From: Maruna, Thomas
Sent: Monday, February 06, 2017 2:18 PM
To: Ammons, Stanley
Cc: Peng, Ze; Patel, Sapana; George, Bindu; Kong, Hyesuk
Subject: 06-Feb-2017 Information Request - BLA 125612.0 - Response due 20-Feb-2017

Importance: High

STN: BL 125612/0
BLA INFORMATION REQUEST

Octapharma Pharmazeutika Produktionsges.m.b.H.
Attention: Mr. Stanley Ammons
February 6, 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:

Clinical

Summary of review findings:

In a substantial number of cases, the Case Report Forms do not record active bleeding at the time of administration of the product but record the type of bleeding 1 day and in one case up to 7 days prior to treatment. In the absence of documentation of active bleeding shortly prior to the infusion of the investigational product, we are unable to determine whether subjects experienced hemostasis prior to the administration of the investigational product. In addition a number of subjects do not have documentation of assessment of the bleeding site of interest. A generalized assessment of all organ systems has been provided without a discussion of findings at the affected site. For example, resolution of hematoma is not expected in one day, however the generalized assessment in some cases notes that the physical examination was normal.

Please note that per the protocol specified criteria:

- The eligibility criterion for FORMA 02 study requires inclusion of subjects with acute bleeding either spontaneous or traumatic and
- The primary efficacy endpoint for assessment of hemostasis for the first bleeding event is based on assessment of hemostasis 24 hours from the last infusion.

Please note that the comments below refer to the first bleeding episode.

1. Subjects (b) (6) had history of hematoma or bruising or bleeding in most cases at least 1 day prior to the administration of the product, but no documentation of active bleeding on the day of administration. In order to assess whether the hemostasis is attributable to the product, evidence of bleeding should at the very least be present at the time of administration of the product. Please provide documentation of active bleeding at the time of administration of your product for the subjects mentioned above.

2. For Subject (b) (6), please provide documentation of the primary efficacy assessment of hemostasis of the R ankle joint one day following infusion. The CRF documents normal exam for all systems without mention of the ankle joint.

3. Subject (b) (6) was noted to have ecchymosis of the legs and pubic area prior to treatment.

    a. However the assessment performed one day post infusion notes presence of the ecchymosis in the legs, without mention of the status of the pubic hematoma. Please provide documentation of active bleeding at the time of the infusion for both lesions, and the status of the pubic hematoma 1 day after the infusion.

    b. Please clarify whether the second infusion was administered as a result of ongoing bleeding.

4. For subject (b) (6) and (b) (6) the primary efficacy assessments for hemostasis were performed 4 days after the last infusion. Please provide documentation of hemostasis assessment as per the protocol specified period of 24 hours following the last dose. Please also clarify whether the study drug was administered (we note that an entry for administration was made on September 3, 2015) to Subject (b) (6) since elevation in fibrinogen levels were not noted post infusion.

5. Subject (b) (6) was noted to have a history of groin hematoma on December 7, 2015. Subject (b) (6) was noted to have calf muscle bleeding on December 12, 2015. However for both these subjects, the physical exam on ecember 13, 2015, (day of infusion) and December 15, 2015, (24 hour post infusion assessment) reveals a normal exam. Please provide documentations of bleeding site assessments for the date of infusion and the protocol specified assessment at 24 hours post infusion for the above two subjects.

(b) (4) Endotoxin Testing for licensing support testing

6. CBER assessed your five conformance lots (i.e., lot numbers: A423A3472, A441A3474, A425A3471, A440A3472, and A433A3473) for (b) (4) endotoxin using a (b) (4) method and had valid results using the (b) (4) sample testing dilution, as selected in your method qualification report (000VAL162FC

34x IP13 34x /01.rep). However, the results as indicated in their lot release protocols submitted to CBER were generated using a sample testing dilution of (b) (4). Please explain why the (b) (4) dilution was used for testing, which CBER agrees represent a more appropriate dilution to evaluate samples, compared to the (b) (4) test dilution.

Device/Combination Product

7. You have provided medical device specifications of the proposed filter to be used in your copackaged combination product. It is unclear of your in process controls that are in place to ensure that the files meet your specifications when received from your supplier. Please describe the in process controls you have in place to ensure that the device will meet your specifications.

8. You have provided in Section 3.2.P.7 the material requirements for the Octajet. You state the Water spike/Powder spike is composed of (b) (4). In your response to Question 1 in the information request response on received on January 5, 2017, It is stated in Annex 5 that the water spike material is (b) (4) and the powder spoke is (b) (4). It is unclear if your material requirements are met by the proposed transfer device. Please clarify if your material requirements are met by the supplier of the Octajet. If the materials differ, please provide a rationale to why the device is considered acceptable if the requirements differ.

<u>Performance testing of combination product:</u>

9. Performance testing was provided in the January 5, 2017, response to Information Request which included the following tests:

   Testing of Attachment Force
   Withdrawal of (b) (4) from vials via Luer Lock syringes

   a. You have provided attachment force testing which compares the Octajet to the (b) (4) device and meets your acceptance criteria of an attachment force of (b) (4). You have not performed this testing with your drug vial. We recommend that your performance testing is completed with all constituents of the combination product to ensure that your device performs as expected when used as a system. Please provide testing that supports that the attachment force when used with your drug vial still meets your criteria of (b) (4).

   b. You have not provided attachment force testing for the water spike and you stated that testing of the attachment force of the water spike would not support any conclusions on the safety of your device. We do not agree with this rationale. We recommend to ensure that the design characteristics and input requirements of the water spike are appropriate for use with currently available 50ml diluent vials. We also recommend that you provide testing to

support that the diluent vial will not leak during normal use of the device after complete penetration of the stopper.

10. You have provided in your response to Question 1 received January 5, 2017, a test report in Annex 18A that states if all components of the Octajet are produced according to the specifications and assembly is done according to validated procedures , the device can properly connect to both vials. We expect that your combination product which includes information on your proposed device that is designed and manufactured per the requirements of 21 CFR 820 Quality Systems Regulations. Please provide a summary of the design controls of the device constituent.

11. In your test report in Annex 18B, you state that the thread on your device should meet ISO 594-1 and ISO 594-2 requirements. Please clarify the meaning of "should" We recommend that you perform testing as per ISO 594 and ensure that your device meets the requirements.

12. You also stated in that due to the specific design of you the device not all defined dimensions can be measured on the final device. We do not agree with your rationale as part of the Design Control requirements we expect that you address all design control issues through the initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that meets the proposed intended use of the final combination product.

13. You have provided in your response received by the Agency on January 23, 2017, that batch analysis for the syringe filter and Octajet. We believe there is a misunderstanding. We expect that you provide lot release documentation to ensure that future devices are verified to meet specifications prior to distributions. Please provide a lot release protocol which will be utilized to verify new devices are manufactured per your specifications. The lot release data should be justified as statistically acceptable.

14. In you Human Factor Study, you stated to mitigate the risk of a leaking product vial after reconstitution a syringe filter was implemented. It is unclear if the product vial was leaking after reconstitution when attached to a syringe or if the user was inverting the product vial upside down after reconstitution. We recommend you assess the cause of the leakage with the product vial attached. We believe that the Octajet is an open luer connector which is expected to leak when inverted and connected to a drug vial. We believe that the leakage can be mitigated by providing clear instructions to the user to connect a syringe prior to inverting the vial to withdraw the fluid. Please review your instructions for use and consider revising them to provide clarity. We are unclear of the purpose of the syringe filter if the syringe is attached prior to inverting the vial.

15. You have provided a leakage test report in Exhibit 18A, the method used to assess leakage testing is unclear within the submission. Please provide the test method

used to assess for leakage and the rationale for use of the method. We recommend you perform air leakage testing to ensure there is no leakage between the vial, transfer device and syringe and the device performs as intended.

Labeling:

16. You have provided labeling for the Octajet device in you January 5, 2017, response. It is unclear if the labeling will be included in your combination product. Please clarify if you intend to include the Octajet device labeling with your combination product.

Stability Data:

17. We are unable to locate stability or shipping validation studies of your copackaged combination product. We expect that you perform assessments of the device constituent over time to assess the system functionality of your device through the drug product expiration. We also expect that to support functionality of your combination product after shipping, that you provide evidence that your system is capable of withstanding the effects associated with shipping which may include temperature excursions, withstanding vibrational and atmospheric effects.

18. You stated in your January 5, 2017, response that additional testing is ongoing. Please provide a summary of additional tests that you are performing on your device. Please note that (b) (4) , and we expect your test reports to be submitted to the BLA. Please also note that we expect that the tests that you have performed to the specifications of your combination product.

The following additional deficiencies are related to the information request response received by the Agency on January 5, 2017:

19. In Annex 1, Device Description, Table 11B, you have provided Specifications and Engineering Drawings for the Octajet and the Exhibit Locations for each drawing. We are unable to locate the Exhibits in your January 5, 2017, response. Please provide the Exhibits for review.

Cleaning, Disinfection, Sterilization, Shelf-Life and Reuse:

20. You have stated that your sterilization method was validated using the (b) (4) method. However, you have not indicated if you intend to perform regular dose audits on your validated sterilization method. Please be advised that per ISO 11137-1, "once the sterilization dose has been established, periodic sterilization dose audits shall be carried out to confirm the continued appropriateness of the sterilization dose. The frequency at which sterilization dose audits are carried out shall be in accordance with ISO 11137-1:2006, 12.1." As stated in ISO 11137-1:2006, "to demonstrate continued validity of the sterilization dose, sterilization

dose audits are carried out at a pre-defined interval of time. Historically, a three-month time interval has been used to detect seasonal variations in bioburden." Therefore, please state the time intervals at which you plan to perform dose auditing on the validated sterilization method.

21. In Annex 4, Section 14- Sterilization and Shelf life you have referenced Exhibit 14A, 14B, 14E, and 13D however we are unable to locate the Exhibits in this response. Please provide the referenced Exhibits to adequately review the information.

Biocompatibility:

22. You have provided justification as to why biocompatibility testing was not performed on the subject device. In the absence of biocompatibility testing, you indicate that testing according to European Pharmacopoeia 01/2009 was performed. However, to demonstrate the pharmaceutical quality of a device, we recommend testing according to USP <661> Containers-Plastics. Therefore, the provided justification is incomplete and additional information is needed to assess the safeness of device. To demonstrate that your device is inert and will not alter the drugs transferred, please provide testing according to USP <661>. Alternatively, if European Pharmacopoeia 01/2009 is comparative to USP<661> testing and specifications, you may provide a thorough comparative analysis between European Pharmacopoeia 01/2009 and USP <661>. The comparison should include justification on how the results obtained from European Pharmacopoeia 01/2009 testing compare to the standard requirements of USP <661>.

23. In Annex 5, Biocompatibility you reference Exhibit 15B which includes the Biocompatibility Evaluation however we are unable to locate this Exhibit in your response. Please provide the location of the Exhibit or provide a copy for review.

24. We have observed that you have provided (b) (4) testing to demonstrate that the device contains acceptable levels of bacterial endotoxins. However, it is not clear whether it is your intent to make non-pyrogenic claims. To support non-pyrogenic claims, bacterial endotoxins and material-mediated pyrogenicity should be evaluated. To evaluate material-mediated pyrogenicity, we recommend USP <151> rabbit pyrogen testing be performed. Therefore, if it your intent to label your device as non-pyrogenic, please provide rabbit pyrogenicity testing according to USP <151> Pyrogen Test.

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. If we receive your major amendment during the last three months of the review period, we will extend the review period an additional three months.

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** February 20, 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
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Senior Regulatory Management Officer

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