**From:** Maruna, Thomas
**Sent:** Saturday, April 01, 2017 7:07 PM
**To:** Ammons, Stanley
**Cc:** Mayerhofer, Juliane (juliane.mayerhofer@octapharma.com); Patel, Sapana; Peng, Ze
**Subject:** 01-Apr-2017 Information Request - BLA 125612.0 - Response due 07-Apr-2017

**Importance:** High

STN: BL 125612/0
**BLA INFORMATION REQUEST**

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

Additional Deficiencies regarding the Octajet device:

1. In your response to FDA Question 17, you stated "*additional obtained data prove a shelf for up to* (b) (4) *. The stability test plan and report (MA0019929879S709-03-PVP and MA0019929879S709-03-PVR, respectively) are enclosed. Furthermore transportation and handling testing was conducted demonstrating that the packaging remained in a satisfactory condition with no evidence of damage to the primary packaging. Please find enclosed the Packaging Transport Validation report, MA001992989S709-02-PVR.*" However, the information that you provided is not sufficient to support a (b) (4) shelf life claim. Please address the following concerns:

    a. You have not provided package integrity testing to demonstrate that the device packaging maintains a sterile barrier throughout the claimed shelf life. Please consider conducting the most appropriate package integrity testing for your package type, seal integrity, and barrier performance as referenced in ANSI/AAMI/ISO 11607-1:2006/(R)2010, Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems, and packaging systems. We recommend that your testing include bubble leak or dye penetration according to ASTM D2096, Standard Test Method for Detecting Gross Leaks in Packaging by Internal

Pressurization (Bubble Test) or ASTM F1929-15, Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration, respectively. Testing should be conducted on the final, packaged device at the end of the claimed (b) (4) shelf life, and should be conducted separately for (b) (4) sterilized devices. Please ensure that you conduct real time aged testing in tandem with testing on accelerated aged devices.

b. It is not clear how the information in the stability test plan and report (MA0019929879S709-03-PVP and MA0019929879S709-03-PVR) supports your claimed shelf life. The test reports alternate between multiple languages and are difficult to interpret. The test report indicates that bioburden testing was conducted (b) (4) and sterility testing was performed (b) (4). However, the results of the bioburden testing could not be located and the protocol for sterility testing was not included. Additionally, it is not clear how this information is intended to validate that your device will remain sterile throughout a (b) (4) shelf life. Please clarify how bioburden testing (b) (4) and sterility testing (b) (4) supports your claimed (b) (4) shelf life. Please also update your test reports to include the complete protocols and test results for bioburden and sterilization of (b) (4) sterilized devices.

c. You stated that transportation and handling testing was conducted to demonstrate that the packaging remained in a satisfactory condition with no evidence of damage to the primary packaging, and you referenced the Packaging Transport Validation report, MA001992989S709-02-PVR. However, the Packaging Transport Validation that you provided does not indicate whether the validation was conducted on accelerated aged or real-time aged devices. Therefore, this information is not sufficient to support your claimed shelf life of (b) (4). Please clarify whether your transportation and handling testing was conducted on devices at the end of the (b) (4) shelf life. Please also provide justification that devices tested were representative of aged samples, addressing factors such as potential material deterioration or damage to packaging.

2. The document titled Amendment #0034 includes Bioburden Certificates for (b) (4) test samples in Exhibit 14B. However, within Section 14 – Sterilization and Shelf Life – (eCTD sequence #0028) you stated that bioburden testing was conducted on (b) (4) samples from (b) (4) separate batches. You also stated that the average bioburden from the (b) (4) batches was used to calculate the (b) (4) based on (b) (4). Please provide the bioburden test certificates for each of the (b) (4) samples from the other (b) (4) test batches to support your claim that (b) (4).

3. The document titled Amendment #0034 includes Endotoxin (b) (4) testing for the Octajet device in Exhibit 14E. However, Exhibit 14E does not clearly indicate how many device samples were tested for (b) (4). Additionally, Exhibit 14E does not

address whether you intend to conduct (b) (4) testing on every batch. Please note that the FDA Sterility Guidance document recommends that you provide confirmation that endotoxin testing will be conducted on every batch. Please clarify how many devices were tested for (b) (4) and provide a scientific justification that the sample size tested is sufficient to verify (b) (4) endotoxin limits are within the acceptable range for your subject device. Please also confirm whether you intend to conduct endotoxin (b) (4) testing on every batch, as recommended in the FDA Sterility Guidance Document. You may refer to the Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile Guidance for Industry and Food and Drug Administration Staff for additional information.

4. In the your Response to Information Requested on February 06, 2017; in response to FDA question 22, you state the following:

   Certification according to ISO 10993 which confirms the biocompatibility of the device (please refer to Table 15B of document "15_Biocompatibility).

   However, based on the information provided, biocompatibility testing according to ISO 10993 was not performed. Rather, a European Standard test method (i.e. European Pharmacopoeia 01/2009) was performed. Therefore, the meaning of the above statement is not clear. Please clarify.

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 April 7, 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
Senior Regulatory Management Officer

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