From: Maruna, Thomas
Sent: Thursday, February 09, 2017 4:45 PM
To: Ammons, Stanley; Mayerhofer, Juliane (juliane.mayerhofer@octapharma.com)
Cc: Melhem, Randa
Subject: 09-Feb-2017 Information Request - BLA 125612.0 - Response due 20-Feb-2017

STN: BL 125612/0
BLA INFORMATION REQUEST

Octapharma Pharmazeutika Produktionsges.m.b.H.
Attention: Mr. Stanley Ammons
February 9, 2017
Sent by email

Dear Mr. Ammons:

We are reviewing your biologics license application (BLA) dated June 9, 2016, for Fibrinogen Concentrate (Human), and have determined that the following information is necessary to take complete action. Please promptly submit your written response to the following items so that we may continue evaluating your BLA:

1. Container Closure Integrity Testing
   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.

   a. Please explain.

   You provided the (b) (4) measurements at two 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.

   b. Please explain how you ruled out that the increase could be due to a very small leak which decreased the (b) (4) during the 6 months period. Please justify your response.

   c. 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**.

2. Equipment Qualification/Cleaning

(b) (4)

[redacted]

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

(b) (4)

3. Filtration
Sterilization Filters

a. 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) .

b. Please include number of filters (lots) used for the validation studies, the testing parameters, acceptance criteria and results.

(b) (4)

Nano Filters
Planova Nanofilters: For integrity testing using the (b) (4)

d. 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.

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

Pegasus Nanofilters: (b) (4)

f. 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.

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

4. Process Validation

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.

a. Please submit the (b) (4) transport validation by **March 31, 2017**.

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).

b. The CpK acceptance limit is low. Please provide the rationale for considering Cpk (b) (4) acceptable to demonstrate process consistency.

5. HVAC/Environmental Monitoring

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.

a. 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.

b. 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.

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.

c. 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.

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.

d. 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.

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.

e. Please provide the non-viable sampling performed and the data collected during the manufacturing of the conformance lots and media simulations.

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.

f. 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.

6. Visual Inspection

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.

7. Comment

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.

Please submit your response in a timely manner, as noted below, so we may continue the review of your application. If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your responses as an amendment to this file **NO-LATER-THAN March 15, 2017 (except where noted above)**, referencing the date of this request.

The action due date for these files is June 9, 2016.

If you have any questions, you may contact me directly.

Very Respectfully,

Thomas J. Maruna, MSc, MLS(ASCP), CPH
Lieutenant Commander, U.S. Public Health Service
Senior Regulatory Management Officer

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