

From: Thompson, Edward
Sent: Wednesday, July 17, 2013 2:28 PM
To: 'Jennifer Spinella (jspinella@raretx.com)'
Cc: Waites, Nancy; Kennedy, Michael
Subject: Information Request for BL 125488/0

Contacts: Jennifer Spinella

Dear Ms. Spinella:

We are reviewing your March 16, 2013 biologics license application (BLA) for Crotalidae (pit viper) Immune F(ab')₂ (Equine) Injection. We are providing the following comments and request for additional information to continue our review:

Drug Product

1. In section 3.2.P.5.6, sterility test, (b) (4) are referenced. Please indicate which (b) (4) test is used for sterility testing? In addition, for pyrogen testing you reference 21 CFR 613.13, which does not exist. Please clarify if this was a typographical error and you meant to reference 610.13 (b) in addition to (b) (4)

Multi-product Facility

2. You provided a list of major equipment used in the manufacture of the drug product and indicated which equipment was shared or dedicated. Please provide a list of the other products manufactured in the facility.

Environmental Monitoring Qualification for the (b) (4) Facility

3. You state the following in the description of the EM qualification of the (b) (4) facility: "It is important to mention that the floor plan above corresponds to the plan that will be effective (b) (4) Please indicate when the (b) (4) (b) (4) is scheduled to occur.

Equipment

4. Cleaning validation studies were only provided for the lyophilizer. Please provide cleaning validation studies for all major product contact equipment used in the manufacture of the drug product.

Shipping of Drug Product

5. In Section 2.3.P.2.4.1 and 3.2.P.2.4.1 you state that a partial shipping validation report for the shipping results of winter 2012-2013 will be submitted to the BLA. Please submit the report.
6. Please indicate what would happen to the shipment if there was evidence of a deviation in temperature, humidity or impact requirements.

7. Please provide additional information on the monitors placed on the shipping containers. Please specify how often they are calibrated and if they are on a preventive maintenance schedule.

Receipt of Drug Substance from Tlalpan

8. Please describe the maximum length of storage time and the storage conditions for the drug substance once it is delivered from the Tlalpan facility to the (b) (4) facility.

Autoclave

9. In reference to Pro-Val-005, Performance Qualification (PQ) Protocol of the Autoclave (b) (4) Code : (b) (4) please submit the following:
 - i. Only the results for autoclave load patterns 4 and (b) (4) were submitted to the BLA. Please submit the results for patterns 1-3 to the BLA. Please also clarify which load pattern the filling needles are part of.
 - ii. The PQ of the load patterns states that a heat penetration study was performed; however, based on the description provided, it seems as if the (b) (4)

 - iii. Please identify the validated autoclave cycles including process parameters for each validated load pattern. The process parameters would include duration of sterilization time, sterilization temperature, time to obtain sterilization temperature, pressure and vacuum cycles, cool down time, etc.
 - iv. Please indicate if empty chamber mapping of the autoclave was performed and provide a short summary of the mapping results and the procedure for the temperature mapping.
 - v. Please indicate if there were any deviations during the execution of the PQ for the autoclave and describe any investigations, if applicable.

Filling

10. For the qualification of the filling line, it is unclear if the weight check station was qualified. Specifically, filled vials deviating from the acceptable fill range are removed at the reject station. If a vial fails the weight check, (b) (4)
 Please provide the qualification for the weight check station.

11. The stopper (b) (4) described as placing the (b) (4). Since the vials are lyophilized, please clarify how the partial insertion of stoppers into the vials was qualified. It also is unclear if stopper placement was qualified along with the filling qualification. Based on the description provided in the BLA, only weight verification was performed for the filling PQ.
12. Please indicate if the fill line, capping machine and the lyophilizer are physically separated from the surrounding room.

Crimping Machine

13. In the description of the crimping machine, you state the machine has the ability to (b) (4). The qualification of this capability was not included in this application. Please provide a description of the qualification and the results.
14. The vials are not capped and crimped (b) (4) as described in the application. Please provide a description of the process of how vials are (b) (4).
15. Please indicate if the crimping process is a manual or an automated process for the lyophilized vials.
16. Please specify the process settings for the crimping machine, as applicable, for main drive speed, plunger pressure, cap rotation, seal pressure, etc. Please indicate if residual seal force testing was performed.
17. Please confirm the installation qualification and the operational qualification for the capping machine were performed by providing the dates they were performed and please confirm that any deviations, if applicable, were appropriately investigated and closed out.

Dry Heat Oven

18. Information regarding the dry heat oven appears to be missing from the application. Please indicate the location of this information in the BLA or provide the information to the application.

Vial Washer

19. In PRO-VAL-004/I Performance Qualification (PQ) of the Vials (b) (4), you state that minimum operating conditions were used during the studies. Please specify the minimum operating conditions. In addition, please provide the operating conditions used during routine production.
20. Please indicate the quality specifications for the (b) (4) the vials.

21. Please specify the water quality used for washing and rinsing of the vials; specifically, is (b) (4) water used for the final rinse?
22. In your description of the washing process you state, in summary, the vials are (b) (4) (b) (4) “with different means of cleaning and treatment”. Please provide a more detailed description of the “different means of cleaning and treatment”. Are cleaning agents used?
23. Please indicate if you have bioburden or endotoxin specifications for vials (b) (4)

Depyrogenation Tunnel

24. The summary report for the Performance Qualification of the depyrogenation tunnel is incomplete. Please prove a short summary of the following:
- i. Temperature Distribution Mapping
 - ii. (b) (4) Temperature Verification and Temperature Control Verification
 - iii. (b) (4) Temperature Profile Verification
 - iv. (b) (4) Testing and (b) (4) Challenge
 - v. Dry Heat (b) (4) Testing
 - vi. (b) (4) Reduction Testing

Compressed Air

25. It appears that the qualification reports included in the BLA for the compressed air are for the Tlalpan facility only. Please indicate the location of the qualification information for the compressed air for the (b) (4) facility in the BLA or please submit the information to the application.

Container Closure

26. Please specify if a bioburden and endotoxin specification exists for the incoming vials and stoppers.
27. In sections 2.3.P.5.2.20 and 3.2.P.5.2.20 Leak Test M-FQ-030, (b) (4) different methods of leak testing of the final container are described. Please indicate which leak test is used for the Anavip final product.

Environmental Monitoring

28. Environmental monitoring (EM) results performed during some qualification studies could not be located in the application. Please provide the following EM results or specify where in the submission the information can be located:

- i. Qualification of the ^{(b) (4)} system (water specification results for the (b) (4) (b) (4))
- ii. Qualification of the Compressed Air System (for use in (b) (4))

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 August 7, 2013 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.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is March 18, 2014.

Please send an email message acknowledging receipt of this request.

If you have any questions, please contact me at (301) 827-9167.

Sincerely,

Edward Thompson
Regulatory Project Manager
FDA/CBER/OBRR/DBA/RPMB