

Appendix 6

Review of Amendment 29 Response to FDA Information Request Dated 16 Oct 2013

Recommendation: I reviewed the response in Amendment 29 requested an Information Request be sent to the company. The remaining responses were acceptable.

Review

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

Drug Product

1. Environmental Monitoring Action Levels for Aseptic Area

For environmental monitoring, the action levels for the Grade (b) (4) area are acceptable (b) (4) for non-viable particulates, and (b) (4) for viable particles); however the environmental monitoring action levels for the viable particulates of the surrounding areas appear to be incorrect. The non-viable particle action level for a Class (b) (4) area is correct at (b) (4) but the viable monitoring action level is (b) (4) for surrounding areas. This is typically the action level for a Class (b) (4) area. The action level for a Class (b) (4) area is (b) (4). Please confirm this is a typographical error and the surrounding areas meet Class (b) (4) recommendations for both viable and non-viable monitoring.

Instituto Bioclon Response:

Instituto Bioclon confirms that it was a typographical error and the surrounding areas meet Class (b) (4) recommendations and comply with the following criteria: (b) (4) (b) (4) (air environmental monitoring) and (b) (4)

FDA Response: This response is acceptable. I do not have any further questions or comments. The room classifications of the aseptic area and other support rooms for the filling of Anavip are qualified and routinely monitored at an acceptable level.


2. Vial Defect Allowances

You state that the Critical defect specification during visual inspection is (b) (4) ” and the Major defect specification is “(b) (4)

**Typically, the critical defect allowance is tighter than the major defect allowance.
Please provide the rationale for your specifications.**


Instituto Bioclon Response:

Specifications for critical defects, major and minor were obtained by a statistical analysis of batches produced between 2006 and 2009. The specifications were established for the process of (b) (4) product in Tlalpan. (b) (4)

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(b) (4)

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FDA Response: Bioclon is stating that the specifications are only the preliminary specifications set until they have manufactured at least ^{(b) (4)} lots of Anavip in the (b) (4) and 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) fill and (b) (4) crimping process.

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

In your response, you indicated that the acceptance criteria are based on statistical analysis of batches 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) 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) fill and (b) (4) crimping process. The process in the (b) (4) facility is

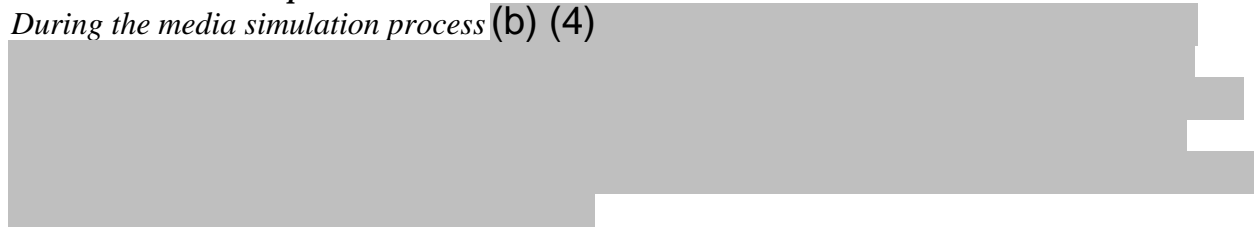
an (b) (4) fill and crimp capping process. Please indicate if an AQL sampling for visual inspection is being performed for the final container (vial) after the 100% visual inspection and prior to release? If so, what are your sample size and acceptance limits?

3. Media Simulation

The description of the media simulation does not provide a sufficient amount of detail of the simulated lyophilization process. Please provide a description of the simulated lyophilization process. It is unclear if a vacuum was pulled, if there was any kind of temperature control or temperature setting in the lyophilizer, or if the shelves were raised to fully stopper the vials at the completion of the simulated process.

Instituto Bioclon Response:

During the media simulation process (b) (4)



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

4. Lyophilization

- a. **Please provide the glass transition temperature of your product and explain how the recipe for Anavip accommodates this temperature.**

Instituto Bioclon Response:

The glass transition temperature for Anavip is (b) (4). The low temperature thermal analysis was not conducted. The parameters for the recipe were transferred from the recipe used in Tlalpan. Final product was evaluated for (b) (4) after lyophilization and all were found acceptable (within pre-established specifications). The recipe used this temperature to solidify the product during freezing process; the solidification temperature is (b) (4). The transition temperature is used in the (b) (4) drying during (b) (4).

FDA Response: This response is acceptable. I do not have any further questions or comments. The lyophilization recipe used in the (b) (4) facility was the same recipe used in the Tlalpan facility. Bioclon demonstrated product acceptability through final product evaluation including the ability of the product to meet release specifications.

- b. Please indicate if temperature of the product was monitored during the lyophilizer qualification. Also, please indicate if the temperature of the product is monitored during routine lyophilizer operations.

Instituto Bioclon Response:

No, the temperature of the product was not monitored during the lyophilizer qualifications. The product temperature is monitored during routine lyophilizer operations (b) (4) temperature sensors located in the chamber of the lyophilizer: (b) (4) containing product.

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

- c. Please provide the graph printout for the Anavip cycle run during the placebo run during the lyophilizer qualification. In addition, provide the graph printout from all three conformance runs.

Instituto Bioclon Response:

Graph printout for the Anavip cycle run during the placebo run during the lyophilizer qualification and the three conformance runs are shown below

FDA Response: This response is acceptable. I reviewed the graphs provided and all of the graphs are similar in their cycle pattern no outstanding issues or deviations were noted. The graphs depicted cycles run using the specifications outlined in the application. I do not have any further questions or comments.

5. Biological Indicators

Please provide the D-value of the biological indicators used in the autoclave and lyophilizer qualification tests.

Instituto Bioclon Response:

The D-value of the biological indicators used in the autoclave and lyophilizer qualification tests is (b) (4)

FDA Response: This response is acceptable. D values are typically a minimum of (b) (4) minutes.