

From: Hooban, Christopher
Sent: Thursday, June 11, 2015 7:25 AM
To: Ammons, Stanley
Cc: Cagungun, Nannette
Subject: Information Request - BL 125587/0; Original BLA; Octapharma; ADD 14-APR-2016

Our Reference: BL 125587/0

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 determined that the following information is necessary to continue our review:

OSA Lingolsheim, France – Information Request

Equipment Cleaning and Sterilization

1. The information in the BLA submission included a very brief summary of the results for various cleaning validations. As these summaries do not provide sufficient information for us to evaluate your cleaning validations for equipment used in the manufacture of NewGam at OSA, please provide the following:

a. Validation protocols and reports for equipment cleaning validations to include the number of runs per piece of equipment, the soiling agent (and why it is worst case), the cleaning steps and conditions (and why they are considered worst case), the rationale for samples collected and an explanation as to why (b) (4)

sampling was not included for every piece of equipment. Additionally, please provide the rationale for not conducting (b) (4) sampling.

b. Justification for not testing for the (b) (4) during the vial washing validation (only a (b) (4) study was included).

c. For the equipment washing machines, please provide the cleaning validations for the different loads.

d. A description of routine cleaning (step-by-step to include time, temperature, pressure, and flow), reagents (and their concentration), and the drying methods for each piece of equipment.

e. For each validation study, please include all deviations and how they were investigated and resolved.

2. A number of non-US approved products are manufactured in the Lingolsheim (OSA) facility. Please clarify whether non-US approved plasma is used in the manufacture of these products. Additionally, please clarify if any equipment is shared between products containing US and non US plasma. If so, please provide the validation for prion (mitigate TSE concerns) removal during cleaning of shared equipment that is in contact with US and non-US plasma and its fractionation intermediates.

3. With regard to sanitization, sterilization, and depyrogenation of equipment, your BLA submission included brief summaries of the studies conducted for equipment used in the manufacture of NewGam at OSA. As these summaries do not provide sufficient information for us to evaluate your processes, please provide the

following:

- a. Protocols and summary reports for validation of the sanitization and sterilization of equipment. This should include qualification of the autoclaves (including empty chamber mapping) and validation of the sterilization cycles for the different loads (if applicable). Please include the number of runs per load per autoclave or (b) (4) per tank/piping, the location of the TCs (and BIs if applicable), and the rationale for choosing these locations as worst case. Please provide justification for the validation cycle parameters and indicate how they compare to routine sterilization parameters. Additionally, please include any deviations and how they were investigated and resolved. Were any repeat validation runs performed to ensure that the issues were resolved?
- b. A description of the BIs (type and number of spores) used to include D-value, Z-value, and vendor.
- c. The validated sterile hold time.
- d. A description of the depyrogenation tunnel and its qualification (including cleaning/sterilization of the cool zone). Please provide the protocols and summary reports for validation of the depyrogenation of the different vial sizes with schematic representation of the TC and EI locations in each run (and the rationale for each location as worst case). Additionally, please provide a description of the EI used as well as summaries of the endotoxin recovery studies conducted to ensure accuracy of the log reduction.
- e. Conditions/parameters for the routine depyrogenation process and how these compare to the validated process.

4. For each piece of equipment, please provide (in tabular format) the following information: method of cleaning, method of sanitization/sterilization, dirty hold time, clean hold time, and sterile hold time.

5. Please provide the revalidation protocols for cleaning (b) (4), the equipment washing machine, the vial washer, and the manual cleaning process), sterilization (b) (4) and autoclave), sanitization/disinfection (b) (4) and autoclave), and depyrogenation/dry heat.

Line Clearance

6. Please provide line clearance procedures associated with the production of NewGam. Please clarify whether rooms, working surfaces, and equipment are cleaned between different batches of NewGam or only between manufacture of different products. Please justify your response.

Aseptic Process Validation/Process Validation

7. Please provide the following SOPs associated with the performance of media fill simulations: 711SOP008, 711SOP009, 757SOP040, and 757SOP032.

8. Please provide a list of the media fill simulation studies conducted to support validation of the NewGam aseptic manufacturing processes. Additionally, please provide the aseptic media simulation protocol for the initial validation and the (b) (4) requalification of the aseptic process (Document No. 757PQP005/23).

9. Please provide the report from the second media fill test (MFT) run (March 2015) conducted in accordance with protocol 757PQP005/23.

10. You reported that Fill Line (b) (4) in the OSA facility is utilized for filling of NewGam and

other non-US approved products; however, it is not clear what conditions (e.g., (b) (4) filling) and vials and stoppers ((b) (4)) are applicable to NewGam. Please provide the aseptic manufacturing operation for NewGam to include container closure (different presentations and stoppers), filling equipment, filling time, single or double aseptic filling operations, and maximum number of vials filled per presentation.

11. Please provide the protocol and report for the validation of sterile filtration of NewGam prior to filling. Additionally, please provide the SOPs and study results to demonstrate sterile filter integrity before and after sterilization.

12. Please provide the qualification of the filling equipment to include changes to the format parts needed to accommodate different vial sizes.

13. Please provide the normal/maximum/minimum batch size for each of the six NewGam presentations.

14. For the conformance and validation batches filled at the OSA and Vienna (OPG) facilities, please provide the lot number, the number of vials filled per size, the number of vials that were visually inspected, and the number of vials that passed visual inspection criteria.

15. Please provide clarification of the visual inspection activities performed at the OPG and Dessau, Germany (ODE) facilities. Specifically, do both facilities conduct primary (100%) visual inspection activities for all NewGam vial presentations? Are the processes and equipment identical?

16. With regard to prevention of cross-contamination, you stated that after processing, the respective bulk solution is transferred (b) (4) to the department of aseptic production. Please confirm which process applies to production of NewGam.

Container Closure for both OSA and OPG (Vienna) – Information Request

17. In the submission, you stated that the vials used for Vienna Line-^{(b) (4)} are (b) (4). However, the vials for Line-^{(b) (4)} are only (b) (4). Please clarify why there is a difference between the two filling operations, and how that would impact the container closure and product. Please provide data and justify your response. Also, clarify whether the vials filled at OSA are (b) (4) as well. Please justify your response.

18. You also stated that stoppers used for filling on Vienna Line-^{(b) (4)} are (b) (4) to sterilize, or the stoppers (b) (4) sterilization. Please explain the use of two types of stoppers, and provide data to demonstrate that the difference has no impact on the container closure and final product. Please justify your response.

19. You reported in the submission that the stoppers used at OPG are 20mm or 32mm light grey ((b) (4) coating), while the stoppers used at OSA are 32mm light grey ((b) (4)). Please explain why different stoppers are used at the two facilities.

20. Stability data is supportive of container closure integrity; however, it is not sufficient to validate the process. You need to provide the protocol and results for container closure integrity testing to demonstrate that the different combinations of vials

(different sizes with some (b) (4) and some not), and stoppers (different sizes and coatings) maintain integrity during handling, transportation and throughout the shelf life of the products. Please provide data to support the minimum critical leak detected ((b) (4)), and the sensitivity of the CCIT method.

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 June 26, 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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