From:	Wood, Lorraine
To:	Ammons, Stanley
Subject:	Information Request for BLA 125612: Follow up Information Request from October 6 Telecon
Date:	Wednesday, October 12, 2016 11:09:00 AM
Attachments:	image001.png image002.jpg image003.jpg image004.jpg image005.jpg image006.jpg
Importance:	High

Dear Mr. Ammons,

As a follow-up to our discussion on October 6, 2016, 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 and (b) (4) facilities (BLA STN 125612/0).

I. General Comments

Each BLA is a standalone submission. As we discussed during the telecon, the submission does not have all the information to demonstrate qualification of equipment and validation of the processes to support the manufacturing of fibrinogen at your Vienna and (b) (4) facilities.

1. You listed in *20160323_347_32A13_Annex_OPG_00.docx* all the equipment used for the manufacture of fibrinogen. You indicated that many pieces of equipment were already submitted, reviewed and approved in association with other US licensed products. For these pieces of equipment, please provide a brief description of the equipment and include the STN and approval date of the submissions where the information was initially submitted; also list the most recent re-qualification protocol/report. For other equipment (not associated with US licensed products), please provide description of the equipment and the respective qualification/validation studies and results.

II. The submission has errors and inconsistencies, below are few examples: Please clarify/update

a. The Dirty hold time for vessel (b) (4) is reported to be (b) (4) in the summary table (*20160323_347_32A13_Annex_OPG_00.docx*) which is different than the (b) (4) dirty hold time stated in report *087RPQ15241.000*. Also, you attached study plan *087STD09260.000* as supportive for (b) (4) dirty hold time, when the document does not include information about the dirty hold time.

b. Fibrinogen is filled in 100mL bottle. The bottle is reported to be (b) (4). You stated in report *089PPQR14007.106_US* (p.52), that the (b) (4) bulk is aseptically filled into (b) (4), sterilized 100 mL glass vials (b) (4). However, you reported in document *087RPQ15222.000* that (b) (4) vials are used for (b) (4) and Fibrinogen (Table 6, p 14). Please explain.

c. eCTD title : (b) (4) -ioq-report is applicable to (b) (4)

d. eCTD title: b) (4) - pq-report sterilization is for the maximum load ((b) (4)).

e. eCTD (b) (4) -pq-report life-cycle and b) (4) -pq-report life-cycle; the protocols were attached instead of the reports.

f. You listed in document *20160323_347_32A13_Annex_OPG_00.docx* the dirty and clean hold times for the equipment. However, I noted discrepancies between the listed DHT and CHT provided in this report and the data presented in the submitted reports. Please review and update the data provided to ensure accuracy.

III. <u>Please provide additional information about the following:</u>

-

2. **<u>HVAC system and Environmental Monitoring (EM)</u>**
You reported that you installed (b) (4) new air handling units: AHU (b) (4) , but you did not provide EMPQ to qualify the respective areas. In addition, you did not describe the environmental monitoring program you did not submit environmental monitoring data during the Drug Substance (DS) and Drug Product (DP) production, and filling of the fibrinogen conformance lots and (b) (4) lots (b) (4)). Please provide the qualification of the areas. In addition, please provide the environmental monitoring performed to demonstrate that the different areas are in a state of EM control during the manufacturing of the DS and DP used for the conformance lots. Also provide the EM Data collected during the aseptic filling/transfer to lyo and lyo operations of the conformance lots and .

3. **<u>Bottle/vial washer</u>**: Please provide description, initial qualification/validation and the most recent requalification using 100mL bottles.

4. If the 100mL bottle is (b) (4) , you need to provide qualification of the (b) (4) functionality, and the validation the (b) (4) process for the 100mL vials, to ensure that the equipment (bottle washer) can perform both cleaning and b) (4) (appropriate coverage).

5. **<u>Depyrogenation Tunnel</u>**: Please provide description, initial qualification/validation, and the most recent validation using the 100mL bottles. Also include the validation of the sterilization of the (b) (4) .

6. **<u>Filling line</u>**: filling/stoppering/capping. Please provide description and qualification including b) (4) …

7. (b) (4) : Please provide description, qualification, cleaning, (b) (4)

8. **<u>Transfer area to lyophilizer</u>** b) (4) (additional information submitted in amendment 125612/0.7). You provided report *080RPQ12393.000,* Validation of Bio-decontamination of loading room b) (4) . Please provide information about the (b) (4)

(b) (4)

9. **Crimping and Coding Machine**

a. Please provide a description of the equipment and the qualification/validation of the crimping process and subsequent inspection ((b) (4)) to separate the rejects from the accepted vials.

b. You provided *OPG_VVKM7022_IQOQ*. Please provide narrative and a schematic diagram showing the transfer of the 100mL partially stoppered filled vials from (b) (4) to Lyo b) (4), and the transfer of the lyophilized and fully stoppered vials to the crimping capping station.

c. Please describe the verification steps (inspection of the filled vials by (b) (4), if performed, with justification.

10. **Visual inspection, labeling and packaging**

a. Please describe the visual inspection lines and equipment used for packaging and labeling for fibrinogen.

b. Please describe AQL sampling performed, and results.

c. You stated during the 06Oct2016 telecon, that all (b) (4) conformance batches were visually inspected, packaged and labeled at OPG Vienna facility, and that none of the batches were sent to b) (4), as the equipment were not completely qualified. As we discussed during the telecon, for the (b) (4) facility to be approved for visual inspection, packaging and labeling of fibrinogen, you need to provide data to demonstrate that you successfully validated the visual inspection, packaging and labeling of Fibrinogen at the (b) (4) facility.

-

IV. Qualification of Additional Equipment

-

(b) (4)

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

V. Cleaning and Sterilization

18. Cleaning

a. Please provide data to demonstrate that (b) (4) is worst case soil.

b. Please list all the b) (4) units used for cleaning the equipment used during manufacturing of fibrinogen. Please provide the studies performed ((b) (4)) to demonstrate that the cleaning process covers all product contact surfaces, and provide supportive data.

c. I noted during the review of the cleaning validation studies that (b) (4) is not monitored in the final rinse for several pieces of equipment. Please explain and justify your response.

d. During the 06Oct2016 telecon, we briefly discussed the cleaning of the equipment, and you stated that the (b) (4) inactivation equipment are cleaned in separate areas. However, on page 6 of eCTD *section 3.2.A.1.4, Procedures to Prevent Cross-Contamination*, you reported "*"Dirty" equipment from the* (b) (4) *area as well as* (b) (4) *inactivation area is transferred to room* (b) (4) *(Washing) and cleaned according to written procedures*". Please explain and justify your response.

(b) (4)

Please explain.

-

(b) (4)

g. Cleaning of Lyo (b) (4)

i. Please provide the protocol and results for the studies performed to demonstrate that the (b) (4) covers all areas of the lyophilizer including the (b) (4)

ii. Please provide the (b) (4) cycle parameters for cleaning Lyo (b) (4)

iii. During routine operations, soiling would be the result of a tipped or broken bottle, which is subsequently exposed to the lyophilization process. Please provide the soiling procedure (including soiling locations) and the conditions post soiling (and pre (b) (4)), to verify that the soiling process represents worst case soil.

iv. You reported that (b) (4) sampling is performed at the (b) (4). Please explain the rationale for choosing the (b) (4), and the reasons for considering it worst case location. Please justify your response and provide supportive data.

v. Please clarify if you validated the clean status of the b) (4) which comes in contact with the (b) (4) and justify your response.

vi. You reported that the dirty hold time was verified with (b) (4) on the (b) (4) of the lyophilizer that were subsequently replaced. Please explain the rationale for not repeating the DHT when the b) (4) were replaced and a new validation run was performed.

vii. In report *087RPQ15145.*000, you reported that the (b) (4) is performed after of the Lyo. As will destroy microbial contamination, it is not clear why you consider that this study with

sampling after (b) (4) validates a (b) (4) clean hold time? Please explain and justify your response. Also clarify if the clean hold time is (b) (4) as both are mentioned in report *087RPQ15145.000*.

19. <u>Sterilization</u>

You reported in the BLA submission, that (b) (4) autoclaves are used for the sterilization/sanitization of equipment, and you provided the summary report for the sterilization of b) (4) in autoclave (b) (4):

a. *080RPQ15154.001,* (b) (4) *Sterilizer* (b) (4) *Standard Load 7a "* (b) (4) (b) (4) *" (Maximum Load) Production* , approved 19 Jan 2016.

a. Fig 4 of the report (location of TCs and BIs in Load 7a) did not transfer correctly, please resubmit.

b. Please list if additional equipment is sterilized/sanitized in b) (4). If the validation of the loads and cycles used for the fibrinogen manufacturing equipment have been submitted and reviewed in other submissions associated with US **<u>approved</u>** products, please provide the STN number and approval date; alternatively provide the validation summary reports for the maximum and minimum loads for equipment used during fibrinogen manufacturing, if applicable. Also include schematic diagrams and description/narrative about the placement of Biological Indicators (BIs) and thermocouples (TC) in the load with justification. Please describe the biological indicator used, the number of spores and the Dvalue.

c. Please describe the other autoclave and list the equipment that are sterilized/sanitized in the autoclave. If the qualification of the autoclave and the validation of the loads and cycles used for the fibrinogen manufacturing equipment have been submitted and reviewed in other submissions associated with US **<u>approved</u>** products, please provide the STN number and approval date; alternatively provide the validation summary reports for the maximum and minimum loads, if applicable. Also include schematic diagrams and description/narrative about the placement of Biological Indicators (BIs) and thermocouples (TC) in the load with justification.

d. You reported that the pink (b) (4) rubber stoppers are purchased clean, and are sterilized by (b) (4). Please describe the (b) (4) used and the validation of the b) (4) of the stoppers. Please describe the sampling performed to ensure compliance with sterility and endotoxin specifications.

e. <u>PQ Report 080RPQ15109.000 (</u>(b) (4) <u>of</u> b) (4) <u>)</u>

i. The data provided shows a variation in temperature recording between the different thermocouples and the process sensor, yet you stated that the results met the specification of temperature spread (b) (4). Please explain. In addition, it is not clear from the data presented what was the minimum

pressure ((b) (4)) recorded.

ii. Please describe the biological indicator used, the number of spores and the Dvalue.

f. Sterilization ((b) (4)) of Lyo (b) (4)

i. You reported that Lyo (b) (4) is a (b) (4) Lyo as shown in the (b) (4) PQ report, and a (b) (4) Lyo as referred to in the (b) (4) PQ report PQ Report *080RPQ 15046.000*, where the (b) (4) . Please explain the (b) (4) validation strategy.

ii. Please provide the studies performed and the data to demonstrate that the (b) (4) TCs and (b) (4) BIs were placed in the worst case locations within lyo (b) (4) .

iii. Please clarify what are the parameters for the routine and validation (b) (4) cycle.

iv. The results presented in Table 10 of the report indicate that the (b) (4) is both the Hot and Cold Spot; please explain.

v. You reported that the validation run was performed at the required temperature for (b) (4) ; however the acceptance criterion is (b) (4) . Validation studies are typically performed at worst case conditions; and it is not clear why you would consider a successful (b) (4) . Please explain and justify your response.

vi. You only provided data for one sterilization run – please clarify if this is a requalification run, and provide the dates and summary reports of the previous (b) (4) validation studies using the same (b) (4) unit and cycle.

VI. Please provide additional information about the following Processes:

20. Purification process

a. You reported that the purification of fibrinogen is performed using the production line approved for the pooled plasma product Octaplas® (STN 125416). However the manufacturing of the two products are different. Please explain.

b. Please provide the virus-inactivation achieved using S/D and nanofiltration.

c. Please describe the integrity testing performed for both the Planova and Pegasus nanofilters.

21. (b) (4)

(b) (4)

22. Lyophilization of Fibrinogen

a. You reported that the freeze drying process is monitored by (b) (4)

b. During the 06Oct2016 telecon we discussed the lyophilization process, and you clarified that the fibrinogen clinical lots were lyophilized at (b) (4) facility whereas the conformance lots were lyophilized at the OPG Vienna facility. As the information was not clearly stated in the submission, we agreed that you would provide information to describe the history of the development of the lyophilization cycle (pilot studies, clinical lots and conformance lots).

c. Also during the telecon you indicated that for the lyophilization of fibrinogen, up to (b) (4) shelves can be loaded and lyophilized. However, the conformance lots data showed that (b) (4) was used for each of (b) (4) lots, and (b) (4) shelves were used for the (b) (4) lot. Please provide the data collected using surrogate/product temperature mapping and extended sampling of product of the minimum and maximum loads to validate the lyophilization process of fibrinogen loaded on up to (b) (4) shelves. Please also specify the shelves used for the validation of the maximum and minimum loads.

d. Please provide the studies performed to validate the lyophilization cycle for fibrinogen (number of runs, size of the load, product or surrogate or product/surrogate), and the results of samples collected and tested (location of samples).

e. You reported that the (b) (4) conformance lots were lyophilized at varying shelf (b) (4) to demonstrate robustness of the freeze drying process. You added sampling was performed ((4) vials per frame) with a maximum of (b) (4) frames per shelf. Please describe the loading of the (b) (4) lots and sampling locations (diagrams and narrative), with justification.

f. Please describe, using narrative and schematic diagrams, the loading procedure when the number of vials (per lot) does not completely fill a frame. Would you use empty vials (to complete the number of vials per frame), would the filled vials be placed at specific positions in the frame, etc…? Please justify your response.

g. You reported in validation report *089PPQR14238.106_US*, that "*According to standard operating procedure 084SOP028/12 'Validation of Freeze Drying Process for Freeze Driers* b) (4) *' vials have to be drawn from each frame loaded. However, to enable parallel analyses at Octapharma Vienna (OPG) and* (b) (4) , (b) (4) *vials instead of* (b) (4) *vials were sampled per loaded frame*." Please explain why some samples were sent to b) (4) for analysis. In addition, where would you routinely analyze the samples for fibrinogen? Please explain and justify your response.

h. You also reported **deviation 36817** where the results for solubility samples (using a (b) (4) to deliver the diluent) performed in Vienna did not meet the acceptance criteria, and as such you reported that you accepted the results of solubility testing performed in b) (4) (using a device) as those met the acceptance criteria for reconstitution time. The information presented demonstrates that the reconstitution of the conformance lot samples was not validated at the OPG Vienna facility. Please provide justification for accepting the (b) (4) results. Please provide additional data to demonstrate that the fibrinogen solubility testing performed in Vienna is successfully validated.

i. In validation report *089PPQR14238.106_US* (5.16.1 Process Control Parameters for Process Step Freeze Drying; p 107) the results of the measurement of the) (4) –seems to be in increments of b) (4). Please clarify.

j. Please provide the following documents referenced in the lyophilization validation report: *080STD13183.000* and *080RPQ12375.000.*

k. You stated that the stoppers are pushed down by shelf pressure – please describe how that functionality was qualified. Did you sample vials from the edges and center of the different shelves to demonstrate consistency in the stoppering force? Please explain.

23. Deviations

Please provide additional information about the investigation and corrective action for the following deviations:

a. **Deviation 34822** (classified as minor) reported for batch (b) (4) for the loss of the "(b) (4) "

b. **Deviation 34913** (classified as minor) reported for batch (b) (4) for exceeding the limits for fibrinogen.

c. **Deviation 34941** (classified as minor) reported for batch (b) (4) , regarding the filling of the bottles. Please clarify if the determination of the filling of the vials – Is it by weight or volume, as it seems to be described differently in different reports. What do you mean by this: Filling b) (4) ?

-

24. Container Closure Integrity Testing

a. You stated that the (b) (4) method is used for validation of the container closure. However you reported that the validation report has not been completed yet. It will be completed by the end of 2016. Please explain.

b. You provided the SOP for 100% testing using (b) (4), and the equipment was qualified at (b) (4) settings ((b) (4)) – what is the acceptance criteria. Please clarify what is the maximum allowed number of rejected vials/bottles before rejecting the batch. Have you performed this testing at the end of shelf life to determine the (b) (4) status throughout the shelf life of the lyophilized product?

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 response to this information request as an amendment to this BLA November 4, 2016, referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

The action due date for this file is June 9, 2017.

Please contact me with any questions.

Thank you

Lorraine D. Wood, MS, MLS(ASCP)CM
Regulatory Project Manager

Center for Biologics Evaluation and Research
Office of Blood Research and Review
U.S. Food and Drug Administration
Tel: 240-402-8439
lorraine.wood@fda.hhs.gov

cid:image001.png@01D1C57E.DFA022A0