

From: Hooban, Christopher
Sent: Wednesday, September 23, 2015 10:14 AM
To: Ammons, Stanley
Cc: Cagungun, Nannette
Subject: Information Request (23 SEP 15) - STN 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:

Dessau Facility

1. The Dessau facility is approved for the visual inspection, packaging and labeling of several US FDA licensed products. However as NewGam is presented in different size vials than those of the already licensed products, please provide the qualification studies performed and the results of the studies (visual inspection, packaging and labeling) to demonstrate that the operations at Dessau can handle the different presentation for NewGam final drug product.

Vienna Facility – Filling Line^(b)₍₄₎

2. Report 089VRE15018.000_US - IVIG 10% (NewGam): Consistency of Filling on Filling Line
(b) (4)

a. In report 089VRE15018.000 there seems to be a discrepancy in the labeling of the conformance lots. On p. 6 of the document, it is stated that “Batches (b) (4), respectively were filled with filling size 5.0 g and batches (b) (4), respectively were filled with filling size 30.0 g”. However, when summarizing the results (p.15): Batches (b) (4) were filled with 5.0g while batches (b) (4) were filled with 30g. Please explain and justify your response. Please send the correct version.

b. (b) (4)

c. (b) (4)

d. (b) (4)

(b) (4)

e. You provided the number of vials rejected during the visual inspection for the different lots. Please provide the number of vials rejected during the filling/stoppering/capping/printing operations and the reason(s) for the rejection.

Vienna Facility – Filling Line-(b) (4)

3. You reported that for filling Line-(b) (4), the bulk solution is sterile filtered and transferred via (b) (4).

a. Please provide the description and validation of the sterile filtration for the bulk that will be filled on filling Line-(b) (4), as well the (b) (4) -filter integrity testing.

b. (b) (4) were used for the bulk associated with the conformance lots manufactured to support qualification of filling Line-(b) (4). Please describe the (b) (4) and provide studies performed and data to support the use of the (b) (4) in the manufacturing process.

c. Please provide media fill studies and results to demonstrate that the (b) (4) can maintain and support aseptic manufacturing.

4. In your response to Q11bi (p. 55/7) of amendment 125587/0/8 regarding the aseptic validation of Line-(b) (4) at the Vienna facility, you stated that “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. Please describe the filling operation to include (b) (4) of the vials, and use of camera(s) for monitoring the filling, stoppering /capping operation. Is there one or more reject stations? Please describe the validated process and specifications. Please describe the frequency of calibration of the (b) (4) stations, counting station and the cameras that monitor the operation.

6. In report OPG_VFVM7031_IQOQ, you reported that the OQ included verification of machinability of the filling machine and filling performance and performance during start mode, verification of the re-dosing, verification of counters and rejects and verification of the machine emptying, and verification of re-stoppering.

a. Please describe these processes and the acceptance criteria and the results obtained to support successful qualification.

b. Please explain “re-stoppering”.

7. You provided protocol and report OPG_(b) (4)_IQOQ for the qualification of the crimping and coding machine (b) (4). Please provide the testing performed to demonstrate the qualification and functionality of the camera system.

8. You provided protocol and report OPG_SVP_LINE_IQOQ for the qualification of the assembled filling Line-(b) (4).

a. Please provide the routine environmental monitoring for the cooling zone in the depyrogenation tunnel.

b. Please provide a summary of the tests performed and data collected during the OQ to verify the functionality of the filling line within the (b) (4).

c. Please explain what you mean by verification of the “(b) (4)

(b) (4) ”?

9. In report 089VRE15012.000/US, IVIG10% (NewGam): Consistency of Filling on Filling Line (b) (4), you presented data to support the filling for the 1.0g and 2.5g filled in 20mL and 30mL injection vials respectively. As NewGam is also filled in 5.0g dose (70mL infusion vial) on filling Line (b) (4) – please provide the data to support the accurate filling of this presentation.

- a. Please clarify whether filling operations on Line (b) (4) incorporate the (b) (4) of each vial before and after filling during routine operations.
- b. There were several deviations raised during the execution of the protocol; please describe the preventive/corrective actions implemented to address the deviations.
- c. Please provide the qualification of the camera and the calibration/testing before and after filling operations to ensure that it is performing as intended.

10. You stated that three runs (PQ_MTC_01 to PQ_MTC_03) were performed for the validation of (b) (4) of MTC and (b) (4) additional runs ((b) (4)) were used for verification of (b) (4) under worst case (b) (4) . Yet the results provided for (b) (4) in report OPG_SVP MTC_PQR_1 (section 7.24; p.24) refer to (PQ_MTC_01 to PQ_MTC_03) for (b) (4) . Please explain.

Vial Washer to support Line (b) (4)

11. For the vial washer, you state that the (b) (4) ; and that the acceptance criterion is (b) (4) . Please justify why the set criterion is so high, considering that the acceptance criterion for (b) (4) , and your testing results showed (b) (4) . Please adjust the acceptance criterion for (b) (4) to meet the standards and the process capability.

Depyrogenation tunnel to support Line (b) (4)

12. Please describe the (b) (4) challenge, (b) (4) recovery, and qualification of Grade (b) (4) in the tunnel.

Cleaning validation

13. For the cleaning validation of vessels (b) (4) , the dirty hold time was evaluated in (b) (4) . The other vessels were not evaluated for the dirty hold time. Please provide and justify your validation strategy. In addition, the dirty hold time was not reported for any of the vessels following routine soiling with product, and no data was reported for cleaning following NewGam 10% production. Please explain.

14. The maximum dirty hold time was also validated for vessel (b) (4) , but not for (b) (4) – please explain and justify your validation strategy.

Sterilization

15. The sterilization of vessels (b) (4) is performed in Autoclave (b) (4) (load (b) (4)). You provided the validation of the minimum load. Please provide the validation of the maximum load.

Deviations

16. During the validation of filling Line (b) (4) and filling Line (b) (4) two deviations were raised due to the gloves failing integrity testing:

- * Line (b) (4) : Deviation 37317, (b) (4) failed integrity testing following filling of batch (b) (4)
- * Line (b) (4) : Deviation 37388, (b) (4) failed integrity testing after filling batches

(b) (4)

Please describe the investigations and provide the corrective/preventive measures implemented to avoid/reduce such incidents in the future

Container Closure

17. You reported that in accordance with transport validation protocol 150VPR1308, the container closure integrity will only be tested in the course of the (b) (4) transport validation. Please explain the reasons for performing CCIT following the (b) (4) and not the (b) (4) validation studies and justify your response.

a. You also stated that the results of the (b) (4) transport validation, including the CCIT will be summarized in a final report by the end of September 2015. Please submit the report when it is completed.

18. These studies consist of ground transportation, and do not include air-freight which presents different conditions/challenges. It is not clear from the submitted material whether you plan to perform CCIT following air-freight. Please clarify and justify your response.

19. You reported that the container closure integrity of the final container for NewGam (different presentations including (b) (4) stoppers) is “investigated by (b) (4) with the (b) (4)”. You provided report 009VAL193 (b) (4) (approved 02 Jul 2015). Please clarify when the (b) (4) test method was implemented. Please describe the CCIT validated and tested prior or during the manufacture of the conformance lots in 2013? Please explain and provide supportive data.

20. You use the terms infusion and injection to describe the bottles and stoppers. Please explain the different terminologies and provide a clear and detailed description of an infusion bottle or stopper, and an injection bottle or stopper.

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 October 15, 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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