



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 125668/0 for Immune Globulin Subcutaneous (Human)

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

Through: CDR Qiao Bobo, PhD, Branch Chief, OCBQ/DMPQ/MRBII
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Subject: Review Memo BLA: [Octapharma Pharmazeutika Produktionsges.m.b.H, License # 1646] Approval for Immune Globulin Subcutaneous (Human) liquid preparation supplied in six doses and indicated for the treatment of primary humoral immunodeficiency (PI). Both drug substance and final drug product are manufactured 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: December 29, 2018

ACTION RECOMMENDED:

Recommend Approval with the concurrence of the Product Office.

SUMMARY

CBER received this electronic submission on December 29, 2017. Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma) submitted this BLA to provide information to support US market authorization of an immune globulin subcutaneous (human) (IGSC) indicated for the treatment of primary humoral immunodeficiency (PI) in adults. The proposed proprietary name for IGSC drug product is Cutaquig, and the current IND name is (b) (4). These names will be used interchangeably throughout the memo.

The product is a liquid formulation containing 165 mg of protein per mL, obtained from the normal immunoglobulin fraction of human plasma, and intended for subcutaneous injection. IGSC is available in different doses: 6mL, 10mL and 12mL, 20mL, 24mL and 48mL, which are presented in the following vial sizes: 10mL, 20mL, 30mL and 50mL non-siliconized glass vials ((b) (4)) respectively, all of which are closed with 20mm bromobutyl rubber infusion stoppers and sealed with aluminum caps.

The manufacturing process was developed at Octapharma OPG facility in Vienna, Austria in 2013. The process was then ((b) (4)), where technical batches were produced ((b) (4)) and several campaigns of clinical batches were manufactured ((b) (4)). The process was then transferred to OPG ((b) (4)), for the manufacturing of the conformance lots ((b) (4)).

The manufacturing process of ((b) (4)) is a continuous process performed at OPG Vienna facility (FEI number: 3002809097), and based on the manufacturing process of licensed Octagam 5% and Octagam 10%. The new IGSC product ((b) (4)) is processed from ((b) (4))

as well as three virus reduction steps (precipitation of ((b) (4)), S/D treatment, and pH 4 treatment). The immunoglobulin G (IgG) solution is then ((b) (4)) step, and formulated by addition of maltose ((b) (4)%) and Polysorbate 80, as well as adjustment of the protein concentration to 16.5%, before aseptic filling into glass vials.

((b) (4)) final bulks were ((b) (4)) into ((b) (4)) final drug product lots to support the manufacturing process. Three lots covered each of the minimum (6mL) and maximum (48mL) fill volumes, and one lot covered each of intermediate (10mL, 12mL, 20mL, and 24mL) fill volumes.

Visual inspection, labeling and packaging were performed at OPG Vienna, and Octapharma GmbH Dessau facility (FEI number: 3008923644) located at Otto-Reuter-Str. 3, D-06847 Dessau, Germany (ODE).

The proposed shelf life of ((b) (4)) is 2 years at 2- 8°C; not to be frozen and protected from light. Within its shelf life, the product may be stored at ambient temperature (up to 25°C) for up to 6 months, without being refrigerated again during this period, and must be discarded if not used after the ambient storage.

All drug substance in-process testing, and drug product testing are carried out by Octapharma laboratories in Vienna, Austria, except for the final product testing for Diphtheria Ab, Measles Ab and Polio Ab testing which is carried out by contract laboratories.

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.

Categorical Exclusion from Environmental Assessment

Octapharma submitted a request for a Categorical Exclusion to omit preparation of an Environmental Assessment, under 21 CFR Part 25.31(c). The sponsor stated that to their knowledge, no extraordinary circumstances exist.

Based on the information submitted and the nature of this product, I concluded that the sponsor's request for Categorical Exclusion from an Environmental Assessment under 21 CFR 25.31(c) is justified as this product is composed of naturally occurring substances and manufacturing of this product will not alter significantly the concentration and distribution of the natural substance, its metabolites, or degradation products in the environment. Also, no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment.

INTRODUCTION

In this memo, I review the facilities, equipment, container closure, and manufacturing operations for (b) (4) at the licensed OPG Vienna and ODE Dessau facilities. The following Table lists the address and activities performed at both facilities.

Manufacturing/Testing site	Responsibility
Octapharma OPG Oberlaaer Strasse 235, Vienna, A-1100, AUSTRIA FEI: 3002809097 DUNS: 301119178	<ul style="list-style-type: none"> • Drug Substance: (b) (4) • Drug Product: Final Bulk sterile filtration and aseptic filling on filling Line (b) (4). • Quality Control: in process and final product testing • 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 secondary packaging
(b) (4) 	<ul style="list-style-type: none"> • Final Product testing: Diphtheria Ab
(b) (4) 	<ul style="list-style-type: none"> • Final Product testing: Measles Ab, Polio Ab

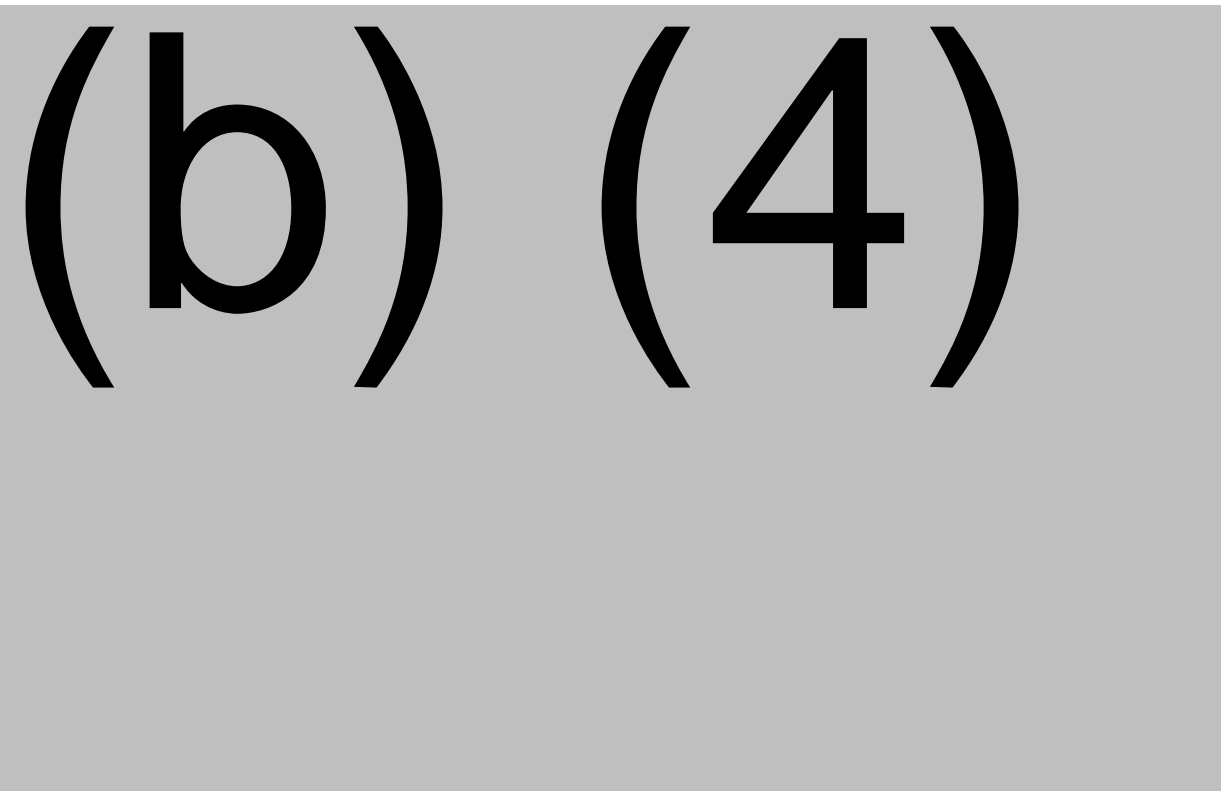
Manufacturing Process

The manufacturing process of (b) (4) is similar to that of Octagam 5% and 10% up to STEP (b) (4). The immunoglobulin G (IgG) solution is then (b) (4) by a (b) (4) step (STEP (b) (4)), and formulated by addition of maltose ((b) (4) %) and Polysorbate 80, as well as adjustment of the protein concentration to 16.5% (STEP (b) (4)), before sterile filtration and filling into glass vials (six fill volumes: 6mL, 10mL, 12mL, 20mL, 24mL, and 48mL).

Octapharma reported that the starting material, human plasma, used in the manufacture of (b) (4) is obtained from U.S. based plasmapheresis centers and community blood banks. All

donations used by Octapharma comply with the requirements of 21 CFR 640.30 and 21 CFR 640.60.

The manufacturing Steps are listed below, Steps (b) (4) are (b) (4) to Octagam production.



FACILITIES AND EQUIPMENT

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 comprises an area of (b) (4), of which the commercially used surface is (b) (4)

. Bldg. (b) (4) includes IT, Materials Management and Logistics, Laboratory QC (Quality Control), and QA (Quality Assurance). Bldg. (b) (4) includes Manufacturing (Visual Inspection and Packaging), Technics, QP, QC, Warehouse, and Building management. Packaging and warehouse areas are located on the first floor.

Octapharma reported that contract warehouse space may also be used. The following contract warehouse is currently used for storage of packed and released finished products at 2 - 8°C:

(b) (4)

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. They provided a site map of the Dessau facility, and the flow diagrams for products and materials, personnel, samples and waste.

Reviewer comments: Review of the manufacturing area shows that several visual inspection (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: Intravenous Immunoglobulin (STN 125062, and STN 125587), Albumin (STN 125154), Factor VIII/von Willebrand Factor (STN 125251), and Recombinant Factor VIII (STN 125555). 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), Recombinant Factor VIII (Simoctocog alfa, and Fibrinogen). 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 comments: The Dessau facility was inspected and licensed by the US FDA for the packaging and labeling of the following products: 5%, (b) (4) 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 was most recently inspected by Team Bio 15-18 February 2016, and resulted in no compliance actions.

The operations performed for the visual inspection, packaging and labeling of Cutaquig at ODE Dessau are similar to those for other US licensed products, and have been reviewed and approved in association with other licensed products. The following sections provide a summary of the operations performed at ODE.

Receipt and Processing of Cutaquig

Products are delivered by refrigerated trucks from the manufacturing site (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.

Octapharma reported that (b) (4) final container is 100% visually inspected at OPG Vienna (manufacturing site) or ODE Dessau.

- For (b) (4) lots that were not visually inspected at OPG, 100% visual inspection is performed at ODE. The product is transported to the visual inspection machine with (b) (4) (room (b) (4), or room (b) (4) for visual inspection), for 100% visual inspection.
- For (b) (4) lots that were 100% visually inspected at OPG Vienna site, an additional visual inspection for transport damages is performed in ODE Dessau site (room (b) (4), Packaging Lines (b) (4))

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

Labeling and packaging are performed on the automatic packaging Lines (b) (4) (room (b) (4)). Alternatively, the final container labeling can be performed on packaging Lines (b) (4) followed by manual packaging. Afterwards a labeling machine can be used for the application of additional labels (e.g. tamper-evident closures). A case-packer supports the packaging of product packages into outer boxes.

After labeling, samples for identity testing are collected and brought to QC (Bldg. (b) (4)) 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, and the respective location(s), and manufacturing operation(s) as presented in the following Table. They also provided a brief description of the equipment and their qualifications. All the equipment is non-product contact, and is shared by the various products (US and non-US licensed products) handled in the facility. The equipment qualifications/ operations have been submitted and reviewed in association with other US licensed products.



Prevention of Cross-contamination/ Mix-up

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

- (b) (4) [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]
- [Redacted]

(b) (4)

Computerized Systems

The computer systems at ODE Dessau includes programmable logic controllers (PLC), and administrative IT systems.

Octapharma stated that the packaging process is manually monitored; however, certain packaging steps are supported by computerized systems. The automated monitoring of the packaging process is integrated in the equipment by PLCs without any external computers. These packaging machines (inspection machines, labeling machines, cartoners, case-packer, and printing machines) are classified in (b) (4), and the computer validations were performed as part of the equipment qualification. where the software and automation hardware are an integral component.

Octapharma added that a SAP system is used 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 in a light industrial area of Vienna's 10th district southern outskirts. The OPG Vienna facility is licensed by the US FDA for the manufacture of the following products: 5%, (b) (4) 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, human fibrinogen (lyophilized). OPG facility is comprised of several buildings located on a (b) (4) area. The manufacturing operations for (b) (4) (drug substance and drug product, quality control, visual inspection, labeling and packaging, and batch release) are carried out in the following buildings:

Building	Activities
Buildings (b) (4)	Pre- v.i. operations (steps (b) (4)), located in Bldg (b) (4) Post v.i. operations (steps (b) (4)), located in Bldg (b) (4) Aseptic operations (step (b) (4), sterile filtration and filling), located in Bldg (b) (4)
Building (b) (4)	QC laboratories, locker rooms, and offices for production management.
Building (b) (4)	Packaging area includes visual inspection of vials, packaging into single cartons, and packaging into transport cartons
Buildings (b) (4)	Administrative functions

Building	Activities
Building (b) (4)	Stability rooms Plasma storage rooms
Building (b) (4)	Main storage area for raw materials

In addition to the on-site storage at OPG, the following contract warehouse space is used for the storage of plasma, intermediates and final product.

Warehouse	Uses
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Storage of plasma at controlled freezer temperature Temperature in the warehouse is under permanent control by calibrated temperature sensors.	

The manufacturing of (b) (4) drug substance is performed in the same areas used for the production of the US licensed Octagam 5% and 10%. The filling operations are performed on the licensed filling Line (b) (4), approved for filling of the US licensed Panzyga (125587) and Fibryna (STN 125612).

HVAC/ Environmental Monitoring

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) 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. Octapharma provided the room classifications for the different areas depending on criticality; they added that the HVAC system provides sufficient air to maintain cascading pressure from the Class (b) (4) → Class (b) (4) → Class (b) (4) as summarized in the following Table. They noted that no specified air pressure differential is maintained between the Class (b) (4) areas and normal atmospheric pressure.

Operations/Criticality	Class	(b) (4) At Rest/ In Operation	Pressure Differential
(b) (4)			

Operations/Criticality	Class	(b) (4) At Rest/ In Operation	Pressure Differential
(b) (4)			

Access to the clean room areas ((b) (4)) is restricted to authorized, trained personnel only.

The supplied air (at least (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. The following areas are supplied with fresh air (no air circulation): Pharmaceutical production areas Class (b) (4) supported by AHU (b) (4) , Packaging area (Class (b) (4)) supported by (b) (4) , and Stairs Hallways (room (b) (4)) and Mat. Locks (Class (b) (4)) supported by (b) (4) . All other areas are supplied with up to (b) (4) recirculated air depending on the activities in the area.

(b) (4)

The HVAC system was validated by IQ/OQ/PQ studies and re-qualification is performed when changes to 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.

Environmental Monitoring

Octapharma described the environmental monitoring program, and the sampling performed (types) in the different class areas, in operation and at rest, and provided the acceptance criteria for the viables and nonviables for the different room classifications as shown in the following Table:

(b) (4)

Octapharma uses the term “Batch monitoring” to refer to EM performed in the aseptic area during filling operations for every batch under dynamic conditions/in operation. They use the term “In Operation” monitoring for EM performed for other processing steps under dynamic conditions.

Reviewer comment: The EM program for the manufacturing operations at Octapharma was previously reviewed and approved. Octapharma included the frequency of sampling and sample locations. Additional information was requested regarding the results for the EM monitoring during the manufacture of the conformance lots and the last APS (Aseptic Process Simulation). The information was submitted in amendments 125688/0.15 and 125688/0.22 and reviewed in **Q3** of the Information Request section below.

Water Systems

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

Potable Water is supplied by the (b) (4)

[REDACTED]

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

(b) (4)

The WFI system validation approach included IQ, OQ and (b) (4) phases of PQ ((b) (4)). The most recent changes were implemented in 2016: Implementation of WFI Still (b) (4) (May 2016), Implementation of new points-of-use in sub-loop (b) (4) (July 2016), and Implementation of new points-of-use Loop (b) (4) (July 2016).

Reviewer comment: The most recent surveillance inspection of the facility was in 2017 (after implementation of the changes) and no objectionable conditions were reported for the water systems.

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).
- Deionized water is sampled (b) (4) throughout the system on a (b) (4). Thus, every sampling point is sampled at least (b) (4). The system is monitored (b) (4).
- The WFI system is monitored according to the following schedule:

(b) (4)

Clean Steam

The clean steam system was initially qualified in November 2001, and a new steam generator (b) (4) was implemented in 2007, and the latest change included implementation of clean steam in “Purification (b) (4)” (August 2009).

Clean steam is monitored (b) (4) at selected sampling points for (b) (4)

Procedures to Prevent Cross Contamination

The OPG Vienna facility has been designed for pharmaceutical manufacturing to accommodate multiple products, and has been licensed by FDA as a multiproduct facility. The procedures for

control of contamination and mix-ups have been reported and reviewed by FDA during the review of the BLAs/supplements and through pre-approval and surveillance inspections. Octapharma described their systems and procedures in place to prevent contamination / cross-contamination of products as summarized below:

- 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
- Use of dedicated equipment, i.e. (b) (4)
- Clear separation of pre-viral inactivation and post-viral inactivation areas: pre-v.i. area is classified as clean room class (b) (4), whereas post-v.i. area is classified as clean room class (b) (4). The pre-v.i. and the post-v.i. areas are physically segregated for each production line (b) (4). Transfer of product from the pre-v.i. area to the post-v.i. area is performed using (b) (4). After transfer is completed, the (b) (4) of in the pre-v.i. area. Therefore, cross-contamination from the pre-v.i. area to the post-v.i. area is prevented. After processing, the respective bulk product is transferred through a (b) (4) to the department of aseptic production.
- HVAC system (multiple AHUs) 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
- 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 (b) (4) or in-house procedures
- Access to the clean Room Areas ((b) (4)) 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 the 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
 - (b) (4)
 - (b) (4)
- Suitable material used for product contact surfaces
- Qualified cleaning procedures for production rooms. The aseptic filling within an (b) (4) is decontaminated by (b) (4)

- Validated cleaning procedures for production equipment
 - The status of each production vessel is clearly defined and labeled for each cleaning and production step
 - Equipment are checked for cleanliness prior to use
 - Samples of final rinse are collected following cleaning from the (b) (4) systems of the pre-v.i. area and the post-v.i. area, (b) (4)
- Validated sanitization and sterilization procedures for production equipment
 - The status of each equipment is clearly marked (e.g. sanitized or sterilized)
- Use of media fills (b) (4) a year to qualify the aseptic processing, and to re-train the aseptic area operators

Octapharma clarified that the changeover steps (bulleted below) are the same after each batch, regardless whether it is followed by a batch of the same or a different product.

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

Cleaning of Production Areas

Octapharma clarified that the cleaning of production areas is performed per validated procedures using qualified disinfectants. They provided the schedules of cleaning for the different areas (depending on classification:

Surface	Class (b) (4)	Class (b) (4)	Class (b) (4)	Class (b) (4)
Working surfaces/benches	(b) (4)			
Laminar flow benches				
Floor				
Handles, handholds, switches				
Doors				
Walls				
Ceiling				

Equipment

Octapharma provided the list of major equipment indicating that all the equipment used for the production of (b) (4) has been qualified previously in association with other US licensed

products. They provided brief descriptions of the equipment, their uses, and their room locations. They also provided the most recent cleaning/sanitization/sterilization validation of each of the already qualified equipment, and listed the validated dirty and clean hold times where applicable. The information is summarized in the following Tables:

(b) (4)

(b) (4)

Reviewer comment: Octapharma referred to equipment as shared, dedicated to US plasma, and shared with Octagam. Clarification was requested during a May 22, 2018 telecon regarding the dedication of equipment to US plasma, or the sharing of equipment with non-US plasma products/intermediates. Also, whether the manufacturing at OPG is performed on a campaign basis.

Octapharma reported in amendment 125668/0.09 that they updated Tables 3-6 of section 3.2.A.1.3 to clarify the usage of the terminology:

- Shared equipment: refers to all products manufactured at OPG (derived from US and non-US plasma sources)
- Shared with Octagam: refers to equipment used to produce Octagam (derived from US and non-US plasma sources) and (b) (4).
- Dedicated to US sourced plasma: refers to equipment used for manufacture of products derived from US sourced plasma only

Octapharma clarified that the manufacturing of (b) (4) is not performed on a (b) (4) basis. They added that their strategies and procedures in place minimize cross

contamination between the different products (derived from US and non-US plasma) at OPG:

- Use of dedicated equipment - (b) (4) are dedicated to US plasma) and (b) (4) dedicated to US Plasma
- Use of (b) (4) is recommended to clean steel surfaces, to achieve the removal of (TSE – potentially present in non-US plasma), and to provide adequate inactivation of adventitious agents.
 - Cleaning/flushing of the product contact surfaces with (b) (4) demonstrate at least (b) (4) log reduction of protein concentration (corresponding to (b) (4) log prion reduction).
 - (b) (4) process applied to equipment used for (b) (4) uses (b) (4) for at least (b) (4) which exceeds the (b) (4) concentration/time/temperature needed for the removal and inactivation of adventitious agents per documented literature.

(b) (4)

Cleaning of Equipment

Octapharma reported the equipment used for the production of (b) (4) at the OPG facility is cleaned either manually or by automated procedures ((b) (4)), or a combination of both.

(b) (4)

Octapharma described their cleaning validation strategy for the product contact equipment used at the OPG Vienna facility. For automatically cleaned vessels, (b) (4)

The cleaning validation studies include demonstration that the equipment can be cleaned (after a defined dirty hold time following soiling with placebo ((b) (4)) or product. The cleaning status is then verified by (b) (4). The clean hold time is also validated by checking the (b) (4) of the equipment following a defined hold time (clean/sanitized/sterilized state).

(b) (4)

(b) (4)

* Testing for (b) (4) is checked for the validation of manual cleaning.

** The (b) (4) are not collected for all cleaning validations, as the (b) (4) in the wash room may impact the results.

Reviewer comment: Octapharma stated during the June 20 and August 3 telecons (Q2 of IR), and subsequently in amendment 125668/0.22 that “If a vessel is used for (b) (4)

”. They clarified that all the vessels used for Cutaquig manufacturing are dedicated to a specific step in the manufacturing process.

They described the (b) (4) cycles used for cleaning of the equipment in the different departments:

(b) (4)

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Manual Cleaning

Manual cleaning includes cleaning of the (b) (4) System, (b) (4) and small equipment parts (e.g. gaskets, tri clamps, etc.) and disassembled major equipment parts.

Reviewer comment: Octapharma confirmed (in response to May 22, 2018 telecon) in amendment 125668/0.09 that there have been no changes to the cleaning and sterilization/sanitization of the equipment. They explained that (b) (4) /Cutaquig manufacturing operations are (b) (4) to those of Octagam 5% and 10% up to Step (b) (4), and thus the same equipment is used. They added that they included the most recent validation reports to support this BLA, for the completion of the file, and not because of any changes.

They added that equipment used downstream of (b) (4) are exposed to product/intermediates which are different than the Octagam/intermediates. Thus, the most recent (b) (4) revalidation reports were submitted to demonstrate adequate cleaning of the equipment following product soiling. The following equipment are used for the downstream steps:

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

I review below the cleaning re-validation reports of the listed equipment (submitted in the initial BLA) following soiling with (b) (4) /intermediates.

- (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

UF^{(b) (4)} System^{(b) (4)}

The UF^{(b) (4)} system ^{(b) (4)} was initially approved for the production of Octagam (STN 125062). The equipment is also used for the manufacturing of ^{(b) (4)} (STEP ^{(b) (4)}) ^{(b) (4)} v.i. for ^{(b) (4)}. Octapharma provided the following PQ report. *The life cycle for the UF^{(b) (4)} is under the purview of the product office, and DMPQ reviews the cleaning of the equipment.*

- 089PQR15310.103/US, Life Cycle Performance Qualification Report Ultra^{(b) (4)} ^{(b) (4)} System ^{(b) (4)} used for Manufacture of Octagam 5%, Octagam 10% and ^{(b) (4)} (approved 05 Jan 2017)

UF^{(b) (4)} system (equipment identifier ^{(b) (4)}) is equipped with ^{(b) (4)}.

For ^{(b) (4)} an initial cleaning is performed (SOP 056SOP104) which follows the following steps:

^{(b) (4)}

Octapharma provided the sampling frequency to evaluate the cleanliness and performance of the UF^{(b) (4)} unit.

(b) (4)

(b) (4)

The UF (b) (4) is monitored by sampling at different timepoints to evaluate the cleaning effectiveness (removal of proteins and prevention of cross contamination), bioburden /endotoxin control, and consistent process performance. The following samples are collected:

- (b) (4)
-
-

(b) (4)

Octapharma provided the results for the testing performed for the (b) (4) used during the manufacturing of Octagam 5%, Octagam 10% and (b) (4). They included the (b) (4).

(b) (4) is collected from the (b) (4) prior to use and is indicative of the effectiveness of cleaning. All (b) (4) results met the acceptance criteria for (b) (4); however, few samples did not meet the acceptance criterion for (b) (4). The range of contamination was (b) (4). Octapharma reported deviations for these excursions which were investigated, and the root cause was determined to be the sampling location. CAPA 38021 was initiated to evaluate a new sampling location. New sampling valves were installed and the WFI rinse flow rate during sampling was adjusted, and the SOPs were updated. Octapharma reported that samples collected from the new sampling

valves complied with the respective acceptance criterion demonstrating adequate preparation, cleaning and regeneration of UF^{(b) (4)} system ^{(b) (4)} .

The results reported for Sample IV for ^{(b) (4)} PPQ lots met the acceptance criteria.

Sterilization of Equipment

Different methods are used for the sanitization/sterilization of equipment:

- Steam sterilization SIP or autoclave
- Dry heat sterilization - oven
- Depyrogenation – depyrogenation tunnel for vials used in filling the final product (reviewed with the filling Line ^{(b) (4)})

The qualifications of the units used for sterilization/ sanitization/ depyrogenation of equipment were previously submitted and reviewed in association with other US licensed products. In addition, Octapharma reported that there have been no changes to the cycles/loads used for the sterilization/ sanitization/ depyrogenation of equipment used for the production of ^{(b) (4)} .

Steam Sterilization

Cleaned equipment used in production is sanitized/sterilized by clean steam (as applicable) prior to use. Octapharma reported that equipment used in the post-v.i. area of “Purification ^{(b) (4)}” and “Aseptic Production” is sanitized/sterilized. In the areas “Basic Fractionation” and pre v.i. area of “Purification ^{(b) (4)}” sanitation/sterilization is not required.

Reviewer comment: Octapharma stated during the May 22 telecon and in amendment 125668/0.09 that “Sanitation/sterilization of equipment used in the pre-v.i. and post-v.i. area is performed ^{(b) (4)} with the difference that equipment used in the pre-v.i. area is ^{(b) (4)}

^{(b) (4)}”. Additional clarification was requested during the May 22 telecon, and Octapharma submitted the response in amendment 125668/0.9 reviewed in this section.

They provided the acceptance criteria for the sanitation/sterilization procedures as summarized in the following Table:

(b) (4)

^{(b) (4)} autoclaves are used for the sanitization and sterilization of equipment. The autoclaves are equipped with interlocking door systems.

- Autoclaves (b) (4), located in room (b) (4), are used for sanitization of miscellaneous production equipment and silicone tubes. The equipment is loaded and unloaded in the same room.
 - These autoclaves are also used for sterilization of the feeding vessels used in the aseptic department. The clean feeding vessels are loaded in room (b) (4) and unloaded in the aseptic area (room (b) (4)) following sterilization.
- Autoclave (b) (4), located in room (b) (4) (Preparation (b) (4)), is used for sanitization of production equipment (post v.i.). The equipment is loaded and unloaded in the same room.
- Autoclave (b) (4), located between cleaning room (b) (4) (washing) on the pre v.i. side and room (b) (4) on the post-v.i. side, is used for sanitization of miscellaneous production equipment (post v.i.) and (b) (4). The equipment is loaded in room, (b) (4), and unloaded in room (b) (4) following sanitization.

Octapharma provided the most recent validation reports as shown in the **Table** above. The qualification of the autoclaves (b) (4) and the validation of the sanitization/sterilizations cycles have been reviewed in association with other US licensed products.

Reviewer comment: Octapharma clarified during the May 22, 2018 telecon that there have been no changes to the autoclaves and the sterilization cycles and loads, and that the reports were submitted for the completion of this new BLA submission. The review of the sterilization reports for (b) (4) is not included in the memo except for the validation of the sterilization of the stoppers, as the reports were not previously submitted in BLA/supplements. However, autoclave (b) (4) was a recently qualified sterilizer (2017), and the validation of the sterilization cycles and loads will be reviewed in this section.

Reviewer comment: Octapharma confirmed (in response to May 22, 2018 telecon) in amendment 125668/0.09 that autoclaves (b) (4) are used by the aseptic department and basic fractionation/purification department. They clarified the flow of equipment (cleaning and sterilization) in the different departments (pre v.i. and post v.i. (including aseptic filling) using diagrams and narrative.

Equipment used in the pre-v.i. area is cleaned in washing room (b) (4) (Grade (b) (4)). Equipment that requires sanitization is transported from washing room (b) (4) through corridors to sterilizer loading room (b) (4) (Grade (b) (4)) where it is loaded into autoclaves (b) (4). The sanitized equipment is unloaded in the same room (b) (4).

Feeding vessels (b) (4) (used in the aseptic area) are cleaned in equipment washing machine (b) (4) located in room (b) (4) (Grade (b) (4)). The clean vessels are assembled, and loaded into autoclaves (b) (4) ((b) (4), Grade (b) (4)). These autoclaves also open to the aseptic manufacturing area. The sterilized vessels are unloaded in the aseptic area ((b) (4), Grade (b) (4)).

Octapharma clarified that feeding vessels (b) (4) are not used in the (b) (4) process.

(b) (4)

Government	Percentage
Current government	85%
Previous government	15%

Government	Percentage
Current government	85%
Previous government	15%

Government	Percentage
Current government	85%
Previous government	15%

CONTAINER CLOSURE

Drug Substance

[REDACTED] (b) (4)
[REDACTED]

Government	Percentage
Current government	85%
Previous government	15%

Government	Percentage
Current government	75%
Previous government	25%

Drug Product

(b) (4) is filled in colorless 10mL, 20mL, 30mL, and 50mL non-siliconized glass (b) (4) vials. The vials are closed with 20mm bromobutyl rubber infusion stoppers (comply with (b) (4)) and sealed with aluminum caps.

Vials: Non-siliconized glass (b) (4) molded clear/colorless , (b) (4)				
Filling sizes	10mL vial	20mL vial	30mL vial	50mL vial
6 mL / 1 g	✓			

Vials: Non-siliconized glass (b) (4) molded clear/colorless , (b) (4)				
10 mL / 1.65 g		✓		
12 mL / 2 g		✓		
20 mL / 3.3 g			✓	
24 mL / 4 g			✓	
48 mL / 8 g				✓
Stoppers: 20mm light grey (b) (4)) Bromobutyl rubber, (b) (4)				
(b) (4) :				
<ul style="list-style-type: none"> Endotoxins (per wash-load): (b) (4) Bioburden Bacteria + Spores (per wash-load): (b) (4) 				
(b) (4) stoppers packed in sterilizable (b) (4) .				
Cap: Aluminum flip off cap 20mm (b) (4)				
blue (plastics component), and the cap is varnished (outside) and gold or blank (inside)				

Octapharma provided schematic diagrams and described the specifications and dimensions of the vials, stoppers and caps.

Reviewer comments:

Additional information about the two stopper specifications was requested, and Octapharma clarified in amendments 125668/0.15 and 125688/0.22 that the stoppers are the same; but they are bagged differently to accommodate the different filling lines. The information is reviewed in more detail in **Q5** of the Information Request section below.

Also, clarification was requested about the vials used, and whether the exact same container closure systems are used for other US licensed products? The information about the vials and container closure were provided in amendments 125668/0.15 and 125688/0.22 reviewed in more detail in **Q4 and Q6** of the Information Request section below.

Container Closure Integrity Testing

Octapharma reported that they evaluated the integrity of the container closure using the (b) (4) method ((b) (4)) in two separate stability studies:

- 000SSR991.16P005.01/INT: *Stability Study Report on Container Closure Integrity of (b) (4) Media Fills manufactured at OPG, Vienna, Primary Packaging System (b) (4), Study no.16P005; 12 months' data* (approved 12 May 2017)

(b) (4) broth was used during media fill simulation of each presentation (10mL, 20mL, 30mL and 50mL glass vials ((b) (4)) with bromobutyl rubber stoppers and caps) for this CCIT study. Octapharma reported that (b) (4) vials of each lot [(b) (4) (10mL); (b) (4) (20mL); (b) (4) (30mL); and (b) (4) (50mL)] were put on stability and tested according to the following schedule under the following conditions:

Storage Conditions: Sealed, dark, inverted	Duration	Testing	No. of Samples	Interim Results	Results
Long-term at 5°C	(b) (4) months	0*, 12, 24, (b) (4) months	(b) (4)	0, 12 months	Pass

Storage Conditions: Sealed, dark, inverted	Duration	Testing	No. of Samples	Interim Results	Results
Long-term at 25°C / (b) (4)	(b) (4) months	0 (b) (4) months	(b) (4)	0, (b) (4) months	Pass
Intermediate at (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Pass
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Pass
Accelerated studies	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Pass
*Samples are tested from each configuration at Time 0, which applies to all conditions. Tolerances: temperature $\pm 2^{\circ}\text{C}$, (b) (4)					

As shown in the above Table, all results passed, indicating the containers are integral at the 12 months' time point.

Reviewer comments:

The validation of the (b) (4) method was previously submitted and reviewed in association with two BLAs: 125587/0 and 125612/0. Thus, using this validated method for CCIT is acceptable.

Octapharma clarified during the June 21, 2018 telecon that the CCIT of media filled vials, was performed as an additional study to demonstrate that filled and stoppered/capped vials can maintain integrity (using (b) (4) method). Moreover, Octapharma provided a summary of the CCIT results (data) in amendment 125668/0.15 reviewed in **Q7** of the information request below. The response is acceptable.

- 000SSR81x.16P011.01/INT, *Stability Study Report on Container Closure Integrity of (b) (4) manufactured at OPG, Vienna Study no.16P011; 12 months' data* (approved 12 May 2017)

This report describes the CCIT study performed during stability of (b) (4) filled and stoppered vials: one batch for each container closure size. Octapharma provided the results for the 12 months' final data of intermediate condition studies ((b) (4)) of the (b) (4) batches. For the long-term condition studies at 5°C and 25°C/(b) (4), only initial data are available at this stage of the study.

Octapharma reported that (b) (4) vials of each lot [(b) (4) (10mL vial, 6mL fill); (b) (4) (20mL vial, 20mL fill); (b) (4) (30mL vial, 24mL fill); and (b) (4) (50mL, 40mL fill)] were put on stability and tested according to the following schedule under the following conditions:

Storage Conditions: Sealed, dark, inverted	Duration	Testing	No. Of Samples	Interim Results	Results
Long-term at 5°C	(b) (4) months	0*, (b) (4) months	(b) (4)	0, Initial (T0)	Pass
Long-term at 25°C / (b) (4)	(b) (4) months	0, (b) (4) months	(b) (4)	0, Initial (T0)	Pass
Intermediate at (b) (4)	12 months	0 and 12 months	(b) (4)	0, 12 months	Pass
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Pass
*Samples are tested from each configuration at Time 0, which applies to all conditions. Tolerances: temperature $\pm 2^{\circ}\text{C}$, (b) (4)					

Reviewer comment: Octapharma provided a summary of the CCIT results (data) in amendment 125668/0.15 reviewed in **Q7** of the information request below. The response is acceptable.

PROCESS VALIDATION

Octapharma provided the following process validation studies to support the validation of the manufacturing process for the drug substance and drug product, and the comparability of the manufacturing of the technical, clinical (b) (4) and conformance batches (OPG) to include validation of drug substance/product manufacturing, validation of the filling operations, and aseptic process validation. They also provided the transport validation of the drug product from OPG to ODE under summer and winter conditions. These validation studies are reviewed below.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

Final Container and Visual Inspection

Octapharma provided in Table 16 of the report the quality test parameters for the final product, the acceptance criteria and the data collected for the (b) (4) lots. I present below the results for the attributes reviewed by DMPQ.

Attribute		Appearance	Endotoxin	Sterility	Extractable Volume
Acceptance criterion		Clear or slightly opalescent and colorless or pale-yellow or light-brown	(b) (4)	Sterile	≥ nominal volume of each filling size
Batch #	Fill volume	Results			
(b) (4)	6mL	Pass	(b) (4)	Sterile	6mL
	48mL	Pass		Sterile	48mL
	6mL	Pass		Sterile	NA
	48mL	Pass		Sterile	NA
	20mL	Pass		Sterile	20mL
	24mL	Pass		Sterile	24mL
	6mL	Pass		Sterile	NA
	48mL	Pass		Sterile	NA
	10mL	Pass		Sterile	10mL
	12mL	Pass		Sterile	12mL

They also provided in Table 17 of the report visual inspection attributes (critical, major, and minor), the acceptance criteria, and the results for the 10 lots including the number of vials inspected, and the % of vials rejected as summarized in the following Table.

Batch	No. vials inspected	Quality Attribute Defects: Glass, Capping, Particles, Product			% Vials rejected
		Critical	Major	Minor	
Acceptance criteria		(b) (4)	(b) (4)	(b) (4)	(b) (4)
Batch # (Fill volume)	Results				
(b) (4) (6mL)	(b) (4)				
(b) (4) (48mL)					
§(b) (4) (6mL)					
§(b) (4) (48mL)					
§(b) (4) (20mL)					
§(b) (4) (24mL)					
§(b) (4) (6mL)					
§(b) (4) (48mL)					
§(b) (4) (10mL)					
§(b) (4) (12mL)					
* Vials inspected at ODE Dessau facility. §Vials inspected at OPG facility.					

No deviations were reported for process step Final Container and Visual Inspection.

Aseptic Process Validation

The aseptic filling line “(b) (4)” at OPG Vienna facility is used for the production of small volume parenterals (10mL – (b) (4)) for liquid infusion solutions or lyophilized products. The initial qualification of the filling line for aseptic processing was performed in 2013, with (b) (4) APS requalification studies to verify aseptic compliance. They provided the results for the APS runs performed during 2013, 2014 and 2015, and all results were compliant.

Octapharma also provided the following two reports and described the equipment used, media used, operators that performed the media simulations as well all the interventions and hold times simulated.

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

(b) (4)

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

- (b) (4)

Ground Transport Validation

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- (b) (4)

(b) (4) runs were performed using the refrigerated trucks between OPG and (b) (4) as summarized in the following Table:

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

(b) (4)

Reviewer Comment: Information about the shipping validation of the final product (air transport) was requested. Octapharma clarified during the June 20, 2018 telecon that they are preparing a shipping protocol for the final product which would be executed with the first shipping of Cutaquig after approval. They provided additional information in amendment 125668/0.15 and is reviewed in **Q12** of the Information Request section below.

Stability Studies

Octapharma reported that they performed stability studies to support the 24 months shelf life of (b) (4) : Long-term at 5°C±3°C and 25°C/(b) (4) , Intermediate-term at (b) (4) and Accelerated studies at (b) (4) . The proposed

shelf life of (b) (4) is 24 months at 2 - 8°C and protected from light. Within its shelf-life, the product may be stored at room temperature up to 25°C for up to 6 months without being refrigerated again during this period, and must be discarded if not used after this ambient storage. They described and provided the results for the following Stability studies:

- 000SSR81x.16P001.02/US, Interim Stability Report (18 months) for (b) (4) Batches manufactured at OPG Vienna in 2015 (approved 14 Dec 2017).

The study includes (b) (4) final container batches manufactured at OPG - (b) (4) batches from each of the smallest (6mL) and largest (48mL) fill volumes. Octapharma considered the study representative of all other fill volumes (10mL, 12mL, 20mL and 24mL) as they are bracketed between the two extremes. Accelerated studies were not performed on these batches, as previous stability studies performed at Octapharma OAB site (12mL and 48mL fill batches) showed reduced stability under accelerated storage conditions (study OC17-0600 reviewed in the subsequent section).

The results provided are for 18 months, and the duration of the study is (b) (4) months for Long-term at 5°C±3°C, (b) (4) months for Long-term at 25°C/(b) (4), (b) (4) months for Intermediate-term at (b) (4), and (b) (4) months for (b) (4) studies at (b) (4).

Batch	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Fill size	6mL	48mL	6mL	48mL	6mL	48mL
Batch size	(b) (4)					
No. of Stability samples						
5°C, dark						
25°C/(b) (4), dark						
(b) (4), dark						
(b) (4) for 12 months, dark, inverted						

The attributes tested during the stability studies included: appearance, pH, molecular size distribution, total protein, protein composition, (b) (4) activity, Fc-function, HBs antibodies, diphtheria antibodies, measles antibodies, polio antibodies, IgG subclasses, maltose, endotoxin, and sterility.

The results of the testing for appearance (clear and colorless; during storage it may turn to slightly opalescent and pale-yellow), sterility ((b) (4)) and endotoxin (b) (4)) which are under DMPQ purview at the different time points met the acceptance criteria. The results of the other product attributes will be covered in the product office reviewer memo.

Octapharma reported that out of specification (OOS) results for Measles Ab were detected after (b) (4) months storage at 25°C/(b) (4) for (b) (4) batches and at (b) (4) for (b) (4) batches. The Measles Ab specification is a product attribute, and the OOS will be covered in the product office memo(s).

- OC17-0600, (b) (4) Human Normal Immunoglobulin Study FFH 1332 Interim report, up to (b) (4) months data for Clinical Batches manufactured at (b) (4) in 2013 and 2015 (approved 13 Oct 2017).

The study includes (b) (4) final container batches manufactured at (b) (4). The report provides the final results ((b) (4) months data) for (b) (4) batches ((b) (4) filled into 12mL and 48mL fill volumes) and interim results ((b) (4) months data) for (b) (4) batches ((b) (4) filled into 12mL and 48mL fill volumes) at the different storage conditions: 5°C±3°C, 25°C/(b) (4) and (b) (4); and after (b) (4) months storage at (b) (4) for all (b) (4) batches as summarized in the following Table:

Batch	(b) (4)
Fill size	
Batch size	
No. of Stability samples*	
5°C, dark, inverted	
25°C/(b) (4), dark, inverted	
(b) (4), dark, inverted	
(b) (4), dark, inverted	
(b) (4), dark, inverted	6 months results (Completed)
*The number of stability sample/storage condition was not included in the report.	

The attributes tested during the stability studies included: appearance, pH, total protein, molecular size distribution, protein composition, (b) (4), Fc-function, HBs antibodies, diphtheria antibodies, measles antibodies, polio antibodies, IgG subclasses, polysorbate 80, maltose, sodium, endotoxin, general safety and sterility.

Appearance, sterility and endotoxin are under DMPQ purview. The results of the testing for sterility (sterile per (b) (4)) and endotoxin (b) (4) at the different time points met the acceptance criteria for all storage conditions. The results for appearance (the liquid formulation is clear and colorless; during storage the liquid may turn to slightly opalescent and pale-yellow) did not meet the specifications after 6 months storage at (b) (4) and after 18 months (and also subsequently 24, (b) (4) months) storage at (b) (4) for all the batches (except batch (b) (4)), as the liquid formulation had a **yellow color** and, and thus did not meet the master product specification. The appearance criterion was met for the other storage conditions.

The results showed OOS for other product related attributes during the stability study which will be covered in the product office memo.

Based on the results of the stability study Octapharma concluded that “*The stability for storage at 5°C/AMB RH for up to (b) (4) months and at 25°C/(b) (4) for up to (b) (4) months could be demonstrated. Based on the current data for (b) (4) the following shelf-life can be supported: 24 months stored at +2°C to +8°C, not to be frozen and protected from light. Within its shelf-life, the product may be stored at room temperature up to +25°C (77°F) for up to 6 months without being refrigerated again during this period, and must be discarded if not used after this*”.

INFORMATION REQUEST

Additional information was requested during a May 22, 2018 telecon, a June 20, 2018 telecon (followed by a June 21, 2018 information request), and an August 3, 2018 telecon. Octapharma submitted their responses in amendments 125668/0.09, 125668/0.15 and 125668/0.22 respectively. The review of the responses to the May 22 telecon are included in the body of the memo. The review of the responses to the June 21 IR and August 3 telecon is either included in the respective sections of the memo, or below.

CBER comments are in bold italics, followed by the sponsor responses in plain lettering.

Cleaning Validation

1. ***Report 087RPQ16012.000: Cleaning validation for Vessel (b) (4) was performed following soiling with (b) (4) /Cutaquig bulk 16.5 %. You reported that the validated dirty hold time is (b) (4) ; however, in the validation run, a DHT of (b) (4) was reported. You justified that the DHT was previously validated for (b) (4) in report 087RPQ09424.000; yet you did not provide the summary report. Please clarify and provide supportive data to demonstrate that cleaning was effective following soiling with (b) (4) /Cutaquig bulk 16.5%, and DHT of at least (b) (4) .***

Response is acceptable, and it was reviewed in the body of the memo.

2. ***You provided the list of major equipment and their uses for (b) (4) Cutaquig production in Annex 1. Some of the equipment is used in more than one manufacturing step. Per your protocol, the cleaning validation should verify cleaning following placebo and product/intermediate runs. You clarified during the June 20 telecon that if a vessel is used for (b) (4) . For each vessel that is used in more than one manufacturing step, please list the intermediate(s)/product(s) that contact the equipment surface, and clarify if the cleaning validation (including DHT) following soiling with the respective product/intermediate was performed. Please justify your response.***

Octapharma stated that vessels used during the manufacturing of Cutaquig are dedicated to (b) (4) . They added that following use, the equipment is (b) (4) . They referred to PQ report 089PPQR15387.103/03/US for a list of the vessels and process steps.

Reviewer comment: Octapharma clarified during the August 3, 2018 telecon and in their written response (amendment 125668/0.22) that all the vessels used for Cutaquig manufacturing are dedicated to (b) (4) in the manufacturing process. They added that, in general, “If a vessel is used for (b) (4)

”.

Response is acceptable.

Environmental Monitoring

3. *You provided in the BLA submission a brief description of the environmental monitoring program. Please provide a summary report of the environmental monitoring performed and data collected during the manufacturing of the (b) (4) Cutaquig conformance lots, and the most recent aseptic process simulation (media fill). Please describe any deviations, the investigations and the corrective actions implemented.*

Octapharma provided summary report, *the Environmental Monitoring during Performance Qualification (PQ) batches of (b) (4)* (issued 28 Jun 2018).

The report summarized the microbiological EM data collected during the aseptic filling of the (b) (4) PQ batches on filling Line (b) (4), and the supportive areas, as well as the microbiological EM results of the most recent APS runs.

Octapharma stated that microbial EM monitoring ((b) (4)) is performed at (b) (4) different positions in the (b) (4). They provided the microbiological EM results for the (b) (4) batches, and all were (b) (4).

The submitted microbiological EM data covered (b) (4) sampling during March, April and June 2016 in the Grade (b) (4) areas (rooms (b) (4)), and all results met the acceptance criteria. However, no EM data was submitted for the EM during the filling operations.

The EM results during the most recent APS runs (2018) were also (b) (4) at all (b) (4) sampling positions for the (b) (4) APS batches (b) (4).

Reviewer comment: Octapharma provided the microbiological EM monitoring; however, they did not provide the non-viable monitoring to demonstrate compliance with room classifications during operations. Additional information was requested during the August 3 telecon, and Octapharma submitted the information in amendment 125688/0.22 and reviewed below.

Non-viable EM results: Octapharma reported that non-viable monitoring is performed during every routine aseptic filling on filling Line (b) (4) at (b) (4) sampling locations based on a risk assessment ((b) (4)). They provided the acceptance criteria for the non-viable particles Grade (b) (4), and a summary of the data collected during the (b) (4) PPQ batches, as well as the summary for non-viable EM data collected during (b) (4) APS (media fills).

The data showed that the non-viable sampling counts were mostly in the (b) (4) range, with few sampling counts in (b) (4) range, and thus meeting the acceptance criteria for all sampling points during the manufacture of the (b) (4) PPQ batches and the (b) (4) APS runs.

Response is acceptable.

Container Closure

4. *You reported that (b) (4) Cutaquig is filled in colorless 10mL, 20mL, 30mL, 50mL non-siliconized glass (b) (4) vials, closed with 20mm bromobutyl rubber infusion stoppers, and sealed with aluminum caps. Are these vials, stoppers and caps the exact types /sizes used for the filling of other US licensed products? Please clarify and list the products and respective STNs and approval dates. If not, please provide the studies used for the qualification of the container closure, and the summary reports for their cleaning and sterilization. If the information is already provided in the BLA submission, please list the report numbers.*

Octapharma stated that two containers (30mL and 50mL vials) are new for the Cutaquig final product. They also listed the vials, stoppers and caps used for other US licensed products as summarized in the following Table.

Container Closure	Use for other US Licensed Products
Vials – Glass (b) (4)	
10 mL	STN 125251/0 (Wilate) on December 04, 2009 – Solvent (b) (4) vial
20 mL	STN 125251/0 (Wilate) on December 04, 2009 – Wilate vial
30 mL	New to Cutaquig
50 mL	New to Cutaquig
Stopper – 20mm Bromobutyl rubber, (b) (4)	
(b) (4)	STN 125062/124 (Octagam 5%) on March 26, 2007 and STN 125062/234 (Octagam 10%) on July 11, 2014
(b) (4)	STN 125062/486 (Octagam 5% and 10%) – Annual Report 2016
Cap – Aluminum flip off cap 20 mm	
20 mm cap	STN 125062/0 (Octagam 5%) on May 21, 2004 and STN 125062/234 (Octagam 10%) on July 11, 2014

Octapharma stated that the integrity of different container closure presentations was demonstrated using the (b) (4) method ((b) (4)) as documented in Stability report 000SSR81x.16P011.01/INT reviewed previously in the body of the memo.

Octapharma also reported that the cleaning/depyrogenation of all the vial presentations were validated, and that the sterilization loads/cycles of the of the stoppers and caps using autoclaves (b) (4) were also validated. The validation reports were submitted in the initial BLA submission and amendment 125668/0.15.

Reviewer comment: The cleaning and depyrogenation of the vials are reviewed in the body of the memo.

The caps are already used for US licensed products, and Octapharma stated previously (amendment 125668/0.9) that there have been no changes to the sterilization process. Thus, these reports are not reviewed in this memo.

Octapharma stated in response to Question 5c below that the sterilization validation of stoppers ((b) (4)) load was not previously submitted to FDA. The sterilization of the 20mm stoppers is reviewed in the body of the memo.

Additional clarification about the vials and stoppers was requested during the August 3, 2018 telecon, and Octapharma submitted their response in amendment 125688/0.22, and reviewed below.

Vials: Octapharma stated that the 30mL and 50mL vials used for Cutaquig, are (b) (4) glass vials, while the vials already approved for Octagam (STN 125062) or Panzyga (STN 125587) are (b) (4) glass. Octapharma clarified during the August 3 telecon and in amendment 125688/0.22, that the validation of the cleaning and depyrogenation of the different vials sizes applies to both glass types ((b) (4)).

Response is acceptable. Octapharma provided CCIT for the new (b) (4) 30mL and 50mL vials. In addition, the cleaning and depyrogenation are covered by the (b) (4) glass validation process.

5. You reported that 20 mm light grey ((b) (4)) Bromobutyl rubber stoppers are used and that they are purchased under the following codes: (b) (4)

a. Please clarify whether the stoppers are tested for endotoxin/bioburden on site, or is it per CoA?

Octapharma stated that endotoxin/bioburden testing is performed by the supplier, and they review at OPG the test results documented in the CoA. They added that (b) (4) revalidation of the certified values on the CoA is performed by in-house testing at Octapharma.

b. From your description, it seems that stoppers (b) (4) are washed and sterilized in-house. Please describe the cleaning and sterilization cycle and the validation of the loads.

Octapharma clarified that the stoppers are supplied ready to sterilize.

c. Also, describe the sterilization cycle for (b) (4) and the validation of the load. If the information has been provided in association with other US licensed product, please provide the STN number(s) and approval date(s).

Octapharma stated that although 20 mm light grey ((b) (4)) bromobutyl rubber stoppers (specification numbers (b) (4)) are licensed for STN 125062 (Octagam), the description of the sterilization cycle for (b) (4) and the validation of the load was not provided in association with other submissions.

Reviewer comment: Octapharma clarified in amendment 125688/0.22 that the information about the sterilization cycle and the validation of the load (22mm stoppers) were reported in the Octagam Annual Report. They added that the sterilization reports were provided in this BLA submission and amendment 125688/0.15.

The stoppers can be sterilized in (b) (4) different autoclaves. The Table below lists the Autoclave, Sterilization load, and the validation reports reviewed in the body of the memo.

Autoclave	Load	Report	Amendment
(b) (4)	Standard Load (b) (4)	080RPQ17086.001	125668/0.15
(b) (4)	Standard Load (b) (4)	080RPQ17102.001	125668/0.15
(b) (4)	Standard Load (b) (4)	080RPQ17398.001	125668/0

Octapharma stated that the sterilization of the stopper loads is revalidated (b) (4) using a (b) (4) to demonstrate effective sterilization.

Reviewer comment: The review of the sterilization validations for the 20mm stopper loads is included in the body of the memo. However, the reports do not state whether the stoppers are (b) (4). Additional information was requested during the August 3 telecon, and Octapharma submitted the information in amendment 125668/0.22 and reviewed below.

Octapharma clarified that stopper specifications (b) (4) include identical 20mm light grey ((b) (4)) bromobutyl rubber stoppers. The only difference is the stopper packaging due to handling characteristics of the filling lines. Cutaquig is only filled on Line (b) (4), and requires stoppers packed in (b) (4) (according to specification (b) (4)). They added these same stoppers are used for filling of Octagam on Line (b) (4), and the studies regarding the sterilization cycle and the validation of the load was performed, but reports were not previously provided to FDA for Octagam due to Annual Report submission. The studies were reviewed in the body of the memo.

Octapharma stated that both specifications were included in the initial BLA submission as the (b) (4) (used for Cutaquig) references information within specification (b) (4). However, to avoid confusion they decided to update specification (b) (4) to include all necessary information without a reference to specification (b) (4). A change control has been initiated and when the final specification will be included in Module 3, section 3.2.P.7, by September 2018.

Octapharma clarified that the specification numbers were not previously included in the sterilization reports, but the stoppers were identified via respective corporate article numbers (CAN). However, since the beginning of 2018, specification numbers have been listed in sterilization cycle validation reports. They provided the most recent validation report 080RPQ18235.001 for standard load (b) (4) covering stoppers according to specification (b) (4).

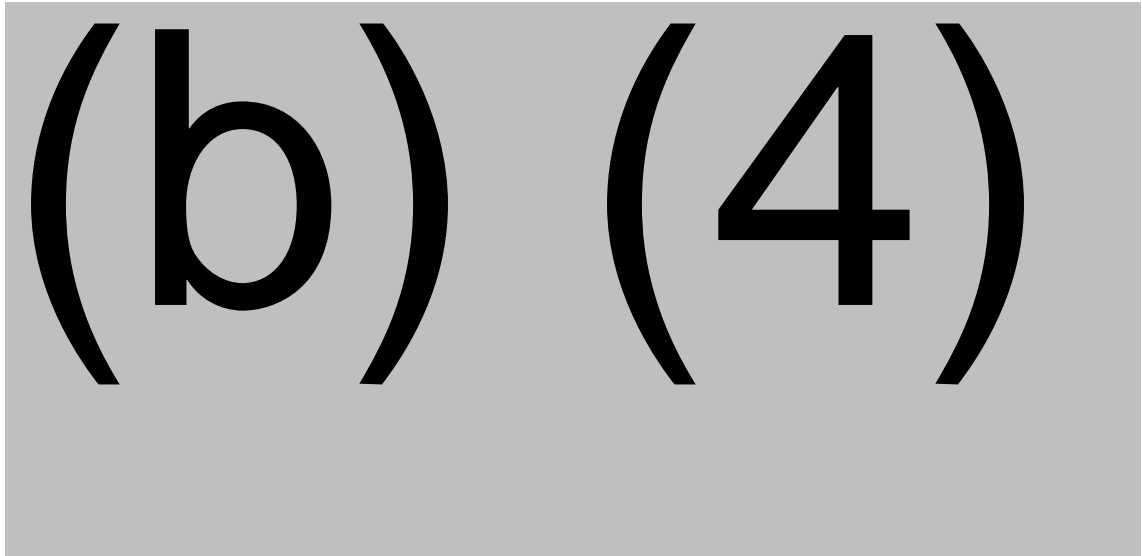
- 080RPQ18235.001, Report Performance Qualification Steam Sterilizer (b) (4) Standard Load (b) (4) "Stoppers 20mm Filling (b) (4)" Sterilization (approved 05 Jul 2018).

The report provides the CAN, description of the stoppers, and lists the stopper specification (b) (4) ((b) (4) stoppers per bag).

Load (b) (4) includes (b) (4) stopper bags, distributed over (b) (4). The validation of sterilization cycle was monitored by (b) (4) TCs and (b) (4) BIs with (b) (4) TCs/BIs on each

(b) (4), and (b) (4) TC/BI in the (b) (4). Also, there were (b) (4) chamber temperature sensors and (b) (4) pressure sensor. The validation cycle was performed at (b) (4) conditions ((b) (4) than the (b) (4) routine cycle). The load is dried with clean air.

Octapharma provided the thermal profile for the sterilization of Load (b) (4) and a summary of the data collected as summarized in the Table below:



The submitted data show that the temperature distribution was uniform (within (b) (4)), and thus, no cold or hot spots were detected. In addition, the process sensors recorded close results to the TCs.

Response is acceptable.

6. You reported that the vials are re-examined after (b) (4) of manufacture. Briefly describe the process and acceptance criteria. What is the shelf life of the vials, stoppers and caps? Please justify your response.

Octapharma explained that the vials are re-examined (b) (4) after first release, where statistical samples are drawn and tested for (b) (4) according to (b) (4). If the vials meet the specified requirements the re-examination date is extended for another (b) (4). The maximum shelf life is (b) (4) as defined by the supplier (as documented in (b) (4), dated 30 Dec 2016).

The shelf life of stoppers is (b) (4) after production according to functional and chemical studies performed by (b) (4) based on the requirements of (b) (4).

The shelf life of caps is (b) (4) according to stability studies conducted by (b) (4) based on chemical, functional and physical characteristics ((b) (4) document dated 27 Jun 2018). Octapharma stated that (b) (4) after first release, they perform a visual reexamination of the caps.

Response is acceptable.

7. *You reported that you evaluated the integrity of the container closure using the (b) (4) method ((b) (4)) in two separate stability studies and provided the following intermediate reports: 000SSR991.16P005.01/INT (media filled vials) and 000SSR81x.16P011.01/INT (product filled vials). You reported that the results passed, yet you did not provide the data (values) obtained for the controls and the test samples. Please provide a summary report of the CCIT data.*

Octapharma provided the following report in amendment 125668/0.15, which summarizes the results of the CCIT testing of media and product filled vials (12 months stability)

- 000SPR991.81x.16P005.16P011.00_INT, CCIT (b) (4) media fills and (b) (4), OPG Studies 16P005 and 16P011, 12 months' numerical results (approved 29 Jun 2018)

As stated previously (body of the memo), Study 16P005 was performed with media fills ((b) (4)), and study 16P011 was performed with (b) (4) Cutaquig final containers.

Octapharma clarified that for the initial testing of the (b) (4) final containers, the number of units sampled for CCIT, is the same as the number of units sampled for sterility (i.e. (b) (4) units). They provided the results ((b) (4)) between beginning and the end of the test time) collected for the negative control, positive controls ((b) (4) vial, and self-test with (b) (4)), and the test samples. The integrity of the container closure is considered validated when the all vials of a tested batch are below the positive controls with the (b) (4). The results for the (b) (4) vials are included for information only.

Octapharma provided the results for the CCIT testing performed for each vial size and incubation conditions/time points. The testing included sampling (b) (4) units, (b) (4) negative controls, and (b) (4) positive controls ((b) (4)). I summarized in the Table below the range of results (Min-Max) for the test samples, the negative controls, the (b) (4) positive control. The CCIT results indicate that the different container closure presentations are integral, as the (b) (4) is closer to the negative control, and way below the (b) (4) of the (b) (4) positive control vials.

The results show that the results for the samples are even lower than those of the (b) (4) positive control vials as summarized in the following Tables.

(b) (4)

9. ***You reported that the (b) (4) Cutaquig final drug product (FC) was evaluated (protein concentration and osmolality) throughout the filling operation. Please provide the frequency of sampling to demonstrate filling consistency throughout the operation.***

Octapharma reported that they sampled throughout the filling process where (b) (4) consecutive samples were collected at (b) (4) of filling process, (b) (4) consecutive samples were collected (b) (4) the product solution, and the (b) (4) consecutive samples of the batch were collected at (b) (4) filling process for a total of (b) (4) samples per batch.

Response is acceptable.

Aseptic Process Simulation (APS)

10. ***You stated in Report 057RPQ_F4_MF_2015-5-iPQ, that the Aseptic Process Simulation was performed for implementation of new filling sizes, yet the report did not specify the new vial sizes and fill volumes.***

- a. ***Please clarify which new vial/fill sizes were validated in this APS.***

Octapharma listed the new filling volume/vial size:

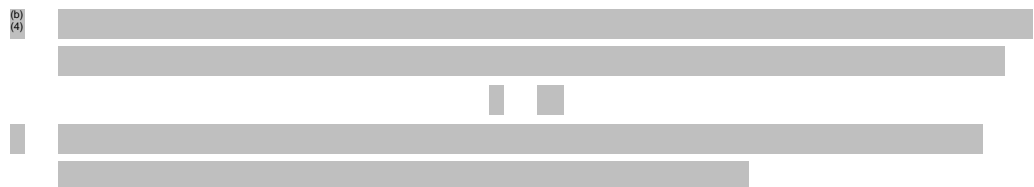
- 6mL in 10mL vials
- 48mL in 50mL vials

They added that 20mL and 30mL vial sizes were previously qualified with (b) (4) initial APS runs, and also as part of the overall qualification program as documented in 057RPQ_F4_MF_2015-5-iPQ.

- 24mL in 30mL vials
- 10/12mL in 20mL vials

- b. ***Also, clarify which of these aseptic process simulations runs were vials filled from (b) (4), and which ones were filled from vessels.***

Octapharma clarified that the media is (b) (4) filtered into the (b) (4), this is followed by one of these (b) (4) steps, and as shown in the flow chart below:



(b) (4)

- c. *You referenced the following two reports for growth promotion testing of the (b) (4) (Report 057RPQ_F4_MF_2015-3 and Report 057RPQ_F4_MF_2015-4). Please provide a summary of the growth promotion testing and results to support the APS study.*

Octapharma explained that growth promotion testing of the spent culture media is performed per SOP 001SOP610 after the last visual inspection of the incubated media filled vials. They briefly described the procedure as follows:

(b) (4)

[REDACTED]

(b) (4)

(b) (4)

Response is acceptable.

11. In report F4_RPQ_ (b) (4) , you described the results for the simulation of (b) (4) product. The report presents a list of the APS runs performed in 2017, indicating whether the filling was performed from a vessel ((b) (4)) or from a (b) (4). All the APS runs resulted in 0 contaminated final container. However, (b) (4) out of (b) (4) APS runs simulating filling from a (b) (4) resulted in deviations – which were not described. Please describe briefly the deviations associated with the media fills reported in Table 12 of the report. Also include the investigation and the corrective actions (if applicable).

Octapharma described the deviations that were raised during the media fills.

APS (b) (4) (Media Fill (b) (4)):

- The media fill was aborted and restarted as (b) (4) due to technical problem with (b) (4). The issue was investigated, determined to be an isolated incident (tubing defect), and not related to the aseptic process. Deviation TW# 74449 was closed.
- During the aseptic filling of APS (b) (4) , technical difficulties were encountered in the depyrogenation tunnel causing blockage and preventing movement of vials. This was also an isolated event, and not related to the media fill process. Deviation TW# 7458 was closed.

Both Media Fill runs were treated as “regular APS” (although (b) (4) duration) and all vials filled until the technical problems occurred, were subsequently incubated, visually inspected and tested in the same way as routinely performed APS, including growth promotion testing. All results met the APS acceptance criteria; however, the number of filled vials did not meet the minimum required filled vials during an APS run.

Octapharma reported that the deviations associated with the other APS runs were not related to aseptic filling process:

Media Fill (b) (4) :

- Wrong batch number logged in LIMS (Deviation T TW# 74617)
- Temperature alarms during the incubation of media filled vials (Deviation TW# 75010)

Media Fill (b) (4) :

- The required vent filter test of the filling (b) (4) could not be performed (Deviation TW# 74583), most likely due to improper filter wetting or accidental contact with media.

Response is acceptable.

Transport of the Final Product

12. *You stated during the June 20 telecon that the ground transport validation studies cover a longer shipping time. You added that you are preparing a protocol for the “shipping to overseas distributors”, and that would be executed with the first shipping of Cutaquig after approval. Please provide a description of the shipping protocol, and how it compares to the shipping process for other US licensed products.*

Octapharma stated that the transport validation protocol for the first shipments of (b) (4) Cutaquig to the USA will include the following elements:

- Transport mode (truck transport, air shipment)
- Packaging configuration (single carton, shipment carton)
- Transport distance
- Transport route
- Position of temperature loggers
- Acceptance criteria (temperature and integrity)

The transport process will be validated by (b) (4) runs during (b) (4) season and (b) (4) runs during (b) (4) season, and will include temperature monitoring, and container closure integrity testing on (b) (4) vials following the transport validation runs.

Octapharma added that the shipping of the final (b) (4) Cutaquig final product is similar to that of Albumin. The labelled and packed (b) (4) Cutaquig final containers will be transported by trucks from the Octapharma packaging site to an international airport in Europe, where they will be reloaded in an aircraft and air transported to an airport in the USA. From the US airport the final product packages will then be transported by trucks to the distribution center.

Response is acceptable.