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 125612/0 for Fibrinogen

From: Randa Melhem, Ph.D., OCBQ/DMPQ/MRBII

Through: Qiao Bobo, Ph.D., Branch Chief, OCBQ/DMPQ/MRBII

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Cc: Ze Peng, Ph.D., OTAT/DPPT/HB
Thomas Maruna, M.Sc., OTAT/DRPM

Subject: **Review Memo BLA:** [Octapharma Pharmazeutika Produktionsges.m.b.H, License # 1646] to include facility and CMC information regarding the manufacturing of freeze dried Fibrinogen supplied in a 100mL vial co-packaged with a reconstitution device and a particle filter. The medicinal product (1 g Fibrinogen per vial) is indicated for the treatment of acute bleeding episodes (b) (4) in adult and pediatric patients with congenital Fibrinogen deficiency, including aFibrinogenemia and hypoFibrinogenemia. Manufacturing of the drug substance and drug product, and visual inspection, packaging and labeling operations of the final drug product are performed at Octapharma OPG facility in Vienna, Austria.

Action Due: June 9, 2017

SUMMARY

CBER received this electronic submission on 09 June 2016. Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma) submitted this BLA to provide information to support US market authorization of Fibryna (also referred to as Octafibrin or Fibrinogen in this memo), a "highly purified concentrate of Fibrinogen for intravenous application, formulated as a lyophilized powder for reconstitution". The product is presented as 1g of Fibrinogen in a 100 mL vial (to be reconstituted with 50 mL Water for Injection, not supplied with the product), and co-packaged with a reconstitution device (Octajet – 510(K) # (b) (4) and a particle filter (510(k) # (b) (4) cleared), and as such it is considered a combination product.

Fibryna is indicated for the treatment of acute bleeding episodes (b) (4) in adult and pediatric patients with congenital Fibrinogen deficiency, including aFibrinogenemia and hypoFibrinogenemia. It has a proposed shelf life of (b) (4) years at 2°C to 25°C.

The manufacturing process of Fibryna was developed at the Octapharma OPG Vienna facility. Starting with US approved plasma, a Fibrinogen containing (b) (4) Fibrinogen is then purified by a sequence of (b) (4) and filtration steps. During the manufacturing process of Fibrinogen, viral reduction is obtained via a combination of two dedicated virus inactivation/removal steps: S/D treatment and a 20nm nanofiltration step. Purification is performed in the manufacturing area approved for the pooled plasma product Octaplas® (STN: BL 125416). Filling in 100mL bottles is performed on (b) (4) ", which is also used to fill (b) (4)). After filling, the product is lyophilized, fully stoppered and capped. The manufacturing of the bulk drug substance and drug product is performed at the OPG Vienna facility in Austria (FEI number: 3002809097). Octapharma stated that visual inspection, packaging and labeling can be performed at either the OPG Vienna facility (b) (4) ; however, as described below, these operations were only validated at the OPG facility. Batch release is performed at OPG.

All drug substance in-process testing is carried out by Octapharma laboratories in Vienna, (b) (4) . All drug product testing is carried out by Octapharma laboratories, except for the *General Safety test* which is performed at a contract laboratory.

Octapharma submitted the results for (b) (4) final product conformance lots to support the US market authorization of Fibryna. However, none of these lots were subjected to visual inspection, packaging and labeling at the (b) (4) facility. ***As Octapharma does not have supportive validation data for visual inspection, packaging and labeling of Fibrinogen at the*** (b) (4) ***facility, they withdrew the*** (b) (4) ***facility from the BLA 125612/0 for Fibrinogen in amendment 125612/0.15 submitted November 10, 2016.***

Octapharma OPG facility in Vienna (Austria) and (b) (4) are US licensed facilities, and the inspections were waived for these facilities (before the withdrawal of the (b) (4) facility) as documented in the respective Inspection Waiver memos.

The information provided in the original BLA submission was brief, and lacked details about the qualification of the facility, equipment and the validation of the manufacturing processes. In addition, the BLA did not provide information to address the combination nature of Fibryna. Additional information was requested on August 1, 2016 (email information request), August 5, 2016 (filing letter), and October 6, 2016 (telecon) followed by information request on October 12, 2016 (email). Octapharma submitted their responses in amendments 125612/0.7, 125612/0.8 and 125612/0.15, which are reviewed in this memo.

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 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, and no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment.

INTRODUCTION

Fibryna, a purified concentrate of Fibrinogen for intravenous application, formulated as a lyophilized powder for reconstitution (1g lyophilized Fibrinogen), is indicated for the treatment of acute bleeding episodes (b) (4) in adult and pediatric patients with congenital Fibrinogen deficiency, including aFibrinogenemia and hypoFibrinogenemia. It has a proposed shelf life of (b) (4) years at 2°C to 25°C.

Fibryna is co-packaged with a reconstitution device (Octajet (b) (4) cleared) and a particle filter (510(k) # (b) (4) cleared). The manufacturing process of Fibryna was developed at Octapharma OPG Vienna facility; and all current commercial manufacturing is performed at the same facility.

In this review memo, I cover the manufacturing process of Fibryna to include the drug substance (purification) and drug product (filling and lyophilization) performed at Octapharma OPG facility in Vienna. My review focused on the facilities and equipment, cleaning and sterilization processes, container closure and container closure integrity testing, and the aseptic filling/stoppering within an (b) (4) and the lyophilization processes.

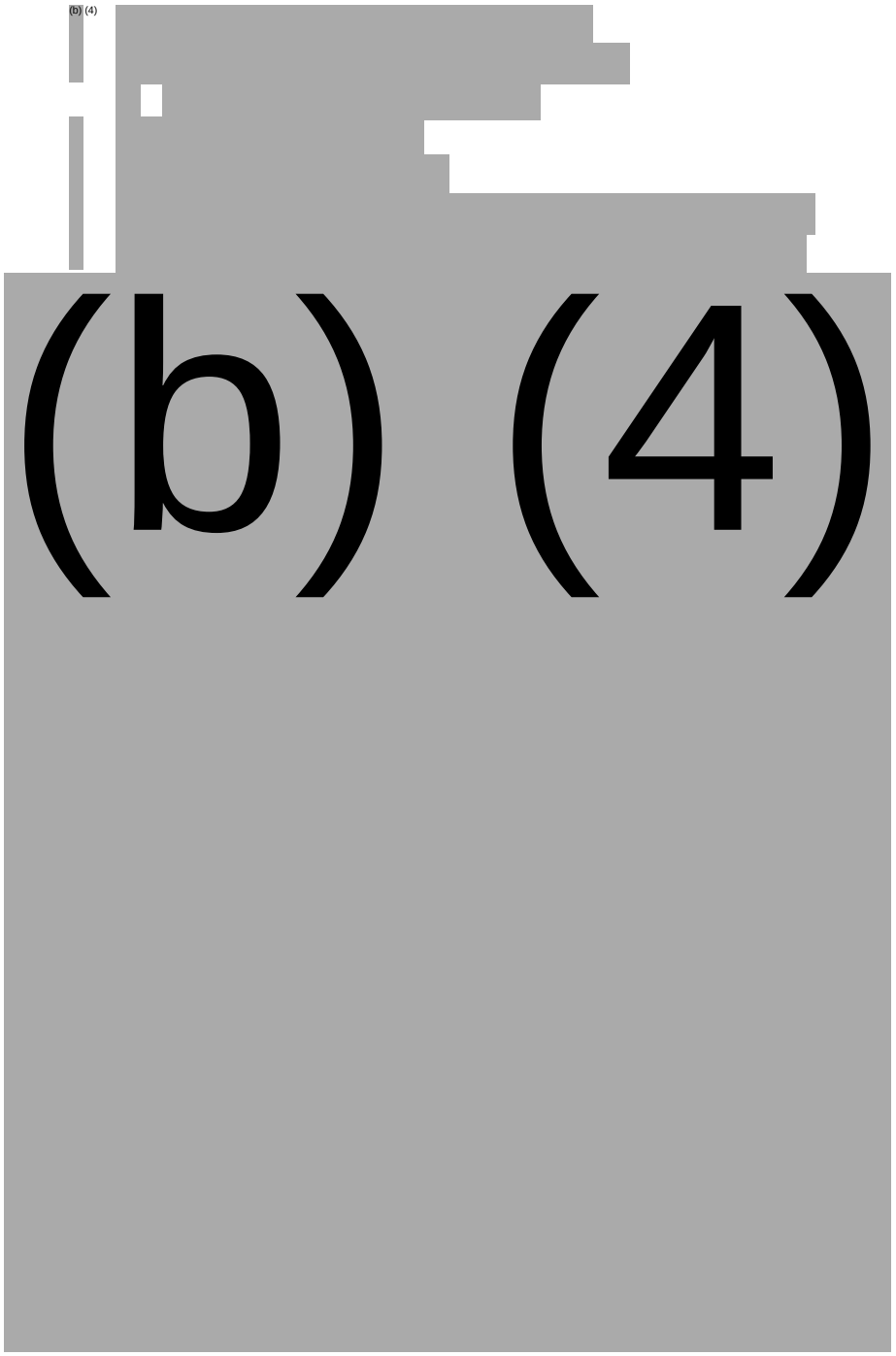
All manufacturing operations are performed at the OPG Vienna facility as summarized below.

Manufacturing site	**Manufacturing Operations**
Octapharma OPG Oberlaaer Strasse 235, Vienna, A-1100, AUSTRIA FEI: 3002809097 Duns: 301119178 Last FDA Inspection 2014.	• (b) (4) • (b) (4) • Quality Control • Visual Inspection • Labeling and packaging • Batch release

The Octapharma Vienna facility (OPG) is a multi-product facility located at Oberlaaer Strasse 235 Vienna, A-1100 Austria, and is licensed by the US FDA for the manufacture of sterile aseptically filled liquid products, terminally sterilized liquid products, and sterile aseptically filled and freeze-dried products to include 5%, 20% and 25% Albumin (Human), 5% and 10% solvent detergent treated intravenous immunoglobulin, and solvent detergent and dry heat-treated von Willebrand Factor/Factor VIII concentrate, and Pooled plasma. In addition, other non-US approved products (b) (4) are manufactured at OPG. Furthermore, other investigational products of human plasmatic origin might be also processed in the same areas. Octapharma reported that no toxic or hazardous

substances (e.g. penicillin, cephalosporins, or cytotoxic substances) are processed or produced at OPG.

Fibrinogen drug substance is manufactured in FDA approved areas used for production of other US and non-US licensed products. The manufacturing process is comprised of (b) (4) steps as shown in the schematic flow chart below and includes:



FACILITY AND EQUIPMENT

The OPG Vienna facility was designed and is licensed by FDA as a multiproduct facility. Octapharma provided narratives and diagrams to describe the flows of product (from plasma receipt, to the final product labeling and packaging), materials, personnel (including gowning) and waste flows, and they appear to be adequate.

The manufacturing operations for Fibrinogen are divided among different departments: pre-virus inactivation area, post-virus inactivation area, aseptic production, and packaging areas as listed in the Table below:

Area	Functions	Building
Pre-virus inactivation areas Steps	(b) (4)	
Post-virus inactivation areas		
Aseptic production area		
Packaging area		

The Quality Control laboratories are located in Building (b) (4). The administrative functions are located in Building (b) (4). The stability rooms are located in Building (b) (4). Plasma storage rooms are located in Building (b) (4). Building (b) (4) houses the main storage for raw materials. All storage rooms are under continuous temperature monitoring. Temperature controls for the (b) (4) rooms are (b) (4). In addition to storage rooms at OPG, Octapharma contracts a warehouse ((b) (4)) for the storage of plasma, intermediates and final product.

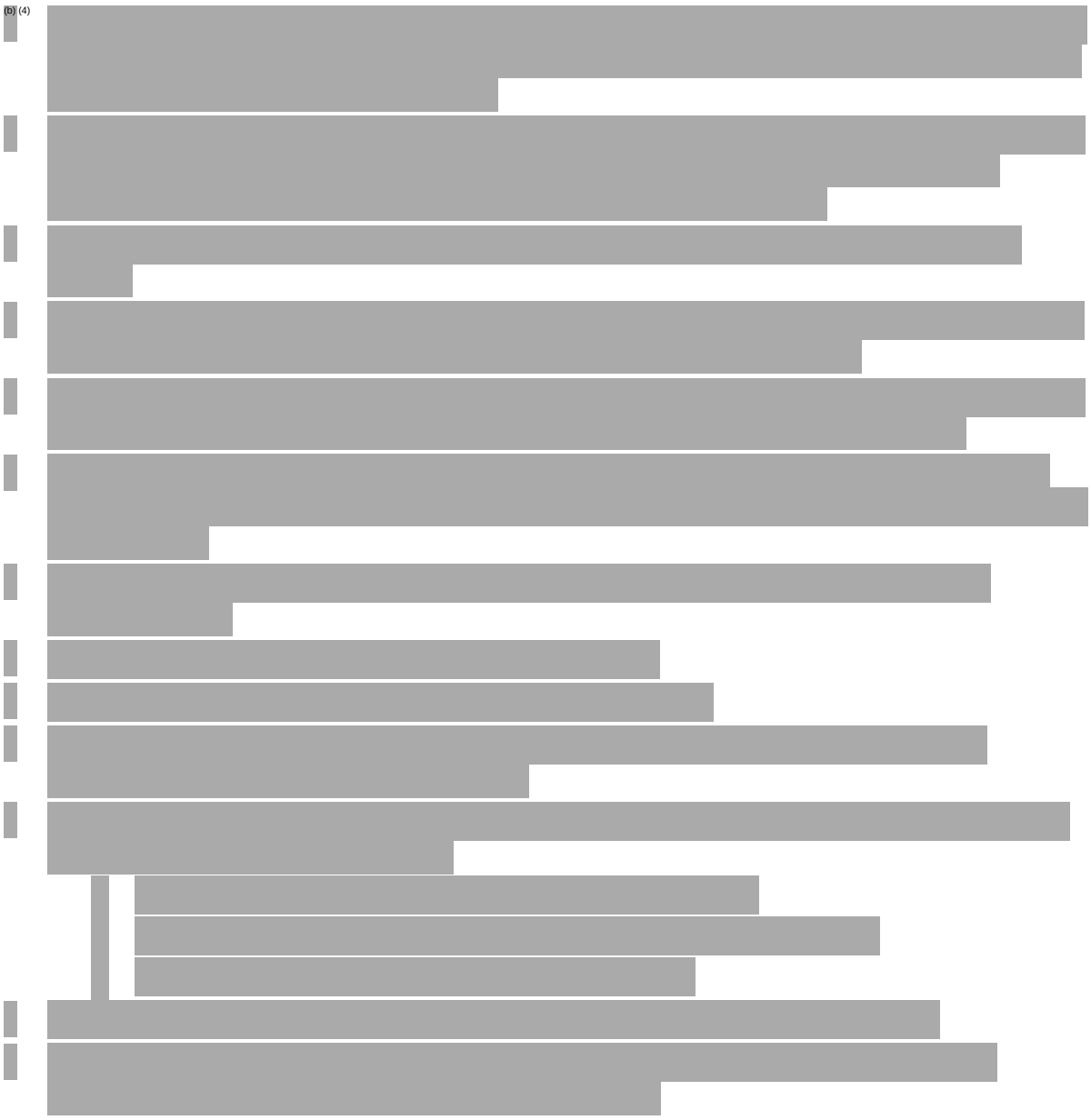
The Fibrinogen manufacturing process includes virus inactivation of enveloped viruses (S/D treatment), step (b) (4), and virus clearance of both enveloped and non-enveloped viruses (nanofiltration), step (b) (4).

- S/D virus inactivation occurs in (b) (4)
- (b) (4) Viral clearance by nano filtration ((b) (4)), (b) (4) are all performed in Building (b) (4) (Octaplas area) room (b) (4).

Octapharma stated that they have the following systems and procedures in place to prevent contamination / cross-contamination of products:

- (b) (4)

(b) (4)



Equipment

Octapharma stated that most of the equipment is shared with other US licensed products, and as such, the qualification of the equipment was already reviewed by FDA. They provided a list of the major equipment used for the manufacturing of Fibrinogen (Basic Fractionation, Purification or Aseptic Production), the manufacturing step and whether the equipment is shared or dedicated. For the dedicated and /or new equipment (not reviewed for licensed US products), Octapharma provided a brief description and qualification of the equipment. I summarize below the list of new equipment (in bold) used for the manufacturing of Fibrinogen.

Process	**Rooms**	**Equipment**	**Manufacturing Step**	**Shared/ Dedicated**
Major Equipment Basic Fractionation	(b) (4)	All equipment are reviewed with other approved products	(b) (4)	Shared

Process	Rooms	Equipment	Manufacturing Step	Shared/ Dedicated
Major Equipment Purification	(b) (4)			Shared
				Dedicated
				Dedicated
				shared
				Dedicated
				Dedicated
Aseptic Production				Shared
Major equipment Aseptic Production				Shared
				Shared
				Shared – Reviewed in BLA (b) (4) (CR status)
				Shared
				Shared
Major equipment VI & Labeling & Packaging				Shared

Octapharma provided the qualification of the new equipment in the original BLA submission 125612/0 and in amendments 125612/0.7 and 125612/0.15, and are reviewed in the equipment section of this memo.

MANUFACTURING PROCESS

Fibrinogen is a plasma-derived, purified concentrate of Fibrinogen for intravenous application, provided as a lyophilized powder for reconstitution (1 g lyophilized Fibrinogen to be reconstituted in 50 mL WFI). A Fibrinogen containing (b) (4) was chosen as starting material, (b) (4) starting material. Fibrinogen is purified by a sequence of (b) (4) and filtration steps. Significant viral

reduction is obtained via a combination of two dedicated virus inactivation/removal steps - S/D treatment and 20 nm nanofiltration. Two alternative nanofilters (Planova 20N and Pegasus SV4) are used, and process validation batches using both nanofilters were produced in (b) (4).

The development of Fibrinogen lyophilized product started in (b) (4) at a laboratory scale at Plasma R&D, OPG Vienna. Octapharma provided the dates and changes during the developmental process as summarized below:

Dev. Phase	R&D	Pilot Batches	Technical Batches	Clinical Batches	Technical Batch	Process Validation Batches
Scale	(b) (4)					
Year						
Process						
Nano-filtration	Planova 20 N Pegasus SV 4	Planova 20 N	Planova 20 N	Planova 20 N optimized	Pegasus SV 4	Planova 20 N Pegasus SV 4

The manufacturing process includes (b) (4)

I summarize below the different manufacturing steps, and the in-process samples collected, noting the in-process microbiological sampling.

Manufacturing Step/Description	Sample/Testing	Comments
(b) (4)		

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(b) (4)

Container Closure – Drug Product

The primary packaging for Fibrinogen includes 100mL (b) (4) vials, 32mm (b) (4) stoppers, and 32mm Flip-Off Caps.

Vials

The 100mL (b) (4) vials (glass (b) (4)) are supplied by (b) (4) (diagram provided below). The vials are (b) (4)

The qualifications of washing, (b) (4) of the vials are described in the equipment section of this memo.

(b) (4)

Lyophilization Stoppers

The stoppers are 32mm in size and are made of brownish red (b) (4) rubber ((b) (4)) with Grade (b) (4), and are supplied by (b) (4) (diagram provided below). The stoppers are (b) (4) at OPG Vienna facility as described in the sterilization section of this memo.

	(b) (4)

Caps (32mm)

The caps are supplied by (b) (4) (diagram provided below). Each cap consists of a white propylene cap, and a (b) (4) aluminum flip-top over cover.

	(b) (4)

The flip-off caps are filled into bags and sterilized by (b) (4) at OPG Vienna facility as described in the sterilization section of this memo.

Container Closure Integrity Testing (CCIT)

Octapharma reported that the integrity of the final product container closure is verified by two methods:

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

CCIT: (b) (4) testing during Stability Studies

Octapharma stated that they performed container closure integrity testing as part of the stability studies for two batches of Fibrinogen using the (b) (4) :

- (b) (4) - manufactured using Planova P20N Nanofilters
- (b) (4) - manufactured using Pegasus SV40 Nanofilters

The stability studies included long-term and accelerated stability conditions. For long term studies, the samples were stored at 5°C, 25°C/(b) (4) or (b) (4) for up to (b) (4) months and tested for CCIT at the start of the study and after 24 months and (b) (4) months storage, and the initial study tests were presented in the BLA. For the accelerated studies, the samples were (b) (4) .

Octapharma provided the following two reports which included the number of samples tested on long term and (b) (4) studies.

- *000SSR347.14P012.00_xxCCIT, Stability Study Report on Container Closure Integrity Testing of Fibrinogen 1g, Primary Packing Systems OPG Planova P20N Nanofilters Study 14P012, (b) (4) months' data* (approved 18 Sep 2015)

Batch (b) (4) ((b) (4) vials) was filled on (b) (4) and released on (b) (4) (b) (4) Octapharma reported that they initiated the stability studies on (b) (4) when samples were stored under the following conditions:

- Long-term Storage Condition 5°C, (b) (4)
- Long-term Storage Condition 25°C / (b) (4)
- Long-term Storage Condition (b) (4)
- Accelerated Storage Condition (b) (4)

Octapharma reported that the results for CCIT at T0 for all storage conditions and the results for CCIT after (b) (4) month of accelerated conditions were acceptable. However, Octapharma did not include validation of the (b) (4) method nor the number of samples tested (or to be tested) per time point.

- *000SSR347.14P013.00_xxCCIT, Stability Study Report on Container Closure Integrity Testing of Fibrinogen 1g, Primary Packing Systems OPG Pegasus SV4 Nanofilters Study 14P013, (b) (4) months' data* (approved 18 Sep 2015)

Batch (b) (4) ((b) (4) vials) was filled on (b) (4) and released on (b) (4) (b) (4). Octapharma reported that they initiated the stability studies on 26 February 2015 when samples were stored under the following conditions:

- Long-term Storage Condition 5°C, (b) (4)
- Long-term Storage Condition 25°C / (b) (4)
- Long-term Storage Condition (b) (4)
- Accelerated Storage Condition (b) (4)

Octapharma reported that the results for CCIT at T0 for all storage conditions and the results for CCIT after (b) (4) month of accelerated conditions were acceptable. However, Octapharma did not include validation of the (b) (4) method nor the number of samples tested (or will be tested) per time point.

Reviewer's comments: Additional information was requested regarding the validation of the method and the number of samples tested per time point. Octapharma submitted their response in amendments 125612/0.7 and 125612/0.15, which is reviewed below.

Additional Information

- (b) (4) Method (protocol)

  (b) (4)

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(b) (4)

QUALIFICATION OF EQUIPMENT

As mentioned previously, a Fibrinogen containing (b) (4) was chosen as starting material for the production of Fibryna; thus all equipment used in (b) (4) were previously reviewed and approved under the (b) (4). In addition, other purification

(b) (4) processes use equipment that have already been approved for the manufacture of Octaplas (BLA 125416).

I list below the equipment used from (b) (4), and describe the qualification of the new/dedicated equipment.

(b) (4)

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(b) (4)

HVAC/ENVIRONMENTAL MONITORING/ ROOM CLASSIFICATIONS

HVAC System

The Vienna Facility is a US licensed facility and the HVAC system has already been reviewed and inspected by FDA in association with other licensed products. Fibrinogen drug substance is manufactured in FDA approved areas used for production of other US licensed products (Octaplas and (b) (4)). The filling and lyophilization is performed in a new (b) (4) (room (b) (4)), (b) (4) transfer area (room (b) (4)) and new lyophilizer (b) (4) (room (b) (4)).

Octapharma provided in the original BLA submission a general description of the process areas, their classifications and monitoring operations. In response to information requests they provided additional details about the qualification of the areas and provided environmental monitoring results which are reviewed in this section.

Clean Room Grades (b) (4) and office areas (Grade (b) (4)) of Production (b) (4) are ventilated by individual Air Handling Units (AHUs) equipped with pre-filters (fine filters) and terminal 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 fine filters are installed.

The supplied air (at least (b) (4) fresh air) is filtered through a pre-filter, heated or cooled as required, and adjusted by constant volume flow regulators installed in the ducts. Incoming air has a constant flow, whereas outgoing air is regulated to assure the required pressure level in the rooms. 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) AHUs that support the different areas, and listed the filters installed and the rate of recirculated air. Pharmaceutical production areas Grades (b) (4) are supported by AHU (b) (4) with up to (b) (4) recirculated air (as of August 2015). The Octaplas line (Production (b) (4)), post-viral inactivation. is supported by AHU (b) (4) with up to (b) (4) recirculation (as of August 2015). All other areas are supplied with (b) (4) recirculated air depending on the activities in the area.

The filling and partial stoppering of Fibrinogen is performed in a Grade (b) (4) area ((b) (4)) under (b) (4) equipped with (b) (4) filters and unidirectional airflow also placed in a Grade (b) (4) environment (Grade (b) (4) in operation). The unidirectional airflow within the (b) (4) maintains

Grade (b) (4) conditions during operations. The pressure differential between the (b) (4) in operation and the surrounding clean room background is adjusted to (b) (4). The partially stoppered vials/bottles are transferred to lyo (b) (4) under Grade (b) (4) environment. Following lyophilization, the stoppered bottles are capped within (b) (4) under Grade (b) (4) air supply.

Octapharma also provided the differential pressure maintained between the different room classifications for the production area. There is no differential pressure between Grade (b) (4) and Grade (b) (4) as shown in the following Table:

(b) (4)

Reviewer's comments: Octapharma reported that a new AHU (b) (4) has been installed to support the Grade (b) (4) area with up to (b) (4) air recirculation, and that AHU (b) (4) has been installed to support the Octaplas line ((b) (4) operations for Fibrinogen) with up to (b) (4) recirculation. However, they did not provide the qualification of the areas following these changes. Octapharma was requested to provide the qualification (static and dynamic environmental monitoring) of the areas after installation of the new AHUs. They provided the information in amendment 125612/0.15 which is reviewed below.

Additional Information

Octapharma clarified that AHU (b) (4) (Octaplas line or Production (b) (4)) were old (since 1986) and were replaced in 2015 per change control: (b) (4) 44479 ((b) (4)) and (b) (4) 44023 ((b) (4)), and according to the user requirement specifications provided in reports 110VFK508 ((b) (4)) and 110VFK509 ((b) (4)).

They stated that the HVAC system is requalified periodically according to SOP *082SOP103*; and that the requalification is performed by the supplier (b) (4). They explained that the HVAC system including HEPA filters, clean room conditions (at rest) and laminar flows was requalified during the summer 2015, and provided in report *080STD15165.000* (approved 02 Dec 2015). The report includes a list of all the areas, HEPA filters, laminar flow units that were requalified and whether they passed or failed. In addition, Octapharma listed the deviations that were initiated during the requalification, and stated that all deviations were investigated according to deviation SOP *011SOP010*, and all affected filters were exchanged and retested successfully.

Reviewer's comment: The report is a brief summary with no data or actions taken, but it gave an overview of the comprehensive requalification effort, and stated that all corrective actions were completed.

Octapharma also provided summary report *080RPQ15395.000* (approved 25 May 2016) for the qualification / calibration of HVAC system ((b) (4) as the rooms or the HVAC systems were modified during summer shut down 2015 according to Change Controls CC 38362, CC 40356, CC 40359, CC 40360, CC 43746, CC 44479 and CC 45507. ***The rooms, in bold are supported by AHU*** (b) (4) ***, as summarized below***:

Room Number	*Definition*	*Clean room class*
(b) (4)		

(b) (4)

(b) (4)

2 pages have been determined to be not releasable: b(4)

(b) (4)

Environmental monitoring

Octapharma provided in the original BLA submission the environmental monitoring schedule and acceptance criteria for the different room classifications used for the fractionation, purification and filling/lyophilization operations, and visual inspection, packaging and labeling of Fibrinogen. The acceptance criteria for the different areas are summarized below:

(b) (4)

Reviewer's comment: Octapharma did not provide any data for the environmental monitoring performed during the manufacturing of the drug substance and drug product of the conformance lots, or the environmental monitoring collected during the media fills for validation of the aseptic processing. The information was requested and submitted in amendment 125612/0.15, and is reviewed below.

- **Environmental Monitoring Program**

  Octapharma reported that they performed a risk analysis to determine the level of environmental monitoring performed in the different areas. The frequency of monitoring depends whether open product is present in the area, and the level of product/personnel/material flow, and each area was assigned high, medium and low risk based on impact to product. They stated that they monitor on a (b) (4) basis (in operation) the high and medium risk areas, and they monitor ((b) (4)) in operation the low risk areas.

  They provided summary report *001*(b) (4) *080914, Batchwise Monitoring and Campaign Monitoring/ Production* (b) (4) *and Octaplas* (approved 12 Sep 2014). The report does not provide any specific information and refers to four annexes that were not submitted.

  - Annex 1: Batchwise Monitoring (b) (4) and Campaign Monitoring (b) (4)
  - Annex 2: Batchwise Monitoring (b) (4) and Campaign Monitoring (b) (4)
  - Annex 3: Batchwise Monitoring (b) (4) and Campaign Monitoring (b) (4)
  - Annex 4: Batchwise Monitoring OCTAPLAS

  Reviewer's comment: Octapharma environmental monitoring program at the OPG Vienna facility has been previously reviewed and approved in association with other

US licensed products. However, the description of the EM program provided in this amendment is not sufficient for evaluation. In addition, Octapharma did not include information about the area classification in the upstream, downstream and filling areas, and whether that plays a role in determining the frequency and level of monitoring performed. Additional information was requested and the information will be reviewed in the addendum memo.

- **Environmental Monitoring Program for** (b) (4)

(b) (4)

1 page has been determined to be not releasable" b(4)

Based on the risk analysis and validation studies, Octapharma stated that they developed their environmental monitoring procedure in report *001*(b) (4) *080914, Batchwise Monitoring and Campaign Monitoring for Production* (b) (4) *and Octaplas at the Vienna Production Site (approved 12 Sep 2014)*

The risk assessment evaluated the microbiological sampling with regard to position, activity, and criticality in relation to potential negative impact on product. If a sampling position was not accepted, a new sampling position is proposed and would be evaluated base on feasibility of location of sampling in the new position without impact on operations or laminar flow; and whether the data collected from this sampling point are useful.

Octapharma listed the different positions (and their criticality: HIGH: (b) (4) ; MEDIUM: (b) (4) and LOW: (b) (4)) and provided a schematic diagram to show the locations on the (b) (4) .

(b) (4)

Their assessment is acceptable.

- **Environmental Monitoring Sampling during** (b) (4) **, and Production of Drug Substance and Drug Product Conformance lots.**

Octapharma provided in amendment 125612/0.15 the results of the environmental monitoring performed during the (b) (4) and during the manufacturing of the conformance lots, and the results are reviewed below:

- (b) (4)

(b) (4)

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(b) (4)

(b) (4)

COMPUTERIZED SYSTEMS

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

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

- (b) (4)

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

Octapharma reported that there is (b) (4) automation for Fibrinogen production operations. They provided the list of manufacturing steps supported by computerized systems as shown in the Table below:

Automated System	Room	Manufacturing Step	Category
(b) (4)			

Automated System	Room	Manufacturing Step	Category
(b) (4)			

WATER SYSTEMS

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

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

Octapharma provided a brief description (with schematic diagrams) of the production and storage of the different water systems ass presented in the following slow chart.

(b) (4)

Each system was validated according to the specific requirements to ensure the appropriate quality requirement is achieved. Moreover, the water system is routinely monitored to ensure consistent water quality.

Water System	Description	Water Use
(b) (4)		

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(b) (4)

CLEANING AND STERILIZATION

Octapharma provided in the initial BLA submission a list of equipment used for the manufacturing of Fibrinogen, they indicated whether the equipment is shared or dedicated. They also reported whether the equipment is (b) (4) or cleaned manually, and reported the dirty and clean/sterile/sanitized hold times. The list was not complete and had a few inconsistencies. Octapharma corrected the discrepancies and submitted the updated document in amendment 125612/0.15.

Several pieces of equipment are shared with other US licensed products, and thus the cleaning/sterilization processes were already reviewed and approved. For new or modified pieces of equipment, Octapharma provided the validation of the cleaning and sterilization/sanitization reports in the original submission and amendment 125612/0.15, and the information was reviewed for the respective equipment.

Cleaning Processes

The OPG Vienna facility is an approved facility for the manufacture of several US licensed products. As such their cleaning and sterilization procedures are mostly reviewed and approved.

I reviewed the cleaning validation of the new equipment in the equipment section of the memo.

I include below a brief summary of the different cleaning procedures used in the different departments for completion of the memo.

Unit	Department/Steps/Equipment	Equipment	Cycle
(b) (4)			

4 pages have been determined to be not releasable: b(4)

Sterilization/Sanitization

Product contact equipment in the pharmaceutical formulation area is autoclaved after cleaning. Clean equipment is loaded into an autoclave in room (b) (4), Class (b) (4) and unloaded in room (b) (4) under (b) (4).

Equipment for sterile filtration and aseptic filling is (b) (4) cleaned, either by using (b) (4), and autoclaved or, in case of format parts used inside the (b) (4), by (b) (4) (described in detail in the (b) (4) section).

Final containers (vials) are washed and depyrogenated; and the stoppers are received clean and are (b) (4) sterilized by (b) (4). The qualifications of these processed are reviewed elsewhere in this memo.

(b) (4) used for product transfers are sanitized prior use and disposed of after use.

Single use sterile filtration sets and filling sets are supplied ready to use ((b) (4)).

Reviewer's comments: Octapharma did not provide in the initial BLA submission a description of the autoclaves or equipment loads. In response to information request, additional information was provided in amendment 125612/0.15 and is reviewed below.

Additional Information

(b) (4) autoclaves ((b) (4)) located in the aseptic department are used for the sterilization/sanitization of the equipment used for manufacturing on filling (b) (4) (Fibrinogen manufacturing).

(b) (4)

The qualification of the (b) (4) sterilizers has been submitted and reviewed in association with other licensed products (Albumin 125154/115, approved on 13 Sep 2011; Wilate, STN 125251/22, approved on 20 Dec 2010 and Octagam, STN 125062/290, Annual report 10 Jun 2011). Octapharma provided a description and photos of the autoclaves and the loads in the different reports reviewed below.

- Octapharma provided the list of all the loads for Autoclave (b) (4), and specified the loads for equipment used during Fibrinogen manufacturing. They included the most recent reports for the sterilization of the relevant loads as summarized below:

(b) (4)

7 pages have been determined to be not releasable: b(4)

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

PROCESS VALIDATION

Drug substance (b) (4) Studies

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Nanofiltration

The nanofiltration viral clearance step was initially qualified using Planova 20N ((b) (4)). However, another nanofilter Pegasus SV4 ((b) (4)) was then qualified. Octapharma provided the following summary report to demonstrate the comparability of Fibrinogen final container manufactured with the two different nanofilters.

- *020STD347 224_01, Biochemical comparison of Octafibrin using different nanofilters* (approved 21 Jan 2014)

The report provides the results of studies performed using both nanofilters:

- Planova 20 N was used for the nanofiltration of (b) (4) batches of Fibrinogen intermediate in 2012 and (b) (4) batches in 2013.

- Pegasus SV4 was used for the nanofiltration of (b) (4) batches in 2013.

Octapharma provided the results of the analytical testing (purview of Product Office) and stated that the data demonstrated biochemical equivalence of all the batches produced using Planova 20N and Pegasus SV4.

In addition, Octapharma provided the following summary report for the evaluation of extractables/leachables for the filters (including nanofilters) as well as product contact plastic material and container closure of the Fibrinogen process.

- *020STD34x.31_00: Assessment of extractables associated with all plastic material used during production including the container closure system for primary packaging of Octafibrin* (approved 14 March 2016)

  Reviewer's comment: Extractables/Leachables is under the purview of the Product Office.

Process Validation - (b) (4)

(b) (4)

(b) (4)

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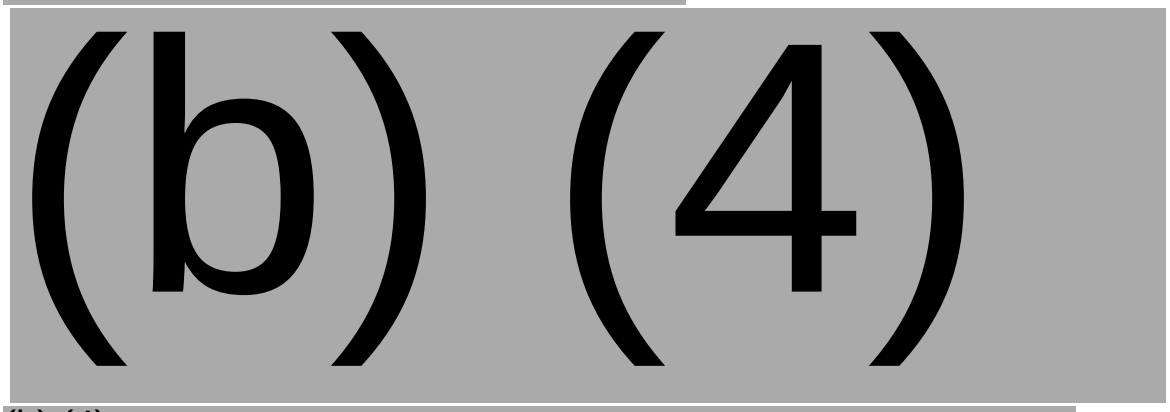
(b) (4)



(b) (4)

Process Validation – Filling Consistency on (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Process Validation – Lyophilization

Octapharma performed the lyophilization PPQ study to demonstrate that the freeze drying parameters and hold times of 1g Fibrinogen in a 100mL vial presentation are adequate and result in a product of consistent quality that meets the acceptance criteria. They provided the results in the following report reviewed below:

- *089VRE14238.106_US - Process Performance Qualification Report for Freeze Drying Process of Fibrinogen 1 g Using Freeze Dryer* (b) (4) (approved 29 Oct 2015)

The lyophilization cycle parameters used for the freeze drying of Fibrinogen in lyo (b) (4) (listed below) are based on the developmental studies results:

(b) (4)

To demonstrate the robustness of the lyophilization process for Fibrinogen (in lyo (b) (4)), Octapharma used (b) (4)

11 pages have been determined to be not releasable: b(4)

Octapharma also provided the results for the lyophilization process and visual inspection of the conformance lots, and final container testing. The same information was also provided in report *089PPQR14238.106_US, Process Performance Qualification Report for Freeze Drying Process of Fibrinogen 1g Using Freeze Dryer* (b) (4) (approved 29 Oct 2016), and is reviewed below.

Visual Inspection

The 100% visual inspection of all the (b) (4) conformance lots was performed at OPG Vienna facility. As mentioned previously, the visual inspection process has been reviewed and inspected in association with other products.

In addition 100% (b) (4) testing was performed on the vials at (b) (4) following crimping.

Octapharma summarized the results of the 100% visual inspection for the batches in Table14 of the report reproduced below:

(b) (4)

(b) (4)

Reviewer's comments:

- Additional information was requested about the AQL sampling performed on the conformance lots. Octapharma provided the responses in amendment 125612/0.15 reviewed in **Q10.b** of the information request section of this memo.
- As Fibrinogen is a lyophilized product, and particles are hard to visualize within the cake, additional information was requested about the visual inspection of reconstituted samples performed (per (b) (4)), the acceptance criteria and the results for the conformance lots for Fibrinogen final product. The information will be reviewed in the addendum memo.

Final Container Release Testing

Octapharma also provided the results for the final container testing, which includes appearance, (b) (4) , solubility, stability of the solution at 20-25°C, residual moisture, sterility, endotoxin, general safety, (b) (4) , Fibrinogen, glycine, citrate, chloride, L-argenine HCL, (b) (4) . The results appear to be within the acceptance criteria, and will be covered in the Product Office review memo. I present below the attributes that are reviewed by DMPQ:

		Min Processing Time		Max Processing Time		Routine Processing time		
Test	**Acceptance Criterion**	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	**Historical Data**
Appearance	A white or pale yellow, hygroscopic powder or friable solid.	conform	conform	conform	conform	conform	conform	conform
Residual Moisture (PPQ)	(b) (4)							
Sterility	**Sterile**	**Sterile**	**Sterile**	**Sterile**	**Sterile**	**Sterile**	**Sterile**	**Sterile**
Endotoxin (b) (4)	(b) (4)							

Two deviations 36215 and 37486 were reported for batches (b) (4) , as well as for batches (b) (4) , respectively, due to increased (b) (4) levels. Octapharma reported that these deviations were minor, as (b) (4) levels found in final container samples are of no clinical relevance. Octapharma added that they initially established the lower limit ((b) (4)) as (b) (4) , used throughout the entire manufacturing process. However, no (b) (4) was observed during manufacture of Fibrinogen batches which exhibited higher levels of (b) (4) ; and as such they increased the QAT level of (b) (4) from (b) (4) . This is a product issue and would be evaluated by the product reviewer.

Process Validation - Combination Product

The lyophilized final product is co-packaged with a reconstitution device (supplied by (b) (4)) and a particle filter (supplied by (b) (4) , and 510(k) cleared -(b) (4)). Octapharma explained that studies showed (b) (4)

Reviewer's comment: The review of the devices and assessment of the combination product is covered in the CDRH consult review memo.

Octapharma provided the following reports to support the compatibility of the reconstitution device and filter with the final Fibrinogen product, and that no absorbance of active ingredient occurs when the device and filter are used.

- *Report 125P58, Compatibility of the Octajet transfer set with Fibrinogen 1g Final Container (347)* (approved 12 Aug 2015).

Octapharma reported that they performed reconstitution of samples from (b) (4) batches of Fibrinogen final containers using (b) (4) and Octajet and tested for the time to reconstitution, (b) (4) . Octapharma provided a summary of the results for each batch as summarized below, indicating that both methods are acceptable; (b) (4) .

(b) (4)

- *Report 012015: Compatibility of Particle Filters* (b) (4) *with Fibrinogen 1g Final Container (34x)* (approved 27 Jan 2015)

The following (b) (4) particle filters are used after reconstitution of the Fibrinogen final product (using Octajet) and prior to infusion to remove any particles.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Transport Validation

(b) (4)

1 page has been determined to be not releasable: b(4)

Reviewer's comment: CBER requested that Octapharma provide the reports when they are available (Reference 01 Aug 2016 IR). Octapharma stated that the results of the transport validation of final containers at (b) (4) will be provided by October 17, 2016 ((b) (4)) and March 20, 2017 ((b) (4)), respectively. The transport validation report was requested and the response will be reviewed in the addendum memo.

STABILITY

Octapharma proposed a (b) (4) months shelf life for the lyophilized Fibrinogen drug product at 2°C to 25°C based on the results of stability studies performed on clinical batches and PPQ batches.

Octapharma provided the summary reports which described the stability protocol and provided the stability data for (b) (4) months for the clinical batches and six months data for the PPQ batches manufactured using both Planova P20N nanofilters and Pegasus SV4 nanofilters.

The stability samples are stored under long-term conditions at 5°C, 25°C/ (b) (4) and (b) (4), and under accelerated conditions at (b) (4).

In addition for PPQ batches, stability of the reconstituted Fibrinogen product was tested at the start of the studies and will be tested after 24 months and (b) (4) months storage at 25°C/ (b) (4) to demonstrate product stability at room temperature for up to (b) (4) hours after reconstitution.

Stability testing is under the purview of the Product Office. I summarize below the results of testing for appearance, residual moisture, sterility and endotoxin (also reviewed by DMPQ) that were provided in the submitted stability reports.

- *000SSR347.14P012.00/US, Stability Study Interim Report for Fibrinogen 1 g, manufactured at OPG using Planova P20N Nanofilters, 6 months data* (approved 02 Oct 2015)

Octapharma initiated the stability study on 26 February 2015 for the following batches: (b) (4). They described the storage conditions and the schedule of testing, and provided the results of testing performed on the stability samples up to six months.

Test/Acceptance criteria	**Acceptance criteria**	**Schedule**	**Schedule**	**Results up to six months for all conditions tested**		
		Accelerated studies	**Long term studies**	(b) (4)	(b) (4)	(b) (4)
Sterility (b) (4)	No growth	(b) (4)	**0,** 24, (b) (4) months	Compliant	Compliant	Compliant
Endotoxin (b) (4)	(b) (4)		**0,** 24, (b) (4) months	(b) (4)	(b) (4)	(b) (4)
Water content (b) (4)	(b) (4)		**0, 6**, 12, 18, 24, (b) (4) months	(b) (4)	(b) (4)	(b) (4)
Solubility ((b) (4))	(b) (4) min at 20-25		**0, 3, 6**, 12, 18, 24, (b) (4) months	compliant	compliant	compliant
Appearance of reconstituted	Almost colorless		**0, 3, 6**, 12, 18, 24, (b) (4) months	compliant	compliant	compliant

solution	and slightly opalescent.					
Stability of reconstituted solution	(b) (4) hours at 20-25°C		**0**, 24 and (b) (4) months	compliant	Not tested	compliant
Testing results presented are for the months shown in bold (**0, 3, 6**) for all storage conditions.						

- *000SSR347.14P013.00/US, Stability Study Interim Report for Fibrinogen 1 g, manufactured at OPG using Pegasus SV4 Nanofilters, 6 months data* (approved 02 Oct 2015)

Octapharma initiated the stability study on 26 February 2015 for the following batches: (b) (4). They described the storage conditions and the schedule of testing, and provided the results of testing performed on the stability samples up to six months.

Test/Acceptance criteria	**Acceptance criteria**	**Schedule**	**Schedule**	**Results up to six months for all conditions tested**		
		Accelerated studies	**Long term studies**	(b) (4)	(b) (4)	(b) (4)
Sterility (b) (4)	No growth	(b) (4)	**0,** 24, (b) (4) months	Compliant	Compliant	Compliant
Endotoxin (b) (4)	(b) (4)		**0,** 24, (b) (4) months	(b) (4)	(b) (4)	(b) (4)
Water content (b) (4)	(b) (4)		**0, 6**, 12, 18, 24, (b) (4) months	(b) (4)	(b) (4)	(b) (4)
Solubility (b) (4)	(b) (4) min at 20-25		**0, 3, 6**, 12, 18, 24, (b) (4) months	compliant	compliant	compliant
Appearance of reconstituted solution	Almost colorless and slightly opalescent.		**0, 3, 6**, 12, 18, 24, (b) (4) months	compliant	compliant	compliant
Stability of reconstituted solution	(b) (4) hours at 20-25°C		**0**, 24 and (b) (4) months	Not tested	compliant	compliant
Testing results presented are for the months bold (**0, 3, 6**) for all storage conditions.						

Moreover, the stability of the reconstituted Fibrinogen was evaluated after the initial solubilization in WFI, and after 4, (b) (4) hours. The reconstituted samples were evaluated by visual inspection, Fibrinogen content and (b) (4) analytical testing. The results for the two batches tested were compliant.

In addition to the stability data for the PPQ batches, Octapharma provided the (b) (4) months stability data for the clinical batches to support the (b) (4) months shelf life of the lyophilized product.

- *000SSR347.11P023.01 US (b) (4) M, Stability Study Report for Fibrinogen 1 g, produced at OPG, Vienna and (b) (4) using Planova P20N Nanofilters, (b) (4) months final data, US version* (approved 16 Nov 2015)

Octapharma reported that for the clinical batches ((b) (4)), the bulk drug substance was manufactured at OPG Vienna, and then shipped for filling and lyophilization at (b) (4) due to manufacturing restrictions. They provided the results for the accelerated and long term stability data in Tables 13.1-13.4 of the report, and the results met the acceptance criteria.
Octapharma noted that for the clinical batches, they performed the six month testing after seven months of storage (planned deviation 13/008) as a worst case condition.

Reviewer's comments: The stability is under the purview of the Product Office.

INFORMATION REQUEST

Additional information was requested on August 1 (email information request), August 5 (filing letter), and October 6 (telecon) followed by an information request on October 12, 2016 (email). Octapharma submitted their responses in amendments 125612/0.7, 125612/0.8 and 125612/0.15.

For clarity of the review, I incorporated most of the information submitted in the amendments in the body of this memo. The rest of the responses are included in this section.

The deficiency outlined in the filing letter (**05 Aug 2015**) pertains to the co-packaging of the product with devices. This review of the combination product is documented in the memo of the CDRH consult reviewer.

While conducting the filing review, we concluded that your product, which will be co-packaged with a transfer device and filter, is a combination product and needs to be in compliance with the following regulations: Management Responsibility (820.20), Design Controls (820.30), Purchasing Controls (820.50), and Corrective and Preventive Action (820.100) as specified in 21 CFR 4.4. Please submit information to demonstrate compliance with the above mentioned regulations which should also include information on the design of the current device, design history, design verification studies, and all Human Factors studies as an amendment to this BLA by September 2, 2016.

01 Aug 2016 IR (Responses Provided in amendment125612/0.7)

Question I
The quality summary for appendices is not included in Module 2.3. Please submit the appendices quality summary.

The correct summary document is now provided in section 2.3.A.

Question II
You reported that container closure integrity testing is performed using the (b) (4) ***method. Please describe the procedure and provide the CCIT validation protocol and report as well the SOP for performing CCIT.***
Please clarify if CCIT is routinely performed on every lot and the number of units tested, and justify your response.

The information provided was included in the body of the memo.

Question III

Octafibrin is a lyophilized product presented in a 100mL bottle. However, the results of media simulation studies provided in the BLA do not include the 100mL lyophilized presentation. Please provide aseptic process validation studies simulating the filling and lyophilization of Octafibrin (100mL bottles) using the same filling line and lyophilizer as the drug product.

The information provided was included in the body of the memo.

Question IV

You provided the German version of document (b) (4) ***-iqoq-report.pdf. Please provide the English translated version of the report.***

The report with annexes translated in English *060ROQ055_Eng* was provided.

Question V

Please provide the protocol and report (including tests performed and results) for the qualification of Lyo (b) (4) ***used for freeze drying of Octafibrin.***

The information provided was included in the body of the memo.

Question VI

You reported that the loading room (including loading and unloading table) was (b) (4) ***. Please describe the changes to the facility and provide the qualification studies performed to ensure the*** (b) (4) ***area meets the room classification. Please justify your response.***

The information provided was included in the body of the memo.

Question VII

You provided the IQOQ report for the (b) (4) ***; however, the document provides a list of the tests performed and concludes that the acceptance criteria were met. Please provide the protocol and results (data) of the tests performed to demonstrate functionality of the equipment.***

The information provided was included in the body of the memo.

Question VIII

You provided the IQOQ studies for the (b) (4) ***vessel*** (b) (4) ***; however, the document provides a list of the tests performed and concludes that the acceptance criteria were met. Please provide the protocol and results (data) of the tests performed to demonstrate functionality of the equipment.***

The information provided was included in the body of the memo.

Question IX

You reported that the transport validation for Octafibrin final containers at (b) (4) ***during*** (b) (4) ***conditions is not available yet but is planned for August 2016 and***

January 2017, respectively. Please provide the results of the transport validation when the studies are completed.

The information provided was included in the body of the memo.

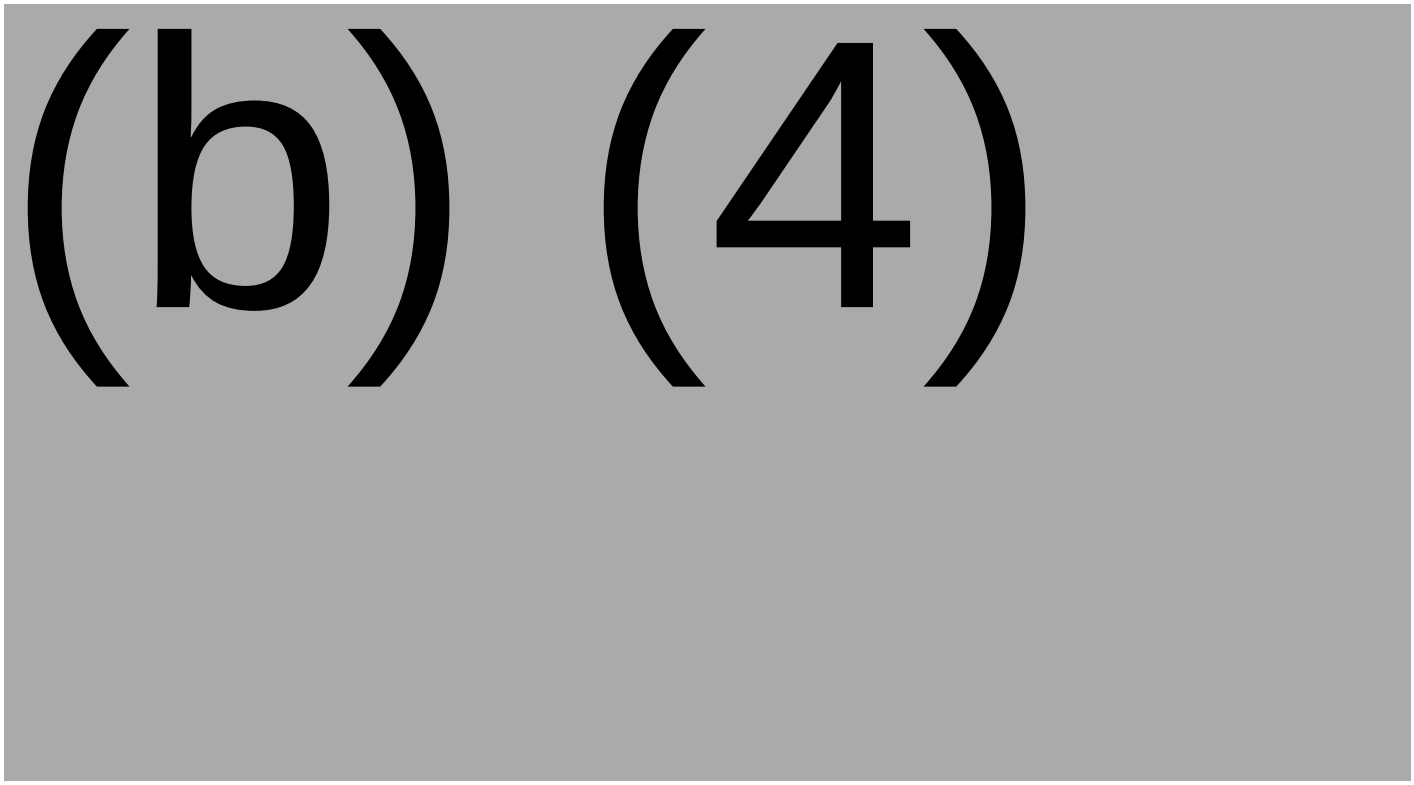
12 Oct 2016 IR (Responses Provided in amendment125612/0.15)

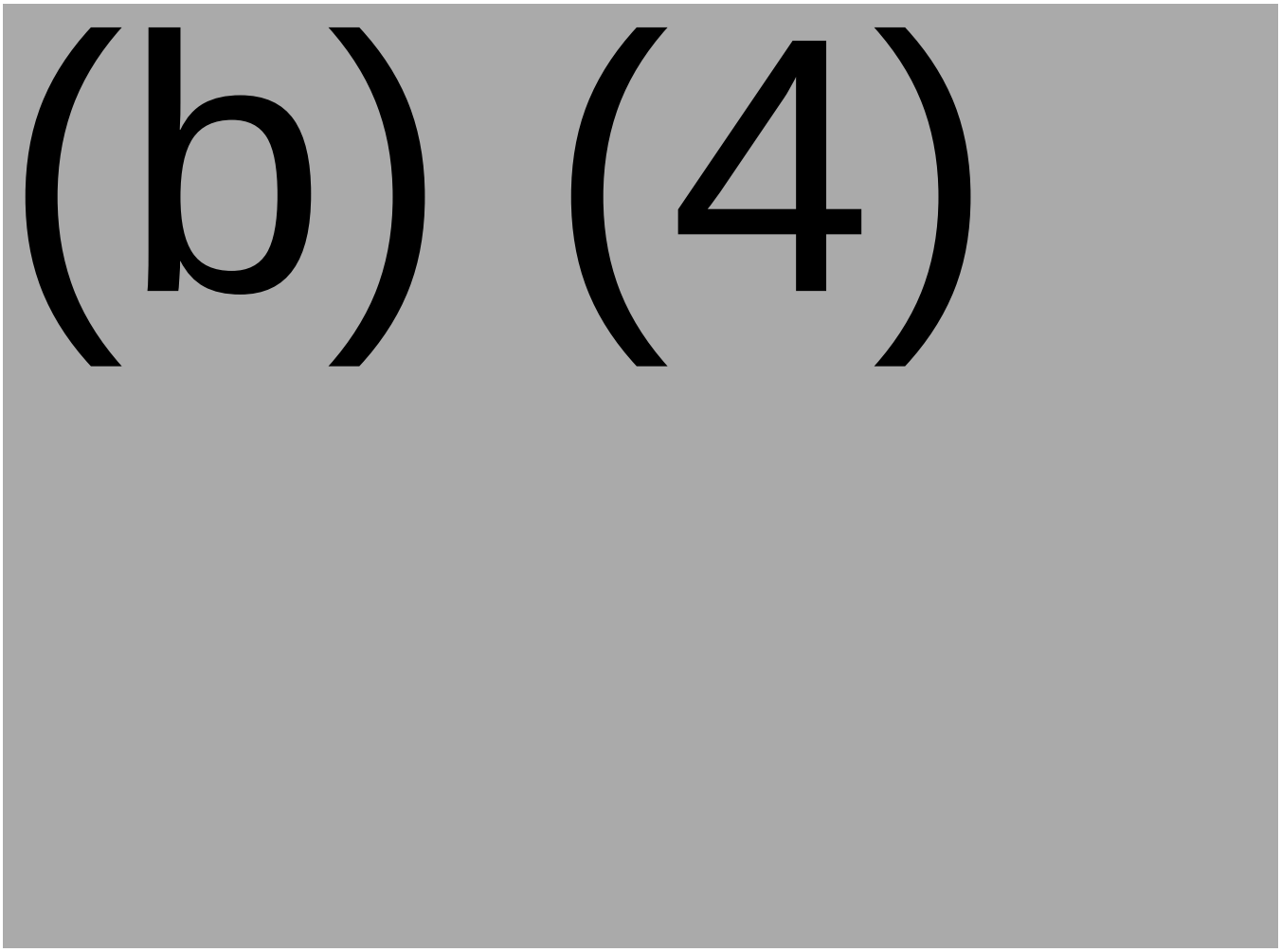
Question 1

You listed in 20160323_347_32A13_Annex_OPG_00.docx all the equipment used for the manufacture of Fibrinogen. You indicated that many pieces of equipment were already submitted, reviewed and approved in association with other US licensed products. For these pieces of equipment, please provide a brief description of the equipment and include the STN and approval date of the submissions where the information was initially submitted; also list the most recent requalification protocol/report. For other equipment (not associated with US licensed products), please provide description of the equipment and the respective qualification/validation studies and results.

Octapharma provided in document *20161107_347_32A13_Annex_OPG_02.00*, an updated Annex 1 in section 3.2.A.1.3 which includes brief description and licensing status for the equipment used in the manufacture of Fibrinogen. Table 1 includes equipment ID and description, the process step where the equipment is used, the qualification status of the equipment (and STN number if applicable), the validation report for cleaning and sterilization including dirty hold time and clean/sterile hold time where applicable.

Octapharma provided the qualification reports and validation of cleaning and sterilization for equipment that have not been reviewed and approved in association with other US licensed products, and has not been submitted previously in the original BLA 125612 and amendments:





Reviewer's comments: The reports were reviewed in the memo, and additional information was requested to clarifying any pending issues as documented in the body of the memo.

The submission has errors and inconsistencies, below are few examples: Please clarify/update

a. The Dirty hold time for vessel (b) (4) is reported to be (b) (4) in the summary table (20160323_347_32A13_Annex_OPG_00.docx) which is different than the (b) (4) dirty hold time stated in report 087RPQ15241.000. Also, you attached study plan 087STD09260.000 as supportive for (b) (4) dirty hold time, when the document does not include information about the dirty hold time.

Octapharma reported that the validated dirty hold time is set at (b) (4) (study performed 2009), even though the cleaning validation was successful after (b) (4) of dirty hold time in (b) (4) validation runs. The (b) (4) dirty hold time is an error, and was corrected.

b. Fibrinogen is filled in 100mL bottle. The bottle is reported to be (b) (4) . You stated in report 089PPQR14007.106_US (p.52), that the (b) (4) bulk is aseptically filled into (b) (4) , sterilized 100 mL glass vials (b) (4). However, you reported in document 087RPQ15222.000 that (b) (4) vials are used for (b) (4) and Fibrinogen (Table 6, p 14). Please explain.

Octapharma clarified that the 100mL bottles used for Fibrinogen are (b) (4), and that the information included in report 087RPQ15222.000 is wrong due to human error.

c. ***eCTD title:*** (b) (4) ***-ioq-report is applicable to*** (b) (4)

The title was corrected.

d. ***eCTD title:*** (b) (4) ***- pq-report sterilization is for the maximum load (***(b) (4)***).***

Octapharma reported that the title is wrong due to human error and was corrected.

e. ***eCTD*** (b) (4) ***-pq-report life-cycle and*** (b) (4) ***-pq-report life-cycle; the protocols were attached instead of the reports***

Octapharma reported that the title of the eCTD is wrong due to human error. This is a life cycle study and is not completed yet. They added that data from initial (b) (4) cycles is available and were provided in report *089PPQR14007.106_US "Process Performance Qualification Report Fibrinogen – From Fresh Frozen Plasma to Final Container*" in Table 47 ((b) (4)) and Table 59 ((b) (4)) of the report.

Reviewer comment: This information was reviewed in the nanofiltration section and deemed acceptable.

f. ***You listed in document 20160323_347_32A13_Annex_OPG_00.docx the dirty and clean hold times for the equipment. However, I noted discrepancies between the listed DHT and CHT provided in this report and the data presented in the submitted reports. Please review and update the data provided to ensure accuracy.***

Octapharma stated that due to human error inconsistent dirty hold times and clean hold times were reported in Annex *20160323_347_32A13_Annex_OPG_00*. They added that the maximum values evaluated for dirty hold times and clean hold times were reported instead of minimum values. In addition the times were rounded up instead of rounded down. They added that they updated 20160323_347_32A13_Annex_OPG_00 to include the correct (minimum) DHT and CHT. In addition, (b) (4) vessels (b) (4) were removed from the annex as they are not used for Fibrinogen manufacturing.

Reviewer comment: The corrected information was reviewed with the respective equipment.

Question 2

HVAC system and Environmental Monitoring (EM)

You reported that you installed (b) (4) ***new air handling units: AHU*** (b) (4) ***, but you did not provide EMPQ to qualify the respective areas. In addition, you did not describe the environmental monitoring program, and you did not submit environmental monitoring data during the Drug Substance (DS) and Drug Product (DP) production, and filling of the Fibrinogen conformance lots and*** (b) (4) ***lots*** (b) (4) ***. Please provide the qualification of the areas. In addition, please provide the environmental monitoring performed to demonstrate that the different areas are in a state of EM control during the manufacturing***

of the DS and DP used for the conformance lots. Also provide the EM Data collected during the aseptic filling/transfer to lyo and lyo operations of the conformance lots and (b) (4)***.***

The information provided was included in the body of the memo.

(b) (4)

Question 3

Bottle Vial Washer: ***Please provide description, initial qualification/validation and the most recent requalification using 100mL bottles***.

The information provided was included in the body of the memo.

Question 4

If the 100mL bottle is (b) (4) ***, you need to provide qualification of the*** (b) (4) ***functionality, and the validation the*** (b) (4) ***process for the 100mL vials, to ensure that the equipment (bottle washer) can perform both cleaning and*** (b) (4) ***(appropriate coverage).***

The information provided was included in the body of the memo.

Question 5

Depyrogenation Tunnel: Please provide description, initial qualification/validation, and the most recent validation using the 100mL bottles. Also include the validation of the sterilization of the (b) (4) ***.***

The information provided was included in the body of the memo.

Question 6

Filling line - filling/stoppering/capping: ***Please provide description and qualification including*** (b) (4) ***.***

The information provided was included in the body of the memo.

Question 7

(b) (4): ***Please provide description, qualification, cleaning,*** (b) (4)

The information provided was included in the body of the memo.

Question 8

Transfer area to lyophilizer (b) (4) **(additional information submitted in amendment 125612/0.7)**. ***You provided report 080RPQ12393.000, Validation of Bio-decontamination of loading room*** (b) (4)***. Please provide information about the*** (b) (4)

(b) (4)

The information provided was included in the body of the memo.

Question 9

Crimping and Coding Machine

a. ***Please provide a description of the equipment and the qualification/validation of the crimping process and subsequent inspection (*** (b) (4) ***) to separate the rejects from the accepted vials.***

b. ***You provided OPG_VVKM7022_IQOQ. Please provide narrative and a schematic diagram showing the transfer of the 100mL partially stoppered filled vials from the*** (b) (4) ***Lyo*** (b) (4) ***, and the transfer of the lyophilized and fully stoppered vials to the crimping capping station.***

c. ***Please describe the verification steps (inspection of the filled vials by*** (b) (4) ***, if performed, with justification.***

The information provided was included in the body of the memo.

Question 10

Visual inspection, labeling and packaging

a. ***Please describe the visual inspection lines and equipment used for packaging and labeling for Fibrinogen.***

Octapharma provided pictures and briefly described the visual inspection lines, vial labeling and packaging and labeling of the secondary packaging.

They stated that 100% visual inspection is performed on a semi-automatic inspection machine either on line (b) (4) in room (b) (4). The semi-automatic inspection lines consist of (b) (4). The vial labeling machine is integrated (b) (4).

Printing of batch data onto the folding cartons is done (b) (4) printing machine.

The labeled vials are manually packed into the preprinted folding cartons together with the leaflet and equipment for dissolution; and tamper evident closures are applied either manually or automatically. The single packs are then put into outer cartons and shipping cartons, and placed on pallets.

Octapharma added that 100mL vials used for Fibrinogen are the same ones used for the (b) (4). Thus the vial label size and material are the same. In addition the same material of the folding carton is used.

All equipment needed for labeling and packaging of Fibrinogen has already been qualified for all existing formats and materials of other US licensed products.

Octapharma provided in *20161107_347_32A13_Annex_OPG_02.00* the list of the most recent qualification documents for equipment used for visual inspection and packaging of Fibrinogen, which have already been submitted and reviewed for other US licensed products.

> **Reviewer's comment**: As Fibrinogen is a lyophilized product, and particles are hard to visualize within the cake, additional information was requested regarding the visual inspection of reconstituted Fibrinogen sample to comply with (b) (4) : sampling plan, the acceptance criteria and the results of all the conformance lots for Fibrinogen.The information will be reviewed in the addendum memo.

b. Please describe AQL sampling performed, and results.

Octapharma provided the following SOP which describes the visual inspection of the final containers including AQL sampling:

- *411SOP001/03, Visual Inspection of Final Containers* (effective 21 Oct 2016)

The visual inspection process performed at OPG including the defect library and the training of inspectors has been reviewed and approved previously. For lyophilized products, in addition to particles, closure and glass defect, lyo-cake and product in the stopper area are evaluated.

Octapharma stated that their procedure allows for re-inspection of vials (2X) if they failed the visual inspection according to the following scheme:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

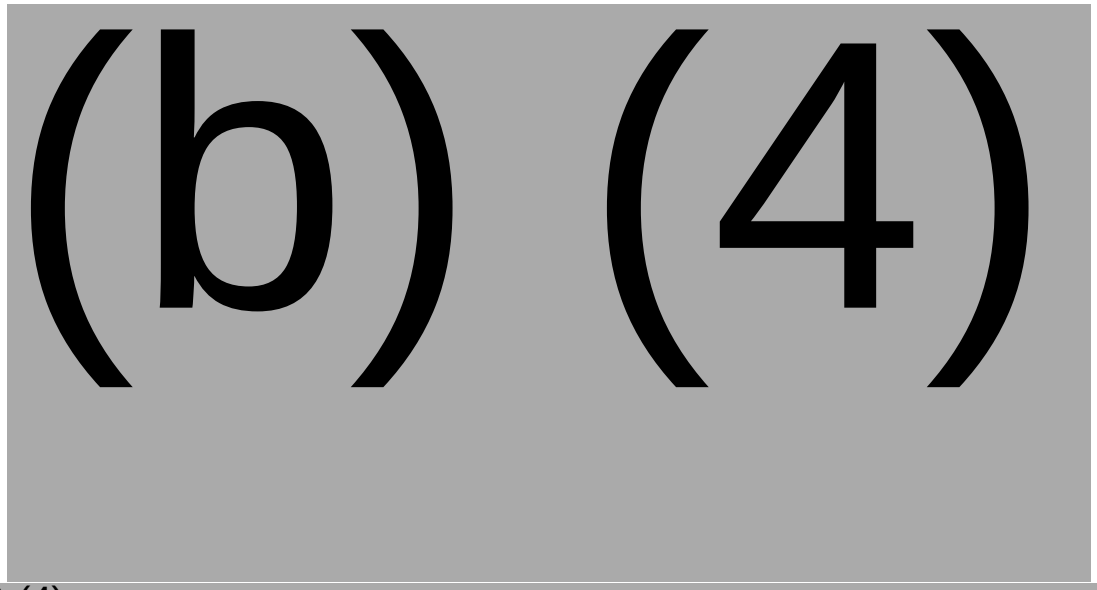
c. You stated during the 06Oct2016 telecon, that all (b) (4) *conformance batches were visually inspected, packaged and labeled at OPG Vienna facility, and that none of the batches were sent to* (b) (4) *, as the equipment were not completely qualified. As we discussed during the telecon, for the* (b) (4) *facility to be approved for visual inspection, packaging and labeling of Fibrinogen, you need to provide data to demonstrate that you successfully validated the visual inspection, packaging and labeling of Fibrinogen at the* (b) (4) *facility.*

Octapharma withdrew the (b) (4) facility from the BLA for the visual inspection and packaging for Fibrinogen, as they do not have supportive validation data.

Question 11

(b) (4)

5 pages have been determined to be not releasable: b(4)



(b) (4)

(b) (4)

Question 18
Cleaning

a. Please provide data to demonstrate that (b) (4) ***is worst case soil.***

b. Please list all the (b) (4) ***units used for cleaning the equipment used during manufacturing of Fibrinogen. Please provide the studies performed (*** (b) (4) ***) to demonstrate that the cleaning process covers all product contact surfaces, and provide supportive data.***

c. I noted during the review of the cleaning validation studies that (b) (4) ***is not monitored in the final rinse for several pieces of equipment. Please explain and justify your response.***

The information provided (a, b, c) was included in the body of the memo.

d. During the 06Oct2016 telecon, we briefly discussed the cleaning of the equipment, and you stated that the (b) (4) ***inactivation equipment are cleaned in separate areas. However, on page 6 of eCTD section 3.2.A.1.4, Procedures to Prevent Cross-Contamination, you reported ""Dirty" equipment from the*** (b) (4) ***area as well as*** (b) (4) ***inactivation area is transferred to room*** (b) (4) ***(Washing) and cleaned according to written procedures". Please explain and justify your response.***

Octapharma clarified in their written response that their statement during the 06 Oct 2016 telecon is applicable only to the production (b) (4) area.

They explained that Fibrinogen is manufactured in (b) (4) different production areas:

(b) (4)

1 page has been determined to be not releasable: b(4)

g. Cleaning of Lyo (b) (4)

i. Please provide the protocol and results for the studies performed to demonstrate that the (b) (4) *covers all areas of the lyophilizer including the* (b) (4)

ii. Please provide the (b) (4) *cycle parameters for cleaning Lyo* (b) (4) *.*

iii. During routine operations, soiling would be the result of a tipped or broken bottle, which is subsequently exposed to the lyophilization process. Please provide the soiling procedure (including soiling locations) and the conditions post soiling (and pre (b) (4)*), to verify that the soiling process represents worst case soil.*

iv. You reported that (b) (4) *sampling is performed at the* (b) (4) *. Please explain the rationale for choosing the* (b) (4) *and the reasons for considering it worst case location. Please justify your response and provide supportive data.*

v. Please clarify if you validated the clean status of the (b) (4) *which comes in contact with the* (b) (4) *and justify your response.*

vi. You reported that the dirty hold time was verified with (b) (4) *on the* (b) (4) *of the lyophilizer that were subsequently replaced. Please explain the rationale for not repeating the DHT when the* (b) (4) *were replaced and a new* (b) (4) *validation run was performed.*

vii. In report 087RPQ15145.000, you reported that the (b) (4) *is performed after* (b) (4) *of the Lyo. As* (b) (4) *will destroy microbial contamination, it is not clear why you consider that this study with sampling after* (b) (4) *validates a* (b) (4) *clean hold time? Please explain and justify your response. Also clarify if the clean hold time is* (b) (4) *as both are mentioned in report 087RPQ15145.000.*

The information provided was included in the body of the memo.

Question 19
Sterilization

You reported in the BLA submission, that (b) (4) **autoclaves are used for the sterilization/sanitization of equipment, and you provided the summary report for the sterilization of** (b) (4) **in autoclave** (b) (4) **:**

- ***080RPQ15154.001,*** (b) (4) ***Sterilizer*** (b) (4) ***Standard Load 7a "***(b) (4) ***" (Maximum Load) Production*** (b) (4)**, approved 19 Jan 2016.**

a. Fig 4 of the report (location of TCs and BIs in Load 7a) did not transfer correctly, please resubmit.

Octapharma resubmitted the report with the schematic Fig 4.

b. Please list if additional equipment is sterilized/sanitized in (b) (4) ***. If the validation of the loads and cycles used for the Fibrinogen manufacturing equipment have been submitted and reviewed in other submissions associated with US approved products, please provide the STN number and approval date; alternatively provide the validation summary reports***

for the maximum and minimum loads for equipment used during Fibrinogen manufacturing, if applicable. Also include schematic diagrams and description/narrative about the placement of Biological Indicators (BIs) and thermocouples (TC) in the load with justification. Please describe the biological indicator used, the number of spores and the Dvalue.

c. Please describe the other autoclave and list the equipment that are sterilized/sanitized in the autoclave. If the qualification of the autoclave and the validation of the loads and cycles used for the Fibrinogen manufacturing equipment have been submitted and reviewed in other submissions associated with US approved products, please provide the STN number and approval date; alternatively provide the validation summary reports for the maximum and minimum loads, if applicable. Also include schematic diagrams and description/narrative about the placement of Biological Indicators (BIs) and thermocouples (TC) in the load with justification.

d. You reported that the pink (b) (4) rubber stoppers are purchased clean, and are sterilized by (b) (4). Please describe the (b) (4) used and the validation of the (b) (4) of the stoppers. Please describe the sampling performed to ensure compliance with sterility and endotoxin specifications.

The information provided (b, c & d) was included in the body of the memo.

e. PQ Report 080RPQ15109.000 (b) (4)

i. ***The data provided shows a variation in temperature recording between the different thermocouples and the process sensor, yet you stated that the results met the specification of temperature spread (b) (4). Please explain. In addition, it is not clear from the data presented what was the minimum pressure (b) (4) recorded.***

Octapharma clarified that qualification sensors are positioned in the (b) (4) whereas process sensor (b) (4) is located in the (b) (4) system. Due to these different positions data recorded by the process sensor are not used to evaluate the temperature spread in the (b) (4). Acceptance criterion of (b) (4) for temperature during the (b) (4) hold-time phase is only applicable for qualification sensors. Therefore, evaluation of respective data does not include data recorded by the process sensor.

ii. ***Please describe the biological indicator used, the number of spores and the D-value.***

The BI used is (b) (4) (Spore Strips) with a population of (b) (4) spores/paper strip, and a and a $D_{121\ value}$ (b) (4), which were certified by incoming goods control. (b) (4) BIs were placed in the vessel to demonstrate sterilization throughout (b) (4) as described in the body of the memo.

f. Sterilization (b) (4)) of Lyo (b) (4)

i. You reported that Lyo (b) (4) is a (b) (4) Lyo as shown in the (b) (4) PQ report, and a (b) (4) Lyo as referred to in the (b) (4) PQ report PQ Report 080RPQ 15046.000, where the (b) (4). Please explain the (b) (4) validation strategy.

ii. Please provide the studies performed and the data to demonstrate that the (b) (4) TCs and (b) (4) BIs were placed in the worst case locations within lyo (b) (4).

iii. Please clarify what are the parameters for the routine and validation (b) (4) cycle.

The information provided (f.i,f.ii. f.iii) was included in the body of the memo.

iv. T*he results presented in Table 10 of the report indicate that the (b) (4) is both the Hot and Cold Spot; please explai*n.

Octapharma explained that the temperature of the (b) (4) reached the highest temperature (hot spot of (b) (4)) at (b) (4). In addition, the lowest temperature (cold spot) was recorded at the (b) (4) at (b) (4).

v. You reported that the validation run was performed at the required temperature for (b) (4); however the acceptance criterion is (b) (4). Validation studies are typically performed at worst case conditions; and it is not clear why you would consider a successful (b) (4). Please explain and justify your response.

Octapharma explained that the sterilization phase is controlled by the process sensor which was (b) (4). However, the qualifying sensors located at the different locations within the lyophilizer reached the (b) (4) before the process sensor which resulted in the (b) (4) sterilization time.

vi. You only provided data for one sterilization run – please clarify if this is a requalification run, and provide the dates and summary reports of the previous (b) (4) validation studies using the same (b) (4) unit and cycle.

Octapharma reported that Lyo (b) (4) was initially validated in October 2012 by (b) (4). The Lyo (b) (4) was then revalidated with one run (January 2014), and with one run (March 2015). All the (b) (4) validation runs were performed on the (b) (4) configuration (used for Fibrinogen production).

Question 20
<u>Purification process</u>

a. You reported that the purification of Fibrinogen is performed using the production line approved for the pooled plasma product Octaplas® (STN 125416). However the manufacturing of the two products are different. Please explain.

Octapharma explained that by using the "Octaplas line" they meant that both Octaplas and Fibrinogen share a manufacturing space (Production (b) (4)), and not a manufacturing process. They added that some tanks are shared during the manufacturing of both products.

b. Please provide the virus-inactivation achieved using S/D and nanofiltration.

Octapharma stated the validation of viral inactivation using S/D and nanofiltration was provided in section 3.2.A.2.4.3 Summary Virus Validation Studies of the original BLA.

Virus inactivation is performed in two steps: the first step (**room** (b) (4) **Grade** (b) (4)**)** is to inactivate most of the enveloped viruses and the second step (**(room** (b) (4) **Grade** (b) (4)**)** is viral clearance of both enveloped and non-enveloped viruses.

Octapharma provided small scale spiking validation studies to demonstrate the efficacy for the inactivation (S/D) and removal (nanofiltration – using two different nanofilters) of viruses.

Table 1: Global reduction factors during Fibrinogen (Octafibrin) manufacturing including the Planova 20N filter for nanofiltration

Production step	In vitro reduction factor [log_{10}]				
	Enveloped viruses			Non-enveloped viruses	
	HIV-1	PRV	BVDV	HAV	PPV
S/D treatment	(b) (4)				
Nanofiltration (Planova 20N)					
Global reduction factor					

n.a.: not applicable

Table 2: Global reduction factors during Fibrinogen (Octafibrin) manufacturing including the Pegasus SV4 filter for nanofiltration

Production step	In vitro reduction factor [log_{10}]				
	Enveloped viruses			Non-enveloped viruses	
	HIV-1	PRV	BVDV	HAV	PPV
S/D treatment	(b) (4)				
Nanofiltration (Pegasus SV4)					
Global reduction factor					

n.a.: not applicable

c. Please describe the integrity testing performed for both the Planova and Pegasus nanofilters.

Octapharma stated that the integrity for both filters was tested (b) (4) nanofiltration; however, they used different methods for testing the integrity of the two filters.

For the Planova filter, the integrity of the filter is assessed by performing a (b) (4) test (b) (4) the nanofiltration. (b) (4) test is performed.

They described the (b) (4) test (performed (b) (4) nanofiltration) which involves (b) (4)

Reviewer's comment: The (b) (4) test depends on the (b) (4) .

Additional information was requested regarding the testing parameters and acceptance criteria performed by the manufacturer, and the studies performed in-house (or at supplier) to determine the testing parameters and acceptance criteria relevant to testing the integrity of nanofilters used for Fibrinogen. More information was also requested regarding the operating parameters, the acceptance criteria and the results obtained for

the (b) (4) testing of the Planova filter. The information will be reviewed in the addendum memo.

The (b) (4) test is performed according to procedure *056SOP314, Filtration – Filter Integrity Testing Planova 20N Using* (b) (4) *Test System (*(b) (4)*)*, or procedure *056SOP310, Filtration - Filter Integrity Testing Planova 20N*, in case of (b) (4) testing, respectively. Octapharma briefly described the (b) (4) test where the filter is (b) (4)

Reviewer's comments: Additional information was requested regarding the operating parameters, acceptance criteria for the (b) (4) testing with justification. Moreover, the results for the (b) (4) testing performed for the Planova filters following nanofiltration during Step (b) (4) of Fibrinogen manufacturing was also requested. The information will be reviewed in the addendum memo.

For the Pegasus filter, the (b) (4) integrity testing is performed by a different method "(b) (4)" using (b) (4). Octapharma stated the (b) (4) has not been reviewed by FDA in association with other licensed products. They provided the following two documents for the qualification and operation of the method:

- *060VFK023, Qualification of* (b) (4) *(supplier) in 2007*.
- *060SOP017, Filter Test – Operation of the Filter Test Device* (b) (4)

(b) (4)

Reviewer's comments:
The (b) (4) test (b) (4) for a filter is dependent of the (b) (4), (b) (4). Additional information was requested regarding the testing parameters and acceptance criteria performed by the manufacturer, and the studies performed in-house (or at supplier) to determine the testing parameters and acceptance criteria relevant to testing the integrity of nanofilters used for Fibrinogen. In addition, more information was requested regarding the operating parameters, the acceptance criteria and the results obtained for the (b) (4) testing of the Pegasus filter. Moreover, an explanation was requested for not performing the (b) (4) method for

testing the integrity of the Pegasus nanofilters. The information will be reviewed in the addendum memo.

(b) (4)

(b) (4)

Reviewer's comment:

(b) (4)

b. (b) (4)

Question 22
Lyophilization of Fibrinogen

a. You reported that the freeze drying process is monitored by (b) (4)

b. During the 06Oct2016 telecon we discussed the lyophilization process, and you clarified that the Fibrinogen clinical lots were lyophilized at (b) (4) ***facility whereas the conformance lots were lyophilized at the OPG Vienna facility. As the information was not clearly stated in the submission, we agreed that you would provide information to describe the history of the development of the lyophilization cycle (pilot studies, clinical lots and conformance lots).***

c. Also during the telecon you indicated that for the lyophilization of Fibrinogen, up to (b) (4) ***shelves can be loaded and lyophilized. However, the conformance lots data showed that*** (b) (4) ***was used for each of*** (b) (4) ***lots, and*** (b) (4) ***shelves were used for the*** (b) (4) ***lot.***

d. Please provide the data collected using surrogate/product temperature mapping and extended sampling of product of the minimum and maximum loads to validate the lyophilization process of Fibrinogen loaded on up to (b) (4) ***shelves. Please also specify the shelves used for the validation of the maximum and minimum loads.***

e. ***You reported that the*** (b) (4) ***conformance lots were lyophilized at varying shelf*** (b) (4) ***to demonstrate robustness of the freeze drying process. You added sampling was performed (*** (b) (4) ***vials per frame) with a maximum of*** (b) (4) ***frames per shelf. Please describe the loading of the*** (b) (4) ***lots and sampling locations (diagrams and narrative), with justification****.*

f. Please describe, using narrative and schematic diagrams, the loading procedure when the number of vials (per lot) does not completely fill a frame. Would you use empty vials (to complete the number of vials per frame), would the filled vials be placed at specific positions in the frame, etc…? Please justify your response.

Vials are loaded (b) (4) onto shelves, and if the number of filled vials does not fill a frame or shelf, (b) (4) vials will be loaded.

g. You reported in validation report 089PPQR14238.106_US, that "According to standard operating procedure 084SOP028/12 'Validation of Freeze Drying Process for Freeze Driers (b) (4) ***' (b) (4) vials have to be drawn from each frame loaded. However, to enable parallel analyses at Octapharma Vienna (OPG) and*** (b) (4) ***, (b) (4) vials instead of (b) (4) vials were sampled per loaded frame." Please explain why some samples were sent to*** (b) (4) ***for analysis. In addition, where would you routinely analyze the samples for Fibrinogen? Please explain and justify your response.***

h. You also reported deviation 36817 where the results for solubility samples (using a (b) (4) ***to deliver the diluent) performed in Vienna did not meet the acceptance criteria, and as such you reported that you accepted the results of solubility testing performed in*** (b) (4) ***(using a device) as those met the acceptance criteria for reconstitution time. The information presented demonstrates that the reconstitution of the conformance lot samples was not validated at the OPG Vienna facility. Please provide justification for accepting the*** (b) (4) ***results. Please provide additional data to demonstrate that the Fibrinogen solubility testing performed in Vienna is successfully validated.***

The information provided (a-h) was included in the body of the memo.

i. In validation report 089PPQR14238.106_US (5.16.1 Process Control Parameters for Process Step Freeze Drying; p 107) the results of the measurement of the (b) (4) –seems to be in increments of (b) (4). Please clarify.

Octapharma reported that the (b) (4) .

j. Please provide the following documents referenced in the lyophilization validation report: 080STD13183.000 and 080RPQ12375.000.

k. You stated that the stoppers are pushed down by shelf pressure – please describe how that functionality was qualified. Did you sample vials from the edges and center of the different shelves to demonstrate consistency in the stoppering force? Please explain.

The information provided (j, k) was included in the body of the memo.

Question 23

Deviations

Please provide additional information about the investigation and corrective action for the following deviations:

a. Deviation 34822 (classified as minor) reported for batch (b) (4) ***for the loss of the "*** (b) (4) ***"***

b. Deviation 34913 (classified as minor) reported for batch (b) (4) ***for exceeding the limits for Fibrinogen.***

c. Deviation 34941 (classified as minor) reported for batch (b) (4), regarding the filling of the bottles. Please clarify if the determination of the filling of the vials – Is it by weight or volume, as it seems to be described differently in different reports. What do you mean by this: (b) (4)?

The information provided was included in the body of the memo.

Question 24

Container Closure Integrity Testing

a. You stated that the (b) (4) method is used for validation of the container closure. However you reported that the validation report has not been completed yet. It will be completed by the end of 2016. Please explain.

Octapharma reported that they test container closure integrity by the (b) (4) method as part of the stability studies.

They stated that the validation was only partially completed due to the limited number of control vials ((b) (4)) and provided report *009VAL193 CCIT (b) (4) Lyo-(b) (4), Container and Closure Integrity Testing of 100ml Glass Vials with Rubber Stoppers for Lyophilized Product by (b) (4) Measurement with the (b) (4)* (approved 03 Nov 2016).

Review of the information provided was included in the body of the memo.

Reviewer's comment: The CCIT validation report was requested and will be reviewed in the addendum memo.

b. You provided the SOP for 100% testing using (b) (4), and the equipment was qualified at (b) (4) settings ((b) (4)) – what is the acceptance criteria. Please clarify what is the maximum allowed number of rejected vials/bottles before rejecting the batch. Have you performed this testing at the end of shelf life to determine the (b) (4) status throughout the shelf life of the lyophilized product?

The information provided was included in the body of the memo.