

Appendix 5

Review of Amendment 28 - Response to FDA Information Request Dated 07 Oct 2013

Recommendation: I reviewed the response in Amendment 28 and request an IR be sent to the company on. All other responses were acceptable.

Review

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

Drug Product

- 1. Please provide the completed batch production record for the visual inspection and packaging and labeling of the vials for the conformance lots manufactured.**

Bioclon Response:

*Bioclon does not have a batch production record for the visual inspection process. The Standard Operating g Procedure contains Formats used to document the visual inspection process. Documents for the visual inspection process are included in Section 3.2R Regional Information; Executed Batch Records; Drug Product: **visual-insp-report-conformance-lots**.*

Product is currently under quarantine. Packaging and labeling process of the vials will be done once the labels are finalized (signed and approved) upon FDA review.

FDA Response: This response is acceptable.

Reviewer Comment: SOP PNO-PBT-035, Visual Inspection of Lyophilized Products, was included in the response. I reviewed the SOP and found it to be acceptable. Per the SOP, the documentation generated during the visual inspection becomes part of the final package for release of the product.

- 2. The information in Section 3.2.P.3.5.1 – Media Fills is incomplete. I reviewed the BPR for the 20 mL vial media fill and found it to be incomplete in the following areas:**
 - a. The Spanish version of the BPR (the executed BPR) is different from the English translation of the BPR used for the media fill. The Spanish version includes information on incubation conditions and time of incubation for the vials in addition to information on growth promotion testing. The Spanish version documented four “observations / non-conformance”; however it is unclear if these observations were noted in the application. All translations must be true and accurate. Please translate the sections of the executed media fill BPR that are not currently translated and please translate the four “observations / non-conformance” statements.**

Bioclon Response:

*The revised media fill BPR containing the translation of the missing section and the four observation/non-conformance statements is included in Section 3.2R Regional Information; Executed Batch Records; Media Fill Process: **media-master-bpr-20ml**. The Spanish version was modified to include the growth promotion testing, however, the English version did not include the growth promotion testing since translation of document was done prior to make the changes.*

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

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 (b) (4), after any intervention to the fill line such as removing vials or clearing a jammed line. Please indicate when personnel monitoring took place.

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.

Please provide the sterile hold times for filling parts and stoppers. Please indicate if these times were challenged during the media fill.

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?

b. Please provide the results from environmental monitoring for rooms and personnel that occurred during the media fill.

Results from environmental monitoring for rooms and personnel that occurred during the media fill are included in Section 3.2A.1 Facilities and Equipment; Facility: **em-rooms-personnel-for-media-fills**.

FDA Response: The following was added to the IR dated 15 Nov 2013:

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.

- c. **Please provide the total number of hours the lyophilization cycle was simulated. From the Spanish BPR it appears the cycle was simulated for (b) (4) Please confirm.**

Instituto Bioclon Response:

Instituto Bioclon confirms that the lyophilization cycle was simulated for (b) (4). The time recorded (b) (4) is the time for all activities related to the lyophilization process, including the filling process, simulated interventions, loading of lyophilizer, etc. Bioclon understand that the BPR is a living document and will review it to include details of each operation to avoid future confusions.

FDA Response: This response is acceptable. (b) (5), (b) (7)(E)

3. **The dates of (b) (4) media lots (b) (4) were provided in the application. Please provide the dates the media were actually used in the media fill and the total number of days held from (b) (4) to use in the media fill in (b) (4)**

Bioclon Response:

(b) (4)

FDA Response: This response is acceptable.

4. For Section 3.2.P.7.3, Container Closure Integrity Testing, please provide the following information:

- a. Please clarify if the test vials and the control vials used in this testing protocol were stoppered and crimped using the (b) (4) equipment used in (b) (4) or the (b) (4) process used in Tlalpan.

Bioclon Response:

Instituto Bioclon confirms that the control vials used in the testing protocol for the container closure studies were stoppered and crimped using the (b) (4) equipment in Tlalpan. However, a follow up using the conformance lots which used the (b) (4) equipment in (b) (4) was evaluated. The summary of the results for the container closure system using the (b) (4) equipment from (b) (4) is included in Section 3.2A.1 Facilities and Equipment; Facility: ccs-(b) (4) -equipment.

FDA Response: This response is acceptable. Both test vials and control vials were capped and crimped at the (b) (4) facility. Conformance Lots (b) (4) were tested. The results for the CCIT are applicable to the (b) (4) facility and met specifications for (b) (4) testing. I do not have any further questions or comments.

FDA Review:

Container Closure Integrity Test – (b) (4)

Conformance Lots (b) (4) were tested for (b) (4). These vials were all filled and capped in the (b) (4) facility and met specification with no deviations noted.

Bioclon evaluated the container closure integrity, per protocol PCB-CC-006, to document the primary packaging of the final product is able to maintain the (b) (4) polyvalent fabootherapeutics (Anavip) under suitable conditions such that the physical, chemical, microbiological and biological properties are not affected.

(b) (4) testing, using three different lots of released product, were performed under different temperature and pressure conditions to evaluate the container closure integrity.

The protocol studies described in the application applied to container closure system:

- Vial of 20 mL Type (b) (4) supplier (b) (4)
- Gray slotted rubber stopper (b) (4)
- Flip-off assembly

The protocol described the preparation of the negative and the positive test controls and the preparation of the (b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5. For the report for (b) (4) Injectable Water System, (b) (4) (PQ), I was unable to locate the WFI sampling results for Phase 3 Qualification of the WFI system. Please indicate the location of the information within the application or please submit a summary of the results including a summary of any deviations and investigations. In addition, please provide the dates the Phase 3 qualification occurred.

Bioclon Response:

Summary of the results for the Phase 3 Qualification of the WFI System is included in Section 3.2A.1 Facilities and Equipment; Facility: wfi-(b) (4)-phase3-results. One deviation was found during the Phase 3 Qualification process and its description is also included in the file. Dates for the Phase 3 qualification are also provided in the summary.

FDA Response: This response is acceptable. I reviewed the data provided and all specifications for (b) (4) water were met. I do not have any further comments or questions. The (b) (4) systems is appropriately qualified.