From: Maruna, Thomas
Sent: Wednesday, May 03, 2017 9:32 AM
To: Mayerhofer, Juliane (juliane.mayerhofer@octapharma.com); Ammons, Stanley
Cc: Melhem, Randa
Subject: 03-May-2017 Information Request - BLA 125612.0 - Response due 08-May-2017

Importance: High

STN: BL 125612/0
BLA INFORMATION REQUEST

Octapharma Pharmazeutika Produktionsges.m.b.H.
Attention: Mr. Stanley Ammons
May 3, 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.

As a follow-up to our telecon on May 2, 2017, (to discuss Octapharma responses to the February 9, 2017, Information Request), we request that you respond to all the issues discussed during the telecon with specific attention to the items listed below. The information requested is necessary to continue our review and evaluation of the manufacturing operations for Fibrinogen at OPG Vienna facility (BLA STN 125612/0). Please promptly submit your written response to the following items so that we may continue evaluating your BLA:

Vessels (b) (4)

1. Octapharma reported in response to Q2h that they performed (b) (4) studies on (b) (4) (as part of OQ studies). However, in response to Q2i, they stated that (b) (4) using (b) (4) was performed (b) (4) . During our May 2, 2017, telecon, you confirmed that (b) (4) studies were performed on (b) (4) vessel. Please describe the (b) (4) studies performed (including the dates), and provide a summary of the data collected to demonstrate (b) (4) .

2. Octapharma reported in response to Q2j that 087SOP032 will be updated by March 31, 2017. You confirmed during the May 2, 2017, telecon that the SOP was revised, and we agreed that you would submit the translated pages of the SOP that will describe the revisions made, and the date the SOP became effective.

Cleaning of Product Contact Equipment in Aseptic Area

(b) (4)

Sterilizing filters

4. 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.

Pegasus Nanofilters

5. 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.

Transport Validation

6. 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.

HVAC/Environmental monitoring

7. 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) 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.

8. 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.

9. 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.

Visual Inspection

10. 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.

11. 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.

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 May 8, 2017**, 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
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