machine and filling performance and performance during start mode, verification of the re-dosing, verification of counters and rejects and verification of the machine emptying, and verification of re-stoppering.
- Please describe these processes and the acceptance criteria and the results obtained to support successful qualification.
 - Please explain “re-stoppering”.
7. You provided protocol and report OPG (b) (4) _IQOQ for the qualification of the crimping and coding machine (b) (4). Please provide the testing performed to demonstrate the qualification and functionality of the camera system.

8. You provided protocol and report *OPG_SVP_LINE_IQOQ* for the qualification of the assembled filling Line (b) (4).
 - a. Please provide the routine environmental monitoring for the cooling zone in the depyrogenation tunnel.
 - b. Please provide a summary of the tests performed and data collected during the OQ to verify the functionality of the filling line within the (b) (4).
 - c. Please explain what you mean by verification of the “(b) (4)”?
9. In report 089VRE15012.000/US, *IVIG10% (NewGam): Consistency of Filling on Filling Line* (b) (4), you presented data to support the filling for the 1.0g and 2.5g filled in 20mL and 30mL injection vials respectively. As NewGam is also filled in 5.0g dose (70mL infusion vial) on filling Line (b) (4) – please provide the data to support the accurate filling of this presentation.
 - a. Please clarify whether filling operations on Line (b) (4) incorporate the (b) (4) of each vial before and after filling during routine operations.
 - b. There were several deviations raised during the execution of the protocol; please describe the preventive/corrective actions implemented to address the deviations.
 - c. Please provide the qualification of the camera and the calibration/testing before and after filling operations to ensure that it is performing as intended.
10. You stated that three runs (*PQ_MTC_01 to PQ_MTC_03*) were performed for the validation of (b) (4) of MTC and (b) (4) additional runs ((b) (4)) were used for verification of (b) (4) under worst case (b) (4). Yet the results provided for (b) (4) in report *OPG_SVP MTC_PQR_1* (section 7.24; p.24) refer to (*PQ_MTC_01 to PQ_MTC_03*) for (b) (4). Please explain.

Vial Washer to support Line (b) (4)

11. For the vial washer, you state that the (b) (4); and that the acceptance criterion is (b) (4). Please justify why the set criterion is so high, considering that the acceptance criterion for (b) (4), and your testing results showed (b) (4). Please adjust the acceptance criterion for (b) (4) to meet the standards and the process capability.

Depyrogenation tunnel to support Line (b) (4)

12. Please describe the (b) (4) challenge, (b) (4) recovery, and qualification of Grade (b) (4) in the tunnel.

Cleaning validation

13. For the cleaning validation of vessels (b) (4), the dirty hold time was evaluated in (b) (4). The other vessels were not evaluated for the dirty hold time. Please provide and justify your validation strategy. In addition, the

dirty hold time was not reported for any of the vessels following routine soiling with product, and no data was reported for cleaning following NewGam 10% production. Please explain.

14. The maximum dirty hold time was also validated for vessel (b) (4), but not for (b) (4) – please explain and justify your validation strategy.

Sterilization

15. The sterilization of vessels (b) (4) is performed in Autoclave (b) (4) (load (b) (4)). You provided the validation of the minimum load. Please provide the validation of the maximum load.

Deviations

16. During the validation of filling Line- (b) (4) and filling Line- (b) (4) two deviations were raised due to the gloves failing integrity testing:

- Line- (b) (4): Deviation 37317, (b) (4) failed integrity testing following filling of batch (b) (4)
- Line- (b) (4): Deviation 37388, (b) (4) failed integrity testing after filling batches (b) (4)

Please describe the investigations and provide the corrective/preventive measures implemented to avoid/reduce such incidents in the future

Container Closure

17. You reported that in accordance with transport validation protocol 150VPR1308, the container closure integrity will only be tested in the course of the (b) (4) transport validation. Please explain the reasons for performing CCIT following the (b) (4) and not the (b) (4) validation studies and justify your response.
- a. You also stated that the results of the (b) (4) transport validation, including the CCIT will be summarized in a final report by the end of September 2015. Please submit the report when it is completed.
18. These studies consist of ground transportation, and do not include air-freight which presents different conditions/challenges. It is not clear from the submitted material whether you plan to perform CCIT following air-freight. Please clarify and justify your response.
19. You reported that the container closure integrity of the final container for NewGam (different presentations including (b) (4) stoppers) is “*investigated by (b) (4) with the (b) (4)*”. You provided report 009VAL193 (b) (4) (approved 02 Jul 2015). Please clarify when the (b) (4) test method was implemented. Please describe the CCIT validated and tested prior or during the manufacture of the conformance lots in 2013? Please explain and provide supportive data.

20. You use the terms infusion and injection to describe the bottles and stoppers. Please explain the different terminologies and provide a clear and detailed description of an infusion bottle or stopper, and an injection bottle or stopper.

29 October 2015 telecon followed by 30 October 2015 information request

Dessau Facility

1. In response to Q-1 of 23Sep2015 information request you provided the most recent (October 2015) qualifications of (b) (4) packaging lines ((b) (4)). In these reports you 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 thus it is not applicable to NewGam.

(b) (4)

You also provided the qualification of the following (b) (4) equipment:

- Summary Qualification Report VAL2015/2-S: (b) (4) for 100 % visual inspection
- Summary Qualification Report VAL2045/2-S: (b) (4) for 100 % visual inspection
- Summary Qualification Report VAL2047/1-S: (b) (4) for 100 % visual inspection
 - a. As we discussed during the 29Oct2015 telecon, it is not clear if all these lines are used for NewGam, and whether the qualification of these lines has been submitted, reviewed by FDA in association with other US licensed products. Please clarify and provide the STN numbers if applicable.
 - b. Please explain the reasons for submitting the qualification of (b) (4) (not listed as equipment used on the packaging lines);

and for not submitting the summary qualification reports for (b) (4) which are used on the mentioned packaging lines. If that was an error, please submit the correct reports.

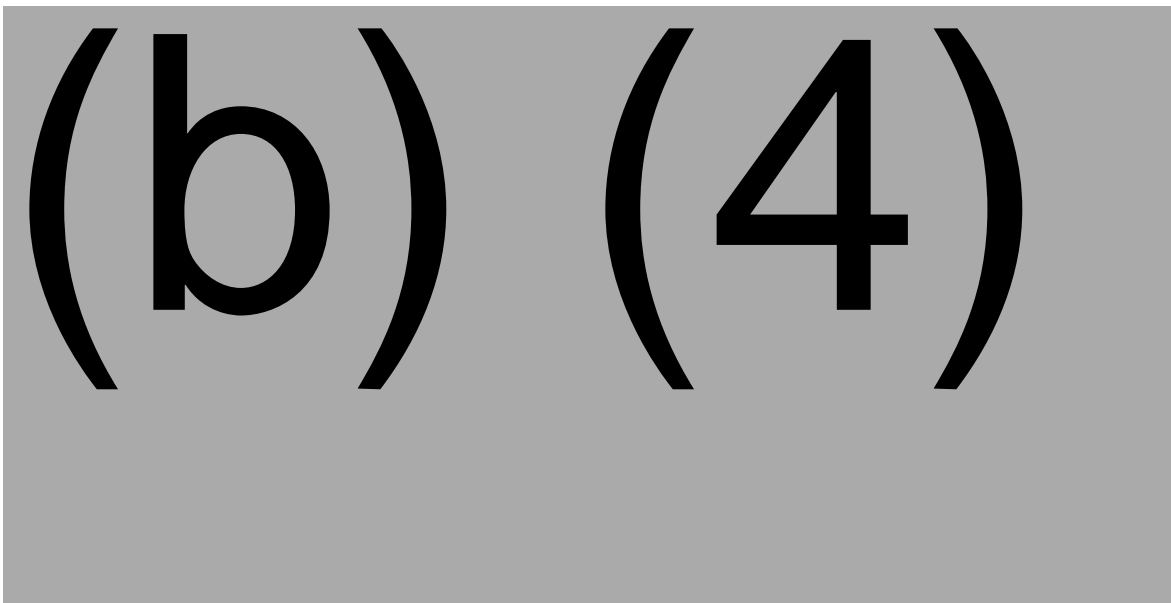
- c. NewGam uses a new bottle size (300mL). You reported in the qualification reports that the cartoner cannot accommodate the 300mL vials. Please describe the process for packaging the 300mL bottles.
- d. Please provide studies performed (using the 300mL vials) to demonstrate that the current packaging lines can accommodate the VI, labeling, cartoning and carton labeling of the 300mL bottles.

Vienna Facility

2. In response to Q-2e of 23Sep2015 information request, you reported in Tables 1 & 2 that (b) (4) vials were rejected for lot (b) (4) and (b) (4) vials were rejected for lot (b) (4) due to printing errors. Please provide the investigation and corrective actions implemented.
3. You reported that for filling Line-^{(b) (4)}, the bulk solution is sterile filtered and transferred via (b) (4) to the filling Line. In response to Q-3e of 23Sep2015 information request, you stated that “Initial and routine media filling on filling line-^{(b) (4)} were carried out without (b) (4) for bulk storage and transfer. However, starting with calendar week 41/2015 first media fills using (b) (4) with subsequent aseptic filling were performed on filling line-^{(b) (4)}. First media fill on filling line-^{(b) (4)} using (b) (4) covered a filling size of (b) (4) in 10 mL vials and (b) (4) in 50 mL vials, respectively. Additional media fills using (b) (4) are already planned and will be performed until end of 2015”.
 - a. Please describe the procedure for sterile filtration into the (b) (4) (including the connections) and the transfer of the product from the (b) (4) to the (b) (4) prior to filling.
 - b. Please describe the media fill studies performed and the results that support this aseptic processing step for filling of NewGam on filling Line-^{(b) (4)}.
4. Your response to Q-4 of 23Sep2015 information request was not adequate as you did not explain your statement “The performance qualification (covering process, filling line, and personnel) demonstrated a sterility assurance level (SAL) of (b) (4) recommended by (b) (4) for aseptic processing”. Please explain.
5. You provided in response to Q-7 of 23Sep2015 information request, the IQ/OQ report and the PQ report. However, there was no information provided in the PQ report except reference to the IQ/OQ report (further qualification) and that all deviations were closed. In that section of the IQ/OQ report it states that (b) (4) defective vials for each size were included and they were correctly identified. Please provide the protocol and report for this study.

6. Your response to Q-13 of 23Sep2015 information request regarding the Dirty Hold Time (DHT) is not adequate. For the (b) (4) vessels, you validated the maximum allowable DHT of (b) (4) for only one run on only one vessel. You applied the same principle for the (b) (4) vessels, where you validated the maximum allowable DHT of (b) (4) for only one run on only one vessel. One run on only one vessel is not adequate validation. Please justify your validation strategy.
7. The same is applicable to your response to Q-14 of 23Sep2015 information request regarding the validation of DHT for the (b) (4) vessels (b) (4) vessels. One run on only one vessel is not adequate validation. Please justify your validation strategy.
8. In response to Q-17 of 23Sep2015 information request you provided report 150VRE1529/00 which would provide CCIT (container closure integrity testing) following transport. The information provided about the CCIT is 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.
9. The response to Q-19 of 23Sep2015 information request was not clear. What method do you currently use for container closure integrity testing for NewGam final container at both OPG Vienna and OSA Lingolsheim. Please clarify.
10. As we discussed during the 29Oct2015 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 studies will be performed to address the deficiencies. Please provide the revised protocol and results of studies performed to demonstrate the container closure integrity for the different presentations used for NewGam.
11. As we discussed during the 29Oct2015telecon, this statement (in 087SOP028.00, Cleaning Validation: Bottle Washing Machine Filling (b) (4) is not clear. (b) (4)
Please explain.
12. You stated in report OPG SVP (b) (4) PQR 2.0.docx that (b) (4)
However, you did not clarify in which load these items (b) (4) were placed, and whether that load was validated. Please explain and justify your response.

13. In response to Q-11c of 23June2015 information request, you provided report 080RPQ13217.000 “*Report Performance Qualification according to Qualification Protocol 080VPQ13217.000 Clean Room "in operation" Filling (b) (4) Change Control CC 7012*”. In this report you presented the acceptance criteria and results for the 1st and 2nd campaign which are summarized below:



- a. Please explain the pressure acceptance criteria, and why the excursions (way outside the set limits) were acceptable. Please justify your response.
 - b. In the same report 080RPQ13217.000, you summarized the non-viable data collected during the manufacture of the three batches during the two campaigns and provided the results in Tables 26 – 29 of the report. Excursions in the particle counts ((b) (4)) in the Grade (b) (4) (Class (b) (4)) occurred during the production of the Batches at (b) (4) monitoring locations. However, you decided to (b) (4) the counts over the span of the monitoring, and concluded that the (b) (4) was within the acceptance limits and thus did not raise a deviation or investigate and determine a root cause. Please explain and justify your response.
14. Please provide studies performed (using the 300mL vials) to demonstrate that the current packaging lines at OPG Vienna can accommodate the visual inspection, labeling, cartoning and carton labeling of the 300mL bottles.

REVIEW OF SUBMITTED INFORMATION

DESSAU FACILITY

The Octapharma Dessau facility (ODE) is located in an industrial area in the western outlying district of Dessau, Germany, and is used for packaging and distribution. ODE comprise an area of (b) (4), of which the commercially used effective surface is (b) (4) in Building (b) (4); and (b) (4) Building (b) (4). Bldg (b) (4) includes IT, Materials Management and Logistics, Laboratory QC, and QA, and Bldg (b) (4) includes Manufacturing (Visual Inspection and Packaging), Technics, QP, QC, and Warehouse.

Octapharma stated that all production areas and warehouses are environmentally controlled. The buildings and all manufacturing and warehousing areas are subject to access controls. The manufacturing personnel enter the manufacturing area through an airlock.

Octapharma provided a site map of the Dessau facility, and the flow diagrams for personnel, sample and waste (Bldg (b) (4)), and flow diagrams for products and materials, and waste (Bldg (b) (4)).

Reviewer's comments: Review of the manufacturing area shows that several VI/packaging and labeling lines are located in Room (b) (4). Octapharma stated that they have implemented physical and procedural barriers to minimize mix-ups as described later in this section of the memo.

The following US licensed products are packaged at the Dessau facility: i.v. Immunoglobulin (STN 125062), Albumin (STN 125154) and Factor VIII/von Willebrand Factor (STN 125251). In addition, other non US licensed products are also packaged at ODE: immunoglobulins, blood coagulation factors (Antithrombin III concentrate, PPSB complex, Factor VIII and Factor IX) as well as Recombinant Factor VIII (Simoctocog alfa). Moreover the facility is also used for handling investigational products (recombinant or plasma derived) and diluents used for reconstitution of lyophilized products - sterile WFI and Solvent (Aqueous 0.1% (w/w), Polysorbate 80 Solution, sterile).

Reviewer's comments: The Dessau facility was inspected and licensed by the US FDA for the packaging and labeling of the following products: 5%, 20% and 25% Albumin (Human), 5% and 10% solvent detergent treated intravenous immunoglobulin (Octagam), and solvent detergent and dry heat-treated von Willebrand Factor/Factor VIII concentrate (Wilate). In 2015, the ODE facility was approved for visual inspection of Albumin and Octagam in association with the following submissions (STN 125154/156; STN 125062/414 and STN125062/440). The facility is scheduled to be inspected by Team Bio early 2016.

Receipt and Processing of NewGam

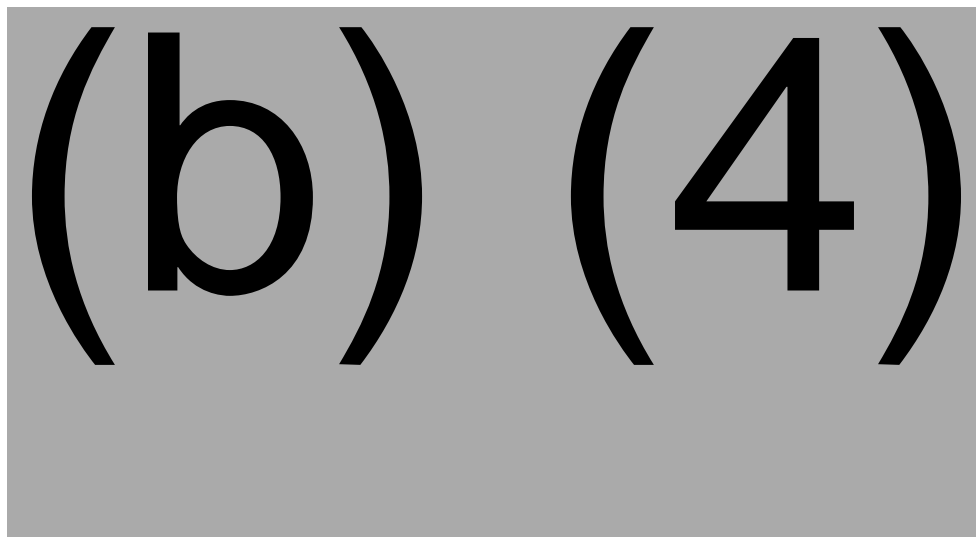
Products are delivered by refrigerated trucks from the manufacturing sites (OSA or OPG) to ODE. The products are subjected to the incoming goods control in the Area Logistics (room (b) (4)). Afterwards they are transported to the warehouse for storage pending release for visual inspection.

After visual inspection the finished products are transferred through the material lock to the warehouse awaiting packaging and labeling.

After labeling, samples for identity testing are collected and brought to QC for verification. Following confirmation of identity, the finished products are packaged and stored in the warehouse awaiting release by QC. The products are then prepared for shipment in the dedicated area of the Area Logistics (room (b) (4)).

Equipment

Octapharma provided a list of equipment, location, and manufacturing operation as presented in the following table. All the equipment is non-product contact and is shared by the different products handled in the facility as shown in the following Table:



They also provided a very brief description of the equipment and their qualifications.

Reviewer's comments: Octapharma provided a very brief description of the equipment and qualification; however, as NewGam is presented in different size bottles (300mL) 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 can handle the different presentations of NewGam. *The information requested is documented in 23 September 2015 and 30 October 2015 information requests. The information provided in responses to these requests will be reviewed in the addendum memo.*

Prevention of Cross-contamination/ Mix-up

Octapharma stated that they have implemented physical and procedural barriers to minimize mix-ups:



Computerized Systems

Octapharma stated that the packaging process is manually monitored; however, certain packaging steps are supported by computerized systems. The packaging machines are often supported by automated monitoring. This monitoring is integrated in equipment by PLC's without any external computers. These packaging machines (inspection machines, labeling machines, cartoner, casepacker, and printing machines) are classified in (b) (4) and the computer validation is performed as part of the equipment qualification where the software and automation hardware are an integral component.

In addition, the Dessau facility has a SAP system for handling administrative operations: packaging orders, warehousing (released or blocked inventory), quality management, tracking and inventory control, etc... They stated that the system is access controlled to ensure that only authorized users perform transactions in SAP. Octapharma added that critical data (recipes, document templates) are controlled by two independent persons and are approved by electronic signatures.

VIENNA FACILITY

The Octapharma Vienna facility (OPG) is located at Oberlaaer Strasse 235 Vienna, A-1100 Austria, and is licensed by the US FDA for the manufacture of the following products: 5%, 20% and 25% Albumin (Human), 5% and 10% solvent detergent treated intravenous immunoglobulin, and solvent detergent and dry heat-treated von Willebrand Factor/Factor VIII concentrate. OPG have several buildings located on a (b) (4) area. The manufacturing operations for NewGam (filling, quality control, visual inspection, labeling and packaging and batch release) are carried out in the following buildings:

Building		Activities
Building (b) (4)		Storage of packaging material
Warehouse	Building (b) (4)	Receipt of NewGam Bulk and shipping of final product
	Building (b) (4)	Storage of NewGam bulk, and final product
Buildings (b) (4)		<p>Pharmaceutical Production</p> <p>Building (b) (4): Plasma storage, fractionation, and purification.</p> <p>R&D laboratories and offices.</p> <p>Building (b) (4) was added in 2004 for the expansion of the filling capacity.</p> <ul style="list-style-type: none">• The (b) (4) houses the gowning facilities, the technical areas for different supply systems, and an archive.• The (b) (4) floor houses the aseptic (b) (4) filling lines (Filling (b) (4)) and (Filling (b) (4)) for infusion bottles. Filling (b) (4) includes an area for bulk holding (b) (4) and for sterile filtration.
Building (b) (4)		QC laboratories, locker rooms, and offices for production management.
Building (b) (4)		Packaging and Storage

Octapharma provided brief summaries about the filling operations for NewGam and associated equipment (including cleaning and sterilization/sanitization) using Line- (b) (4) and Line- (b) (4). Additional information was requested during 10 June 2015 telecon and 23 June 2015 information request by email. Octapharma provided the information in amendment 125587/0/8 received 08 July 2015. Additional information was then requested in a 23 September 2015 information request, and the information was provided in amendment 125587/0/17 on 15 October 2015. The information is reviewed in this memo. ***Further clarification was requested during a 29 October telecon followed by 30 October information request; and the information will be reviewed in the addendum memo.***

Manufacturing Operations of NewGam at OPG Vienna Facility

NewGam drug substance is manufactured at the OSA Lingolsheim facility in France, and either filled at OSA for LVP (large volume parenterals) or shipped (ground transportation) for filling at OPG Vienna facility (Line- (b) (4) for LVP, and Line- (b) (4) for SVP (small volume parenterals)). The

NewGam bulk is received in Receiving/Manipulation (room (b) (4)), and then stored in (b) (4) storage rooms ((b) (4)), and then in Bulk storage rooms (b) (4).

(b) (4)

The sterile filtered product solution is connected to filling Line- (b) (4) under (b) (4) for filling into depyrogenated bottles (SVP). The bottles are sealed with stoppers and crimping caps; and the final containers are placed in closed storage containers and transferred for storage at 2-8°C awaiting visual inspection, labeling and packaging.

Following filling, stoppering, and capping on Line- (b) (4) and Line- (b) (4), the vials are then stored in cool storage awaiting visual inspection performed in either Packaging (b) (4) (room (b) (4)) or Visual Inspection & Packaging (room (b) (4)). Visually inspected and accepted final containers are put into storage containers that are closed and labelled and transferred back to cool storage pending labelling and packaging of final containers in Packaging (b) (4) (room (b) (4)), Packaging (b) (4) (room (b) (4)) or Visual Inspection & Packaging (room (b) (4)). The bottles are inspected and labeled, put into cartons that are sealed by temper-evident labels. Single packs are further packed into multi-packs of 6 or 12 bottles, which in turn are packed into shipping cartons which are then transferred to cooling storage rooms awaiting shipment. The shipping cartons are loaded onto trucks at the exit of Delivery/Manipulation (room (b) (4)).

Octapharma reported that NewGam shares areas and equipment with the following products at the Vienna facility – this includes sterile liquid and lyophilized products aseptically filled as well as terminally sterilized liquid products.

Product	Product Type	Status - Product Licensure
Albumin (STN 125154)	Plasma Protein Fraction	US, CA, EU and other countries
i.v. Immunoglobulin (STN 125062)	Immunoglobulin preparation	US, CA, EU and other countries
(b) (4)	Blood Coagulation Factor	EU and other countries, submitted to (b) (4)
Factor VIII/von Willebrand Factor (STN 125251)	Blood Coagulation Factor Complex	US, CA, EU and other countries
Factor IX	Blood Coagulation Factor	EU and other countries
(b) (4)	Blood Coagulation Factors	EU, CA and other countries; submitted in (b) (4)

Investigational products of human plasmatic origin might be also processed in the same areas.

They provided the list of shared production areas in Table 1 of eCTD section 3.2.A.1.2 – Other products in the same area (Vienna Facility). They also provided a list of equipment used for the production of NewGam at the Vienna facility; and indicated that the equipment was shared with other products manufactured in the facility.

Container Closure

NewGam is a liquid formulation and intended for intravenous injection. It is available in six different presentations 10mL, 20mL, 50mL 100mL, 200mL and 300mL. Octapharma provided the description for the primary packaging (vial, stopper, and cap) for NewGam used at OSA Lingolsheim facility and OPG Vienna facility as summarized below.

Container closure system	Comments
Vials: Glass (b) (4) supplied by (b) (4)	20mL (10mL dose)
	30mL (20mL dose)
	70mL (50mL dose)
	100mL (100mL dose)
	250mL (200mL dose)
	300mL (300mL dose)
Stopper: Bromobutyl rubber, (b) (4) supplied by (b) (4)	20 mm light grey ((b) (4) coating) – used at OPG for the 20-70mL vials.
	32mm light grey ((b) (4) coating) – used at OPG for the 70mL-300mL vials.
	32mm light grey ((b) (4)) – used at OSA for the 100mL-300mL vials.
Cap: Aluminum flip off supplied by (b) (4)	20mm blue cap – used at OPG for the 20-50mL vials.
	32mm white cap – used at OPG and OSA for the 70mL-300mL vials
	32mm red cap – used at OPG for the media fills.

The vials are (b) (4)

(b) (4)

Octapharma also confirmed during the 29Oct 2015 telecon that the washing/sterilization of the stoppers in (b) (4) has been submitted and reviewed by FDA in association with other licensed products.

Container Closure Integrity Testing

In the initial submission, Octapharma reported that container closure integrity testing (CCIT) was performed on NewGam final product during stability studies. They stated that the CCIT using (b) (4) was performed at different time points throughout the studies. Octapharma clarified in amendment 125587/0/8 that for each scheduled CCIT point (b) (4) samples

of each batch and storage condition are tested for container closure integrity by (b) (4) using the (b) (4).

They submitted in the initial submission the reports for the following two studies and stated that both studies are ongoing and will continue throughout the proposed shelf life of the product.

- Report 14P022.00/US, CCIT of IVIG 10 % (NewGam) Intravenous Immunoglobulin Human 10 % SD, OSA, OPG - Initial data (issued 26 Feb 2015)

Octapharma reported that the container closure testing was performed on (b) (4) NewGam final containers put on stability: (b) (4) batches manufactured at OSA Lingolsheim Line-(b) (4), (50mL and 300mL filling sizes), and (b) (4) batches filled at OPG Vienna Line -(b) (4) (10mL and 25mL filling sizes) and (b) (4) batches filled at OPG Vienna Line -(b) (4) (50mL and 300mL filling sizes). All samples are stored in an (b) (4) to assess a possible impact of the stoppers on the product. The product final containers are stored under different conditions as listed below and tested as at the marked (x) time points.

Study	Storage condition	Incubation Time / Months		(b) (4)
	(b) (4), sealed, (b) (4)	0	24	
Long Term	+5°C ± 3°C	x	x	
	+25°C (b) (4)		(b) (4)	
Temperature Excursion	+5°C ± 3°C			
	+25°C (b) (4) (b) (4)			
x = scheduled testing point				

In this study – the initial CCIT performed and the results showed that the container closure integrity of all batches was maintained at the start of the study.

- Report 13P003.00/US, CCIT of IVIG 10 % (NewGam) Intravenous Immunoglobulin Human 10 % SD, OSA, OPG - 6 months' data (issued 24 Feb 2015)

In this study report, Octapharma reported the results of container closure testing at the beginning of the stability study as well as testing performed after six months storage under different conditions. The study includes (b) (4) batches manufactured at OSA Lingolsheim Line-(b) (4), (50mL and 300mL filling sizes), and the batches filled at OPG Vienna Line -(b) (4) (10mL and two 25mL filling sizes) and (b) (4) batches filled at OPG Vienna Line -(b) (4) (50mL and 200mL filling sizes). All samples are stored in an (b) (4) to assess a possible impact of the stoppers on the product. The product final containers are stored under different conditions as listed below:

Study	Storage condition (b) (4), sealed, (b) (4)	Incubation Time / Months				(b) (4)
		0	1	6	24	
Long Term	+5°C ± 3°C	x				(b) (4)
	+25°C/(b) (4) (b) (4)				(b) (4)	
Accelerated	(b) (4)					
	(b) (4)			(b) (4)		

Temperature Excursion	(b) (4)						(b) (4)	
x = scheduled testing point * performed after 9 months storage								

In this study – the initial CCIT performed and the results showed that the container and closure integrity of all batches was maintained at the start of the study.

For the accelerated stability study which has a duration of (b) (4) months, the samples were tested for container closure integrity after (b) (4) months storage (not (b) (4) month), and the results showed that the container closure integrity of all batches was maintained after (b) (4) months storage at (b) (4).

Octapharma did not describe the (b) (4) method and they did not provide validation studies for CCIT in the initial BLA submission. In response to information requests, Octapharma explained in amendment 125587/0/8 that they have been using the (b) (4) test, but decided to switch to the (b) (4) test because it is a (b) (4) physical test which is (b) (4) testing and (b) (4). As the (b) (4) test is (b) (4), the (b) (4) samples collected per time point per batch per storage condition (for CCIT) will be used for other analytical tests and sterility tests performed as part of the stability studies.

They also submitted report 009V AL193 CCIT (b) (4), *Method Validation Report for Container and Closure Integrity Testing of Glass Vials with Rubber Stoppers* by (b) (4) with the (b) (4) (approved 02 Jul 2015).

Octapharma reported that they validated the (b) (4) method using media filled vials of different sizes and the respective closures. The CCIT was performed on (b) (4)

(b) (4)

(b) (4)

(b) (4)

However review of the validated (b) (4) testing (to demonstrate the container closure integrity of the final container) as described in SOP 131SOP021/02, *Container Closure Integrity Test* (effective 31 Oct 2012) indicates the following deficiencies in the testing method:

- The test vials (including positive controls) (b) (4)

- (b) (4)

Reviewer's comments: The (b) (4) method was discussed during the PLI, and Octapharma was informed that the (b) (4) method is inadequate and that this is considered a review issue. This was reiterated during a teleconference on 29 Oct 2015, where the firm was informed that the (b) (4) method is inadequate and Octapharma agreed to revalidate this method. However, in their written response to the information request (amendment 125587/0/28), Octapharma stated that they do not plan to revalidate the (b) (4) test as the container closure integrity was demonstrated by the (b) (4) method using (b) (4). *Further discussion about CCIT will be documented in the addendum memo.*

Qualification of Equipment

Filling Line (b) (4)

(b) (4)

(b) (4)

(b) (4)

Filling/Stoppering/Capping

Octapharma also provided report 057RPQ157_00, *Summary report of IQ/OQ of machines processing 300 mL vials at filling line (b) (4) productions OPG* (approved 23 July 2014). In this translated version (approved 06 July 2015), they listed the tests performed to accommodate the washing, depyrogenation, filling, stoppering and capping of the new 300mL vials, and stated that they were acceptable.

In response to information request, Octapharma provided in amendment 125587/0/17 additional information regarding the filling operation on the Line-^{(b) (4)} and the verification of the filling accuracy. The filled vials are (b) (4)

(b) (4)

Octapharma described in the original BLA submission the qualification of Filling Line-^{(b) (4)} for filling 300mL bottles and submitted the media simulations to demonstrate aseptic filling, and the production of NewGam conformance lots as described below.

Media Fills

(b) (4)

Review of the report demonstrated that results met the acceptance criteria with no contaminated vials.

Conformance Lots:

Octapharma also provided Report 089VRE15018.000_US - IVIG 10% (NewGam): Consistency of Filling on Filling Line (b) (4) (approved 06 Mar 2015) to demonstrate that the filling of NewGam using 300mL vials on filling Line-^{(b) (4)} yields a product of consistent quality.

(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Crimping and Printing

Octapharma provided a schematic diagram of the crimping and printing equipment which includes the directional transport/conveyance of the vials. Prior to capping and crimping, the stoppered vials are checked to ensure proper stoppering. Properly stoppered vials are transported to (b) (4) (Grade (b) (4) air supply) where they are capped and crimped. Incorrectly crimped vials are rejected from the line via reject station (b) (4). Accepted vials are then imprinted with a unique number code. Incorrectly printed vials are rejected via reject station (b) (4). Accepted vials are transported through to the collector table.


The equipment consists of the following stations: (b) (4)

[REDACTED]

In addition the

equipment has few mechanical adjustments thus format changeover (for different presentations) can be carried out rapidly.

Octapharma provided in amendment 125587/0/8 the protocol and report OPG_(b) (4) _IQOQ for the installation and operational qualification of the Fully Automatic Crimping and Coding Machine (b) (4) . The IQ/OQ protocol was created and executed by (b) (4) (the supplier) from 11 Feb to 16 Mar 2013. The IQ included (b) (4)


A large rectangular area of the document is redacted with a solid grey fill, obscuring several lines of text.

Octapharma reported that the IQ/OQ was successfully completed and the deviations were addressed and additional testing performed and was successfully completed.


Reviewer's comments: Additional information about the Qualification of the camera was requested, and the information provided in amendment 125587/0/17 was incomplete. *More information was requested, and the qualification of the camera will be reviewed in the addendum memo.*

IQ/OQ of Assembled filling Line

(b) (4)

A rectangular area of the document is redacted with a solid grey fill, obscuring several lines of text.A rectangular area of the document is redacted with a solid grey fill, obscuring several lines of text.A rectangular area of the document is redacted with a solid grey fill, obscuring several lines of text.

(b) (4)

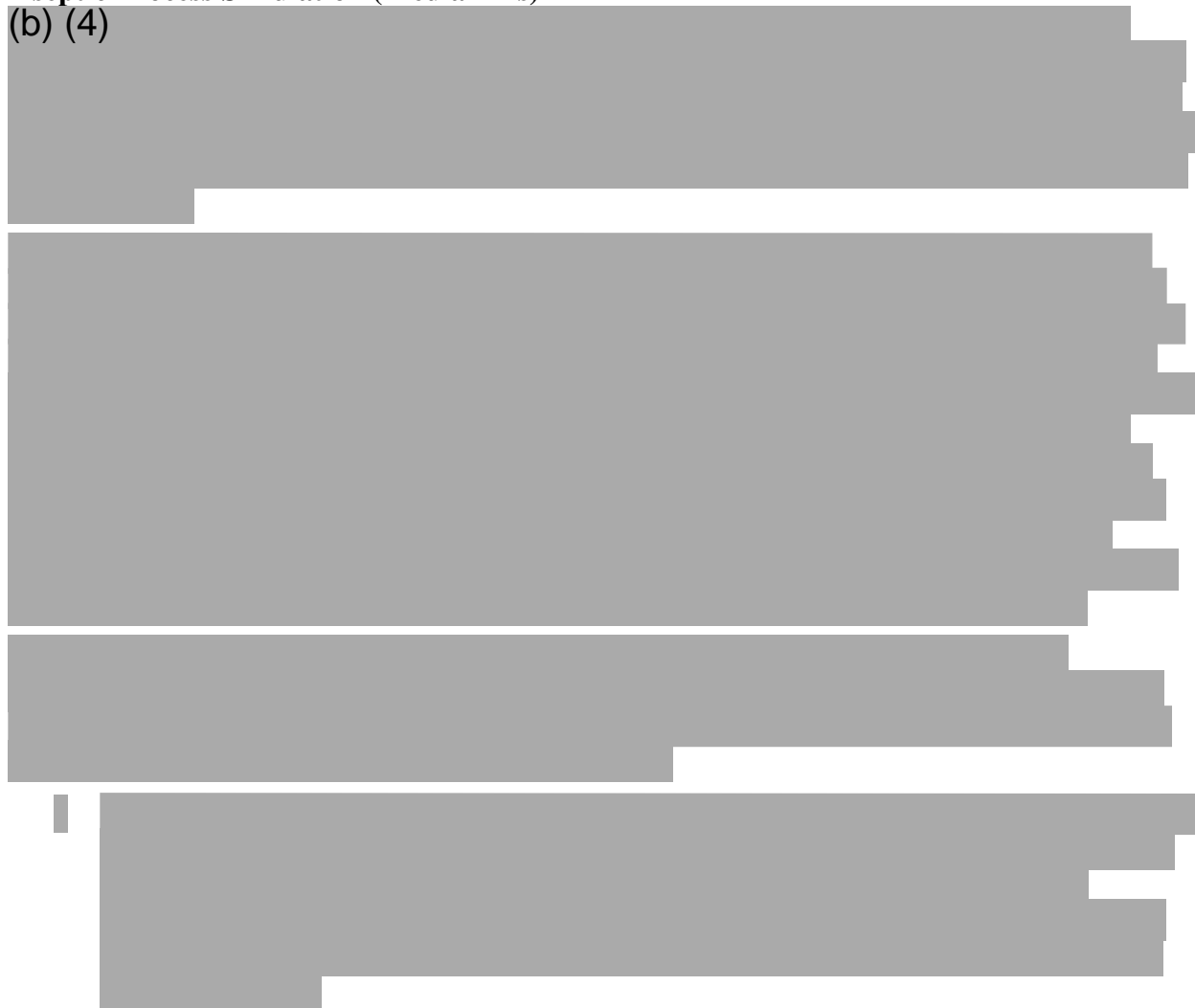


Performance Qualification (PQ) of Assembled Filling Line


For the PQ of filling Line-^{(b) (4)}, Octapharma provided aseptic media simulation studies (20mL, 30mL and 70mL vials) and filling of conformance lots (20mL and 30mL vials).

Aseptic Process Simulation (Media Fills)

(b) (4)




(b) (4)

A large section of the document is redacted with a grey box. The redaction covers approximately the top half of the page, starting below the first (b)(4) label and ending above the Process Validation section.

Process Validation (conformance Lots)

Octapharma provided (in the initial submission) report 089VRE15012.000/US, IVIG10% (NewGam): Consistency of Filling on Filling Line (b) (4) (approved 06 Mar 2015) to demonstrate that the filling of NewGam using filling Line-^{(b) (4)} yields a product of consistent quality.

(b) (4)

A large section of the document is redacted with a grey box. The redaction covers approximately the middle section of the page, starting below the Process Validation paragraph and ending above the large (b)(4) label.

(b) (4)

(b) (4)

(b) (4)

Visual Inspection

Octapharma also reported that (b) (4) batches (b) (4) were visually inspected at OPG and batches (b) (4) were visually inspected at ODE. They provided the list of defects and the acceptance criteria of % rejected vials per critical, major and minor defects, and the visual inspection results for the six batches. All results met the acceptance criteria as summarized below:

(b) (4)

HVAC System

The Vienna Facility is a US licensed facility and the HVAC system has already been reviewed and inspected by FDA in association with other licensed products.

Clean Room Grades (b) (4) and office areas (Grade (b) (4)) of Production (b) (4) are ventilated by individual Air Handling Units (AHU) equipped with (b) (4) HEPA-filters. The Plasma Donation Control area, Packaging area and the Main Storage area specified as Clean Room Grades (b) (4) are supported by separate AHUs, where (b) (4) filters are installed.

The supplied air (b) (4) is filtered through a (b) (4)

A central System for Controlling and Data Acquisition (SCADA) is used for monitoring and controlling temperature, moisture and/or differential pressure in the production rooms of Grades (b) (4).

Octapharma provided a list of (b) (4) AHU that support the different areas, and listed the number of filters installed and the rate of recirculated air. Pharmaceutical production area Grade (b) (4) are supported by AHU (b) (4) with no recirculated air. All other areas are supplied with (b) (4) air depending on the activities in the area.

The filling operations for NewGam are performed on Filling Line- (b) (4) and Filling Line- (b) (4).

(b) (4)

The HVAC system was validated by IQ/OQ/PQ studies and re-qualification is performed when changes on the system are made. The aseptic area is qualified (b) (4) with media fills. In addition routine monitoring is performed depending on the activity and room classifications. Octapharma provided the schedule of monitoring for the different areas and the acceptance criteria. Pressure differential, humidity and temperature are continuously monitored for the aseptic filling area, and air velocity is continuously monitored for the Grade (b) (4) operations.

More detailed information was requested about the classification and monitoring of new filling Line- (b) (4) and Octapharma provided the information in amendment 125587/0.8 reviewed below.

Octapharma provided a schematic diagram of the filling Line- (b) (4) area (presented below) and stated that the filling operations are located within an (b) (4) (Grade (b) (4)) located in room (b) (4) (Grade (b) (4)).

(b) (4)

They added that (b) (4) AHU units are used for the filling operations and supporting areas as summarized below:

(b) (4)

Octapharma listed in chronological order the studies performed to qualify the HVAC system for the new filling Line-^(b)₍₄₎ area and to demonstrate that it can support the required room classification:

(b) (4)

(b) (4)

Report 080RPQ13217.000, Performance Qualification of Clean Room in operation: Filling
Change Control CC7012 (approved 02 May 2014)

The PQ was performed during (b) (4)

(b) (4)

(b) (4)

Environmental Monitoring

In response to information request (23 Jun 2015), Octapharma described the environmental monitoring program with justification for viable and nonviable sampling locations and frequency of sampling.

They explained that the initial sampling locations for viables and non viables during filling operations in the (b) (4) were based on risk assessment 057RAN114 performed on 24 Apr 2012). This included (b) (4) sampling positions for active viable counts and continuous non-viable counts placed in critical areas near filling operations ((b) (4))

(b) (4)

Based on the risk assessment study, Octapharma executed a (b) (4) -phase validation program to evaluate their EM program:

(b) (4)

(b) (4)

(b) (4)


(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)



Validation/Qualification of Equipment

Octapharma provided a list and very brief description of the major equipment used for the manufacture of NewGam at the OPG Vienna facility and stated that the equipment is shared with other products. They provided very brief description of the IQ/OQ/PQ of the bulk holding (b) (4), filling Line- (b) (4) and Line- (b) (4), equipment washing machines, and autoclaves.

They also provided brief description of the cleaning (manual, (b) (4), washing machines) and sanitization/sterilization ((b) (4), autoclaves), depyrogenation tunnels and dry heat ovens as well as (b) (4) of the (b) (4). They provided summary data for with no details. They added that no deviation occurred during the execution of these validations.

The information provided in the initial submission lacked the details for a comprehensive review. In response to information request, Octapharma provided in amendment 1255870.8 the qualification of the equipment as well as the validation of cleaning and sterilization of the equipment used.

Cleaning and Sterilization

Octapharma stated that (b) (4) systems ((b) (4)) are used for cleaning and sanitization of equipment in place such as e.g. stainless steel tanks or other multi-use equipment or piping.

The cleaning & sterilization/sanitization process is performed according to the following sequence: (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's comments: During the PLI at the Lingolsheim OSA facility, I had a discussion with Mr. Christian Weiner (head of Corporate Operation Support, Vienna), regarding the acceptance criteria for the protein (b) (4), and that the acceptance criteria should demonstrate the cleanliness of the equipment to prevent cross contamination between different products that share the equipment. He agreed that they will adjust their acceptance limits.

They also provided the most recent cleaning validation reports for the equipment used for filling Line- (b) (4) and filling Line- (b) (4). However as filling Line- (b) (4) is an approved line, I review below the cleaning validation associated with the equipment of filling Line- (b) (4).

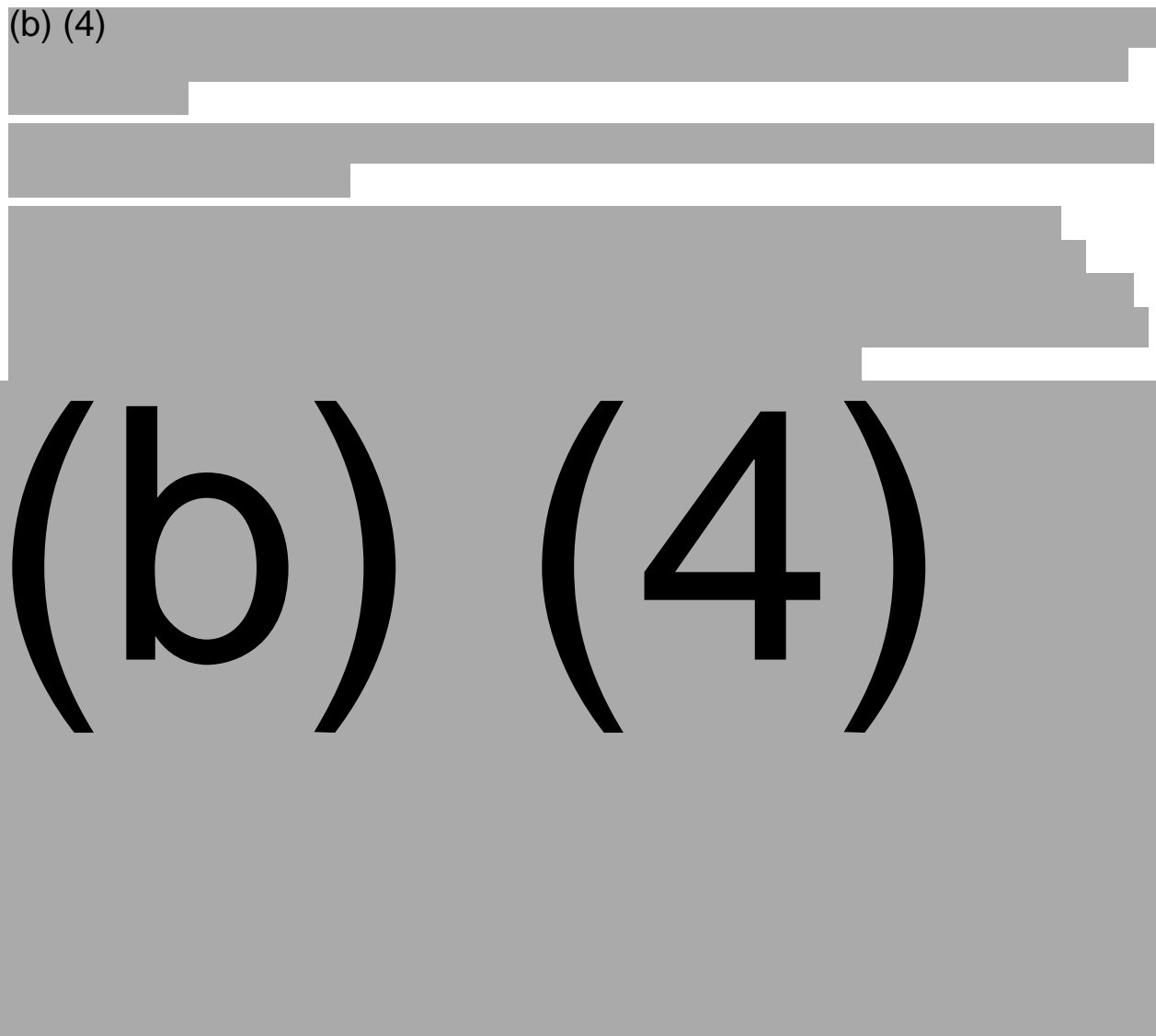
Octapharma clarified during the 10 June 2015 telecon that the (b) (4) stainless steel vessels ((b) (4)) used as (b) (4) vessels for filling on Line- (b) (4), and (b) (4) vessels (b) (4) have not been submitted and reviewed by FDA. They provided the summary reports in amendment 125587/0.8 reviewed below.

(b) (4) Vessels

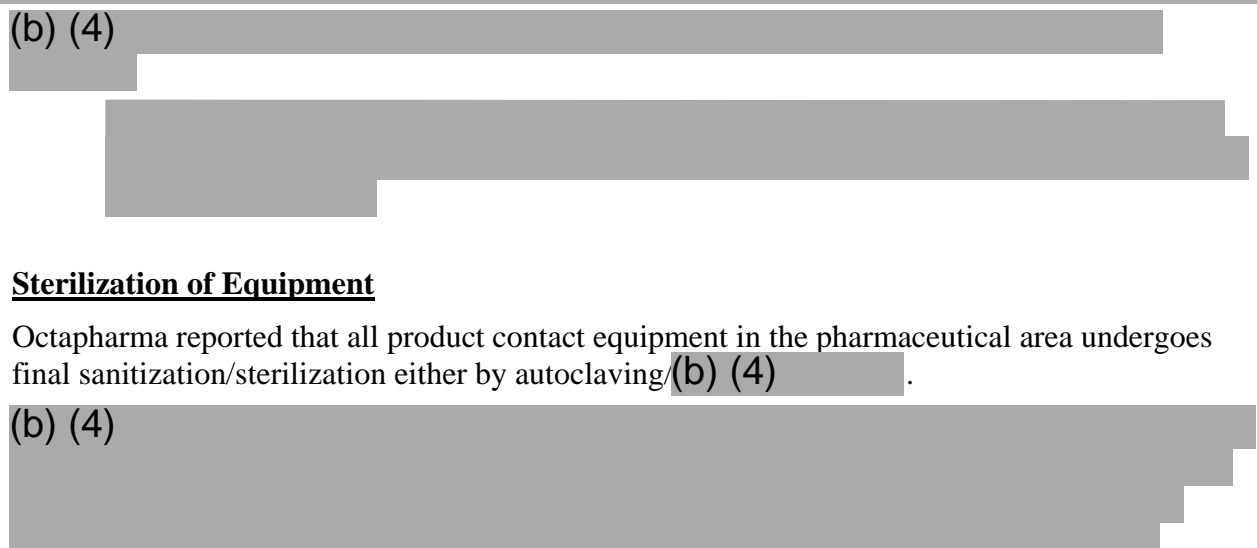
(b) (4)

(b) (4)

(b) (4)



(b) (4)



Sterilization of Equipment

Octapharma reported that all product contact equipment in the pharmaceutical area undergoes final sanitization/sterilization either by autoclaving (b) (4) .

(b) (4)

(b) (4)

Visual Inspection

The visual inspection of the final containers is performed in (b) (4) rooms, also used for Packaging (b) (4) (room (b) (4)) or Visual Inspection & Packaging (room (b) (4)). Following inspection, accepted final containers are put into storage containers that are closed and labelled, and then stored at 2-8°C pending labelling and packaging of final containers. The results for visual inspection of the conformance lots were reviewed in the process validation section.

Labelling and Packaging

For labeling and packaging, the vials are then moved from cool storage to either of these areas Packaging (b) (4) (room (b) (4)), Packaging (b) (4) (room (b) (4)) or Visual Inspection & Packaging (room (b) (4)). The labeled vials are placed into cartons that are sealed by temper evident labels. Single packs are further packed into multi-packs of 6 or 12 bottles, which in turn are packed into shipping cartons. The cartons are then transferred to cool storage waiting to be shipped.

Reviewer's comments: Additional information about the visual inspection, labeling and packaging on the new presentations was requested and will be *reviewed in the addendum memo*.

Procedures to Prevent Cross Contamination

The OPG Vienna facility is a licensed multiproduct facility. Octapharma stated that the facility is designed for pharmaceutical manufacturing to accommodate multiple products; in addition they have the following systems and procedures in place to prevent contamination / cross-contamination of products:

- Only one product is manufactured at a time in the rooms for Filling, Capping, Crimping, and Marking, and in the rooms for Visual inspection, Labelling and Packaging. Line clearance procedures are followed to prevent product mix-up.
- Clear separation of Pre-viral inactivation and Post-viral inactivation areas are: Post-V.I. area is classified as clean room class (b) (4), whereas Pre-V.I. area is classified as clean room class (b) (4).

- HVAC system to provide the rooms with clean air for proper room classifications (Grade (b) (4) depending on criticality of operation) with appropriate differential pressure between the different Grade areas
- Validated routine monitoring programs (environmental monitoring, water and clean steam)
- Raw materials for production are of pharmaceutical grade (where available) or of highest purity obtainable and are tested per USP, EP or in-house procedures.
- Access to the clean Room Areas (A-D) is restricted to authorized, trained personnel only. In addition gowning procedures are established for entering the different areas
- Transfer of personnel between classified areas is possible only through airlocks where staff changes work clothes and footwear according to the gowning procedures outlined in current SOPs.
- Material, product, waste and personnel flow are designed to prevent mix-ups and contaminations.
- Qualified cleaning procedures for production rooms
- Validated cleaning procedures for production equipment
- Qualified sanitization and sterilization procedures for production equipment
- Use of media fills (b) (4) to qualify the aseptic processing, and to re-train the aseptic area operators.


Transport Validation

The NewGam final containers are transported (trucks) between the Octapharma production sites OSA and OPG to the Octapharma packaging sites OPG and ODE for visual inspection packaging and labeling.

Octapharma provided in the original submission transport validation report 150VRE1503/00, *Truck Transport of NewGam Final Containers between the OCTAPHARMA Production Sites OSA and OPG to the OCTAPHARMA Packaging Sites OPG and ODE and OCTAPHARMA Packaging Sites OPG and ODE to Customer / Airports / Distribution Centre during (b) (4) seasons* (approved 03 Mar 2015). They also provided in amendment 125587/0.9 transport validation protocol 150VPR1308.000, *Truck Transport of NewGam Final Containers between the OCTAPHARMA Production Sites OSA and OPG to the OCTAPHARMA Packaging Sites OPG and ODE and OCTAPHARMA Packaging Sites OPG and ODE to Customer / Airports / Distribution Centre during (b) (4) seasons* (approved 12 Mar 2014). They added that the report describing the *NewGam Transport Validation of Real Product – (b) (4) Season* was completed at the end of September 2015. This report was requested as part of 23 Sep 2015 IR, and was submitted in amendment 125587/0/17 and reviewed below.

NewGam is filled in vials of various sizes (20 mL up to 300 mL), and packed (unlabeled) into cartons which are clearly identified and shipped from the manufacturing facilities OSA and OPG to Octapharma packaging facilities in OPG and ODE for visual inspection followed labeling and packaging. The vials are then stored at the packaging facilities pending shipment to distributors/customers.

(b) (4)



For the CCIT, Octapharma reported that (b) (4) vials from each batch ((b) (4) vials in total) were tested for container closure integrity, and they all met the acceptance criteria.

Reviewer's comment: The information provided about the CCIT is deficient. Additional information was requested (29 and 30 Oct 2015), and *the information will be reviewed in the addendum memo.*

Computer Systems

The Vienna Facility is a US licensed facility and the validation approach of the computerized systems has already been reviewed and inspected by FDA in association with other licensed products.

Octapharma have administrative IT system which includes a manufacturing execution system ((b) (4)) and a laboratory management system (LIMS). They also have automated system used for manufacturing operations which are listed below:

- Remote control systems (RCS) used for (b) (4) Systems,
- Sequence control systems (SCS) used for (b) (4)

- Package unit systems (PUS) refers to complex standalone manufacturing equipment supported by automated control systems, where the operational qualification of the computerized functions is performed together with the mechanical part. This category includes (b) (4)

Water Systems

The Vienna Facility is a US licensed facility and the water systems, their uses and monitoring has already been reviewed and inspected by FDA in association with other licensed products.

Potable Water is supplied by the (b) (4) Public Water Supply System and its quality is controlled and certified by the municipal agency. Potable water is used to supply the different water preparation systems for deionized water (b) (4). The system (b) (4) provides water for the WFI stills, which are part of the WFI system (b) (4).

Octapharma provided a brief description (with schematic diagrams) of the production and storage of the different water systems.

The WFI is stored in (b) (4)

The WFI system validation approach included IQ, OQ and three phases of P Q (Phases I, II, and III). The last qualification after implementation of subloop^{(b) (4)} was performed in 2009.

Octapharma provided the routine monitoring schedule for the potable water, deionized water and water for injection as summarized below.

Potable water is monitored for (b) (4) with an acceptable specification of (b) (4). It is also monitored for (b) (4) with an acceptable specification of (b) (4).

Deionized water is sampled (b) (4) throughout the system on a (b) (4) basis on (b) (4) days. Thus, every sampling point is sampled at least (b) (4). Thus the system is monitored (b) (4).

The WFI system is monitored according to the following schedule:

(b) (4)

Octapharma reported that The WFI (b) (4) system is included in the general WFI routine monitoring program and follows the same principles as currently implemented and reviewed/inspected by FDA at the Vienna site:

- Return line: (b) (4) control and (b) (4) control
- Points-of-use: (b) (4) principle for (b) (4) control
- Others (no direct product contact): (b) (4) for microbial and endotoxin control.

In addition temperature, (b) (4) are continuously monitored in line.
