



DEPARTMENT OF HEALTH & HUMAN SERVICES

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 BL 125587/0, panzyga® (Immune Globulin Intravenous, Human 10%)

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Subject: **BLA 125587/0** Review Memorandum – Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma): to provide information for U.S. market authorization for panzyga®, an immune globulin intravenous (human) 10% liquid preparation indicated for the treatment of primary humoral immunodeficiency and chronic immune thrombocytopenic purpura in adults.

Due Date: April 14, 2016

REVIEW RECOMMENDATION

A Complete Response (CR) Letter should be issued to the firm.

CR letter ready comments include the following:

Inspectional Issues

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 the inspection. Your corrective actions do not appear to be comprehensive and address some of the underlying issues. Examples include:
 - The panzyga® process validation lots were manufactured prior to 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 the autoclaves used to sterilize items for use in the aseptic core.
- 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 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.

Review Issues – Please note that Item Nos. 4 and 10 – 12 originated from this memo, while Item Nos. 2, 3, and 5 – 9 are referenced from the addendum memo by Randa Melhem.

2. Please clarify whether the qualifications of the visual inspection/package and labeling for the smaller liquid presentations (20 mL and 30 mL vials) 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, 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. 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).
5. You provided the interim report 087RPQ13210.000 for the qualification of the vial washer at the at the OPG Vienna facility. Please submit the final report.
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 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.
7. As discussed during the 29 Oct 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 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.
8. The CCIT performed following the transport validation study covers only the 20 mL 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.
9. 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)).

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.
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 (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-requirements are determined.
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.

REVIEW SUMMARY

CBER received this electronic submission on April 15, 2015. Octapharma submitted this original BLA to provide information to support U.S. market authorization of panzyga® (working title “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. This product is a liquid formulation intended for intravenous injection. panzyga® will be marketed in the following doses (weight/fill volume): 1.0 g/10 mL, 2.5 g/25 mL, 5.0g/50 mL, 10.0 g/100 mL, 20.0 g/200 mL, and 30.0 g/300 mL.

The panzyga® manufacturing process was developed at Octapharma Pharmazeutika Produktionsges.m.b.H., Oberlaaer Strasse 235, A-1100 Vienna, Austria (OPG). As part of the development process, pilot scale batches were produced at OPG for preclinical and clinical studies. The panzyga® 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). In 2013, results from conformance batches manufactured at OSA Lingolsheim were presented to FDA in a pre-BLA meeting packet. Based on feedback from the Agency, the process was further optimized and consistency (process validation) batches were manufactured at OSA Lingolsheim in November/December 2014.

The panzyga® manufacturing process is a continuous process that utilizes U.S. (b) (4) plasma. Drug substance (plasma to final bulk) is manufactured at OSA Lingolsheim 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 ion exchange (b) (4) chromatography. The final product is formulated in glycine. Final drug product is filled at both OSA Lingolsheim and OPG Vienna. Visual inspection, labeling, and packaging are performed at OPG Vienna and the Octapharma GmbH Dessau facility located at Otto-Reuter-Str. 3, D-06847 Dessau, Germany (ODE).

CBER performed a PLI of the OSA Lingolsheim facility from 10/5-14/2015 in support of the review of original BLA 125587/0. During this inspection, major deficiencies were noted with regard to QA oversight of the panzyga® manufacturing process. Specific examples from the nine-item Form FDA 483 (issued on 10/14/2015) include the following:

- Inadequate oversight of non-conformances associated with PQs of the following equipment/rooms: the HVAC system in the aseptic core; the (b) (4) autoclaves used to sterilize items for use in the aseptic core; and the plasma (b) (4) fractionation areas.
- Failure to ensure timely progression and implementation of corrective actions associated with PQ non-conformances. Of note, none of the PQ non-conformances referenced in the preceding bullet point were corrected prior to manufacture of the panzyga® lots used to support the process validation.
- Inadequate oversight of equipment cleaning validations in that cleaning processes were approved for several pieces of equipment (including those used in the aseptic processing area) despite the equipment being documented as not visibly clean during execution of the protocol. Concurrent use of this equipment (during the associated investigation) and prior to implementation of an effective corrective action.
- Failure to investigate or correct some non-conformances associated with equipment cleaning validations. For example, the firm has not adequately addressed the failed cleaning validations ((b) (4)) associated with the (b) (4) in plasma (b) (4). As noted on the 483, the last successful cleaning qualification for this unit was conducted in 2008.

The firm's response to the 483 was received on 11/4/2015. Review of this submission revealed that the firm's responses were superficial and failed to adequately address the underlying issues (e.g., QA oversight of manufacturing operations) identified during the PLI. Consequently, a Complete Response (CR) Letter should be issued to the firm with a recommendation that more comprehensive corrective actions be implemented to address the underlying issues with QA oversight. The CR Letter should also state that a second PLI will be required to verify the corrective actions once they have been fully implemented.

Inspectional findings are documented in the Establishment Inspection Report (EIR). This PLI was the first FDA inspection of the OSA Lingolsheim facility. Evaluation of the firm's response to the 483 Observations is documented in a separate memo.

Of note, the OPG Vienna and ODE Dessau facilities are U.S. licensed facilities; however, these sites were not inspected in support of the review of original BLA 125587/0. Information regarding the decision to waive the inspections for these facilities is documented in the respective Inspection Waiver memos.

With regard to the original BLA submission, the information provided was brief and resulted in submission of a detailed Information Request (IR) on 6/11/2015. The firm's response to the IR was received on 7/13/2015 in Amendment STN 125587/0.9. This review memo is organized by topic and includes information provided in the initial submission and Amendment STN 125587/0.9. Any unresolved issues will be addressed in the CR letter.

Review of the panzyga® operations conducted at the OPG Vienna and ODE Dessau facilities is summarized in a separate memo.

NARRATIVE REVIEW

This memo encompasses my review of the facilities, equipment, and manufacturing operations for panzyga® at the unlicensed OSA Lingolsheim facility.

Items Reviewed

- STN BL 125587/0 and Amendment STN 125587/0.9

3.2.A.1 – Facilities and Equipment

panzyga® production operations are conducted in Building (b) (4) at the OSA Lingolsheim facility. Production areas within Building (b) (4) are divided as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The firm's Quality Control laboratories and Administrative functions are housed in Buildings (b) (4) and (b) (4), respectively. Figures representing product flow, personnel flow, material flow, waste flow, pressure cascades, and room classifications were included the submission.

3.2.A.1.1 – Production Flow

panzyga® starting material (human plasma) is obtained from U.S. based plasmapheresis centers and community blood banks. The firm's procedures require that all donations utilized in the manufacturing process be in compliance with 21 CFR 640.30 and 21 CFR 640.60. Plasma receiving and storage is performed in the Logistic Building at the Lingolsheim facility (OSA).

The incoming plasma is stored on (b) (4).

Rejected plasma donations are also stored in (b) (4).

(b) (4)

I

I

(b) (4)

- **Step ^{(b) (4)}: Labeling and Packaging** – panzyga® final containers are labeled and packaged at the OSA and OPG facilities. After the vials have been labeled with the batch number and expiry, the vials are placed in cartons with package inserts. The single and multi-packs are then placed in shipping cartons that are subsequently labeled with the product name, batch number, expiry, and storage conditions. The shipping cartons are then visually controlled by Quality Assurance and transferred to a 2°C to 8°C storage area prior to shipping.

A high level flow chart of the manufacturing process and the respective manufacturing sites is as follows:

Figure 1: Flow chart of the panzyga® manufacturing process and manufacturing sites

Manufacturing step	Manufacturing site
Plasma	
↓	OSA, Lingolsheim, France
(b) (4)	
	OSA, Lingolsheim, France
	OSA, Lingolsheim, France
↓	
Filling of bulk solution	<u>OSA, Lingolsheim, France:</u> 50 mL, 100 mL, 200 mL, 300 mL <u>OPG, Vienna, Austria:</u> 10 mL, 25 mL, 50 mL, 100 mL, 200 mL, 300 mL
↓	
Visual inspection	OPG, Vienna, Austria ODE, Dessau, Germany

Reviewer's Comments: The firm was asked to provide clarification regarding the visual inspection activities performed at the OPG Vienna and ODE Dessau facilities. Specifically, the firm was asked if both facilities conduct 100% visual inspection activities for all panzyga® vial presentations. The firm was also asked if the visual

inspection processes and equipment are identical at these facilities. Please refer to IR Question No. 15 for the firm's response.

3.2.A.1.2 – Other Products in the Same Area

In addition to panzyga®, the firm manufactures a number of other products in the Building ^{(b) (4)} production areas. These products include sterile liquid dosage forms (large and small volume parenterals), terminally sterilized liquid dosage forms, and sterile solid dosage (freeze-dried) forms. Specific products are listed in Table 1 below.

Table 1: Building ^{(b) (4)} Product Types and Development Status

Product	Product Type	Development Status	Product Name
PPSB Complex	Prothrombin Complex Concentrate (PCC)	Product registered in the EU, Canada, and other countries	Octaplex
IV Immunoglobulin	Immunoglobulin preparation	Product registered in the EU and other countries	Octagam
Albumin	Plasma protein fraction	Product registered in the EU and other countries	Albunorm
Factor VIII	Blood coagulation factor	Product registered in the EU and other countries	Octanate
Factor IX	Blood coagulation factor	Product registered in the EU and other countries	Octanine F

Reviewer's Comments: The firm was asked to clarify if any non-US approved plasma is used in the manufacture of these products. If so, the firm was asked to confirm if any equipment is shared between the products containing US and non-US plasma. If the presence of shared equipment was confirmed, the firm was asked to provide the validation for prion removal (to mitigate TSE concerns) during cleaning of shared equipment that is in contact with US and non-US plasma and its fractionation intermediates. Please refer to IR Question No. 2 for the firm's response.

No toxic or hazardous substances (e.g., penicillin, cephalosporins, or cytotoxic substances) or veterinary products are manufactured at the OSA Lingolsheim facility.

3.2.P.3.5 – Process Validation and/or Evaluation

The panzyga® manufacturing process was developed at the OPG Vienna facility. As part of the development process, pilot scale batches were produced at OPG Vienna for preclinical and clinical studies. The panzyga® process was then transferred and scaled up to commercial scale at OSA Lingolsheim. In 2013, results from conformance batches manufactured at OSA Lingolsheim were presented to FDA in a pre-BLA meeting packet. Based on feedback from the

Agency, the process was further optimized and consistency (process validation) batches were manufactured at OSA Lingolsheim in November/December 2014. A batch tree of the process validation batches is presented in Table 2 below.

(b) (4)

(b) (4)

Reviewer's Comments: As Filling Line (b) (4) is utilized for panzyga® and other non-US approved products such as Octagam and Albuterm, it is unclear what MFT conditions (e.g., (b) (4)) and vials and stoppers ((b) (4)) are applicable to panzyga®. Consequently, the firm was asked to provide the aseptic manufacturing conditions for panzyga® to include container closure (different presentations and stoppers), filling equipment, filling time, single or double aseptic filling operations, and maximum number of vials filled per presentation. The firm was also asked to provide the following:

- A list of MFTs conducted to support validation of the panzyga® aseptic manufacturing process.
- The protocol for the aseptic media simulation for the initial validation and the (b) (4) requalification of the aseptic process (Document No. 757PQP005/23)
- The report from the 2nd MFT run scheduled for mid-March 2015.

Please refer to IR Question Nos. 8 – 10 for the firm's responses.

- With regard to CAPA-40299, a status update was requested as part of CR Letter Item No. 12.

3.2.A.1.3 – Preparation, Cleaning, and Sterilization of Equipment

The firm provided a description of the major equipment utilized in the production of panzyga®. A complete list of this equipment is as follows:

(b) (4)

103

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The equipment cleaning methods for each production area includes the following:

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1

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101

101

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Journal compilation © 2006 Blackwell Publishing Ltd

103

1001

7

© 2006 The Authors

1

11

100

1

- Pharmaceutical Manufacturing

(b) (4)

According to the firm's cleaning validation strategy, the effectiveness of the cleaning methods must be evaluated for each piece of equipment with direct product or buffer contact. Regardless of the type of contact, batch-to-batch cross contamination must be reduced to an acceptable limit by cleaning. The cleaning method must also ensure that the next batch is not contaminated by residual material from cleaning agents. The quantitative parameters that are considered critical to assessment of the cleaning procedures include (b) (4). The rationale for test and acceptance criteria for the various equipment validations is summarized in the following tables:

Automated Cleaning

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's Comments: The firm was asked to provide justification for not testing for the (b) (4) during the vial washing validation. Please refer to IR Question No. 1 for the firm's response. With regard to (b) (4), the firm was asked to provide a description of this reference as well as the actual acceptance criterion associated with each applicable piece of equipment (see CR Letter Item No. 11). Additionally, the firm was asked to 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 (also part of CR Letter Item No. 11).

Manual Cleaning

Manually cleaned equipment is also challenged with a product run to ensure that the cleaning method is efficient. Miscellaneous equipment cleaned manually is washed with (b) (4) detergent. In (b) (4) fractionation, (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Dirty Hold Time (DHT)

The efficiency of the cleaning process was evaluated for its ability to remove (b) (4) between the end of use of equipment (product or buffer) and cleaning. This evaluation was conducted during the initial cleaning validation for each piece of equipment.

Clean Hold Time (CHT)

The time between cleaning and use was evaluated during the initial cleaning validation for all product contact equipment.

Conclusion

The initial BLA submission included very brief tabular results summaries for each of the equipment cleaning validations. An example of the summary for (b) (4) tank (b) (4) is presented in Table 9 below.

(b) (4)

(b) (4)

Review of the various summaries revealed that each validation met the acceptance criteria for visual cleanliness, residual product, residual cleaning agents, and microbial contamination.

Reviewer's Comments: As the tabular summaries did not provide sufficient information to evaluate the various cleaning validations, the firm was asked to provide the following:

- Validation protocols and reports for equipment cleaning validations to include the number of runs per piece of equipment, the soiling agent (and why it is worst case), the cleaning steps and conditions (and why they are considered worst case), the rationale for samples collected and an explanation as to why (b) (4) sampling was not included for every piece of equipment. The firm was also asked to provide their rationale for not conducting (b) (4) sampling.
- Cleaning validations for the different loads used with the equipment washing machines.
- A list of all deviations from each validation study and how they were investigated and resolved.
- A description of routine cleaning (step-by-step to include time, temperature, pressure, and flow), reagents (and their concentration), and the drying methods for each piece of equipment.

Please refer to IR Question No. 1 for the firm's response.

Sanitization, Sterilization, and Depyrogenation of Equipment

The initial BLA submission included a single report summarizing the validation of (b) (4) disinfection, (b) (4) sterilization, and dry heat depyrogenation for all equipment utilized in the production of panzyga®. A description of the specific methods, tests, and validation acceptance criteria is as follows:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Revalidation

(b) (4) *Sterilization of process tanks*

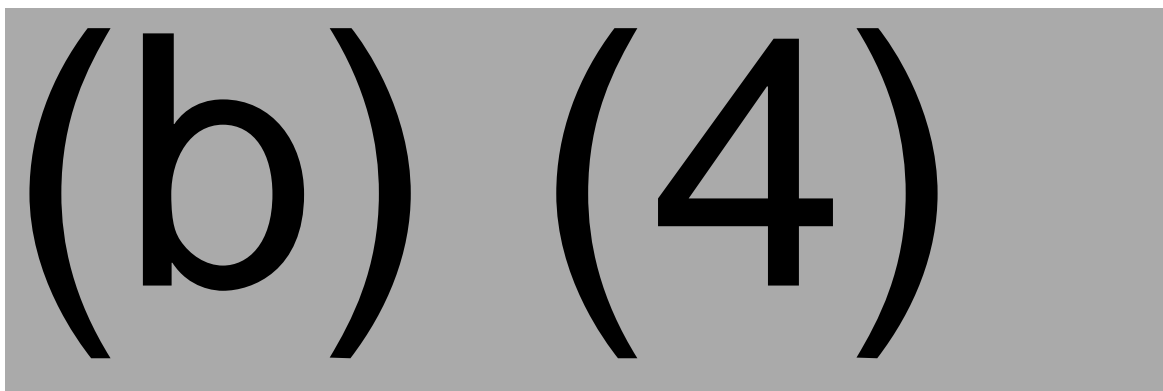
- (b) (4) Fractionation – conducted every (b) (4)
- (b) (4) Purification – conducted every (b) (4)
- Revalidations are also performed if the equipment is changed

Equipment sterilization in (b) (4) sterilizers (autoclaves)

- Autoclaves are revalidated every (b) (4)
- Revalidations are also performed if the equipment is changed or the material loads are modified

Conclusion

As with the cleaning validations, the firm's initial BLA submission included only brief tabular summaries of the disinfection, sterilization, and depyrogenation validation studies. An example of the summary for process tank (b) (4) is presented in Table 21 below.



Review of the various summary tables revealed that all temperature, pressure, and microbial challenges met the pre-defined acceptance criteria for the disinfection, sterilization, and depyrogenation processes utilized in panzyga® production operations.

Reviewer's Comments: As the tabular summaries did not provide sufficient information to evaluate the sanitization and sterilization of equipment, the firm was asked to provide the following:

- **Protocols and reports for validation of the sanitization and sterilization of equipment to include qualification of the autoclaves (including empty chamber mapping) and validation of the sterilization cycles for the different loads (if applicable). The firm was also asked to include the number of runs per load per autoclave or (b) (4) per tank/piping, the location of the TCs (and BIs if applicable), and the rationale for choosing these locations as worst case. Additionally, the firm was asked to provide justification for the validation cycle parameters and indicate how they compare to routine sterilization parameters.**
- **A list of all deviations from each validation study and how they were investigated and resolved.**
- **A description of the BIs (type and number of spores) used to include D-value, Z-value, and vendor.**
- **A description of the depyrogenation tunnel and its qualification (including cleaning/sterilization of the cool zone). The firm was also asked to provide the protocols and summary reports for validation of the depyrogenation of the different vial sizes with schematic representation of the TC and EI locations in each run (and the rationale for each location as worst case). Additionally, the firm was also asked to provide a description of the EI used as well as summaries of the endotoxin recovery studies conducted to ensure accuracy of the log reduction.**
- **Conditions/parameters for the routine depyrogenation process and how these compare to the validated process.**
- **For each piece of equipment, the firm was also asked to provide the following information in tabular format: method of cleaning, method of sanitization/sterilization, dirty hold time, clean hold time, and sterile hold time.**

Please refer to IR Question No. 3 for the firm's response.

3.2.A.1.4 – Procedures to Prevention Cross-Contamination

Clean Room Concept

Production areas in Building (b) (4) are classified according to a clean room concept that is based on the current European guidelines as defined in EU GMP regulations and as applicable to facilities within the EU. An overview of these guidelines is presented in Table 22 below.

Table 22: Assignment of products/processes to appropriate environments

Assignment	Grade
High risk operations (e.g., filling)	Grade (b) (4)
Sterile filtration and background for Class (b) (4)	Grade (b) (4)
(b) (4) purification ((b) (4)) – S/D treatment	Grade (b) (4)
(b) (4) purification ((b) (4)) and (b) (4) fractionation	Grade (b) (4)
Non-critical operations (e.g., storage)	Unclassified

In order to meet both U.S. and EU requirements, the clean room concept was amended by additional control measures. A comparison of the EU and U.S. classifications is as follows:

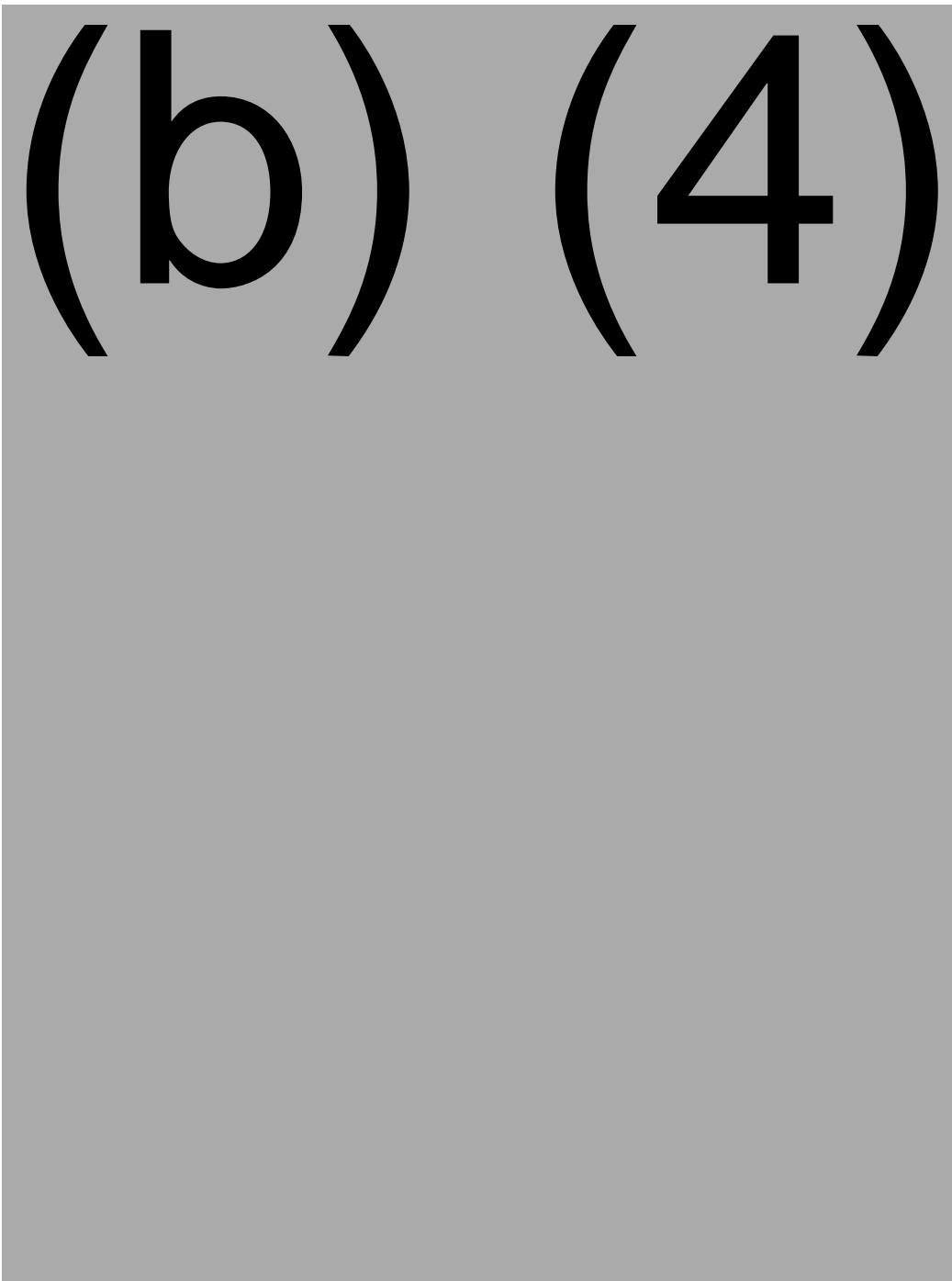
Table 23: Comparison between clean room classifications

Grade	USP <1116>	ISO 14644-1
A	Class 100	5
B	Class 10,000	7
C	Class 100,000	8
D	N/A	N/A

Reviewer's Comments: The firm was asked to provide a detailed summary of the additional control measures that were utilized to amend the clean room concept in order for it to meet both U.S. and EU requirements (see CR Letter Item No. 10).

Personnel Flow and Gowning Requirements

Access to the clean room areas is restricted to authorized and trained personnel. With regard to personnel flow, production employees enter the production area through Room (b) (4) and proceed to the primary gowning facilities (Rooms (b) (4)) where they don plant pants, tops, single-use caps, and clean room shoes. Production employees then enter corridors (b) (4) and proceed to the various production areas. Additional gowning requirements for these areas are presented in Table 24 below.



Clean Room Monitoring

Following validation of the HVAC system, an environmental monitoring (EM) program was established to reflect the assigned classification of each clean room area and the criticality of operations performed therein. Specific monitoring parameters and the corresponding acceptance criteria for each area are provided in the tables below.

(b) (4)

The alert limits are based on historical data and the corresponding action limits. When these limits are exceeded, the firm has a series of actions that are initiated to assess the event. Specific actions are listed in Table 30 below.

(b) (4)

All EM results are made available to Production and Quality personnel for assessment and initiation of any investigations and/or corrective actions. When an action limit is exceeded, the organism is identified to the genus and species level (when possible). Trending of EM data is performed (b) (4) for rooms, operators, surface locations, and batches. Long term trending of all EM and personnel monitoring data is performed (b) (4). The suitability of the alert and action limits is also evaluated (b) (4). Analysis of these data includes an assessment of any changes made during the reporting period as well as any reported deviations, corrective actions, or changes in the microbial flora.

Reviewer's Comments: The summary of actions that are initiated for alert/action limit excursions does not adequately describe when investigations are required or how they are documented. Clarification of these requirements was provided during inspectional review of the SOPs for routine EM, personnel monitoring, trending, and investigations. Inspectional coverage also included review of EM trending reports for each panzyga® production run and the (b) (4) preceding the inspection. Please refer to the EIR for more information regarding EM procedures, investigations, and trending reports for the manufacturing areas.

Product Segregation

Products are processed/manufactured one at a time in the rooms for (b) (4) purification, filling, capping, cramping, marking, and crating. Contamination by other products is also minimized by use of dedicated equipment (e.g., (b) (4)), single-use materials (e.g., filter (b) (4), nanofilters, tubing, bags), and validated cleaning procedures for shared equipment.

With regard to panzyga®, (b) (4) purification ((b) (4)) activities are conducted in rooms dedicated to Immunoglobulin products. The (b) (4) areas are clearly segregated from other production lines and operations are performed in closed containers/systems. Additionally, transfer of product from (b) (4) purification is conducted with (b) (4)

Cleaning, Sanitization, and Sterilization of Equipment

Cross-contamination from equipment is minimized through use of established and validated procedures for cleaning, sanitization, and sterilization of equipment. The risk of equipment contamination is further minimized by clearly identifying the status of each piece of equipment (e.g., sanitized or sterilized). Material and equipment in use is also labeled to indicate its status with regard to cleaning or production step.

Room Cleaning

The risk for contamination of rooms is minimized by the following procedures:

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Standard procedures for room cleaning and disinfection, frequency of cleaning, use of detergents and disinfecting agents, and application of microbial contamination specifications have been established in each operating department. The firm's submission also indicated that the disinfectants utilized in each production area are rotated periodically and their effectiveness has been demonstrated with efficacy studies. Sporocidal agents are also utilized according to defined schedules; however, these agents may be used more frequently based on EM data. Although each department has specific SOPs for surface cleaning, each area follows the general schedule as outlined in Table 31 below.

Table 31: General schedule for surface cleaning in clean room areas

Cleaning item	Grade (b) (4)	Grade (b) (4)	Grade (b) (4)	Grade (b) (4)
Equipment	(b) (4)			
Working surfaces				
Contact points (Handles, switches...)				
Floor				
Walls (and Doors)				
Ceiling				

Extended cleanings are performed after a clean room area has been comprised (e.g., after the summer shutdown) or when deemed necessary (e.g., corrective action associated with an investigation).

3.2.A.1.5 – HVAC System

The HVAC systems for the clean room areas in OSA Lingolsheim are designed to heat, cool, dehumidify, supply clean air, dilute contaminants, capture airborne particles, and create room differential pressure. Air is supplied to the different production areas (Clean Room Grades (b) (4) [REDACTED] is provided by (b) (4) air handling units (AHUs) equipped with (b) (4) [REDACTED]

filters) and terminal HEPA filters installed in the ceiling of each production room. (b) (4) air is provided by specific AHUs. A description of the system for supplying (b) (4) air to the panzyga® clean room areas is as follows:

(b) (4)

(b) (4)


Of note, the air pressure differential between the clean room grade areas is monitored by air pressure differential gauges. The temperature, moisture, and air pressure differentials in these areas are also monitored by a central system for controlling and data acquisition (SCADA) system.

A complete list of the AHUs that service the panzyga® manufacturing areas was provided in the initial BLA submission. Specific information regarding the AHUs for Filling Line (b) (4) (Room (b) (4)) is provided in Table 32 below.

Table 32: Identification of individual AHUs that service the panzyga® Grade (b) (4) filling area

(b) (4)

(b) (4)



Acceptance criteria for pressure differential between the clean room areas have been established. These include the following:

(b) (4)

Preventive and unscheduled maintenance of the HVAC system is managed in the computerized maintenance management system (CMMS). Specific requirements within the preventive maintenance program include the following:

- (b) (4) air (b) (4)-filters are changed at least (b) (4)
- (b) (4) air (b) (4)-filters are changed on demand in accordance with the clogging monitoring program
- HEPA filters within the Grade (b) (4) areas are integrity tested (b) (4)
- HEPA filters within the Grade (b) (4) areas are integrity tested (b) (4)
- Replacement of the terminal HEPA filters is conducted from the clean side of each Production room

Validation of the HVAC System

The firm's submission indicated that validation of the HVAC system was performed in three stages (IQ, OQ, and PQ) for all clean room areas specified with Grades (b) (4). Results of the IQ, OQ, and PQ activities were summarized in reports and archived in the Validation Department. The firm also noted that requalifications are performed whenever changes are made

to the system. As noted above, an EM monitoring program was implemented for each clean room area following completion of the HVAC validation.

Reviewer's Comments: The HVAC validation reports referenced above were not submitted with the initial BLA submission. To ensure that the HVAC system could support the assigned room classifications under both static and dynamic conditions, these reports were reviewed during the site inspection. Major deficiencies were noted with the airflow patterns in the Class (b) (4) areas surrounding the Line (b) (4) filling unit in Room (b) (4) (Observation Nos. 1 and 2(b)). Deficiencies were also noted with the qualification status of Fractionation and Plasma (b) (4) Rooms (b) (4) in that air exchange rate excursions were not corrected in a timely manner (Observation No. 2(c)). Subsequent review of the firm's 483 response revealed that the implemented corrective actions failed to adequately address the deficiencies identified during the PLI. Consequently, a CR Letter should be issued to the firm with a recommendation that more comprehensive corrective actions be implemented to address the underlying issues with QA oversight. The CR Letter should also state that a second PLI will be required to verify the corrective actions once they have been fully implemented. Please refer to the Form FDA 483, the 483 response memo, the CR Letter, and the EIR for more information.

3.2.A.1.6 – Water System

The potable water used to feed the Lingolsheim Purified Water (PW) system is supplied by (b) (4)

A description of each loop and its application is as follows:

- (b) (4)
 - -
 -
 -
- -
 -
 -
- -
 -
 -

(b) (4)

Reviewer's Comments: Validation reports for sanitization of the PW and WFI distribution systems and qualification of the clean steam generation system were not provided in the initial submission. These studies were reviewed during the inspection and will be summarized in the EIR.

Maintenance of Water Systems

Preventive and curative maintenance events are documented in the Computerized Maintenance Management System (CMMS). The initial BLA submission indicated that written procedures were established for the preventive maintenance program based on a risk analysis approach.

Validation of the PW and WFI Systems

The PW system was described as operating in a validated state and providing water of a specified quality ((b) (4)). The initial IQ/OQ of the PW system was performed in 1992 and completed in 2004. Subsequent major modifications performed on this system are provided in Table 35 below.

Table 35: Major Modifications Performed on the PW system

(b) (4)

(b) (4)

The (b) (4) WFI system was also described as operating in a validated state and providing water of a specified quality ((b) (4)). The initial IQ/OQ of the (b) (4) WFI system was performed in 1992 and completed in 2004. Subsequent major modifications performed on this system are provided in Table 36 below.

Table 36: Major Modifications Performed on the (b) (4) WFI system

Date of Approval	Action	Validation References
1992	Implementation of the initial system by the supplier	N/A
2004	System Quality Review	776RQS001/00
2005	Retrospective Qualification Report	776RQR001/00
2007	(b) (4)	776RQI004/02
2009	(b) (4)	776RQM004/05

As with the preceding water systems, the (b) (4) WFI system was also described as operating in a validated state and providing water of a specified quality ((b) (4)). The initial IQ/OQ of the (b) (4) WFI system was performed in 2008. Validation references associated with the implementation and initial qualification of this system are provided in Table 37 below.

Table 37: Major Modifications Performed on the (b) (4) WFI system

Date of Approval	Action	Validation References
2008	Implementation and Qualification of the initial system	776PQI009/00 (IQ) 776PQO009/00 (OQ automation) 776PQO010/00 (OQ production & distribution) 776RQP007/00 (Production) 776RQP008/00 (Distribution) 776RQP009/00 (cleaning)

Reviewer's Comments: Validation studies were not provided for the PW or WFI systems. These reports were reviewed during the site inspection and will be summarized in the EIR.

Routine Monitoring

The firm's routine monitoring program is based on in-line monitoring and sampling results from the QC laboratory. Sampling intervals are based on the quality and criticality of the water system involved.

Potable Water (City Water)

Routine monitoring of potable water includes a (b) (4) test for (b) (4). Specifications are provided in Table 38 below.

(b) (4)

A certificate of analysis (CoA) containing data from chemical analyses is also obtained monthly from the regional institute of health.

Purified Water ((b) (4))

Routine monitoring of the PW system also includes testing for (b) (4). Sampling is performed (b) (4) throughout the system on a (b) (4) basis on (b) (4). (b) (4) from select locations are also tested for (b) (4). Specifications are provided in Table 39 below.

(b) (4)

WFI ((b) (4))

Routine monitoring of the WFI systems includes testing for (b) (4). Sampling is performed (b) (4) throughout each system on a (b) (4) basis on (b) (4) to ensure that each sampling point is sampled/tested at least (b) (4). (b) (4) samples from select locations are also tested for (b) (4). Specifications are provided in Table 40 below.

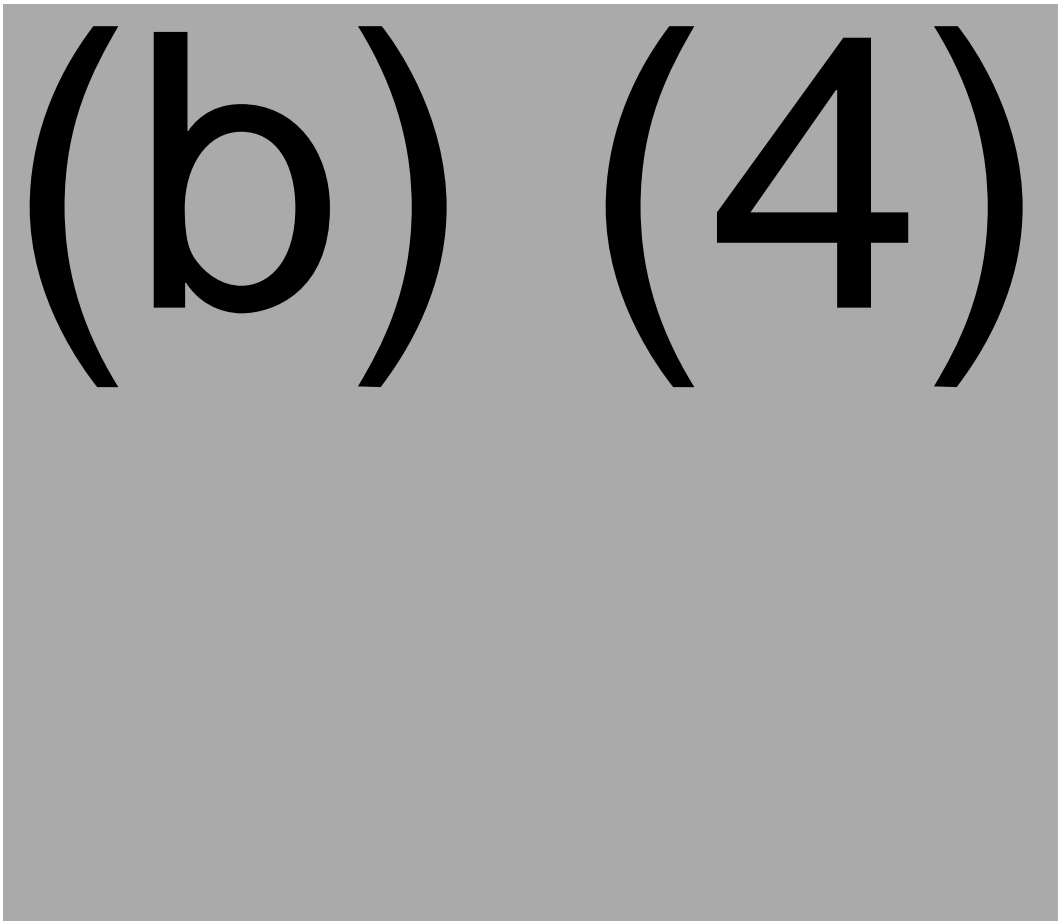
(b) (4)

Clean steam condensates are monitored as (b) (4) as part of a (b) (4) sampling program. Each main steam distribution line is (b) (4). As indicated previously, clean steam is supplied (b) (4).

Reviewer's Comments: No trending data were provided to demonstrate that any of the water systems were in compliance with the routine monitoring acceptance criteria. With regard to the clean steam system, no information was provided regarding qualification of this system, routine monitoring, acceptance criteria, or trending of monitoring data. The water system trending reports and clean steam information were reviewed during the site inspection and will be summarized in the EIR.

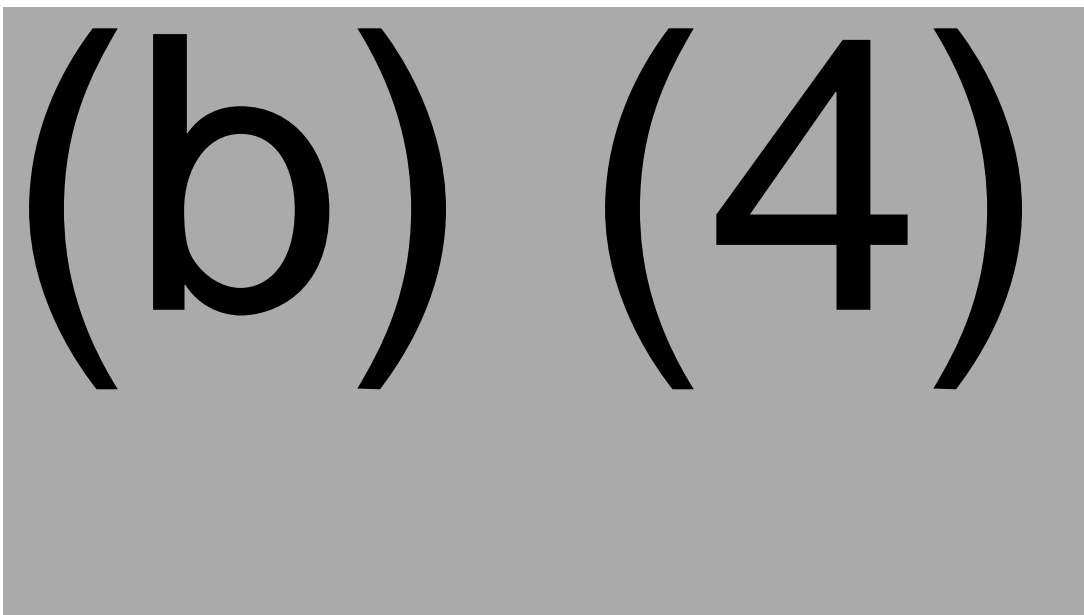
The monitoring program results are reviewed weekly for all in-line data. Furthermore, all monitoring data are reviewed by the Quality Unit (QU) and Process Utilities. When warning limits are exceeded, an investigation is performed at the QC level with Process Utilities informed. When action limits are exceeded, Production and the QU are notified while a deviation is initiated with immediate corrective actions and investigation performed at the QC and Process Utilities levels. A complete list of the action plans that are initiated when limits are exceeded is provided in Table 41 below.

(b) (4)



3.2.P.7 – Container Closure System

The immediate packaging of panzyga® is comprised of glass vials (glass (b) (4)) and bromobutyl rubber stoppers ((b) (4)). Stoppered vials are sealed with an aluminum flip off cap. An overview of the container closure system for panzyga® is as follows:



(b) (4)

Reviewer's Comments: As noted in the table above, stoppers used at OPG Vienna are 20 mm or 32 mm light grey (b) (4) coating), while the stoppers used at OSA Lingolsheim are 32 mm light grey (b) (4)). The firm was asked for clarification regarding the use of different stoppers at the two facilities. Please refer to IR Question No. 18 for the firm's response.

Container Closure Integrity

The initial BLA submission included the following reports to support container closure integrity:

- Stability Study Report on Container Closure Integrity of IVIG 10% (NewGam) Primary Packaging Systems OSA and OPG, Study No. 13P003 (6 month time point data from conformance batches produced at OSA Lingolsheim in 2013)
- Stability Study Report on Container Closure Integrity of IVIG 10% (NewGam) Primary Packaging Systems OSA and OPG, Study No. 14P022 (initial data from consistency batches produced at OSA Lingolsheim in 2014)
- Study Report for the Extractable and Leachable Assessment of Bromobutyl Rubber Stoppers used for NewGam

Stability Study No. 13P003 was implemented in 2013 with (b) (4) conformance batches manufactured at OSA Lingolsheim. Of note, (b) (4) of these batches were filled at OSA Lingolsheim (50 mL fill and 300 mL fill), while the remaining (b) (4) batches were filled at OPG Vienna ((b) (4) fill). Additionally, a number of vial/stopper combinations were utilized to simulate the intended marketing for the product. These include the following:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

*The (b) (4) batches from OPG Vienna Filling Line (b) (4) were included as supportive data as this line is not part of BLA 125587

The filled final containers were (b) (4) under long-term (5°C and 25°C/(b) (4)), intermediate ((b) (4)), and accelerated ((b) (4)) storage conditions. Subsequent evaluation of container/closure integrity is performed with (b) (4) at the following intervals:

(b) (4)

Results from the initial and 6 month time points showed that all vials met the acceptance criteria for (b) (4) measurement.

Stability Study No. 14P002 was implemented in 2014 with (b) (4) consistency (process validation) batches manufactured at OSA Lingolsheim. (b) (4) of these batches ((b) (4) fill volume) were filled at OSA Lingolsheim and (b) (4) were filled at OPG Vienna ((b) (4) fill). The vial/stopper combinations utilized in this study include the following:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The filled final containers were (b) (4) under long-term storage conditions (5°C and 25°C/(b) (4)). Subsequent evaluation of container/closure integrity is performed with (b) (4) at the following intervals:

(b) (4)

Results from the initial time point showed that all vials met the acceptance criteria for (b) (4).

The extractable/leachable study for the bromobutyl stoppers was performed to evaluate the potential for volatile, semi-volatile, and non-volatile compounds to migrate into the final product. The compounds identified ((b) (4)) and quantified during this study were forwarded to the firm's Toxicology Department for a toxicological risk assessment. The exposure scenario calculated during this risk assessment showed that the margins of safety for the preceding compounds were high enough for the firm to conclude that no toxicity risk is expected for patients exposed to possible leachables present in panzyga®. Furthermore, the stopper formulation passed the biological reactivity (in vitro) (b) (4) test according to (b) (4) as well as the biological reactivity test (in vivo) system (b) (4) test in (b) (4) according to (b) (4). According to the report, these results confirm that toxic effects are not expected from the stopper compounds. The firm's analysis concluded that the bromobutyl stoppers ((b) (4) coatings) are suitable for use during manufacturing operations for panzyga®. The detailed review of extractable/leachable study and biological tests of the stoppers is deferred to the product reviewer.

Reviewer's Comments: Although the stability data provided is supportive of container closure integrity, it is not sufficient to validate the process. The firm was asked to provide the protocol and results for container closure integrity testing (CCIT) to demonstrate that the different combinations of vials (different sized with some (b) (4) and some not) and stoppers (different sizes and coatings) maintain integrity during handling, transportation, and throughout the shelf life of the product. Please refer to IR Question No. 19 for the firm's response.

3.2.A.1.7 – Computerized Systems

The firm's computerized systems are divided into two groups:

- Administrative IT systems

- Automated systems used in the manufacturing process

Administrative IT Systems

Administrative IT systems include the Manufacturing Execution System (MES), the Laboratory Information Management System (LIMS), and CMMS.

MES

The following activities are supported by the MES (b) (4) :

- Plasma donation control and administration
- Inventory administration and warehouse management
- Identification and tracking of material with barcode labels
- Tracking of material flow within the facility
- Product history from plasma donation through distributed final product

With regard to plasma donations, (b) (4) allows the firm to compare individual donation numbers with the corresponding electronic list provided by blood banks and plasmapheresis centers. Look back data are also administered with this system. Additionally, all materials used in production are tracked and controlled with (b) (4) .

LIMS

The following activities are by (b) (4) :

- Collection, evaluation, and reporting of analytical data for products (in-process and final container), non-biological components, stability studies, EM, and utilities
- Laboratory equipment management
- QC employees qualification management
- Management of OOS test results
- Archiving of QC data
- Document generation
- Automating laboratory workflow
- Information management

CMMS

The following activities are supported by CMMS:

- Asset management

- Maintenance plans
- Preventive and corrective maintenance
- Maintenance task lists
- Work order documentation

Reviewer's Comments: The initial BLA submission indicated that all applications within (b) (4) CMMS had been successfully validated; however, no protocols or reports were submitted in support of this claim. Review of computerized systems was conducted during the site inspection and will be summarized in the EIR.

Automated Systems used in the Manufacturing Process

Although the initial BLA submission described the panzyga® manufacturing process as being under manual control with a low degree of automation, a number of manufacturing steps are supported by computerized systems. The automated systems associated with this process are divided into three categories: remote control systems (RCS), sequence control systems (SCS), and package unit systems (PUS). A brief description of each system and the operations they support is as follows:

RCS

RC systems are based on programmable logic controls (PLCs) with a user interface such as a control panel or a computer. Mechanical functions (e.g., control valves or dosage ports) are visualized on the user interface and allow operators to direct actions on components or operations such as opening and closing valves (after a predefined amount agent has been added), setting and maintaining process tank temperatures, starting stirrers, entering weight data, and initiating filling or emptying operations.

SCS

SC systems are based on PLCs with user interfaces that allow a functional sequence of multiple steps to be performed under programmed control (including the transition between steps). The operator initiates a program sequence with a functional sequence that runs until the last program step is completed. SCS examples include the (b) (4).

PUS

Complex stand alone manufacturing equipment is often supported by automated control systems. As the OQ of the computerized functions is performed in conjunction with mechanical qualification, these systems are described a package units. Examples of processes supported by PUS include (b) (4) steps, (b) (4).

Validation of computer systems is based on Good Automated Manufacturing Practice (GAMP) guidelines.

REVIEW QUESTIONS

A teleconference regarding the initial BLA submission was held with the firm on 5/26/2015. The corresponding IR was sent to the firm on 6/11/2015. The firm provided its response on 7/13/2015 in Amendment STN 125587/0.9. A summary of my questions (in *Italics*), Octapharma's responses (in regular text), and my comments (in **bold**) is provided below:


Equipment Cleaning and Sterilization

1. *The information in the BLA submission included a very brief summary of the results for various cleaning validations. As these summaries do not provide sufficient information for us to evaluate your cleaning validations for equipment used in the manufacture of NewGam at OSA, please provide the following:*
 - a. *Validation protocols and reports for equipment cleaning validations to include the number of runs per piece of equipment, the soiling agent (and why it is worst case), the cleaning steps and conditions (and why they are considered worst case), the rationale for samples collected and an explanation as to why (b) (4) [REDACTED] sampling was not included for every piece of equipment. Additionally, please provide the rationale for not conducting (b) (4) [REDACTED] sampling.*


The firm's response included cleaning validation protocols and reports for all major equipment used in the following production areas: Plasma (b) (4) ; Fractionation and Purification (b) (4) [REDACTED] ; and Aseptic Production. Specific protocols and reports are listed in the tables below.

(b) (4)

(b) (4)



(b) (4)



Reviewer's Comments: The cleaning validation protocols and reports were reviewed upon receipt of Amendment STN 125587/0.9. During the inspection, select reports were also discussed and verified with the firm. A number of major deficiencies were identified and subsequently listed on the Form FDA 483. Specific examples include the following:

- Several pieces of equipment were documented as not visibly clean during execution of cleaning validation protocols; however, the cleaning processes were still approved (Observation No. 4(a)). Examples include the following:

(b) (4)



As indicated previously, the firm's failure to adequately address the deficiencies identified during the PLI should result in issuance of a CR Letter. Please refer to the Form FDA 483, the 483 response memo, the CR Letter, and the EIR for more information.

- b. *Justification for not testing for the (b) (4) during the vial washing validation (only a (b) (4) study was included).*

The firm's response indicated that testing was not performed for (b) (4) during the vial washing validation as (b) (4) that was previously validated for a (b) (4). However, the firm committed to testing for (b) (4) during the next qualification of the vial washing machine (due before the end of 2015).

Reviewer's Comments: During the inspection, the firm indicated that testing for (b) (4) had been completed. These results were reviewed and appeared acceptable.

- c. *For the equipment washing machines, please provide the cleaning validations for the different loads.*

The firm's response included protocols and reports for the (b) (4) equipment washing machines at OSA Lingolsheim. As indicated previously, these units are located in the (b) (4)

Reviewer's Comments: The validation reports were reviewed and confirmed as acceptable.

- d. *A description of routine cleaning (step-by-step to include time, temperature, pressure, and flow), reagents (and their concentration), and the drying methods for each piece of equipment.*

The firm's response included tabular summaries for the following production areas: Plasma (b) (4); Fractionation and Purification for Manufacture (b) (4); and Aseptic Production. Specific cleaning processes are listed in the tables below

(b) (4)

Detergents utilized during routine cleaning of equipment include the following:

- (b) (4)
- Manual cleaning
(b) (4)
- Equipment washing machines – (b) (4)

Reviewer's Comments: The firm's response is acceptable.

- e. *For each validation study, please include all deviations and how they were investigated and resolved.*

A list of cleaning validation deviations was provided as part of Amendment STN 125587/0.9.

Reviewer's Comments: The list of deviations was reviewed upon receipt and during the inspection. Of note, a number of non-conforming results associated with equipment cleaning validations did not appear on this list as these events were not investigated or corrected (Observation No. 6(a)). Please refer to the Form FDA 483, the 483 response memo, the CR Letter, and the EIR for more information.

2. *A number of non-US approved products are manufactured in the Lingolsheim (OSA) facility. Please clarify whether non-US approved plasma is used in the manufacture of these products. Additionally, please clarify if any equipment is shared between products containing US and non US plasma. If so, please provide the validation for prion (mitigate TSE concerns) removal during cleaning of shared equipment that is in contact with US and non-US plasma and its fractionation intermediates.*

The firm's response confirmed that non-US approved plasma is used in the Lingolsheim facility during production of non-US approved products. The firm also acknowledged that equipment is shared between products containing US and non-US approved plasma. A list of the shared equipment is provided in the table below.

(b) (4)

(b) (4)


Reviewer's Comments: The (b) (4) treatment conducted during the (b) (4) for shared equipment appears to be adequate for inactivation of prions. It is also noted that the panzyga® manufacturing process has two consecutive (and dedicated) virus and prion removal steps (IEC (b) (4) and 20 nm nanofiltration) to further mitigate TSE risk concerns. With regard to manual cleaning of shared equipment, the firm presented additional studies to demonstrate effective prion removal during the inspection. Please refer to the EIR for more information.

3. *With regard to sanitization, sterilization, and depyrogenation of equipment, your BLA submission included brief summaries of the studies conducted for equipment used in the manufacture of NewGam at OSA. As these summaries do not provide sufficient information for us to evaluate your processes, please provide the following:*
 - a. *Protocols and summary reports for validation of the sanitization and sterilization of equipment. This should include qualification of the autoclaves (including empty chamber mapping) and validation of the sterilization cycles for the different loads (if applicable). Please include the number of runs per load per autoclave or (b) (4) per tank/piping, the location of the TCs (and BIs if applicable), and the rationale for choosing these locations as worst case. Please provide justification for the validation cycle parameters and indicate how they compare to routine sterilization parameters. Additionally, please include any deviations and how they were investigated and resolved. Were any repeat validation runs performed to ensure that the issues were resolved?*

The firm's response included validation protocols and reports for equipment sanitization and sterilization. Specific reports are listed in the tables below.



(b) (4)

(b) (4)



- b. *A description of the BIs (type and number of spores) used to include D-value, Z-value, and vendor.*

(b) (4)

Reviewer's Comments: The firm's response is acceptable.

- c. *The validated sterile hold time.*

Please refer to the firm's response for IR Question No. 4 for more information.

- d. *A description of the depyrogenation tunnel and its qualification (including cleaning/sterilization of the cool zone). Please provide the protocols and summary reports for validation of the depyrogenation of the different vial sizes with schematic representation of the TC and EI locations in each run (and the rationale for each location as worst case). Additionally, please provide a description of the EI used as well as summaries of the endotoxin recovery studies conducted to ensure accuracy of the log reduction.*

The depyrogenation tunnel is divided into (b) (4) zones:

(b) (4)



- e. *Conditions/parameters for the routine depyrogenation process and how these compare to the validated process.*

As noted above, the routine depyrogenation cycle is conducted with a heating zone temperature of (b) (4) (versus (b) (4) for validation studies). The firm's response also noted that conveyor speeds for the 70 mL, 100 mL, 250 mL, and 300 mL vial formats are the same for both routine operations and validation activities.

Reviewer's Comments: The firm's response is acceptable.

4. *For each piece of equipment, please provide (in tabular format) the following information: method of cleaning, method of sanitization/sterilization, dirty hold time, clean hold time, and sterile hold time.*

The firm's response included tabular summaries for major equipment in the following production areas: Plasma (b) (4); Fractionation and Purification for Manufacture of (b) (4); (b) (4); and Aseptic Production. Specific cleaning methods and hold time parameters are listed in the tables below.

(b) (4)

(b) (4)

Reviewer's Comments: The firm's response is acceptable.

5. Please provide the revalidation protocols for cleaning (b) (4), the equipment washing machine, the vial washer, and the manual cleaning process), sterilization (b) (4) and autoclave), sanitization/disinfection (b) (4) and autoclave), and depyrogenation/dry heat.

The preceding protocols were submitted as part of the firm's responses to Questions 1 and 3.

Reviewer's Comments: The firm's response is acceptable.

Line Clearance

6. Please provide line clearance procedures associated with the production of NewGam. Please clarify whether rooms, working surfaces, and equipment are cleaned between

different batches of NewGam or only between manufacture of different products. Please justify your response.

The firm's response included a translated version of SOP 710SOP050/00, Line Clearance. In brief, this procedure requires that all products, documents, and components be removed from equipment and associated workstations at the conclusion of batch manufacturing activities. Operators are then required to document completion of these activities in the Master Batch Record (MBR). Line clearance activities are then verified and documented in the MBR by a (b) (4) operator prior to initiation of another production batch. Specific instructions and photographs for conducting line clearance activities in "complex" manufacturing areas such as Filling Line (b) (4) are also provided in Appendix 3 of SOP 710SOP050/00.

(b) (4)

Reviewer's Comments: The firm's response is acceptable.

Aseptic Process Validation/Process Validation

7. *Please provide the following SOPs associated with the performance of media fill simulations: 711SOP008, 711SOP009, 757SOP040, and 757SOP032.*

The requested SOPs were provided as part of Amendment STN 125587/0.9

Reviewer's Comments: The preceding SOPs were reviewed upon receipt and discussed during the inspection. Please refer to the EIR for more information.

8. *Please provide a list of the media fill simulation studies conducted to support validation of the NewGam aseptic manufacturing processes. Additionally, please provide the aseptic media simulation protocol for the initial validation and the (b) (4) requalification of the aseptic process (Document No. 757PQP005/23).*

A tabular summary of the media fills that were performed in support of the validation of the panzyga® aseptic manufacturing process is as follows:

Table 59: Media Fills Performed in support of the panzyga® Aseptic Manufacturing Process

(b) (4)

The firm's response also included translated versions of the initial validation protocol for the aseptic process (Document No. 757PQP024/00) and the protocol for the 2015 (b) (4) requalification of the aseptic process (Document No. 757PQP005/23).

Reviewer's Comments: The protocols for the initial validation and the 2015 (b) (4) requalification activities were reviewed and verified during the inspection. Please refer to the EIR for more information.

9. Please provide the report from the second media fill test (MFT) run (March 2015) conducted in accordance with protocol 757PQP005/23.

The firm's response included the PQ report (No. 757RQP005/24) from the second MFT run conducted on Line (b) (4) in March 2015. As noted in the firm's response to IR Question No. 8, this MFT run was comprised of (b) (4) in the 300 mL format. This MFT run also included requalification of all routine parameters that were not qualified during the 1st MFT run conducted in January 2015. These include the following:

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

Of note, the processing time parameter (minimum (b) (4)) that was to be requalified during this MFT run was not evaluated as processing of Batch No. (b) (4) did not exceed (b) (4). As qualification of processing time was valid through 9/20/2015, the firm decided to requalify this parameter as part of its August 2015 MFT run.

The filled vials from Batch No. (b) (4) were processed in accordance with the requirements outlined in Document No. 757PQPP005/23 (as described previously). Results from examination of these vials after the (b) (4) incubation periods showed no microbial contamination. The (b) (4) test for this batch also met acceptance criteria.

Reviewer's Comments: The firm's response is acceptable.

10. You reported that Fill Line (b) (4) in the OSA facility is utilized for filling of NewGam and other non-US approved products; however, it is not clear what conditions (e.g., (b) (4)) and vials and stoppers ((b) (4)) are applicable to NewGam. Please provide the aseptic manufacturing operation for NewGam to include container closure (different presentations and stoppers), filling equipment, filling time, single or double aseptic filling operations, and maximum number of vials filled per presentation.

A summary of the aseptic manufacturing operations for panzyga® is as follows:

(b) (4)

(b) (4)

(b) (4)

Reviewer's Comments: The firm's response is acceptable.

11. *Please provide the protocol and report for the validation of sterile filtration of NewGam prior to filling. Additionally, please provide the SOPs and study results to demonstrate sterile filter integrity before and after sterilization.*

The firm's response included the protocol and final validation report for sterilization of panzyga® by aseptic liquid filtration (b) (4)

Reviewer's Comments: Following review of the sterile filtration validation reports performed by (b) (4) (for OSA Lingolsheim) and (b) (4) (for OPG Vienna), a discrepancy was noted with regard to the bactericidal effects

of NewGam. Consequently, clarification was requested by Randa Melhem as part of CR Letter Item No. 3. Additionally, the firm was asked to confirm which product filters are used for sterile filtration of NewGam on Line (b) (4) at the OSA Lingolsheim facility (see CR Letter Item No. 4).

12. Please provide the qualification of the filling equipment to include changes to the format parts needed to accommodate different vial sizes.

The firm's response included the summary report (No. 757RVP032/01) for validation of (b) (4) during filling of panzyga® vials in the 70 mL, 100 mL, 250 mL, and 300 mL formats. In brief, three runs were performed for each of the worst case formats (70 mL (smallest vial) and 300 mL (largest vial)), while (b) (4) runs were performed for the 100 mL and 250 mL formats. To evaluate the (b) (4) of these runs, (b) (4) samples were collected from the (b) (4) of each fill and tested for (b) (4). (b) (4) checks were also performed for each of the (b) (4) samples to determine the adequacy of filling. Results showed that all vials met the acceptance criteria for (b) (4) tolerances.

The firm also noted that changes to the format parts for different vial sizes are evaluated as part of the MFT program.

Reviewer's Comments: The firm's response is acceptable.

13. Please provide the normal/maximum/minimum batch size for each of the six NewGam presentations.

The firm's response indicated that the size of panzyga® bulk batches is dependent on a number of variables within the manufacturing process. These include the following:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

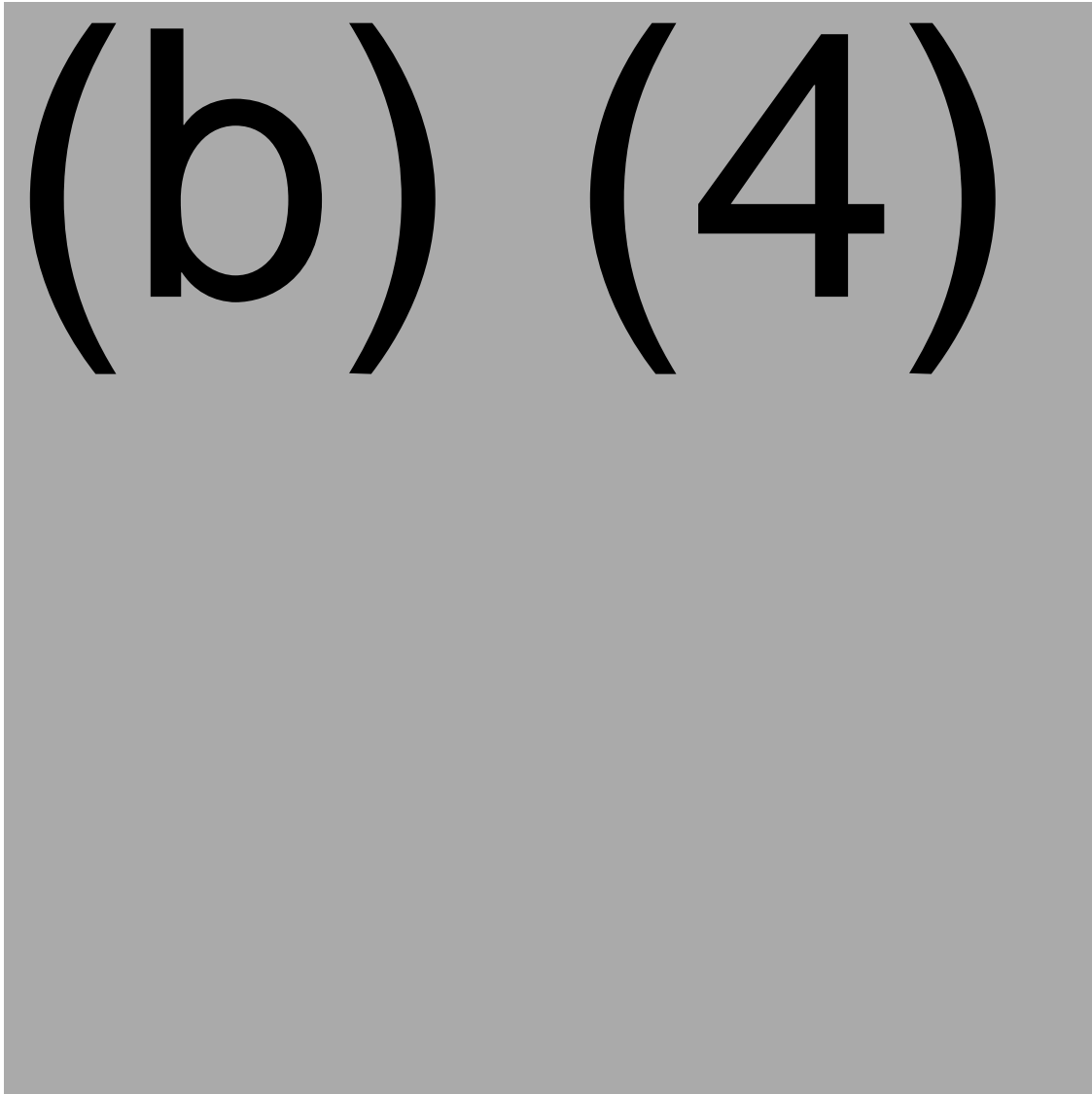
(b) (4)

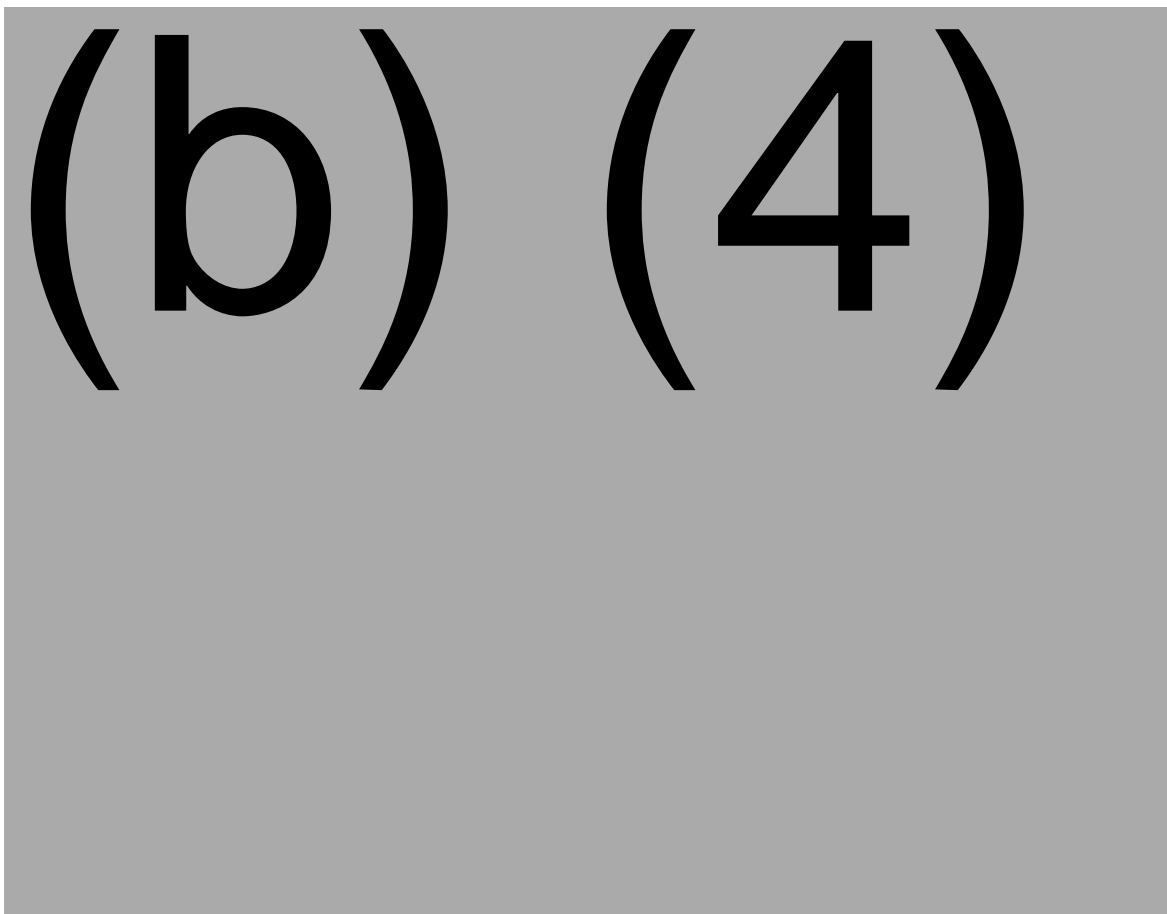
(b) (4)

Reviewer's Comments: The firm's response is acceptable.

14. For the conformance and validation batches filled at the OSA and Vienna (OPG) facilities, please provide the lot number, the number of vials filled per size, the number of vials that were visually inspected, and the number of vials that passed visual inspection criteria.

A tabular summary of the conformance and validation batches filled at OSA Lingolsheim and OPG Vienna is provided below.





Reviewer's Comments: It was noted that each defect classification (e.g., critical, major, and minor) had only one acceptance criterion for the sum of all defects (glass, capping, and product). It was also noted that each criterion for sum of all defects was met during inspection of the conformance and validation batches; however, the firm will need to implement an acceptance criterion for each defect category based on historical data (after an appropriate number of batches have been inspected during routine operations).

15. *Please provide clarification of the visual inspection activities performed at the OPG and Dessau, Germany (ODE) facilities. Specifically, do both facilities conduct primary (100%) visual inspection activities for all NewGam vial presentations? Are the processes and equipment identical?*

The firm's response confirmed that both facilities (OPG Vienna and ODE Dessau) conduct primary (100%) visual inspection activities for all panzyga® vial presentations.

With regard to transportation logistics, vials filled at OSA Lingolsheim may be shipped to OPG Vienna or ODE Dessau for primary (100%) visual inspection. Vials filled at OPG Vienna may be visually inspected at this site or shipped to ODE Dessau for primary (100%) visual inspection.

The firm's response also indicated that the visual inspection processes and equipment are identical at the OPG Vienna and ODE Dessau facilities. Of note, the OPG Vienna facility was previously approved as a visual inspection site for OCTAGAM (STN 125062/0 and STN 125062/234) and ALBUMIN (STN 125154/0). With regard to ODE Dessau, this facility was previously approved as a visual inspection site for OCTAGAM 5% (STN 125062/414) and ALBUMIN (STN 125154/156). Additionally, a submission (STN 125062/440) for ODE Dessau as a visual inspection site for OCTAGAM 10% has been submitted and is pending.

Reviewer's Comments: The firm's response is acceptable.

16. With regard to prevention of cross-contamination, you stated that after processing, the respective bulk solution is transferred through (b) (4) to the department of aseptic production. Please confirm which process applies to production of NewGam.

The firm's response confirmed that after processing, panzyga® bulk solution may be transferred to the Aseptic Production Department through (b) (4).

Reviewer's Comments: The firm's response is acceptable.

Container Closure for both OSA and OPG (Vienna) – Information Request

17. In the submission, you stated that the vials used for Vienna Line (b) (4) are (b) (4). However, the vials for Line (b) (4) are only (b) (4). Please clarify why there is a difference between the two filling operations, and how that would impact the container closure and product. Please provide data and justify your response. Also, clarify whether the vials filled at OSA are (b) (4) as well. Please justify your response.

The firm's response confirmed that the vials used for filling of panzyga® on Vienna Lines (b) (4) are not (b) (4). The firm also acknowledged that the initial BLA submission (Section 3.2.A.1.3.1.1) erroneously stated that vials used for filling of panzyga® on Vienna Filling Line (b) (4). Furthermore, the firm clarified that the description of the Line (b) (4) vials should have stated that "bottles are (b) (4)."

The firm's response also reiterated that the vials used for filling of panzyga® on OSA Lingolsheim Line (b) (4) are not (b) (4).

Reviewer's Comments: The firm's response is acceptable.

18. You reported in the submission that the stoppers used at OPG are 20mm or 32mm light grey (b) (4) coating), while the stoppers used at OSA are 32mm light grey (b) (4). Please explain why different stoppers are used at the two facilities.


The firm's response only indicated that the (b) (4) stoppers are utilized at OSA Lingolsheim as they ensure adequate machineability and closure integrity with the equipment on Filling Line (b) (4). No studies or data were submitted to support these claims.

Reviewer's Comments: The firm's response did not adequately address why different stoppers are used at the two facilities. This topic was addressed during the inspection and will be summarized in the EIR.

19. *Stability data is supportive of container closure integrity; however, it is not sufficient to validate the process. You need to provide the protocol and results for container closure integrity testing to demonstrate that the different combinations of vials (different sizes with some (b) (4) and some not), and stoppers (different sizes and coatings) maintain integrity during handling, transportation and throughout the shelf life of the products. Please provide data to support the minimum critical leak detected (b) (4), and the sensitivity of the CCIT method.*

The firm's response reiterated that the various vial/stopper combinations listed in stability reports Nos. 13P003 and 14P022 represent the intended marketing of the product. The firm also noted that these studies are ongoing and will continue throughout the proposed shelf life of the product.

With regard to CCIT of the various vial stopper combinations, the firm submitted Validation Report No. 009VAL193 CCIT (b) (4), Container and Closure Integrity Testing of Glass Vials with Rubber Stoppers by (b) (4)



The firm also submitted a validation protocol (150VPR1308) for transport of panzyga® in the (b) (4) seasons. Results of this validation were pending at the time of Amendment STN 125587/0.9.

Reviewer's Comments: During the inspection, the firm indicated that only the (b) (4) method is used at Lingolsheim for CCIT. The firm also acknowledged that (b) (4) with the (b) (4) is currently being validated and is only used at the OPG Vienna facility for non-routine testing. Additionally, the (b) (4) testing that is performed in conjunction with the (b) (4) testing was found to be inadequate with regard to the procedure for generating a positive control. Specifically, the (b) (4)

At the conclusion of the inspection, the firm was informed that the (b) (4) method is inadequate and that this is considered a review issue. This inadequacy of this method was reiterated during a teleconference on 10/29/2015 and the firm agreed to revalidate the procedure. Please refer to the addendum memo from Randa Melhem regarding final resolution of the firm's CCIT method.