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

John Eltermann, Jr., R.Ph., M.S., Director, OCBQ/DMPQ

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

Subject: **Addendum 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 (1g 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

ACTION RECOMMENDED

Based on the information provided in the original BLA submission and amendments submitted in response to the information requests, I recommend approval of this submission.

SUMMARY

CBER received this electronic submission on June 9, 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 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 100mL vial (to be reconstituted with 50mL Water for Injection, not supplied with the product), and co-packaged with a reconstitution device (Octajet) 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, (b) (4) was chosen as starting material. (b) (4) 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 new filling line "(b) (4), 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 or the (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, Austria, (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) (b) (4) are US licensed facilities, and the inspections were waived for these facilities (before the withdrawal of the (b) (4)) 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 final product.

Additional information was requested on August 1, 2016 (email information request), August 5, 2016 (filing letter), October 6, 2016 (telecon) followed by information request on October 12, 2016 (email), February 8, 2017 (telecon) followed by February 9, 2017 information request and a May 2, 2017 (telecon) followed by May 3, 2017 information request. Octapharma submitted their responses in amendments 125612/0.7, 125612/0.8, 125612/0.12,125612/0.15, and 125612/0.39, 125612/0.40 and 125612/0.54. The information provided in the initial BLA submissions and amendments 7, 8 & 15 were reviewed in a March 16, 2017 memo. The responses submitted in amendments 12, 39, 40 and 54 are reviewed in this addendum memo.

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) 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.

The Octajet reconstitution device was submitted to FDA for 510(k) clearance (b) (4) . The facilities, associated with the manufacturing and sterilization for the Octajet device were reviewed by CDRH/OC consult, and the consult reviewer recommended inspection as documented in her review memo. CBER/OCBQ/DMPQ recommends that the facilities be inspected post approval based on the following considerations:

- The device was accepted for review as a 510(k) device (b) (4)
- According to FDA guidance, a pre-approval inspection is not required for clearance of a 510(k) submission
- FDA can schedule the inspections for the locations associated with the device manufacturer at a later date
- The device was used for the reconstitution of Fibrinogen lots and the product results met the release criteria

REVIEW OF AMENDMENTS

In this addendum memo, I review Octapharma's responses to the CBER Information Requests submitted in amendments 125612/0.12, 125612/0.39, 125612/0.40 and 125612/0.54.

CBER comments are in bold, followed by the sponsor's response in plain lettering.

CONTAINER CLOSURE INTEGRITY TESTING

Question 1a

You provided report *009VAL193* CCIT (b) (4) Lyo/(b) (4) (approved November 3, 2016) where you presented preliminary results for the CCIT of the lyophilized 100mL vials. The results show that the (b) (4) measurements for the samples are less than the positive control; however they are almost twice the value of the negative control. Please explain.

Octapharma explained that the negative control (b) (4)

Response is acceptable.

Question 1b

You provided the (b) (4) measurements at (b) (4) time points (March and August 2016), and the results show that the (b) (4) measurements for the August 2015 samples are much higher than those of the March 2015 samples. You attributed the increase to humidity. Please explain how you ruled out that the increase could be due to a very small leak which decreased the (b) (4) during the (b) (4) months period. Please justify your response.

Octapharma explained that comparing the March and August results showed that the negative controls ((b) (4)) as well as the tested samples (b) (4) .

They added that the positive controls ((b) (4)) had much (b) (4) values than the tested samples and negative controls, which indicate that the tested samples could not have a (b) (4) or (b) (4) .

Response is acceptable.

Question 1c

Please provide the final report for Container and Closure Integrity Testing of 100mL Glass Vials with Rubber Stoppers for Lyophilized Product by (b) (4) Measurement with the (b) (4) , that had a target completion date December 2016 (as reported in amendment 125612/0.7), by March 31, 2017.

Octapharma provided the final CCIT validation report:

- ***009VAL193 CCIT (b) (4) Lyo/(b) (4) ,*** *Container and Closure Integrity Testing of 100 mL Glass Vials with Rubber Stoppers for Lyophilized Product by (b) (4) Measurement with the (b) (4)* (approved 10 Mar 2017)

The validation plan for the CCIT using the (b) (4) was submitted and reviewed in the March 16, 2017 memo. According to the validation plan, test runs using (b) (4) different sets of leak vials ((b) (4)) are required for the validation. These positive controls are provided by the supplier. The first set was tested in October 2016, and the results documented in report *009VAL193 CCIT (b) (4) Lyo/(b) (4)* reviewed in March 16, 2017 memo, and the results showed the (b) (4) can detect a leak of (b) (4).

The second set was tested in February 2017, and the results also showed that the equipment can detect an (b) (4) breach.

Octapharma summarized the results for both validation studies (October 2016 and February 2017) in the following Table:

(b) (4)

(b) (4)

The studies performed and the data collected demonstrate that the (b) (4) can detect a (b) (4) breach (leak), and that (b) (4) are suitable to use for the positive and negative controls.

Octapharma provided the results of CCIT testing performed at T-24 months on final product placed on long term stability in the following two reports:

- 000SSR347.14P012.01, *CCIT of Fibrinogen 1g, OPG Planova P20N Nanofilters Study 14P012 24 months' data* (approved 08 Mar 2017)
- 000SSR347.14P013.01, CCIT of Fibrinogen 1g, *OPG Pegasus SV4 Nanofilters Study 14P013 24 months' data* (approved 08 Mar 2017)

(b) (4) of Fibrinogen (1g in 100mL vials) prepared using the Planova P20N nanofilters (b) (4) using the Pegasus SV4 nanofilters ((b) (4)) were put on stability and tested for container and closure integrity using (b) (4) measurement at selected time points throughout the studies. The samples are being monitored over a total storage period of (b) (4) months for the long-term condition studies at +5°C, +25°C/(b) (4) and (b) (4) . The accelerated condition studies at (b) (4) were completed after (b) (4) months and reviewed in the March 16, 2017 review memo.

For each batch the following samples were tested for CCIT after 24 months of the long term stability:

- Long-term storage condition 5°C, (b) (4) Samples
- Long-term storage condition 25°C / (b) (4) samples
- Long-term storage condition (b) (4) samples

Octapharma reported that the results showed the container closure integrity was maintained throughout the 24 months period for all conditions, and that no deviations were observed. They added that the studies are ongoing and the samples will be tested again after (b) (4) months storage.

Response is acceptable.

EQUIPMENT QUALIFICATION/CLEANING

We discussed during the February 8, 2017, teleconference, that the qualifications of certain equipment were not completed prior to manufacturing of the conformance lots. Here are some examples:

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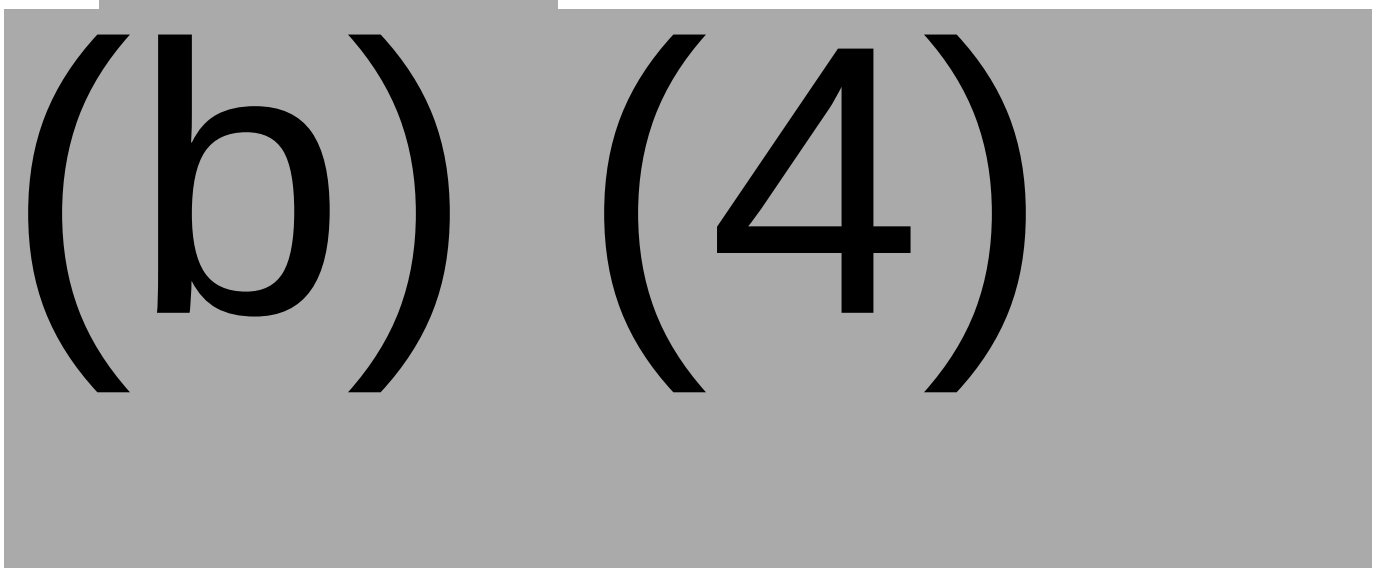
(b) (4)



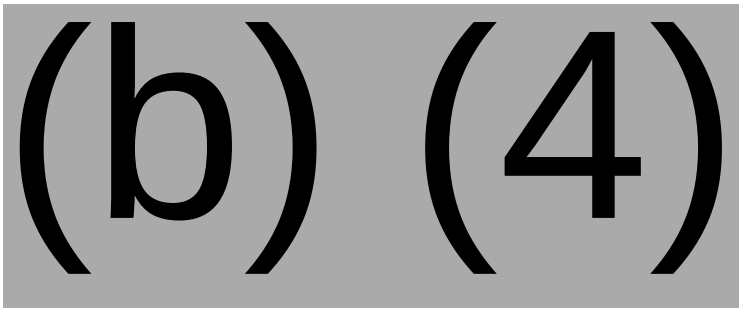
Response is acceptable.

FILTRATION

Question 3a & 3b: Sterilization Filters

Please describe the sterile filtration process (parameters) and provide the validation of the sterile filtration for the Fibrinogen drug product, and the validation of integrity testing performed (b) (4) **. Please include number of filters (lots) used for the validation studies, the testing parameters, acceptance criteria and results.**

(b) (4)



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(b) (4)

Response is acceptable.

(b) (4)

Response is acceptable.

Question 3d & 3e: Planova Nanofilters

For integrity testing using the (b) (4)

Please provide a brief summary of the testing parameters and acceptance criteria performed by the supplier, and the studies performed in-house (or at supplier) to demonstrate that the testing parameters and acceptance criteria are applicable to the nanofilter integrity testing method used for Fibrinogen.

Please provide the results obtained for the (b) (4) **integrity testing of the Planova filter for the Fibrinogen lots**.

(b) (4)

(b) (4)

Response is acceptable.

Question 3f & 3g: Pegasus Nanofilters

(b) (4)

. Please provide a brief summary of the testing parameters and acceptance criteria performed by the supplier, and the studies performed in-house (or at

supplier) to demonstrate that the testing parameters and acceptance criteria are applicable to testing the integrity of nanofilters used for Fibrinogen. Please provide the results obtained for the (b) (4) integrity testing of the Pegasus filter for the Fibrinogen lots.

(b) (4)

Response is acceptable.

PROCESS VALIDATION

Question 4a : Transport Validation

You stated in response to 01 August 2016 information request (amendment 125612/0.7), 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. You stated during the February 8, 2017, teleconference that you submitted the (b) (4) validation report in October 2016 (sequence 13), and that the (b) (4) report would be available in March 2017. Please submit the winter transport validation by March 31, 2017.

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

Reviewer's comment: Octapharma clarified in amendment 125612/0.54 that the final container specification for Fibrinogen lyophilized product (Fibryna) can be stored at 2°C to 25°C up to (b) (4) months. Thus the storage conditions at 2-8°C or ambient are acceptable. The information provided regarding the storage conditions are reviewed in **Q6** of the Information Request section below, and the response is acceptable.

Question 4b: Filling Consistency

In report 089VRE14237.106 (approved May 27, 2015), you concluded that the filling process was consistent as determined by CpK ((b) (4)) thus meeting the acceptance criteria (b) (4). The CpK acceptance limit is low. Please provide the rationale for considering Cpk (b) (4) acceptable to demonstrate process consistency.

Octapharma explained that the Cpk index for two-sided limits is a measure for how close a process is running to its target and how consistent it is. They added that a process with CpK value (b) (4) indicate that the process is performing better than the required specifications.

They stated that for the filling process on (b) (4), 100% of filled vials are routinely (b) (4). Thus filled vials not meeting predefined (b) (4) specifications are automatically rejected from the filling line. They added that a Cpk index of (b) (4) represents a process with (b) (4) of values meeting predefined specifications. Therefore, a Cpk index (b) (4) is considered adequate to demonstrate process consistency.

Response is acceptable.

HVAC/ENVIRONMENTAL MONITORING

Question 5a

You reported that AHU (b) (4) was replaced in 2015. The AHU supports the Grade (b) (4) areas with up to (b) (4) air recirculation in "Production (b) (4)" areas. You provided in amendment 1225612/0.15 summary report 080RPQ15395.000 (approved May 25, 2016) for the qualification / calibration of the HVAC system.

The results for room qualification in operation were presented only for room (b) (4), room (b) (4) and room (b) (4), and not for all the rooms supported by AHU (b) (4) .Please explain and justify your response.

Octapharma stated that all the rooms were qualified for maintaining the required clean room class and air exchange rates (b) (4). However, the modified rooms were also qualified in operation. They explained that the un-modified rooms were not qualified in operation as the "(b) (4) " qualifications have already demonstrated that the same quality air and classification was achieved as before the replacement of the AHU (b) (4) .

Response is acceptable.

Question 5b

Please also provide studies and data (acceptance criteria and results) to demonstrate that the new AHU can support the required air changes per hour, and the recovery studies performed to determine the time required to restore room classification following an excursion or shut down.

Octapharma provided the acceptance criteria and the results for the Air changes per hour (ACH) for the different rooms supported by AHU (b) (4) . The data presented show that the acceptance criteria (b) (4) ACH for most of the rooms; and for those rooms the actual results were (b) (4) ACH. However, for the following (b) (4) rooms (Grade (b) (4) and Grade (b) (4)), the acceptance criteria and results are lower ((b) (4) ACH).

Room	Classification	Description	Acceptance Criteria (ACH)	Actual Results (ACH)
(b) (4)				

Reviewer's comment: In response to information request, Octapharma submitted additional information in amendment 125612/0.54 stating that the acceptance criteria of ACH for rooms (b) (4) were revised to (b) (4) ACH, and that the 2016 testing results met the acceptance criteria. The information provided is acceptable, and is reviewed in **Q7** the Information Request section below.

Octapharma reported that recovery time studies at Vienna OPG facility are performed initially within the scope of new facilities or production rooms, and are not performed for qualification or a after a shutdown. They explained that all clean rooms are requalified "(b) (4)" after each shut down before the rooms are released for production. The qualification includes the following tests:

(b) (4)

Reviewer's comment: Octapharma justification for not performing recovery studies is acceptable, as the testing performed following shutdown indicates that areas are in a state of environmental control.

Question 5c

You also reported that AHU (b) (4) was replaced in 2015. The AHU supports the "Production (b) (4)" areas including room (b) (4) used for the (b) (4) processes of Fibrinogen. You provided summary report 080RPQ15398.000 (approved May 12, 2016) for the qualification of clean rooms in Octaplas line following the modifications. Please provide studies and data (acceptance criteria and results) to demonstrate that the new AHU can support the required air changes per hour, and the recovery studies performed to determine the time required to restore room classification following an excursion or shut down.

Octapharma provided the acceptance criteria and the results for the air changes per hour (ACH) for the different rooms supported by AHU (b) (4). The acceptance criteria for the different rooms vary from (b) (4) ACH to (b) (4) ACH, and the ACH data presented for the various rooms met the respective room acceptance criteria.

- The ACH data for Room (b) (4), which is used for several manufacturing steps of Fibrinogen production (Production (b) (4)) was (b) (4) ACH, which met the acceptance criterion of that room (b) (4) ACH.

Regarding recovery studies, Octapharma reiterated that they do not perform recovery studies following a shut down, but they qualify the rooms "(b) (4)" as described in response to Q5b above.

Response is acceptable.

Question 5d

You presented in the report the qualification of room (b) (4) under dynamic conditions, and presented the sampling locations. Room (b) (4) is used for the manufacturing of several products that require different equipment, manufacturing steps and personnel. Please provide the rationale for the sampling locations selection, and describe the manufacturing steps performed, the number of personnel in the area during the (b) (4) qualification, and how that is representative or applicable to Fibrinogen manufacturing in the area. Please justify your response.

Octapharma explained that they performed a risk assessment to identify the sampling locations for environmental monitoring during clean room qualification and during dynamic operations. They submitted the risk assessment report *001RAN06072016, Risk Assessment for In Operation Monitoring at the Vienna Production (b) (4) and Octaplas* (approved 19 Jul 2016). The study evaluated the critical processes, room classifications, and the probability of potential negative product impact and detectability of potential bioburden as well as the efficacy of the selected microbiological sampling points. Based on the results of the risk assessment, they established the sampling frequency, and the number and location of sampling points.

Octapharma stated that room (b) (4) is subjected to (b) (4) in operation microbiological monitoring: (b) (4)

Octapharma added that the number of personnel present during the (b) (4) qualification period was the maximum shift load of (b) (4) Operators (applicable for both Octaplas and Fibrinogen production.

> **Reviewer's comment**: In response to information request, Octapharma clarified in amendment 125612/0.54 that Octaplas manufacturing was performed during the (b) (4) dynamic monitoring, which they considered applicable to Fibrinogen manufacturing operations. The additional information was reviewed in **Q8** of the information request section below.

Question 5e: Environmental Monitoring (EM)

You provided the microbial EM results during the manufacturing of the conformance lots and media fills. However, you did not describe the non-viable monitoring during the drug substance production ((b) (4)) or drug product filling, lyophilization and capping/crimping operations to assure that clean the rooms are compliant with their area classifications. Please provide the non-viable sampling performed and the data collected during the manufacturing of the conformance lots and media simulations.

(b) (4)

(b) (4)

(b) (4)

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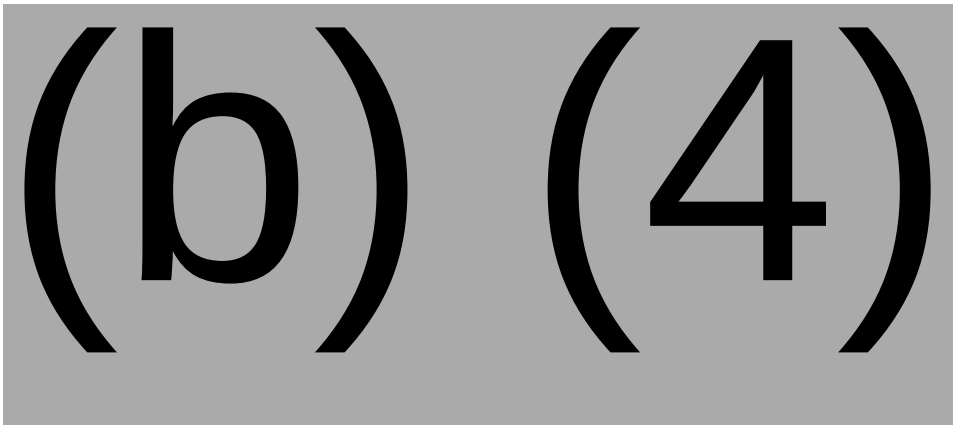


Response is acceptable.

Question 5f

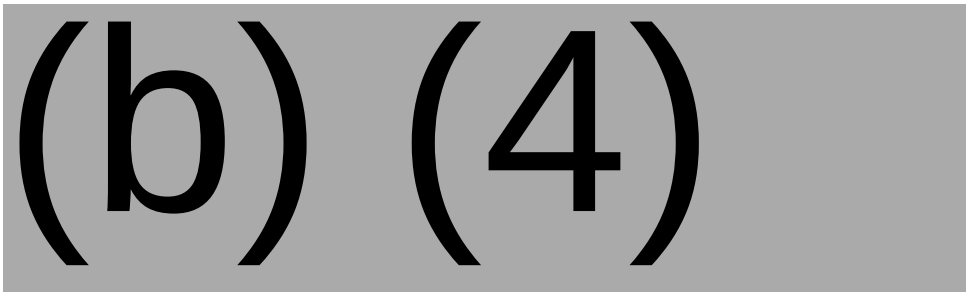
You reported that a risk assessment was performed to determine the level of environmental monitoring performed in the different areas. You stated that the frequency of monitoring depends whether open product is present in the area, and the level of product/ personnel/ material flow. Please explain with justification if the area classification (A, B, C, D, E), and the manufacturing operation: fractionation, purification, formulation, filling operations were included in the risk assessment to determine the frequency and number of sampling locations, and justify your response.

Octapharma provided risk assessment report *001RAN05072016, Batchwise Monitoring and Campaign Monitoring /Production* (b) (4) *and Octaplas* (approved 19 Jul 2016) used for the mapping and classification of the routine environmental monitoring performed during every aseptic filling operation, and at the end of a campaign.

The environmental monitoring of the areas is based on the criticality of the area:

- High risk - (b) (4)
- Medium risk - (b) (4)
- Low risk - (b) (4)

They listed he acceptance criteria for microbial monitoring as shown below:



They also listed the selection criteria for the sampling positions in the area:

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

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

Reviewer's comment: Additional information was requested, and Octapharma reported in amendment 125612/0.54 that the Environmental Monitoring program for the clean room classification and "in operation" PQ (A, B, C, D+ and D) is defined according to Risk Assessment *001RAN27062016*. They added that the number of microbiological samples – including active air samples and contact plates for surface control – is defined based on the room space. The information provided is acceptable, and it is reviewed in **Q9** of the Information Request section below.

VISUAL INSPECTION

Question 6

As Fibrinogen is a lyophilized product, and particles are hard to detect within the lyo cake, reconstitution of lyophilized samples followed by visual inspection is required per USP<790>. Please describe the visual inspection of reconstituted samples performed including number of samples tested and acceptance criteria, and provide the results for the conformance lots for Fibrinogen final product.

Octapharma provided SOP *130SOP006,Visual inspection of freeze-dried products,* (b) (4) *and WFI used for reconstitution and verification of solubility of freeze-dried products* (v.7, effective 25 Feb 2016). The SOP looks as a draft (v.7) as the changes included are in blue.

Octapharma reported that following reconstitution of the Fibrinogen cake, visual inspection is performed for (b) (4) .

They stated that they determined the sample size for reconstituted Fibrinogen according to (b) (4) for reduced sampling, and with an AQL level of (b) (4). They justified their sampling plan based on the premise that the visual inspection of a reconstituted lyophilized product is a destructive method, and pharmaceuticals manufactured from plasma are assessed as very valuable due to the limited material of origin. In addition, the reconstituted Fibrinogen solution is filtered before application to the patient, therefore an AQL level of (b) (4) is considered appropriate.

Octapharma reported that (b) (4) vials per final product batch are subjected to visual inspection. In addition to solubility and appearance, the presence of any particles is recorded. Solutions with particles have to be filtered (pore size e.g. (b) (4)) using the appropriate transfer set and have to be visually inspected again after filtration.

Reviewer's comment: In response to information request, Octapharma clarified in amendment 125612/0.54 that SOP *130SOP006* is not a draft, and "*that all changes to a previously effective SOP are written in blue in the new version*". They added that the SOP *130SOP006* was updated to version 8 which became effective 22 Dec 2016.

Octapharma reported that final release testing is only performed on reconstituted Fibryna (b) (4), and that batches that contain visible particles (b) (4) are rejected. Please refer to **Q11** in the Information Request section below.

Response is acceptable.

COMMENT

Question 7

You presented the results of the initial (b) (4) of the (b) (4) area in report 057RPQ_F2_MF_2012-02, Requalification of the Aseptic Filling Line (b) (4) (approved 08 Nov 2012). In the report you stated that for all Media Fill runs of the (b) (4) media simulations, "the recommended acceptance criteria were fulfilled. For the aseptic filling line (b) (4), the sterility assurance level (SAL) of (b) (4) could be demonstrated, as recommended by (b) (4) for aseptic processing". As we discussed during the February 8, 2017, teleconference, this statement is not correct, as the (b) (4) does not recommend (SAL) of (b) (4) for aseptic processing. Please update your reports.

Octapharma explained that they have already corrected the Media Fill Policy *011SOP204* in 2016, and revised the SOP (effective June 10, 2016) to eliminate reference to the stated SAL level of (b) (4). They stated that the (b) (4) media fills reports submitted to support this BLA were issued before June 2016. They added that both reports were corrected and the reference to the SAL level of (b) (4) was deleted.

Response is acceptable.

INFORMATION REQUEST

Additional information was requested by telecon on May 2 followed by an information request on May 3, 2017 (email). Octapharma submitted their responses in amendment 125612/0.54 on May 8, 2017 and is reviewed below.

All responses are acceptable.

(b) (4)

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(b) (4)

(b) (4)

Response is acceptable.

Question 4: Sterilizing filters

Octapharma reported in response to Q3a and Q3b that the validation studies were performed at (b) (4) ; yet the routine studies are conducted at (b) (4) . Please explain and justify your response.

Octapharma provided the results of additional studies performed at (b) (4) .

Response is acceptable and included in the body of the memo.

Question 5: Pegasus Nanofilters

Octapharma reported in response to Q3f and Q3g that the (b) (4) integrity test is performed per Octapharma's 060SOP017. Please provide the date the SOP became effective.

Octapharma stated that SOP *060SOP017, Filter Test – Operation of the Filter Test Device* (b) (4) was effective 14 May 2014.

Response is acceptable and included in the body of the memo.

Question 6: Transport Validation

Octapharma reported different storage conditions at (b) (4) and OPG facilities for the 100mL vials prior to transportation. You explained during the May 2, 2017, telecon that the vials can be stored at (b) (4), and thus the storage conditions: (b) (4) , depend on storage room availability at the different facilities. Please describe the storage areas and conditions used for the storage of the 100mL vials (under routine operations), as well as the maximum allowable time for storage of the vials under these conditions. Please justify your response.

Octapharma reiterated that the lyophilized Fibrinogen final container can be stored at 2°C to 25°C for up to (b) (4) month. Thus the brief storage of the Fibrinogen final containers during the transport validation at (b) (4) and OPG Vienna ((b) (4)) is compliant with

the product specifications. They added that the storage rooms ((b) (4)) are temperature controlled and validated.

- The (b) (4) room at (b) (4) is (b) (4) and monitored to maintain the storage temperature at (b) (4) in the entire room.
- The storage room at OPG is equipped with a (b) (4) system, and is monitored to maintain the storage temperature at (b) (4) .

Both (b) (4) storage areas are designed for the storage of pallets and that racks are installed for the storage on different levels.

Response is acceptable.

Question 7: HVAC/Environmental monitoring

In response to Q5b regarding ventilation and air changes per hour (ACH), Octapharma provided the acceptance criteria and actual results obtained for the different areas. I stated during the May 2, 2017, telecon that the ACH acceptance criteria and results collected for the following rooms are quite low and requested an explanation.

Room	Classification	Description	Acceptance Criteria (ACH)	Actual Results (ACH)
(b) (4)				

You stated that the results presented were for 2015; and that the results for 2016 show ACH (b) (4) for these areas. I further commented that the acceptance criteria were set quite low for a (b) (4) unloading area and asked for justifications. Please provide the rationale for setting low acceptance criteria for the rooms. Also provide the modifications implemented to the system that led to an increase of the ACH (b) (4) for these areas. Please state what are the current ACH acceptance criteria and provide the actual ACH results. Please justify your response.

Octapharma explained that the acceptance criteria listed in the question above were based on the technical capacity of AHU (b) (4) per "(b) (4)" qualification study ((b) (4) _*Produktion*(b) (4)) and "(b) (4) " qualification study (*080RPQ15395.000*), which indicated that the set ACH were sufficient for the areas to meet "*the acceptance criteria for particle,* (b) (4) ".

They added that during the summer shutdown of 2016, (b) (4) in room (b) (4), (b) (4) in room (b) (4) and (b) (4) in room (b) (4) were installed, and the acceptance criteria were increased to at least (b) (4) ACH in cleanroom Class (b) (4) and Class (b) (4) . The ACH in the rooms were then requalified per study (b) (4) _*Production*(b) (4), and the results met the acceptance criteria as summarized in the following Table:

Room	Classification	Description	Acceptance Criteria (ACH)	2016 Results (ACH)
(b) (4)				

Octapharma added that each of the (b) (4) rooms has a (b) (4) installed, and that (b) (4) operations are done under the (b) (4) (Grade (b) (4)). They provided the ACH acceptance criteria and actual values for the Laminar Flow areas as summarized in the following Table:

Room	(b) (4) (Grade (b) (4))	Description	Acceptance Criteria (ACH)	Jan/Feb 2017 Results (ACH)
(b) (4)				

Octapharma also provided a summary of the environmental monitoring viable results during routine monitoring of production rooms (b) (4) during 2015 and 2016 and all results were within acceptable limits. They concluded that the low ACH acceptance criteria and actual levels before the implemented changes in 2016 did not adversely impact the areas' environmental conditions.

Response is acceptable.

Question 8: HVAC/Environmental monitoring

In response to Q5d regarding the manufacturing operations during the dynamic qualification of room (b) (4), Octapharma did not address the question and specify which product was manufactured in the area during the dynamic monitoring. I noted that several pieces of equipment used for Fibrinogen manufacturing in room (b) (4) were not included in the sampling scheme. You explained during the May 2, 2017, telecon that the (b) (4) dynamic environmental monitoring was performed during Octaplas manufacturing operations. We discussed during the telecon that Fibrinogen manufacturing equipment and processes are different than those of Octaplas, and thus it is not clear whether the (b) (4) qualification (under Octaplas manufacturing) would be valid for Fibrinogen manufacturing. Please provide the assessment performed with justification to assure that the results collected during (b) (4) room qualification (Octaplas manufacturing) would have provided similar passing results during Fibrinogen manufacturing.

Octapharma clarified that Octaplas product was manufactured in the area during the (b) (4) qualification "(b) (4)" of (b) (4)-Room (b) (4). The room is used for manufacturing of Fibrinogen and Octaplas. They stated that the qualification was performed with the fixed shared equipment, and the mobile dedicated equipment used in Octaplas production.

They listed the stationary equipment in the room which is shared for the production of both products: (b) (4) . They also listed the dedicated mobile equipment used for Fibrinogen production (b) (4)).

Octapharma stated that the differences in the dedicated mobile equipment, with respect to physical and microbial burden are negligible, and as such the (b) (4) qualification under dynamic

conditions (equipment and personnel) is applicable to both manufacturing operations. Octapharma added that routine environmental monitoring during manufacturing operations is within acceptance limits and as such the area is in a state of control.

Response is acceptable.

Question 9: HVAC/Environmental monitoring

The response to Q5f, regarding the factors included in the risk assessment for environmental monitoring, did not address the question. Please explain with justification if the area classification (A, B, C, D, E), and the manufacturing operation: fractionation, purification, formulation, filling operations were included in the risk assessment to determine the frequency and number of sampling locations, and justify your response.

Octapharma provided risk assessment report *001RAN27062016, Risk Assessment for PQ In Operation, Clean Room Qualification, In Operation Monitoring and Particle Monitoring at Vienna Production Site - Production* (b) (4) *and Production Octaplas* (approved 08 Jul 2016).

The number of sampling locations during the PQ is based on area classification and room space as shown in the following Table:

(b) (4)

(b) (4)

(b) (4)

Response is acceptable.

Question 10: Visual Inspection

In response to Q6, Octapharma submitted 130SOP006, Visual inspection of freeze-dried products, (b) (4) and WFI used for reconstitution and verification of solubility of freeze-dried products (v.7, approved on February 23, 2016, but no effective date). The SOP looks as a draft (v.7) as the changes included are in Blue. Please clarify if the SOP was finalized and provide a copy including the date the SOP became effective.

Octapharma submitted the requested information.

Response is acceptable and included in the body of the memo.

Question 11: Visual Inspection

Please provide the visual inspection results of the reconstituted product (b) (4) . What are the rejection criteria for a batch based on presence of particles in the vials? Please justify your response.

Octapharma stated that for every batch, they visually inspect (b) (4) final product vials after reconstitution (b) (4) , and record the results for solubility and appearance and presence of any particles. They added that the visual inspection of the vials (b) (4) for all conformance lots ((b) (4)) did not show any particles.

Octapharma reiterated that the final release testing of every batch is performed on (b) (4) vials of (b) (4) product of that batch, and the presence of particles (b) (4) are investigated, and batches that contain visible particles (b) (4) are rejected.

Response is acceptable.