

Appendix 2

Review of Amendment 8 - Responses to Information Request Dated 08 April 2013 for Review Issues

Recommendation: I reviewed the response in Amendment 8 and found them to be acceptable. I do not have any further comments or questions related to this amendment.

Review

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

Module 1 Contents

1. Please amend your request for a categorical exclusion. The request was made under the correct exclusion, 21 CFR 25.31 (c); however, the wording accompanying the request was incorrect.

Instituto Bioclon Response:

The request for categorical exclusion has been amended with correct wording and is provided in Module 1, Section 1.12.14 Environmental Impact Analysis.

Reviewer Comment: The response is acceptable. Refer to approved CE memo dated 20 May 2013.

**2. The following hyperlinks appear to be broken:
Section 3.2.S.2.4 has a hyperlink to Section 3.2.R Executed Batch Records
Section 3.2.8.2.5 has a link to 3.2.S.4.4 Batch Analysis**

Instituto Bioclon Response:

The hyperlinks noted above have been fixed.

Reviewer Comment: The response is acceptable.

Module 2 Contents

3. It is unclear if all applicable facility and equipment information is included in the submission. A list of equipment and utilities was supplied for the Tlalpan facility; however only a list of utilities was included in the submission for the (b) (4) facility. Please provide a list of all major equipment used in the (b) (4) facility for the fill finish of the Anavip drug product and indicate if the equipment is shared or dedicated to Anavip.

Instituto Bioclon Response:

The list of all major equipment used in the (b) (4) facility for the fill finish of the Anavip drug product and indication if the equipment is shared or dedicated to Anavip are included in Module

3, Section 3.2.A.1 Facility and Equipment; Equipment; (b) (4) Facility: list-of-major-equipment-(b) (4)

Reviewer Comment: This response is acceptable. The review of this information is part of the Primary Review memo and is located within the appropriate sections of the review memo. Any additional questions will be asked during the Primary Review, if necessary.

Module 3 Contents: Drug Substance

4. The (b) (4) bulk drug substance is shipped to (b) (4) for final fill and finish. Please provide the shipping validation for shipping of (b) (4) bulk drug substance from Tlalpan to (b) (4). Please include a description of the packing and shipping procedures.

Instituto Bioclon Response:

Bioclon did not perform a formal validation of the transportation of the bulk drug substance from Tlalpan to (b) (4) since the shipments are monitored and evaluated individually (all shipments).

The transportation of the bulk drug substance is performed according to the standard operating procedure (SOP) P-AL-056 for the preparation and transfer of Material packaging and bulk to the (b) (4) plant". The justification for the shipping process is included in Module 3, Section 3.2.A.1 Facility and Equipment; Equipment; (b) (4) Facility: shipping-process-of-the-bds.

Reviewer Comment: This response is acceptable. The review of this information is part of the Primary Review memo and is located within the appropriate sections of the review memo. Any additional questions will be asked during the Primary Review, if necessary.

Module 3 Contents: Drug Product

Container Closure

5. Please provide additional information on the stoppers and vials used as the container closure for the final drug product such as line drawings with measurements indicated. Please provide the acceptance specifications for the materials. Please provide a description for the process for the receipt of these materials. Is any testing conducted prior to release into production? Please provide a brief description of raw material qualification performed for these materials.

Instituto Bioclon Response:

Additional information for the container closure system for Anavip is provided in Module 3, Section 3.2.P.7 Container Closure System. The following additional information is provided:

- a brief description of the stoppers and vials used*
- a description for the process for the receipt of these materials*
- table of specifications and SOP used for testing are also included.*
- diagram showing the dimensions of rubber stopper,*

- diagram showing the dimensions of the glass vial

Reviewer Comment: I reviewed all of the above information and found it to be acceptable. The contents of my review are located in the Primary Review memo.

Process

6. Please confirm the manufacture of the bulk drug substance will only occur in the Talpan facility and the filling and lyophilization will only occur in the (b) (4) facility.

Instituto Bioclon Response:

The Instituto Bioclon S.A de C.V confirms that the manufacturing of the bulk drug substance for Anavip will be done in the Talpan facility and the filling and lyophilization will occur in the (b) (4) facility.

Reviewer Comment: This is acceptable.

7. Please provide a description of the receipt process of the bulk drug substance at (b) (4) Please indicate where the material is stored and under what conditions.

Instituto Bioclon Response:

The reception of all material received at the (b) (4) are done according to the SOP PNO-INS-001 for the inspection of orders supply. The bulk containers are (b) (4)

The SOP is included in Module 3, Section 3.2.R Regional Information; method validation; standard operating procedures: pno-ins-001.

Reviewer Comment: This response is acceptable. I reviewed SOP PNO-INS-001 and found it to be acceptable. The review of the SOP can be found in the Primary Review memo in the Section discussing the final product container.

8. Please describe the process for transferring the bulk drug substance to the filling machine; specifically, describe the container for the BDS and how it is connected to the filling machine. For example, is the BDS in a tank and then an aseptic or sterile connection is made from the tank to the filling machine?

Instituto Bioclon Response:

The process for transferring the bulk drug substance to the filling machine, description of the container for the bulk drug substance and how it is connected to the filling machine is provided in Module 3, Section 3.2.A.1 Facility and Equipment; Facility: description-of-bulk-connection-to-filling-line. The BDS is in a (b) (4). The process is illustrated in Figure 11.

Reviewer Comment: This response is acceptable. I reviewed the description provided by Bioclon for connecting the bulk drug substance (b) (4) to the filling line and I do not have any comments. The description of the process can be found in the Primary Review memo in the

Section discussing the manufacturing process.

9. Please provide a more detailed description of the types of gowning used and of the gowning process prior to entrance into the aseptic filling area.

Instituto Bioclon Response:

To enter the aseptic area it is necessary to make a (b) (4) change of clothing, this is done in the gowning room of aseptic area. (b) (4) head covers are used previously (b) (4); the dress technique is described in the SOP PNO-PBT-002: Personnel Access to Aseptic Area and PNO-PBT-048: Use of Uniform for Entering the Aseptic Area. Staff entering the aseptic area is for qualified personnel only. The training records for qualified personnel are found in the training department. SOPs PNO-PBT-002 and PNO-PBT-048 are included in Module 3, Section 3.2.R Regional Information; method validation; standard operating procedures: pno-pbt-002 and pno-pbt-048.

Reviewer Comment: This response is acceptable. I reviewed SOP PNO-PBT-002: Personnel Access to Aseptic Area and SOP PNO-PBT-048: Use of Uniform for Entering the Aseptic Area and they were acceptable. The review of the SOPs can be found in the Primary Review memo in the Section discussing the manufacturing process.

10. Please clarify (b) (4)

. If this is not included in the media simulations, please provide the rationale for not including this step.

(b) (4)

11. Please clarify where labeling of the vials will occur. Please describe the labeling process and the vial visual inspection process.

Instituto Bioclon Response:

Visual examination of the vials will be held in the "Revision Area" of the (b) (4) using the (b) (4); the review process is carried out according to the SOP PNO-PBT-035: visual inspection of freeze-dried products. The area is classified as Class (b) (4)

*The labeling of the products will be done in the "Packaging Area" of the (b) (4)
The labeling and packaging of the product is carried out according to the SOP PNO-ACO-001:
Labeling and Packaging of Final Products. The area is classified as Class (b) (4)
SOPs PNO-PBT-035 and PNO-ACO-001 are included in Module 3, Section 3.2.R Regional
Information; method validation; standard operating procedures: pno-pbt-035 and pno-aco-001.*

Reviewer Comment: This response is acceptable. I reviewed SOPs PNO-PBT-035 and PNO-ACO-001 and they were acceptable. The review of the SOPs can be found in the Primary Review memo in the Section discussing the visual inspection process.