

**From:** Thompson, Edward  
**Sent:** Friday, November 15, 2013 11:02 AM  
**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')<sub>2</sub> (Equine) Injection. We are providing the following comments and request for additional information to continue our review:

1. The following questions are based on Amendments 14, 16, 28, and 29 which were submitted to STN 125488/0.

**a. Amendment 14 (response to IR dated 21 Jun 2013)**

**Response to question #7**

- 1) In your summary description for the cleaning of the (b) (4) tank used to hold the (b) (4) (b) (4), which is shipped to Tlalpan for use in manufacture of Anavip, you state that the final rinse of the tank post-cleaning uses (b) (4). This is not acceptable. The final rinse of the (b) (4) tanks should be with (b) (4). Please confirm that the final rinse of the tank will be with (b) (4).
- 2) Please provide the following information:
  - a) clean hold time for the (b) (4) tanks
  - b) hold time between cleaning and sanitization
  - c) hold time between sanitization and filling the tank with (b) (4)
- 3) Please clarify what is meant by the terms “sanitizing identification, and verification, (b) (4) final rinsing, assembly, identification, verification, validity and registration.”

**Response to question # 8**

- 4) For process tank (b) (4) please clarify what product was used to evaluate the cleaning and sanitization of the tank. Please indicate the validated dirty and clean hold times.
- 5) The following abbreviations were not defined. Please define the following: (b) (4)

**b. Amendment 16 (response to IR dated 17 Jul 2013)**

**Response to question #4**

- 1) This response is NOT acceptable. Some type of cleaning validation must be performed on the equipment even if it is dedicated to a specific product. You still must demonstrate effective cleaning procedures since this may have an impact on sterilization of the equipment prior to the next fill due to any residual dirt which may harbor bacteria or shield it from complete steam penetration. Bioclon still needs to have clean and dirty hold times, and hold times post-cleaning prior to sterilization, and sterile hold times for the (b) (4) and other product contact equipment. Please indicate if any type of sampling, such as rinse water sampling, was performed to confirm equipment was clean and any detergents used were fully rinsed away.

**Response to question #9i**

- 2) The sterilization time for Load Pattern 1 was (b) (4). The sterilization time for Load Pattern 2 was (b) (4). Please provide an explanation for the changes in sterilization times within Load Pattern 1 and Load Pattern 2.

**Response to question #9iii**

- 3) A time to reach sterilization temperature was originally requested for each load. This information was not provided. Please provide the requested information.
- 4) The sterilization time listed for Load Pattern 1 is (b) (4); however, Load Pattern 1 was validated for a minimum of (b) (4). Please explain why the sterilization time used for routine sterilization of Load Pattern 1 is less than the time that was validated.

**Response to question #16**

- 5) After the list for the operation parameters for the crimping machine, there is a note stating, (b) (4).  
" Please define the term "vensor".

**Response to question #22**

- 6) Please define "PW". In one instance in your response it is defined as purified water and in another instance it is defined as potable water.

**Response to question # 25**

- 7) I am unable to locate the document "*Compress Air Summary for* (b) (4)." The link to the document is broken and I am unable to find the document within the documents contained in 3.2.A.1 in the original submission. Please fix the link, provide the exact title of the document, or provide the document.

**Response for 28ii**

- 8) Your response is unclear. You state, “*Compressed air is used for the* (b) (4) .” Did you intend to state that compressed air is not used for (b) (4) process?

**c. Amendment 28 (response to IR dated 07 Oct 2013)**

**Response to question 2a**

- 1) The media fill batch product record was translated as requested. I have the following questions about the media fill since the BPR is deficient in the description of the media fill:
  - a) Please indicate if a line stoppage was simulated. If so, how long was the stoppage? Please indicate if your filling SOP, or other applicable SOP, describes the procedure for operators to follow during a line stoppage.
  - b) It is unclear if during a line stoppage or during a change in differential pressure if any vials are removed from the line. Please comment.
  - c) There is no indication in the BPR when personnel are monitored so I am unable to determine if there was any personnel monitoring. We would expect personnel monitoring, at a minimum, in the following areas: after set up of the filling line, after adding stoppers to the stopper bowl, after any intervention to the fill line such as removing vials or clearing a jammed line. Please indicate when personnel monitoring took place.
- 2) The BPR does not capture who sets up the filling machine or capping machine. It also does not capture who adds stoppers to the (b) (4) . Please revise your batch record to capture all critical information.
- 3) Please provide the sterile hold times for filling parts and stoppers. Please indicate if these times were challenged during the media fill.
- 4) Please indicate if (b) (4) of bulk drug substance can be used for the filling of a lot. If so, was this simulated during the media fill?

**Response to question 2b**

- 5) The results for personnel monitoring of the (b) (4) filling operators were provided as requested; however, there is no indication of when the monitoring occurred since it is not captured in the BPR. Please indicate when the personnel monitoring occurred during the media fill.

**d. Amendment 29 (response to IR dated 17 Oct 2013)**

**Response to question #2**

- 1) In your response, you indicated that the acceptance criteria are based on statistical analysis of (b) (4)

(b) (4) The specifications are only the preliminary specifications set until you have manufactured at least (b) (4) lots of Anavip in the (b) (4) (b) (4) and then the specifications will be subject to review. The specifications were set for the vials that are filled in the Tlalpan facility which is a (b) (4) crimping process. The process in the (b) (4) facility is an (b) (4) fill and crimp capping process. Please indicate if an AQL sampling for visual inspection is being performed for the final container (vial) after the 100% visual inspection and prior to release? If so, what are your sample size and acceptance limits?

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 December 6, 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