

Appendix 4

Amendment 16 - Response to Information Request Dated 17 Jul 2013

Recommendation: I reviewed the responses in Amendment 16 and request an information request be sent to the company. I have one possible PMC. The remaining responses were acceptable.

Possible PMC for response to #4 - equipment cleaning validation.

Review

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

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)

Instituto Bioclon Response:

- a) (b) (4) is used for sterility test.
- b) For pyrogen testing, the Agency is correct there was a typographical error we meant to 610.13(b) in addition to (b) (4) The correct reference was listed at the narrative written part; however, the references listed at the tables were incorrect. The Tables in section 3.2.P.5.6 Justification of Specifications has been corrected with the proper references.

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

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.**

Instituto Bioclon Response:

A table with other products listed that will be manufactured at the facility was submitted to the Agency on July 15, 2013 in sequence 0015, Section 3.2.A.1 Facility and Establishment; Equipment; Tlalpan Facility: list-of-other-products question #3. The list of products also applies for the (b) (4) facility

FDA Response: This response is acceptable. Note, however, that only Anavip has currently

been manufactured in the (b) (4) facility so it is not a true multi-product facility at this time. (b) (4). I do not have any further comments.

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) is scheduled to occur."

Instituto Bioclon Response:

(b) (4)

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

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.

Instituto Bioclon Response:

For the manufacture of Anavip Drug Product, (b) (4)

All of the accessories used for the operation of this equipment are exclusive to each product. That is, the (b) (4) are dedicated solely for each product. In addition, the (b) (4) are disposable. Therefore, we did not perform any cleaning validation since all the accessories in contact with the drug product all exclusive for each product and the (b) (4) are one time use.

FDA Response: The following was included in the IR dated 15 Nov 2013:

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 filling needles 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.

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.

Instituto Bioclon Response:

The winter phase of the protocol was not performed; it is scheduled to start on December 1, 2013 and finalize on February 15, 2014. The report will be submitted before the action date for the submission (March 18, 2013).

FDA Response: We will accept the summary of the winter shipping validation in an annual report. The US Agent for Bioclon was notified by e-mail on 29 Oct 2013. I do not have any further comments.

6. Please indicate what would happen to the shipment if there was evidence of a deviation in temperature, humidity or impact requirements.

Instituto Bioclon Response:

Experience with the shipments made for clinical trials (using the same shipping configuration planned for commercialization) resulted in no deviations from temperature, humidity or impact. If there were to be a deviation, we would evaluate it and generate a CAPA to include possible modifications to the secondary and tertiary package design and/or changes in the couriers that are contracted.

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

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.

Instituto Bioclon Response:

The monitor that will be used is a (b) (4). The vendor suggests recalibration of the monitors (b) (4) after purchase. The equipment was purchased on April 2013, the re-calibration will occur in (b) (4). Certificate of calibration is included in 3.2.R Regional Information; Certificate of Analysis: (b) (4)-calibration-certificate.

FDA Response: The response is acceptable. I reviewed the certificate of calibration form the company and the monitors were calibrated for (b) (4). As noted in the Primary Review, the shipping of the drug product is monitored for temperature and (b) (4). I do not have any further comments.

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.

Instituto Bioclon Response:

Once the bulk product has been received to the (b) (4) facility, the bulk container is stored in (b) (4) designed for bulk product storage. The product is store at (b) (4) until use. The bulk product is used within (b) (4).

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

Autoclave

9. In reference to Pro-Val-005, Performance Qualification (PQ) Protocol of the Autoclave (b) (4) Code : (b) (4) please submit the following:
- 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.

Instituto Bioclon Response:

Autoclave (b) (4) has (b) (4) validated patterns: Load Pattern 1 includes the (b) (4) Results for the load pattern 1-3 are submitted in this sequence, in section 3.2.A.1 Facility and Equipment, Equipment, (b) (4) Facility: additional-autoclave-info-load1-3

FDA Response: The following was included in the IR dated 15 Nov 2013:

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.

FDA Review:

PRO-VAL-005/I PERFORMANCE QUALIFICATION (PQ) OF THE AUTOCLAVE
(b) (4) CODE: (b) (4)

(b) (4)

(b) (4)

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.

Instituto Bioclon Response:

Qualification is provided in 3.2.A.1 Facility and Equipment, Equipment, (b) (4)

Facility: addendum-filler-check-weight-stopper.

FDA Response: This response is acceptable. See comments for Question 11 since the qualification of the weight check station and stopper insertion were part of the same report. I do not have any further comments.

11. The stopper (b) (4) were described as placing (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.

Instituto Bioclon Response:

Qualification is provided in 3.2.A.1 Facility and Equipment, Equipment, (b) (4)

Facility: addendum-filler-check-weight-stopper.

FDA Response: This response is acceptable. I do not have any further comments. The filling and stoppering line have been successfully qualified.

FDA Review:

Bioclon submitted the report, PRO-VAL-003/I: Performance Qualification (PQ) for the Filler (b) (4), to document the filling and stoppering machine

- (b) (4) [REDACTED].

12. Please indicate if the fill line, capping machine and the lyophilizer are physically separated from the surrounding room.

Instituto Bioclon Response:

The capping machine is (b) (4) [REDACTED]

FDA Response: This response is acceptable. I have no further comments.

Crimping Machine

13. In the description of the crimping machine, you state the machine has the ability to

(b) (4) [REDACTED]

The qualification of this capability was not included in this application. Please provide a description of the qualification and the results.

Instituto Bioclon Response:

The description of the qualification to (b) (4) [REDACTED] is provide in the 3.2.A.1 Facility and Equipment; Equipment; (b) (4) Facility: crimper (b) (4) [REDACTED] qualification-study

FDA Response: This response is acceptable. I do not have any further comments. The crimping machine has been qualified in an acceptable manner.

FDA Review:

Bioclon submitted report, PRO-VAL-001: Report of the Addendum to the Performance Qualification of the (b) (4) [REDACTED] Model (b) (4) [REDACTED] Code (b) (4) [REDACTED], to provide additional information for the qualification of the Capping / Crimping machine.

(b) (4) [REDACTED]

14. The vials are not capped and crimped (b) (4)

(b) (4) as described in the application. Please provide a description of the process of how vials are (b) (4)
(b) (4)

Instituto Bioclon Response:

(b) (4)

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

15. Please indicate if the crimping process is a manual or an automated process for the lyophilized vials.

Instituto Bioclon Response:

The crimping process for the lyophilized vials is an (b) (4) process.

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

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.

Instituto Bioclon Response:

Operation parameters for the crimping machine are:

(b) (4)

(b) (4)

The (b) (4) testing is not performed.

FDA Response:

This response is acceptable. While we would typically like to see (b) (4) testing performed for an (b) (4) crimper to be part of the PQ, in this case; however, this is acceptable to not perform the (b) (4) testing since the product is a lyophilized product and it is tested for residual moisture at the time of release and during stability studies. (b) (4) would be important if (b) (4) crimpers were being compared to show equivalence; however, the crimping of the vials in the currently approved process is a (b) (4) process thus there is no direct comparison between the two mechanisms of crimping.

The following point of clarification was included in the IR dated 15 Nov 2013:

After the list for the operation parameters for the crimping machine, there is a note stating, (b) (4)

Please define the term “vensor”.

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.

Instituto Bioclon Response:

TITLE	COMPLETED DATE	CODE	DEVIATION
Installation Qualification Protocol of (b) (4) Capping Machine (b) (4)	august / 15 / 11	BT/PCE-VA-007	NONE
Installation Qualification Report of (b) (4) Capping Machine (b) (4)	march / 14 / 12	BT/PCE-VA-007/I	NONE
Operation Qualification Protocol of (b) (4) Capping Machine (b) (4)	august / 17 / 11	BT/PCE-VA-008	NONE
Operation Qualification Report of (b) (4) Capping Machine (b) (4)	may / 08 / 12	BT/PCE-VA-008	NONE

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

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.

Instituto Bioclon Response:

Information on the Dry Heat Oven for (b) (4) Facility was not provided in the BLA. The Performance Qualification for the Dry Heat Oven (b) (4), CODE: (b) (4) is provided in 3.2.A.1 Facility and Equipment, Equipment, (b) (4) Facility: (b) (4) -pq-report.

FDA Response: The response is acceptable; however, I discovered this is not captured in their BPR for Anavip. I will have a telecon with Bioclon to discuss the importance of capturing all information in the BPR. They used the BPR for Anascorp, which is acceptable, but Bioclon needs to understand that the filling and preparation for Anavip in the (b) (4) is completely different so the BPR should reflect that. We expect final BPRs to be sued during conformance lot manufacture.

FDA Review:

QUALIFIED EQUIPMENT DATA AND GENERAL DESCRIPTION

Equipment Name: (b) (4)

Code: (b) (4)

Location: (b) (4)

Department: PRODUCTION

Plant: (b) (4)

EQUIPMENT DESCRIPTION

(b) (4)

QUALIFICATION OBJECTIVE

The objective of the performance qualification (PQ) is to verify and document that the (b) (4) (b) (4) Depyrogenation oven, code: (b) (4) can successfully run Load Pattern 1 and Load Pattern 2. The acceptance criteria were all thermocouples during the depyrogenation cycle must not be (b) (4) at the end of each cycle of depyrogenation should obtained a value of FH (b) (4) and all (b) (4) indicators must be (b) (4) to consider the run successful.

All acceptance criteria were met and no deviations were recorded. Load Patterns 1 and 2 are qualified for a (b) (4) depyrogenation cycle.

(b) (4)

Vial Washer

- 19. In PRO-VAL-004/I Performance Qualification (PQ) of the Vials Automatic (b) (4) Washing Machine Code (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.**

Instituto Bioclon Response:

The minimum operating conditions established in the “Report for the Performance Qualification (PQ) for the (b) (4) automatic washing machine of vials, Code (b) (4) PROVAL-004/I001 are:

(b) (4)

(b) (4)

FDA Response:

This response is acceptable. I do not have any further comments. The vial washer has been qualified in an acceptable manner.

20. Please indicate the quality specifications for the compressed air (b) (4)

Instituto Bioclon Response:

The quality for the compresses air used (b) (4) is pharmaceutical grade; specifications are listed in the table below:

(b) (4)

(b) (4)

FDA Response: This response is acceptable. Bioclon provided document titled, Summary of Results of the Tests Carried Out in Compressed Air, to discuss the qualification of the compressed air.

During the qualification, the level of contaminants (b) (4) and determination of (b) (4) count were performed.

(b) (4) meets Grade (b) (4) specifications. I do not have any further comments.

21. Please specify the water quality used for washing and rinsing of the vials; specifically, is (b) (4) used for the final rinse?

Instituto Bioclon Response:

The final rinse of the vials is performed using (b) (4) .

FDA Response: This response is acceptable.

22. In your description of the washing process you state, in summary, the (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?

Instituto Bioclon Response:

Initially the vials are (b) (4)

No cleaning agents are used, only (b) (4) is used to clean the vials.

FDA Response: The following was included in the IR dated 15 Nov 2013:

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.

23. Please indicate if you have bioburden or endotoxin specifications for vials (b) (4)

Instituto Bioclon Response:

There are no specifications of endotoxin and bioburden for the vials (b) (4).

FDA Response: This is acceptable. Samples of the vials that (b) (4) are tested in-process for (b) (4). This ensures the (b) (4) levels of the vials entering the depyrogenation tunnel are not too high.

Depyrogenation Tunnel

24. The summary report for the Performance Qualification of the depyrogenation tunnel is incomplete. Please prove a short summary of the following:

Instituto Bioclon Response:

Summary report for the Performance Qualification of the depyrogenation tunnel was update with the requested information. See 3.2.A.1 Facility and Equipment, Equipment, (b) (4) Facility: summary-for-depyro-equipment.

i. Temperature Distribution Mapping

Instituto Bioclon Response:

See 3.2.A.1 Facility and Equipment, Equipment, (b) (4) Facility: summary-for-depyroequipment.

FDA Review:

Temperature Distribution Mapping

(b) (4)

FDA Review:

Dry Heat (b) (4) Testing

(b) (4)

vi. (b) (4) Testing

Instituto Bioclon Response:

See 3.2.A.1 Facility and Equipment, Equipment, (b) (4) Facility: summary-for-depyroequipment.

FDA Review:

(b) (4)

Testing

(b) (4)

FDA Response: The response to question 24 is acceptable. Based on the information included in the primary review and the additional information provided by this response, the depyrogenation tunnel is considered to be qualified in an acceptable manner.

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.

Instituto Bioclon Response:

*A summary of the compressed air for the (b) (4) Facility was submitted in the original application and it is located at 3.2.A.1 Facility and Equipment; Equipment; Facility: **Compress Air Summary for (b) (4) Facility.***

FDA Response: The following was included in the IR dated 15 Nov 2013:

I am unable to locate the document “Compress Air Summary for (b) (4) Facility.” 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.

Container Closure

26. Please specify if a bioburden and endotoxin specification exists for the incoming vials and stoppers.

Instituto Bioclon Response:

Instituto Bioclon does not have specifications for the bioburden and endotoxins for the incoming vials and stopper. The following specifications are provided by the vendor in a certificate of analysis.

Microbiological

<i>Determination</i>	<i>Specification</i>
(b) (4)	

A certificate of analysis is provided in section 3.2.R Regional Information; Certificate of Analysis: (b) (4) -stoppers.

FDA Response: Bioclon does not test the incoming stoppers for the above tests, but rely on the results from the manufacturer. (b) (4) stoppers have not historically posed problems with bioburden and endotoxin levels; usually problems arise when the purchaser stores the raw materials inappropriately. Bioclon did not provide any information for the vials; however, it was stated in the primary review that the vials were not tested by Bioclon for endotoxin or bioburden, but Bioclon performs extensive testing on the incoming vials and performs a number of in-process tests to determine (b) (4) (sterile) of the vials and performs in-process testing for (b) (4) using the vials and stoppers. Thus, both the stoppers and vials are controlled.

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.

Instituto Bioclon Response:

The method used for the leak testing in the Anavip finished products is the method II, (b) (4)

FDA Response: This response is acceptable. The vials are being tested to confirm they still (b) (4). If the vial integrity was compromised, then there would not be a vacuum and the test would fail. This test along with the residual moisture test that is performed upon release and during stability studies demonstrates that the vials are integral.

FDA Review:

2.3.P.5.2.20 and 3.2.P.5.2.20 Leak Test M-FQ-030

The procedure for the Leak Determination is described in section 3.2.P.5.2

Method II: (b) (4)

(b) (4)

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))**

Instituto Bioclon Response:

Microbiological results of the EM during the qualification of the (b) (4) autoclave

Microbiological results of EM during steam qualification are shown in the following table:

(b) (4)

(b) (4)

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

ii. **Qualification of the Compressed Air System** (b) (4)

Instituto Bioclon Response:

Compressed air is used for (b) (4) .

FDA Response: The following was included in the IR dated 15 Nov 2013:

Your response is unclear. You state, “Compressed air is used for the (b) (4)