

Appendix 3

Review of Amendment 14 - Responses to Information Request Dated 21 June 2013

Recommendation: I reviewed the response in Amendment 14 and request an Information Request be sent. The remaining responses are acceptable.

Review

The FDA questions are in **bold** font and Bioclon's responses are in *italicized* font.

Drug Substance

1. **The equipment information provided in the BLA was for the equipment qualification studies from 2009 – 2010. Please provide the most recent requalification summary reports for the following equipment to demonstrate the equipment has been run in a controlled manner and as qualified. Please include in the summary acceptance criteria and discuss any deviations that occurred, if applicable.**
 - a) **Depyrogenation Oven, Oven (b) (4)**; specifically, the load pattern used for the depyrogenation of the (b) (4) containers used to (b) (4)
 - b) **Autoclave Type (b) (4)** specifically, the load pattern(s) for the (b) (4) container, and the (b) (4)

Instituto Bioclon Response:

The most recent requalification summary reports for Depyrogenation Oven, Oven (b) (4) specifically, the load pattern used for the depyrogenation of the (b) (4) containers used to (b) (4) and Autoclave Type (b) (4) specifically, the load pattern(s) for the (b) (4) container, and the (b) (4) (b) (4) are included in 3.2.A.1 Facility and Equipment; Equipment; Tlalpan Facility. See Files: update-(b) (4) and update-autoclave-(b) (4)

FDA Response: This response is acceptable. I have reviewed the documents provided in response to Question 1a and 1b and find them to be acceptable. The equipment remains in working condition and the load patterns are still acceptable. Of note, however, is the load pattern for Load 13 of the autoclave has changed by (b) (4). The acceptance criteria for the load continue to be met.

FDA Review

Question 1a:

I reviewed the summary document, DRY HEAT OVEN, (b) (4), and found it to be acceptable. The summary report was specific for Load 3 which is the load pattern for the

depyrogenation of the (b) (4) used to (b) (4). The summary report provided a picture of the (b) (4) in the dry heat oven and the load consists of (b) (4). These are the only items in the dry heat oven for that load. The parameters for the Load 3 cycle are the following:

PARAMETERS:

- (b) (4)

The re-qualification for the oven was performed in Dec 2011 and (b) (4). The next scheduled re-qualification is to be performed (b) (4).

The documents referenced in the summary are the following. The documents were not provided, but the summary data for the three cycles ran for Load 3 were provided.

Document Reference	
Protocol for the validation process of the depyrogenation Dry Heat Oven (b) (4)	PROVAL-158-11
Report for the validation process of the depyrogenation Dry Heat Oven (b) (4)	
Temperature distribution profile for the Depyrogenation Dry Heat Oven	PROVAL-152-12
Report for the validation process of the depyrogenation Dry Heat Oven (b) (4)	

(b) (4)

(b) (4)

Conclusions

(b) (4)

Reviewer Comment: I reviewed the summary document, DRY HEAT OVEN, (b) (4) and found it to be acceptable. The summary report was specific for Load 3 which is the load pattern for the depyrogenation of the (b) (4) used to (b) (4) e. All acceptance criteria were met. (b) (4)

FDA Review:

Question 1b:

I reviewed the summary document, Autoclave (b) (4) Load 5 and Load 13, and found it to be acceptable. The summary report was specific for Load 5 and Load 13. The descriptions of the loads are provided below in the review memorandum.

Autoclave (b) (4) Load 5

The summary report provided a picture of the items in Load 5 as they are in the autoclave. Load 5 is the load which contains the (b) (4). The load consists of the following:

DESCRIPTION for Load 5:

- (b) (4)

The parameters for the Load 5 cycle are the following:

PARAMETERS:

- (b) (4)

- (b) (4)

The re-qualification for the autoclave was performed in Nov 2011 and (b) (4) . The next scheduled re-qualification is to be performed (b) (4) .

The documents referenced in the summary are listed below. The documents were not provided, but the summary data for the (b) (4) cycles ran for Load 3 were provided.

Document Reference	
Protocol of the validation for sterilization process by (b) (4) in an Autoclave	PROVAL-155-11
Report of the validation for the sterilization process by (b) (4) in an Autoclave (b) (4)	
Report of the validation for the sterilization process by (b) (4) in an Autoclave (b) (4)	PROVAL-150-12

(b) (4)

(b) (4)

Conclusions

All acceptance criteria were met for Load pattern 5. All (b) (4) bioindicator results were (b) (4) and all thermocouples met the specifications for temperature. No deviations were recorded by Bioclon.

Reviewer Comment: I reviewed the summary document, Autoclave (b) (4) Load 5, and found it to be acceptable. The summary report was specific for Load 5 which is the load pattern for the (b) (4) container. All acceptance criteria were met. (b) (4)

Autoclave (b) (4) Load 13

The summary report provided a picture of the items in Load 13 as they are in the autoclave. Load 13 is the load which contains the (b) (4) . I note that the load pattern was changed

during the requalification of the load in 2013. The change consisted of the (b) (4) to the load.

The load for 2011 and 2012 consisted of the following:

DESCRIPTION for Load 13:

- (b) (4)

The load for 2013 consisted of the following:

DESCRIPTION:

- (b) (4)

The parameters for the Load 13 cycle for all years are the following:

PARAMETERS:

- (b) (4)

The re-qualification for the autoclave for Load 13 was performed in May 2011, (b) (4). The next scheduled re-qualification is to be performed (b) (4).

The documents referenced in the summary are listed below. The documents were not provided, but the summary data for the (b) (4) cycles ran for Load 3 were provided.

Document Reference	
Protocol of the validation for sterilization process by (b) (4) in an Autoclave	PROVAL-081-11
Report of the validation for the sterilization process by (b) (4) in an Autoclave	PROVAL-074-12
Report of the validation for the sterilization process by (b) (4) in an Autoclave	
Protocol of the validation for sterilization process by (b) (4) in an Autoclave	PROVAL-064-13
Report of the validation for the sterilization process by (b) (4) in an Autoclave	

(b) (4)

(b) (4)

Reviewer Comment: I reviewed the summary document, Autoclave (b) (4) Load 13, and found it to be acceptable. The summary report was specific for Load 13 which is the load pattern for the (b) (4). The load pattern was changed in 2013 by the (b) (4) (b) (4) to bring the total of (b) (4) autoclaved in the same load to five. All acceptance criteria were met. All (b) (4)

2. Please indicate if there have been any changes to the equipment cleaning procedures since cleaning was initially validated.

Instituto Bioclon Response:

Yes, there have been several changes on the Standard Operating Procedures related to the cleaning of equipment procedures. An update of the cleaning validation and a short description of the changes are included in 3.2.A.1 Facility and Equipment; Equipment; Tlalpan Facility: update-eq-cleaning-proc

FDA Response: This response is acceptable. I do not have any further questions or comments.

FDA Review

I reviewed the document, “Status Report of the Cleaning and Sanitization Validation Process of the Equipment Used in the Manufacture of the Fabotherapics Products” dated June 2013, and found it acceptable. No changes to the cleaning process itself occurred. Only changes to the SOPs for updating the “Valid date” and updating some wording occurred. Although Bioclon’s statement that there have been changes to the cleaning procedures is technically correct, they misunderstood the scope of my query. I was asking in reference to the specific cleaning procedure / process itself and not so much in relation to changes to the SOPs specifically. Bioclon provided a summary report for the requalification of the manual cleaning procedures for the equipment in Tlalpan. The report concluded that based on test results after cleaning, the

current cleaning procedures are acceptable for the cleaning of the equipment. No changes to the actual procedure itself were necessary and the current cleaning procedures are still acceptable.

3. Please provide a list of other products manufactured in the Tlalpan facility and indicate if the equipment used in the manufacture of Anavip is dedicated or shared.

Instituto Bioclon Response:

A list of other products manufactured in the Tlalpan facility and statement if the equipment used in the manufacture of Anavip is dedicated or shared is provided in 3.2.A.1 Facility and Equipment; Equipment; Tlalpan Facility: list-of-other-products

FDA Response: This response is acceptable. Bioclon provided a list of equipment and a list of products manufactured in the facility. There are no changes to the list of shared equipment and products manufactured in the facility since the approval of Anascorp in 2011.

4. The utility information provided in the BLA was for qualification studies performed in 2009 – 2010. Please provide the following information, since 2012, to demonstrate the facility and utilities have been run in a controlled manner and as qualified:

- a) **Summary of EM data for the manufacturing rooms and aseptic area including a summary of any major deviations and their investigation. Please include acceptance criteria.**
- b) **Summary of testing results for the (b) (4) used in manufacturing including a summary of any deviations and their investigations. Please include acceptance criteria.**

Instituto Bioclon Response:

Summary of EM data for the manufacturing rooms and aseptic area including a summary of any major deviations and their investigation is included in 3.2.A.1 Facility and Equipment; Facility: update-em-2012.

Summary of testing results for the (b) (4) used in manufacturing including a summary of any deviations and their investigations is included in 3.2.A.1 Facility and Equipment; Facility: update-(b) (4)-2012.

FDA Response: This response is acceptable.

FDA Review

I reviewed the following documents:

Trend Analysis of the Results of Environmental Monitoring in the Manufacturing and Aseptic Area for Production of the Anavip Product

This document was a trend analysis of the microbiological results obtained during routine environmental monitoring of the manufacturing areas and Aseptic Area (b) (4) for Anavip. The monitoring period analyzed for the Aseptic Area (b) (4) covered August 23, 2012 to July 01, 2013 while the data analyzed for the manufacturing areas for the bulk drug substance covered January 2012 to June 2013.

All results met predetermined specifications for the area of classification. The rooms continue to meet room classifications and the cleaning procedures continue to be effective. No deviations were noted by Bioclon.

Trend Analysis of the Results from the (b) (4) Chemical Analysis Used in the Manufacturing of Fabotherapics Products

This document was a trend analysis of the chemical and microbial results for (b) (4) in 2012.
(b) (4)

- 5. Please list any changes or improvements in the manufacturing processes or facility for the manufacture of the (b) (4) bulk drug substance since 2011.**

Instituto Bioclon Response: There have been no changes in the manufacturing process or the facility for the manufacturing of the (b) (4) Bulk Drug Substance since 2011.

FDA Response: This response is acceptable.

- 6. Please provide a short description for the procedure for receipt and storage of the horse plasma at the Tlalpan facility.**

Instituto Bioclon Response: A short description for the procedure for receipt and storage of the horse plasma at the Tlalpan facility is included in 3.2.A.1 Facility and Equipment; Facility: rec-and-storage-horseplasma.

FDA Response: This response is acceptable. I reviewed the provided summary of the procedure and it is similar to the procedure for transport of the (b) (4) bulk drug substance from Tlalpan to (b) (4). The plasma is transported in (b) (4) and QA is involved in oversight of the shipments. All shipping and receipt are documented.

- 7. The (b) (4) is manufactured at the (b) (4) facility and transported to the Tlalpan facility for use throughout the manufacturing process. Please provide the following information:**

- a) Description of the tank used to hold the (b) (4)**

- b) A summary of the tank cleaning and sterilization validation including any deviations and investigations, if applicable
- c) Summary of the qualification studies for the expiration date of the (b) (4)
- d) Summary of the procedure for shipping and receipt of the (b) (4) from (b) (4) to Tlalpan

Instituto Bioclon Response: A description, summary of cleaning and sterilization, summary of qualification for the expiration date for using the (b) (4) and a summary of the shipping receiving is included in 3.2.A.1 Facility and Equipment; Facility: (b) (4) -desc-summary

FDA Response: Some points of this response need to be clarified. The following was included in an IR dated 15 Nov 2013:

In your summary description for the cleaning of the (b) (4) tank used to hold the bulk (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) water.

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)

Please clarify what is meant by the terms “sanitizing identification, and verification, (b) (4) (b) (4) final rinsing, assembly, identification, verification, validity and registration.”

FDA Review:

I reviewed the document provided, Cleaning, Sanitization, Shipment and Receipt of (b) (4) Tanks Grade (b) (4) and found it to be acceptable with the exception of the final rinse step in the cleaning procedure where the final rinse of the tank post-cleaning is with (b) (4) (b) (4). The final rinse should be with (b) (4) since the tank will be holding (b) (4) (b) (4). The document summarized the validation for cleaning and sanitization of the (b) (4) tanks, summarized the study performed to determine the length of time the (b) (4) can be stored in the tanks, and summarized the shipping procedure for the tanks to be shipped from (b) (4) to Tlalpan. The hold period for the (b) (4) in the tanks was qualified out to (b) (4); however, Bioclon has set the hold time at (b) (4).

Cleaning and Sanitization Procedure Description

Protocol PVA-AC-006 was used for the validation process of the sanitization of the (b) (4) tanks and to establish a hold period for the (b) (4) stored in the tanks.

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Reviewer Comment: Shipping and receipt of the (b) (4) tank is acceptable.

8. In Stage (b) (4) [Redacted], the description in the BLA states that (b) (4) [Redacted] process, the product in the (b) (4) [Redacted]. This step does not appear to be captured in either the English translation of the BPR or the Spanish BPR which is actually used in production. Please indicate where in the BPR this step is captured. In addition, please provide additional information on tank (b) (4) specifically:
- a) A description of the tank
 - b) A summary of the cleaning and sanitization/ sterilization qualifications.

Instituto Bioclon Response: The Agency is correct, the step “the product in the (b) (4) [Redacted]” is NOT (b) (4) [Redacted]

included in the BPR. Instituto Bioclon recognizes that the Master BPR is a living document and will take into account this missing step when reviewing the MBPR.

Description and a summary of the cleaning and sanitization of the (b) (4) (b) (4) is included in Appendix 3.2. A.1 Facility and Equipment; Equipment; Tlalpan Facility: description-(b) (4)-tank

FDA Response: Some points of this response need to be clarified. The following was included in an IR dated 15 Nov 2013:

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. The following abbreviations were not defined. Please define the following: (b) (4)

FDA Review

TANK DESCRIPTION

A figure of the tank is included in the response. The tank is described as a (b) (4)

VALIDATION PROCESS OF THE CLEANING AND SANITIZATION OF TANK

(b) (4)

The objective of the validation process of cleaning and sanitizing of the equipment used in the manufacture of Fabotherapics, is to verify that the procedures used for the cleaning and sanitizing are reliable, safe and reproducible. In addition, the objective is to demonstrate control of the cleaning and sanitization process to prevent the cross-contamination between products manufactured, as well as reduces the microbial load.

The worst case conditions were chosen, these conditions are those in which the cleaning process represents greater challenges. For this case, the conditions selected for the validation of cleaning process study were the conditions considered to be critical factors such as: product to evaluate, detergent and manufacturing equipment.

Residues of proteins were evaluated by the (b) (4) test method, the traces of detergent-sanitizer were analyzed by (b) (4) and a microbiological analysis was performed to assess the microbial load in the manufacturing equipment.

The Cleaning Validation Protocol establishes the steps to follow for the validation of the cleaning and sanitizing process; as well as the equipment used in manufacturing, the analytical methods, the detergent used to clean, the sanitizer used for microbiological control and the responsibilities of the personnel involved in validation.

RESULTS

