

From: Hooban, Christopher
Sent: Friday, October 30, 2015 1:19 PM
To: Ammons, Stanley
Cc: Krammer, Marlene; Cagungun, Nannette
Subject: Information Request (October 30, 2015) - BLA 125587/0

Our Reference: BL 125587/0
Original BLA

Octapharma Pharmazeutika Produktionsges.m.b.H.

Dear Mr. Ammons:

We are reviewing your April 15, 2015 biologics license application (BLA) for Immune Globulin Intravenous, Human 10%. We are providing the following comments and request for additional information to continue our review:

As a follow-up to our discussion on October 29, 2015 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 NewGam (panzyga) at OPG Vienna and ODE Dessau. We agreed the information will be submitted within two weeks, except for those questions that require additional studies.

Dessau Facility

1. In response to Q-1 of 23Sep2015 information request you provided the most recent (October 2015) qualifications of (b) (4) packaging lines ((b) (4) (b) (4)). In these reports you listed the visual inspection equipment, labeler and cartoner used on each line and the vial/bottle sizes that can be accommodated. Packaging line (b) (4) is used for lyophilized products and thus it is not applicable to NewGam.

(b) (4)

(b) (4)

(b) (4)

You also provided the qualification of the following (b) (4) equipment:

- * Summary Qualification Report VAL2015/2-S: (b) (4) for 100 % visual inspection
- * Summary Qualification Report VAL2045/2-S: (b) (4) for 100 % visual inspection
- * Summary Qualification Report VAL2047/1-S: (b) (4) for 100 % visual inspection

a. As we discussed during the 29Oct2015 telecon, it is not clear if all these lines are used for NewGam, and whether the qualification of these lines has been submitted, reviewed by FDA in association with other US licensed products. Please clarify and provide the STN numbers if applicable.

b. Please explain the reasons for submitting the qualification of (b) (4) (not listed as equipment used on the packaging lines); and for not submitting the summary qualification reports for (b) (4) which are used on the mentioned packaging lines. If that was an error, please submit the correct reports.

c. NewGam uses a new bottle size (300mL). You reported in the qualification reports that the cartoner cannot accommodate the 300mL vials. Please describe the process for packaging the 300mL bottles.

d. Please provide studies performed (using the 300mL vials) to demonstrate that the current packaging lines can accommodate the VI, labeling, cartoning and carton labeling of the 300mL bottles.

Vienna Facility

2. In response to Q-2e of 23Sep2015 information request, you reported in Tables 1 & 2 that (b) (4) vials were rejected for lot (b) (4) and (b) (4) vials were rejected for lot (b) (4) due to printing errors. Please provide the investigation and corrective actions implemented.

3. You reported that for filling Line-(b) (4), the bulk solution is sterile filtered and transferred via (b) (4) to the filling Line. In response to Q-3e of 23Sep2015 information request, you stated that "Initial and routine media filling on filling line-(b) (4) were carried out without (b) (4) for bulk storage and transfer. However, starting with calendar week 41/2015 first media fills using (b) (4) with subsequent aseptic filling

were performed on filling line-(b) (4). First media fill on filling line-(b) (4) using (b) (4) covered a filling size of (b) (4) in 10 mL vials and (b) (4) in 50 mL vials, respectively. Additional media fills using (b) (4) are already planned and will be performed until end of 2015”.

a. Please describe the procedure for sterile filtration into the (b) (4) (including the connections) and the transfer of the product from the (b) (4) to the (b) (4) prior to filling.

b. Please describe the media fill studies performed and the results that support this aseptic processing step for filling of NewGam on filling Line-(b) (4).

4. Your response to Q-4 of 23Sep2015 information request was not adequate as you did not explain your statement “The performance qualification (covering process, filling line, and personnel) demonstrated a sterility assurance level (SAL) of (b) (4) recommended by (b) (4) for aseptic processing”. Please explain.

5. You provided in response to Q-7 of 23Sep2015 information request, the IQ/OQ report and the PQ report. However, there was no information provided in the PQ report except reference to the IQ/OQ report (further qualification) and that all deviations were closed. In that section of the IQ/OQ report it states that (b) (4) defective vials for each size were included and they were correctly identified. Please provide the protocol and report for this study.

6. Your response to Q-13 of 23Sep2015 information request regarding the Dirty Hold Time (DHT) is not adequate. For the (b) (4) vessels, you validated the maximum allowable DHT of (b) (4) for only one run on only one vessel. You applied the same principle for the (b) (4) vessels, where you validated the maximum allowable DHT of (b) (4) for only one run on only one vessel. One run on only one vessel is not adequate validation. Please justify your validation strategy.

7. The same is applicable to your response to Q-14 of 23Sep2015 information request regarding the validation of DHT for the (b) (4) vessels (b) (4) vessels. One run on only one vessel is not adequate validation. Please justify your validation strategy.

8. In response to Q-17 of 23Sep2015 information request you provided report 150VRE1529/00 which would provide CCIT (container closure integrity testing) following transport. The information provided about the CCIT is minimal. Please provide the protocol and report for the CCIT to include the positive controls and the critical leak detected. The transport was performed using 20mL vials. Please provide the studies performed to demonstrate container closure integrity for all NewGam vial/stopper presentations.

9. The response to Q-19 of 23Sep2015 information request was not clear. What method do you currently use for container closure integrity testing for NewGam final container at both OPG Vienna and OSA Lingolsheim. Please clarify.

10. As we discussed during the 29Oct2015 telecon the (b) (4) method used for CCIT is not adequate as the method does not test the exposure of the vials to contamination (b) (4) to simulate shipping conditions, and does not identify the critical leak detected. It was agreed that new container closure studies will be performed to address the deficiencies. Please provide the revised protocol and results of studies performed to demonstrate the container closure integrity for the different presentations used for NewGam.

11. As we discussed during the 29Oct2015 telecon, this statement (in 087SOP028.00,

Cleaning Validation: Bottle Washing Machine Filling (b) (4) is not clear. (b) (4)

Please explain.

12. You stated in report OPG SVP (b) (4) PQR 2.0.docx that “(b) (4)

”.

However, you did not clarify in which load these items ((b) (4)) were placed, and whether that load was validated. Please explain and justify your response.

13. In response to Q-11c of 23June2015 information request, you provided report 080RPQ13217.000 “Report Performance Qualification according to Qualification Protocol 080VPQ13217.000 Clean Room "in operation" Filling (b) (4) Change Control CC 7012”. In this report you presented the acceptance criteria and results for the 1st and 2nd campaign which are summarized below:

(b) (4)

(b) (4)

(b) (4)

a. Please explain the pressure acceptance criteria, and why the excursions (way outside the set limits) were acceptable. Please justify your response.

b. In the same report 080RPQ13217.000, you summarized the non-viable data collected during the manufacture of the three batches during the two campaigns and provided the results in Tables 26 – 29 of the report. Excursions in the particle counts ((b) (4)) in the Grade (b) (4) (Class (b) (4)) occurred during the production of the Batches at (b) (4) monitoring locations. However, you decided to (b) (4) the counts over the span of the monitoring, and concluded that the (b) (4) was within the acceptance limits and thus did not raise a deviation or investigate and determine a root cause. Please explain and justify your response.

14. Please provide studies performed (using the 300mL vials) to demonstrate that the current packaging lines at OPG Vienna can accommodate the visual inspection, labeling, cartoning and carton labeling of the 300mL bottles.

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 file by November 13, 2015 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 April 14, 2016.

If you have any questions, please contact me at (240) 402-8376 or christopher.hooban@fda.hhs.gov.

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