

From: Trayer, Amanda
Sent: Thursday, June 21, 2018 9:15 AM
To: stanley.ammons@octapharma.com
Cc: 'Serro, Xenia'; Melhem, Randa (Randa.Melhem@fda.hhs.gov); Thompson, Edward
Subject: Information Request for BLA 125668/0-follow up to teleconference on June 20, 2018

Mr. Ammons-

As a follow-up to our discussion on June 20, 2018, the review committee requests that you respond to the items listed below. The information requested is necessary to continue our review For Original BLA STN 125668/0.

The review of this BLA 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 file by July 6, 2018, 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 December 29, 2018.

Cleaning Validation

1. Report 087RPQ16012.000: Cleaning validation for Vessel (b) (4) was performed following soiling with (b) (4) /cutaquir (b) (4) 16.5 %. You reported that the validated dirty hold time is (b) (4) ; however, in the validation run, a DHT of (b) (4) was reported. You justified that the DHT was previously validated for (b) (4) in report 087RPQ09424.000; yet you did not provide the summary report. Please clarify and provide supportive data to demonstrate that cleaning was effective following soiling with (b) (4) /cutaquir (b) (4) 16.5%, and DHT of at least (b) (4) .
2. You provided the list of major equipment and their uses for (b) (4) /cutaquir production in Annex 1. Some of the equipment is used in more than one manufacturing step. Per your protocol, the cleaning validation should verify cleaning following (b) (4) . You clarified during the June 20 telecon that if a vessel is used for more than one step, a cleaning validation run will be performed following (b) (4) . For each vessel that is used in more than one manufacturing step, please list the intermediate(s)/product(s) that contact the equipment surface, and clarify if the cleaning validation (including DHT) following soiling with the respective product/intermediate was performed. Please justify your response.

Environmental Monitoring

3. You provided in the BLA submission a brief description of the environmental monitoring program. Please provide a summary report of the environmental monitoring performed and data collected during the manufacturing of the (b) (4) /cutaquin conformance lots, and the most recent aseptic process simulation (media fill). Please describe any deviations, the investigations and the corrective actions implemented.

Container Closure

4. You reported that (b) (4) /cutaquin is filled in colorless 10mL, 20mL, 30mL, 50mL non-siliconized glass (b) (4) vials, closed with 20mm bromobutyl rubber infusion stoppers, and sealed with aluminum caps. Are these vials, stoppers and caps the exact types /sizes used for the filling of other US licensed products? Please clarify and list the products and respective STNs and approval dates. If not, please provide the studies used for the qualification of the container closure, and the summary reports for their cleaning and sterilization. If the information is already provided in the BLA submission, please list the report numbers.
5. You reported that 20 mm light grey ((b) (4)) Bromobutyl rubber stoppers are used and that they are purchased under the following codes: (b) (4) .
 - a. Please clarify whether the stoppers are tested for endotoxin/bioburden on site, or is it per CoA?
 - b. From your description, it seems that stoppers (b) (4) are washed and sterilized (b) (4) . Please describe the cleaning and sterilization cycle and the validation of the loads.
 - c. Also, describe the sterilization cycle for (b) (4) and the validation of the load. If the information has been provided in association with other US licensed product, please provide the STN number(s) and approval date(s).
6. You reported that the vials are re-examined after (b) (4) years of manufacture. Briefly describe the process and acceptance criteria. What is the shelf life of the vials, stoppers and caps? Please justify your response.
7. You reported that you evaluated the integrity of the container closure using the (b) (4) method ((b) (4)) in two separate stability studies and provided the following intermediate reports: 000SSR991.16P005.01/INT (*media filled vials*) and 000SSR81x.16P011.01/INT (*product filled vials*). You reported that the results passed, yet you did not provide the data (values) obtained for the controls and the test samples. Please provide a summary report of the CCIT data.

Validation of the Filling Process on Line-

8. Report 089PQR15517.103/US was submitted and included summary results of studies performed to demonstrate the homogeneity and consistency of filling for all filling sizes: 6mL, 10mL, 12mL, 20mL, 24mL, and 48mL. In the study, you provided the CpK for each fill volume, and they ranged from (b) (4) , except for the 30mL presentation (20mL fill volume), with a CpK of (b) (4) . Please describe the issues encountered with the 20mL fill volume, and how they were resolved. Please justify your response.

9. You reported that the (b) (4) /cutaquir final drug product (FC) was evaluated (protein concentration and osmolality) throughout the filling operation. Please provide the frequency of sampling to demonstrate filling consistency throughout the operation.

Aseptic Process Simulation (APS)

10. You stated in Report 057RPQ_F4_MF_2015-5-IPQ, that the Aseptic Process Simulation was performed for implementation of new filling sizes, yet the report did not specify the new vial sizes and fill volumes.
- Please clarify which **new** vial/fill sizes were validated in this APS.
 - Also, clarify which of these aseptic process simulations runs were vials filled from (b) (4), and which ones were filled from vessels.
 - You referenced the following two reports for growth promotion testing of the (b) (4) (Report 057RPQ_F4_MF_2015-3 and Report 057RPQ_F4_MF_2015-4). Please provide a summary of the growth promotion testing and results to support the APS study.
11. In report F4_RPQ_K735B99I, you described the results for the simulation of (b) (4) product. The report presents a list of the APS runs performed in 2017, indicating whether the filling was performed from a vessel ((b) (4)) or from a (b) (4). All the APS runs resulted in 0 contaminated final container. However, (b) (4) out of (b) (4) APS runs simulating filling from a (b) (4) resulted in deviations – which were not described. Please describe briefly the deviations associated with the media fills reported in Table 12 of the report. Also include the investigation and the corrective actions (if applicable).

Transport of the Final Product

12. You stated during the June 20 telecon that the ground transport validation studies cover a longer shipping time. You added that you are preparing a protocol for the “shipping to overseas distributors”, and that would be executed with the first shipping of cutaquir after approval. Please provide a description of the shipping protocol, and how it compares to the shipping process for other US licensed products.

Please confirm that you have received this email and contact me with any questions about this Information request.

Thank you-

Amanda

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