

Memorandum

**Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality**

To: 125335/0/38 Centruroides (Scorpion) Immune F(ab)2 Intravenous
(Equine)

Rare Disease Therapeutics, Inc. (RDT) U.S. License # 1860

From: Nancy Waites, Facility Reviewer, MRB1/DMPQ/OCBQ/HFM-675

Through: Carolyn Renshaw, Branch Chief /MRB1/DMPQ/OCBQ/HFM-675

Cc: Debbie Cordaro, RPM, OBRR/DBA/RPMB /HFM-380
Robert Fisher, PhD, Chair, OBRR/DH/LPD /HFM-345

Subject: Review of the CR letter response submitted by RDT for Bioclon, received
01 Feb 2011.

Recommendation: I have reviewed Bioclon's response to the CR letter items that were applicable to DMPQ and found them to be acceptable. I recommend approval of this submission.

Review Narrative and Comments

Overview

On 23 July 2009, a CR letter was sent to Bioclon for STN 125335/0. On 01 Feb 2011, we received a response to our letter, STN 125335/0/38. I have reviewed the responses in the CR letter that were specific to DMPQ and I found them to be acceptable. I do not have any questions or comments for this submission.

Utilities Summary

Bioclon provided utility validation information for the HVAC, compressed air, and RO/DI system. The HVAC was shown to be capable of maintaining specified room classifications and humidity control. The RO/DI system met (b)(4)- purified water specifications and the compressed air met the required specifications depending on room classification. All three systems are monitored on a routine basis per specified criteria.

NOTE: There was one unusual aspect of the review for the Water for Injection (WFI).

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Equipment and Cleaning Validation Summary

Process validation for major manufacturing equipment such as the autoclave, filling apparatus used in the manual filling process, lyophilizer, (b)(4)- vial washer, and the depyrogenation oven was provided in this response. Cleaning validation was provided for the filling apparatus, (b)(4)- system, various tanks, and filter housings. The validation of the equipment demonstrated the equipment could be run and maintained in such a manner as to provide acceptable final product. It was also demonstrated through the cleaning validation that the equipment could be cleaned to an acceptable level with established clean hold times and dirty hold times.

Media Fill Summary

Information for media fills and routine environmental monitoring was provided in the response and the most recent media fill conducted in Aseptic Area (b)(4) (June 2011) was reviewed during the inspection. Media fills appropriately mimic the actual filling and a simulated lyophilization. Full lots of vials are filled and since the number of vials filled is ----- (b)(4) -----, EM trend data was reviewed during the inspection too. Both the media fills and EM data were acceptable. Media fills are performed ----- (b)(4) -----.

Container Closure Summary

The container closure system used for Anascorp is the exact same system used for Alacramyn (scorpion antivenin licensed for Mexico). It consists of a 10 mL Type (b)(4) clear glass vial, (b)(4) grey bromobutyl rubber stopper, and a (b)(4) aluminum crimp cap. The fill volume is (b)(4)- mL prior to lyophilization.

Based on the information provided by Bioclon in this submission, the container closure system appears to be compatible with the final product, Anascorp. The system is not additive or absorptive nor can the stoppers adversely affect the finished product as demonstrated by extractable (b)(4). The container closure was shown to be integral through (b)(4) testing. The (b)(4) test did not show evidence of (b)(4) in the vial after visual inspection and the vials consistently met the final product release specification for moisture which is (b)(4).

NOTE: Bioclon did not test the sensitivity of the (b)(4) test for CCIT; however, after discussing this with Carolyn Renshaw, Branch Chief, and Deborah Trout, Team Lead, it was decided that this was acceptable since the (b)(4) test is a better test for lyophilized products. Bioclon will not have to determine the sensitivity of the (b)(4) test since they perform the (b)(4) moisture test.

Bioclon also provided data to demonstrate the container closure system is compatible with Anascorp. The quality attributes tested during this study were those that would reflect any change resulting from the interaction between the product and the container-closure system. The quality attributes evaluated were as follows: appearance of reconstituted material, proteins content, (b)(4), safety, (b)(4). All specifications were the final release specifications of the product during routine manufacturing.

Shipping Validation Summary

Bioclon provided their shipping validation protocol and executed validation report in this submission. The vials were packed and shipped according to approved SOPs. The lyophilized vials are shipped in a cardboard carton without any cold packs or other type of material to keep the boxes cool; however, the shipping validation demonstrated that the product met release testing specifications pre- and post-shipment even though the environment around the shipped containers reached a maximum temperature of 36°C.

The shipping validation was performed in the summer from 19 June - 10 July 2009, thus the package would have been exposed to possible high heat conditions. The vials were shipped from Mexico to the distribution warehouse in Tennessee; from Tennessee to Arizona; from Arizona back to Tennessee; and from Tennessee back to Mexico. The shipment went through Customs twice (once to the US from Mexico and once from the US into Mexico) where the outer box was opened for examination. A temperature data logger and shock monitor were included in the packaging. The maximum temperature reached was 36°C and the minimum temperature reached during shipment was 18 °C. Per Bioclon, this meets their specification of (b)(4). The product was tested

per release specifications prior to shipment from Bioclon and post-shipment when the material was returned to Bioclon. All final product release specifications were met.

Pre-License Inspection

A pre-license inspection was performed 13-17, 20-22 June 2011 and a ten item Form FDA 483 was issued. The inspection was classified as VAI. The Form FDA 483 observations from the inspection in 2009 were reviewed and it was determined that the observations had been addressed in an acceptable manner.

Review and Comments

The following review is specific for CR letter issues pertaining to DMPQ purview. The DMPQ issues are written in **bold** followed by Bioclon's response in *italics*. The FDA response to the information provided by Bioclon follows Bioclon's response.

CR# 37

The facilities and process information is not sufficiently detailed and descriptive to permit a comprehensive review. Please note that you should include only applicable information within an application and you should not include any information based on future proposals. You should present the information in a coherent and cohesive manner and include dates, data, specifications/action levels, acceptance criteria, rationales for specifications/action levels and acceptance criteria, and copies of approved protocols with accurate summaries of results. Please amend your application accordingly.

Bioclon Response

*The facilities and process information was not sufficiently detailed. The SUV report attached to **CR#1** provides brief descriptions of each production area. The validation of the classified areas is provided in **CR#43 and #53**. The non-classified areas which constitute the majority of the production areas have associated cleaning and sanitization procedures and associated environmental monitoring results with alert and action levels specified, but do not have validation criteria.*

FDA Response CR#37

I reviewed the sections of **CR#1** that were applicable to DMPQ and found them to be acceptable. I reviewed **CR#43** and **CR#53** and found the responses to be acceptable. Therefore, Bioclon's response to CR#37 is acceptable.

CR #1

You should manufacture your conformance lots on the scale that you intend to market them in the United States.

Bioclon Response

The ^{(b)(4)} scale-up verification (suv) batches (commercial scale but not for human use) were completed during the months of August to November of 2010 using the instruction sets

and documentation requirements detailed in the newly revised BPR - DM-ID-011 Rev. B. (b)(4) of the (b)(4) batches were combined (see CR #15) which resulted in the filling and lyophilization of (b)(4) full scale batches. The SUV runs (aka engineering runs) were conducted to ensure that the defined process and the new BPR are appropriate and acceptable at the commercial scale. Conformance batches are scheduled for the first or second quarter of 2011 will be manufactured using the commercial scale (----- (b)(4) -----) that was verified with the (b)(4) SUV runs and will use the current version at the time of production of the applicable BPRs.

Refinements to the BPR (a living document) have been identified and will be incorporated as result of the SUV runs and the first hand experience with the completion and review of the document. Thus, the conformance batches will be conducted with a newer version of the fractionation and sterile bulking BPR as well as the filling, lyophilization and packaging BPR to ensure a more compliant completion and documentation of the initial batches which may be released for distribution upon agency approval. The SUV report is attached providing the results of the processing parameters intended to be entered into a tracking database and statistically trended to demonstrate process consistency with respect to the individually validated processes and equipment.

FDA Response

I reviewed the sections of the SUV report in CR#1 that pertained to the description of each production area. I did not review the sections on process validation that fall under the purview of the Product Office. I found the area descriptions coupled with the floor plans provided to be acceptable.

FDA Review CR#1

CODE: PTP-ID-1000/FDA/01 Scale-up Verification (SUV) Run Summarization Report listing the Processing Parameters documented in the revised BPR for each Stage of the Fractionation, Purification, ----- (b)(4) -----, Final Formulation and Sterile Bulk for the (b)(4) Full Scale Runs of Anascorp

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----- (b)(4) -----
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Manufacturing Overview

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Redact 2 pages (b)(4)

(b)(4)

(b)(4)

(b)(4)

CR #43

Utility qualification for all utilities used in the production of Anascorp must be completed. Please submit detailed descriptions and data from these qualifications. This includes, but is not limited to water, compressed gas and the HVAC system. Please provide information on all utility qualification and validation even if it was previously included in the original BLA and/or amendments.

Bioclon Response

The HVAC system has been re-qualified after -----(b)(4)----- . The RO/DI and Compressed Air Systems were also validated. Description and data from these qualifications are included.

FDA Response CR #43

I have reviewed the documentation provided for the validation of the HVAC, RO/DI water, and the compressed air system and found them to be acceptable. I do not have any questions or comments.

The information for the RO/DI system was included in the response under **CR# 51**. These three systems were also reviewed during the Pre-License inspection and found the validation data and routine monitoring data to be acceptable. The HVAC was shown to be capable of maintaining specified room classifications and humidity control. The RO/DI system met (b)(4) purified water specifications and the compressed air met the required specifications depending on room classification. All three systems are monitored on a routine basis per specified criteria.

FDA Review CR #43

Compressed Air

- **PCS-VA-005/I – Compressed Air System Installation Qualification (IQ) Report**
PD1327

Issue Date: 16 Mar 2010 – This was a 20 page report documenting the Installation Qualification of the compressed air system for the Tlalpan facility. I reviewed the document and do not have any comments. The document was acceptable.

- **PCS-VA-014/I – Compressed Air System Operation Qualification (OQ) Report, PD1327**

Issued 18 Mar 2010 - This was a 21 page report documenting the Operation Qualification of the compressed air system for the Tlalpan facility. I reviewed the document and do not have any comments. The document was acceptable.

- **VAL-459, Compressed Air System Performance Qualification (PQ) Report Code (NE)**

Issue Date: 19 Mar 2010 – This was an 11 page report summarizing the Performance Qualification for the Compressed Air system at the Tlalpan facility.

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----- (b)(4) -----.

- **Statement of Compliance for Compressed Air Viable Particles Determination (March 29, 30, & 31, 2010)**

----- (b)(4) -----

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HVAC

- **PCS-VA-007 – Aseptic Area (b)(4) Air Conditioning System (HVAC) Installation Qualification Protocol**
- **PCS-VA-007/I – Report for the Aseptic Area (b)(4) Air Conditioning System (HVAC) Installation Qualification (IQ)**

I reviewed these two documents together. The IQ Protocol (Date 11 AGO 2009 – 11 AGO 2011) was a 25 page document describing the HVAC system components and features that were expected. The IQ Report Date 14 AGO 2009) was a 21 page document that confirmed the parts of the HVAC that were expected were installed properly. This document appears to be acceptable. I do not have any comments. Aseptic Area (b)(4) is used for Anascorp manufactured for the US.

- PCS-VA-013 - Protocol for the Aseptic Area (b)(4) HVAC OQ
- PCS-VA-013-I - Report for the Aseptic Area (b)(4) HVAC OQ

I reviewed these two documents together. The OQ Protocol was a 16 page document dated 12/AGO/2009 through 12 Ago 2011. The report was an 8 page document dated 20 Ago 2009. The OQ documented the installation qualification for the HVAC system for Aseptic Area II. The OQ tested the functionality of all major HVAC components such as

----- (b)(4) -----
-----, The document appears to
be acceptable.

- **PCS-VA-012 Protocol for the Aseptic Area (b)(4) HVAC Performance Qualification (Dated 17 Aug 2009 through 17 Aug 2011)**
- **Performance Qualification (PQ) Report, code QV-PHARMA-RPQHvac-0609-R01 (Dated 21 Aug 2009)**
- **Addendum to Aseptic Area (b)(4) air conditioning system (HVAC) PQ Report, code PCS-VA-01(1) (Dated AUG 2009 to Feb 2010)**

I reviewed these three documents together and found them to be acceptable. Per the HVAC PQ Protocol, the HVAC system will be requalified every --(b)(4)--.

The aseptic area (b)(4) air conditioning system (HVAC) must guarantee that the following conditions are complied according to the guideline NOM-059 as described in the following table:

----- (b) (4) -----

Results

All of the acceptance criteria were met for room classification, differential pressure, and HEPA filter testing. Viable and non-viable particulate monitoring was performed in Aseptic Area (b)(4) under both static and dynamic conditions and all acceptance criteria were met.

The PQ report provided results and raw data to support the following conclusions:

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The Addendum performed the following tests and all specifications were met:

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- -----(b)(4)-----
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CR # 51

You state in your February 19, 2009, submission that a copy of the RO/DI system validation report is included in Appendix 1. A copy of this report was not included. Please provide a copy of this validation report.

Bioclon Response

The RO/DI validation report is attached. -----
----- (b)(4) -----
----- The requested reports (PCS-VA-003/I-001 - Results Report for the Reverse Osmosis Water System - April-Dec 2008, PCS-VA-003/I-001 - Results Report for the Reverse Osmosis Water System Jan-March 2009 and PCS-VA-003 - Results Report of Performance Qualification (PQ) of the Reverse Osmosis Water System) are attached.

FDA Response

I reviewed the RO/DI validation information and found it to be acceptable. I do not have any comments.

FDA Review

▪ PCS-VA-003 - Results Report of Performance Qualification (PQ) of the Reverse Osmosis Water System Revision A

FIRST PHASE

During the month of January 2008, the appropriate limits (Action and Alert) were established for the operation of the Reverse Osmosis Water System. -----

----- (b)(4) -----

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1 page redacted (b)(4)

CR # 53

Please provide data to support conclusions obtained in the water system validation report and the HVAC system validation report. Also, please reference the meeting minutes dated April 10, 2009, in which CBER/DMPQ stated that a retrospective data review for the water system may not be an acceptable validation of the system. Please provide a justification for performing only a retrospective data review for validation of the water system.

Bioclon Response

*HVAC System has been re-validated as described in **CR#43**. WFI is purchased from -----(b)(4)----- as described above; therefore this observation has been resolved in a different mode than the requested justification since the retrospective aspect no longer applies.*

FDA Response CR#53

The HVAC system validation was described and is acceptable. The RO System PQ was described and alert and action levels were set. Trend data for the first quarter of 2009 was submitted and it was acceptable. The data for the purchased WFI was reviewed during the Pre-License inspection and found to be acceptable.

CR#38

The FDA held two Type C meetings (January 8, 2008 and April 10, 2008) with your firm in which we specifically stated what type of information you needed to submit to the BLA. You proposed to follow these guidance documents:

- **Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice**
- **Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products**

You did not submit all information as put forth in these guidance documents and as specified in the Type C meetings. This includes, but is not limited to, providing validation data for hold time for water used in production that is held in secondary containers and providing information on container/closure integrity testing such as CCI testing results and CCI validation and summary results. Please review all meeting minutes, guidance documents, and additional information requests and provide all information as requested. If information is not available for a requested item, please state that no information is available for the requested item. The information submitted must be detailed, concise, and coherent. Please submit the information even if you already believe the information is contained in the BLA or the amendments. The information as provided in the original BLA and amendments is not presented in a detailed, concise, coherent manner that allows for a timely and

accurate review of the submission. We are unable to come to an informed conclusion and recommendation on adequacy given the information you previously provided.

Bioclon RESPONSE

This response summary provides amended and more detailed descriptions of the production areas and each stage of the production process beyond the original BLA submission (BLA STN 125335/0).

FDA Response CR#38

This statement appears to be an accurate statement. The response is accepted.

CR #39

Please provide the registration number for your Tlalpan facility.

Bioclon Response

The Establishment Registration number has not been assigned for the Tlalpan facility to date although we have confirmation of current Drug Firm Annual Registration status as of November 8, 2010.

Attachment - Drug Firm Annual Registration Status – printed November 8, 2010 and Establishment Registration SPL - submitted August 23, 2010.

FDA Response

The FEI Number for Bioclon is 3007581821

CR #40

You must resolve all outstanding inspectional observations listed on FDA Form 483. For example, Bioclon's RESPONSE to FDA Form 483 Item #1 is unacceptable. An acceptable inspection of your facilities is required prior to licensure.

Bioclon Response

We have responded to the Agency's inspectional observations (FDA Form 483) as a separate document. A portion of the 483 responses are identical or paraphrased from this document to provide consistency.

FDA Response:

FDA performed a Pre-License Inspection at the Bioclon Facility 13-17, 20-22 June. A ten item Form FDA 483 was issued at the conclusion of the inspection. The inspection was classified as VAI. The responses to the 483 were received 06 July 2011 and they were acceptable. The prior Form FDA 483 observations from the 2009 inspection were reviewed during the current inspection and it was determined the observations were addressed in an acceptable manner.

CR #41

CMC information provided to the BLA should be applicable to the conformance lots. If there were process improvements since the manufacture of the conformance lots, please provide detailed descriptions of these improvements including their date(s) of implementation.

Bioclon Response

The validated process has not had significant process changes. Improvements or enhancements to generate a more consistent process were incorporated into the revised BPR. As noted above, the completion of the SUV runs provided additional enhancements and necessary documentation changes to improve and provide a higher level of standardization to the process execution and documentation. Processes of this nature frequently encounter minor changes that may or may not require validation activities. Regardless, any changes are to be managed in accordance with the Change Control procedure. Prior to the initiation of the conformance batches the necessary documentation changes will have been implemented.

FDA Response

This response is acceptable.

CR #6

You should complete process validation. This includes, but is not limited to, time limits for holding of production water in secondary containers, aseptic processing, room environment qualification under dynamic conditions, and cleaning of the vials and stoppers including -----(b)(4)----- reduction validation. Please provide detailed descriptions and data summaries.

Bioclon Response

The SUV report attached with CR#1 above addresses each of the critical aspects of the fractionation, purification, ----(b)(4)----- and sterile bulk process as well as monitoring systems to ensure a consistent operation. Responses to the specific examples listed above are used to demonstrate the more comprehensive process control and documentation managed by the enhanced BPR. WFI hold times are discussed in CR# 49, media fills to support the aseptic processing is provided in CR#58, dynamic room qualification is included in CR#48 and cleaning of vials are discussed in CR#5b and stoppers information are provided in CR #45.

Individual validation activities have continued since the prior plant inspection and implementation of the process tracking system has been implemented ----(b)(4)----- to provide continuous statistical and trending process assessment using statistical tools as more data is obtained from normal operation. Examples of the additional validation activities are provided throughout this document (See CR # 40-45).

FDA Response CR # 6

I reviewed the responses to **CR #1, CR #49, CR #48, CR #5(b), CR #45, and CR # 40-45** and found them to be acceptable; therefore the response to **CR #6** is acceptable. The reviews for the listed CR responses are contained within this review memo.

CR # 49

-(b)(4)-

Bioclon Response

-(b)(4)-

FDA Response:

No data was included with this submission so I reviewed the WFI testing during the Pre-License inspection and found it to be acceptable.

During the inspection I reviewed the specifications and data supporting a -(b)(4)- hold time (expiration date) for the purchased WFI.

-(b)(4)-

- (f) Neither the MBPR nor the FBPR record the actual number of vials filled for the media fills. The FBPR records “theoretical volume” and a “no. of theoretical pieces,” but you did not record actual fill volume and actual number filled. You recorded the number of vials incubated, but not the number filled.
- (g) Please provide additional information describing how the media fill and the actual aseptic fill are similar. In areas that are not similar, please provide the justification for their applicability and/or acceptability.

Bioclon Response 58 (a)

The Filling and Lyophilization BPR is being revised with the new format as with the provided examples. The corrections for this observation will be included in the latest revision and will be used for the conformance batches. A brief comment is that the SOP listed above should have been “13 instead of “31”.

Bioclon Response 58 (b)

During the review of both BPRs, SOP P-PB-054 is for the operation of the --(b)(4)-- washer machine and Bioclon currently uses the --(b)(4)-- washer machine for both applications (production and media fill), hence the SOP reference has been removed from the Media fill and aseptic filling process BPRs.

Bioclon Response 58 (c)

The BPRs (Production Filling and Lyophilization and the Media Fill BPR) have been reviewed and are being revised to accommodate these changes for the conformance and on-going production process. The instruction sets are similar for both BPRs which will utilize the following format.

Bioclon Response 58 (d)

SOP P-PB-029 is correct and SOP-PB-056 will be revised so the two documents are equivalent.

Bioclon Response 58(e)

Both BPRs were reviewed and are being revised to provide similar instructions both

Bioclon Response 58 (f)

Both BPRs were reviewed and are being revised to provide similar instructions for both BPRs.

Bioclon Response 58 (g)

SSR and Rational (study design) to be included in the Media Fill BPR

FDA Response CR # 58 (a) – 58 (g)

Bioclon’s response is acceptable for CR# 58 (a) – 58 (g). Media fills were reviewed during the most recent inspection.

In the BLA narrative, the cleaning procedure only describes the vials placed and washed in the -(b)(4)- washing machine; however, the actual vial washing procedure starts out with a --(b)(4)-- cleaning of the vials prior to placement into the --(b)(4)-- washer. Please comment.

Bioclon Response

*The cleaning procedure (P-PB-013) indicates that only -(b)(4)- is used for the cleaning process which is technically only a rinse process. No vial cleaning is done prior to placement in the -(b)(4)- washer. ------(b)(4)-----
------. The error was in the batch record DA-PB-002 Rev A, which has been revised.*

FDA Response

The validation of the -(b)(4)- washer was reviewed during the Pre-License inspection and found to be acceptable.

CR #45

In the Additional Information Request dated February 6, 2009, we asked you to provide additional information for the container closure system. You provided a partial response.

- (a) Please provide the finalized approved protocol for the container closure system assessment along with a detailed summary of the executed protocol and data to support your conclusions.**
- (b) In your response you reference a stopper extractable ------(b)(4)----- test report performed by (b)(4). Please provide a rationale for how the extractable studies for the stoppers (as performed by (b)(4)) apply to your product.**
- (c) Validation of container closure integrity testing was not provided as requested.**
- (d) You state that leak testing is performed per the ------(b)(4)-----
------. Please provide an explanation how the leak test as performed per the ------(b)(4)----- is equivalent to microbial or dye ingress leak testing. Please provide evidence of validation of the container closure integrity test.**

Bioclon Response 45 (a)

A description of the container and closure system, and its compatibility with the biological substance is provided in the compatibility report which includes detailed information concerning the supplier, address, and the results of compatibility, toxicity and biological tests. Results of the container closure integrity are included as well. The lyo stoppers are -(b)(4)- Gray bromobutyl which are compliant with the requirements for a Type (b)(4) closure. The attached copy of the DMF (-(b)(4)-) letter provides reference

the closure details (CR#45b). The Container Closure System assessment was completed and details summary of the executed protocol along with data are attached. Responses to “b” and “c” below comprise the entire response with respect to the closure system compatibility and integrity.

Attachment

- *PCB-CC-004 - Container Closure System Validation Protocol*
- *PCB-CC-004-I004 – Container Closure (CC) System Validation Report.*
- *PCB-CC-003 – Protocol for Evaluation of Compatibility of Container-Closure System for Anti-Scorpion Polyvalent Fabotherapics (Alacrity/Anascorp)*
- *PCB-CC-003-I003 - Scorpion Container Closure System Report.*

Bioclon Response 45 (b)

An important aspect of the stopper application is that the stopper and product contact is minimal. Only to (b)(4) of product is added to the 10mL vial prior to lyophilization. After freeze drying, the cake remains in the bottom of the vial prior to re-constitution (dissolution) immediately before use. Once dissolved, the product is dispensed from the single dose vial within minutes, due to the urgency of the application for patient treatment. The dissolved fluid is --- (b)(4) --- and does not contain aggressive chemicals that would generate leachable or extractable concerns outside the challenged elements of the DMF and the internal testing conducted in accordance with the attached compatibility protocol. The (b)(4) authorization for the FDA to review the DMF --- (b)(4) ---, the formulation characteristics for the -(b)(4)- Gray stopper and the --- (b)(4) --- study results are attached.

Bioclon Response #45 (c)

----- (b)(4) -----

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----- (b)(4) -----

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Bioclon Response #45 (d)

----- (b)(4) -----

(b)(4)

FDA Response CR # 45

I reviewed the responses for CR # 45 (a) – (d) and found them to be acceptable. In addition, this information was reviewed during the Pre-License inspection and found to be acceptable. I do not have any questions.

FDA Review CR #45 (a)

I reviewed the attachments listed above and the extractable --- (b)(4) --- information provided by (b)(4) for the stopper and found it to be acceptable. Based on the information provided, the container closure system consisting of a 10 mL Type (b)(4) clear glass vial, (b)(4) grey bromobutyl rubber stopper, and a (b)(4) aluminum crimp cap is acceptable for use with Anascorp. Bioclon provided container closure integrity testing which is performed by ----- (b)(4) ----- testing. The test met the specifications ----- (b)(4) -----, which is the release specification for final product.

Bioclon also provided data to demonstrate the container closure system is compatible with Anascorp. The quality attributes tested during this study were those that would reflect any change resulting from the interaction between the product and the container-closure system. The quality attributes evaluated were as follows: appearance of reconstituted material, proteins content, -----(b)(4)-----
-----, safety, -----(b)(4)----- . All specifications were the final release specifications of the product during routine manufacturing.

NOTE: Bioclon did not test the sensitivity of the ---(b)(4)--- test for CCIT; however, after discussing this with Carolyn Renshaw, Branch Chief, and Deborah Trout, Team Lead, it was decided that this was acceptable since the -----(b)(4)----- test is a better

test for lyophilized products. Bioclon will not have to determine the sensitivity of the -----(b)(4)-- test since they perform the ---(b)(4)--- test.

- ***PCB-CC-003 – Protocol for Evaluation of Compatibility of Container-Closure System for Anti-Scorpion Polyvalent Fabotherapics (Alacrity/Anascorp)***
- ***PCB-CC-003-1003 - Scorpion Container Closure System Report.***

I reviewed the two above listed documents together and found them to be acceptable. I do not have any questions or comments. The unexecuted protocol and the report generated from the execution of the protocol were provided. The purpose of the study was to evaluate the compatibility between the container closure system and Anascorp. The container closure system that had product contact consisted of the following:

- 10 mL Type (b)(4) vial, supplied by -----(b)(4)-----.
- Gray rubber slotted stopper. -----(b)(4)-----.

The quality attributes tested during this study were those that would reflect any change resulting from the interaction between the product and the container-closure system. The quality attributes evaluated were as follows: appearance of reconstituted material, proteins content, -----(b)(4)-----, safety, -----(b)(4)----- . All specifications were the final release specifications of the product during routine manufacturing. There must be no significant difference between control group and test groups and results must comply with specifications, as stated for Anascorp.

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---(b)(4)---

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Vials from three lots were tested and all acceptance criteria were met.

The results demonstrate that the contact between the reconstituted product with the vial and the stopper does not affect the product potency as all the tested groups comply with the product specifications. In some cases, there are variations detected between the control and the test group. These variations are related to the analytical method, so the product maintains its required potency for administration to patients. In conclusion, the experimental study shows that under these conditions the vial and the stopper do not affect the product potency in the three lots tested.

The following conclusions are determined after the study:

- The components of the container closure system are compatible with the reconstituted product.

Attachment

- *PEE-AC-001/E - Shipping Validation Protocol*
- *PEE-AC-001/ER - Shipping Validation Report*
 - *Appendices*
 - *Appendix 1. Protocol Flowchart*
 - *Appendix 2. Box Diagrams*
 - *Appendix 3. Label, box and package insert specifications*
 - *Appendix 4. Label contents approval forms*
 - *Appendix 5. Materials' approval forms*
 - *Appendix 6. Pictures*
 - *Appendix 7. Shipping Log*
 - *Appendix 8. Temperature and RH shipping logs*
 - *Appendix 9. Certificate of Analysis of pre-shipment samples*
 - *Appendix 10. Certificate of Analysis of shipped samples*
 - *Appendix 11. Certificate of Analysis of control samples*

FDA Response:

I reviewed the above protocol and validation report summary along with the appendices and found the procedure to be acceptable. The product met release testing specifications pre- and post-shipment and even though the environment around the shipped containers reached a maximum temperature of 36°C, the product was not adversely impacted.

FDA Review

A summary of the shipping validation was included in the response. The product was shipped according to Bioclon's packaging and shipping SOPs and shipped from Mexico to the distribution warehouse in Tennessee; from Tennessee to Arizona; from Arizona back to Tennessee; and from Tennessee back to Mexico. The shipment went through Customs twice (to the US from Mexico and from the US into Mexico) where the outer box was opened for examination. The shipping validation was performed in the summer from 19 June to 10 July 2009, thus the package would have been exposed to possible high heat conditions. A temperature data logger and shock monitor was included in the packaging. The maximum temperature reached was 36°C and the minimum temperature reached during shipment was 18 °C. Per Bioclon, this meets their specification of -----(b)(4)-----. The product was tested per release specifications prior to shipment and post-shipment when the material was returned to Bioclon. All release specifications were met. The product was shipped in a cardboard carton without any cold packs or other type of material to keep the boxes cool.

CR #42

You should complete equipment qualification on all major manufacturing equipment used in the production of Anascorp. Please provide detailed descriptions and data summaries. This includes, but is not limited to, cleaning validation with appropriate clean and dirty hold times. Please provide information on all equipment qualification and cleaning validation even if it was previously included in the original BLA and/or amendments.

-----,

----- (b)(4) -----

Conclusions

The --(b)(4)-- washing machine (----(b)(4)----) performance qualification (PQ) was performed on 03/JUN/09. The PQ work showed that the equipment complies with the performance conditions and acceptance criteria set forth in the Performance Qualification protocol.

----- (b)(4) -----

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----- (b)(4) -----

CR #47

Please provide additional information on your equipment cleaning validation and sanitization qualification, such as information on swab recovery studies, and a clear, detailed description of the cleaning process used for equipment cleaning validation and how it is applicable to the actual cleaning procedure used during manufacturing. You provided a small diagram in an amendment depicting the swab sample areas for a -----(b)(4)-----, but no narrative descriptions or justifications of the sample areas. Please provide this information.

Bioclon Response

-----*(b)(4)*-----
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-----*(b)(4)*-----
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-----*(b)(4)*-----

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References

- *PVL-VA-002 - Equipment Used for the Manufacture of Fabotherapeutic Products Cleaning and Sanitization Protocol Addendum*
- *PVL-VA-002/I001 - Report for the Cleaning and Sanitization Validation of Equipment Used for the Manufacture of Fabotherapeutic Products for the Protocol Addendum*
- *PVL-VA-005 - Validation Protocol of the Cleaning Process of the --(b)(4)- System Equipment*
- *PVL-VA-005/I001 - Validation Process Report of Cleaning and Sanitization from the Equipment --(b)(4)- System*
- *P-PB-082 - Standard Operating Procedure for Cleaning and Sanitization of the -----*(b)(4)*-----*

FDA Response

I reviewed the listed attachments and found them to be acceptable. Appropriate cleaning validation was performed and clean hold times and dirty hold times were established. I do not have any questions.

FDA Review

- *PVL-VA-002 - Equipment Used for the Manufacture of Fabotherapeutic Products Cleaning and Sanitization Protocol Addendum*
- *PVL-VA-002/I001 - Report for the Cleaning and Sanitization Validation of Equipment Used for the Manufacture of Fabotherapeutic Products for the Protocol Addendum*

The purpose of the protocol was to validate the cleaning of the following pieces of multi-product equipment used in the Fabotherapeutics manufacture and packaging processes:

-----*(b)(4)*-----

1 page redacted (b)(4)

Each piece of equipment met their respective acceptance criteria. -----

----- (b)(4) -----

----- (b)(4) -----

- **PVL-VA-005 - Validation Protocol of the Cleaning Process of the --(b)(4)-- System Equipment**
- **PVL-VA-005/I001 - Validation Process Report of Cleaning and Sanitization from the Equipment --(b)(4)-- System**

These two documents were reviewed together as one was the unexecuted protocol and the second document is the report that resulted from the execution of the protocol. Both documents were acceptable.

The purpose of the cleaning validation was to demonstrate the cleaning and sanitization process of the -(b)(4)- System equipment used in the Fabotherapeutic products manufacturing is reproducible, reliable and meets the acceptance criteria established. Since this -(b)(4)- System is a multi-product system, the cleaning procedure was also intended to show that there is sufficient removal of any residual product to ensure there isn't any cross contamination.

The process validation of cleaning and sanitization from the -(b)(4)- System equipment used in the Fabotherapeutic products manufacturing process involved the analysis of the ----- (b)(4) -----.

The protocol established the steps for the cleaning and sanitization process validation, as well as the equipment used in manufacturing, the analytical methods to be used, the detergent employed for cleaning and the sanitizing used for microbiological control and the responsibilities of the staff involved in validation.

The cleaning validation consisted of using "worst case" conditions since these conditions represent the greatest cleaning challenge. This validation study was performed with 3 manufacturing batches.

For the cleaning validation the condition of worst case will be selected and they are those under which the cleaning process represents a higher challenge, in this study will be considered the critical factor which in the case of this equipment it is only the product to be tested.

----- (b)(4) -----
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(b)(4)

----- (b)(4) -----
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Results

All acceptance criteria were met. The residual product values are below the acceptance criterion established demonstrating that the procedure used for cleaning is reproducible, reliable and guarantees that the residual product levels are kept within the allowable limits and thus, the cross-contamination of the products is avoided. The ----- (b)(4) ----- tests also met specifications.

■ P-PB-082 - Standard Operating Procedure for Cleaning and Sanitization of the

----- (b)(4) -----

----- (b)(4) -----

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----- (b)(4) -----
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CR #5 (a)

The information in the original application and amendments appear contradictory or inaccurate.

**The narrative in the BLA for the room classifications does not match the room classifications described in the HVAC validation summary such that -----
------(b)(4)----- in the
narrative; however, in the HVAC validation summary both of these sample points are described as ---(b)(4)---. Please comment.**

Bioclon Response

*The BLA room classifications described in the HVAC validation summary were correct at -----
------(b)(4)-----, whereas the room classification described in the Amendment was incorrect. The diagram states -(b)(4)- whereas the description is correct at -----
------(b)(4)-----.*

FDA Response

This response is acceptable.

CR #7

**Please establish sufficient in-process controls to demonstrate that you have a controlled manufacturing process. For example, in-process specifications or action levels should be set based in part on process validation and equipment qualification. Specific examples include -----
-----(b)(4)----- and the allowable failure rate for the number of vials not passing specifications after washing or depyrogenation. The specifications and/or action levels and results must be captured in the applicable batch production record. Please provide a justification for your in-process specifications and/or action levels.**

Bioclon Response

In the revised BPRs for the conformance batches and ongoing for each of the critical in-process control elements is to be documented and the specified acceptance criteria listed. Some examples within this document provide the format that will continue to be used in any future revisions. For non in-process testing, such as EM action alert and action levels, the data will be statistically assessed on an ongoing basis to establish more appropriate levels if needed.

------(b)(4)-----:

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----- (b)(4) -----:

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FDA Response

This response is acceptable.

CR #46

You should establish a final specification or action level for the total number of filled drug product vials that may be rejected during final visual inspection before a lot must be held and a determination is made to discard the entire lot. Please submit this specification or action level.

Bioclon Response

SOP for visual inspection was modified to establish a final specification or action level for the total number of filled drug product vials that may be rejected during final visual inspection. P-PF-062 – Standard Operation Procedure for Visual Inspection of Fabotherapeutics is attached.

FDA Response

I reviewed the supplied SOP and found it to be acceptable. The SOP listed types of defects such as critical, major, and minor along with associated alert and action levels.

----- (b)(4) -----

CR #12

In your April 6, 2009, response to our request for additional information for filter compatibility testing, you stated that you used the information provided by --- (b)(4) -- to determine the compatibility of the filter with the product. Additionally, you stated you used the filters for - (b)(4) - for the same process and the finished product was compliant with the quality specifications. Please justify why information obtained by -- (b)(4) -- is applicable to your product. Please provide the

approved protocol you used and the summary of the report written to document that the --(b)(4)-- filters are acceptable for use without performing compatibility testing.

Bioclon Response

(b)(4)

(b)(4)

----- (b)(4) -----

------(b)(4)-----

(b)(4)

FDA Response

This response is acceptable.

CR #11 (d)

Regarding filtration steps:

In your April 6, 2009, response, you state that if a filter becomes blocked while in use, -----(b)(4)----- . Please note that this practice is unacceptable. Developmental studies should be performed to determine the adequate filter size to prevent clogging. Process validation of filtration should demonstrate that the filters are adequately sized to perform the function required without clogging. If any filter becomes clogged or if the time to filter increases during the manufacture of the drug substance or final drug product, we will consider this a deviation requiring an investigation.

Bioclon Response

-(b)(4)-

FDA Response

This response is acceptable.

CR # 50

-(b)(4).

Bioclon Response

-(b)(4)-

FDA Response

-(b)(4).

CR # 52

You provided a list of sample ports and a list of specifications for each port during the validation of the RO/DI systems. It appears some ports may have two different specifications for microbial limits (WFI and Purified Water). Please provide rationale for the two different specifications and provide the justification for the use of two different specifications for the same sample port.

Bioclon Response

There is only one specification for the RO system. -----

----- (b)(4) -----

----- WFI is treated and handled completely separate as described above in CR#49.

FDA Response

This response is acceptable.

CR # 53

Please provide data to support conclusions obtained in the water system validation report and the HVAC system validation report. Also, please reference the meeting minutes dated April 10, 2009, in which CBER/DMPQ stated that a retrospective data review for the water system may not be an acceptable validation of the system. Please provide a justification for performing only a retrospective data review for validation of the water system.

Bioclon Response

HVAC System has been re-validated as described in CR#43. WFI is purchased from ----- (b)(4) ----- as described above, therefore this observation has been resolved in a different mode than the requested justification since the retrospective aspect no longer applies.

FDA Response

This response is acceptable.

CR # 54

On page 32 of 44 of the original submission you state that the differential pressure between each room is --- (b)(4) --- monitored. On page 2 of 42 of the February 19, 2009, amendment you state that it is a -- (b)(4) -- observation. This information appears to be contradictory. Please clarify how differential pressure is monitored between adjacent manufacturing rooms.

Bioclon Response

----- (b)(4) -----

FDA Response

----- (b)(4) -----

FDA Response

This response is acceptable.

CR # 56

Please clarify if you perform routine environmental monitoring during dynamic or static conditions.

Bioclon Response

Routine Environmental Monitoring is conducted under both static and dynamic conditions as addressed in CR# 43 and CR# 48 above.

FDA Response

This response is acceptable.

CR # 57

We requested that you submit additional information on the HVAC system in our March 25, 2009, information request. Your April 6, 2009, RESPONSE included summaries of typical results obtained during three separate drug product manufacturing runs. We cannot discern the acceptability of the data provided in the tables because the sample points are identified in the diagrams with numbers and the results are identified with a description. You provided personnel monitoring results in three tables. It appears the monitoring was for three different batches; however, only one set of results is provided. It is not clear if only one person was

monitored or if these tables are the results of all personnel monitored during the fill. We were unable to determine if you monitored all sample points. You provided acceptance criteria for Class (b)(4) areas; however, it appears Sample 3 is located in a Class (b)(4) area. Please clarify this information and provide a response in a detailed, concise, and coherent manner.

Bioclon Response

The tables below are corrected and slightly modified versions of the previously submitted tables. The listed results (----- (b)(4) -----) are identical to the original data. A significant error in the diagrams is that the classified areas were improperly labeled. The gowning and degowning listed as Class (b)(4) should have been Class (b)(4). Similarly, the use of the term “----- (b)(4) -----” is incorrect as ----- (b)(4) -----.

Environmental Monitoring Results

----- (b)(4) -----

Redact 1 page (b)(4)

This response is acceptable.

CR # 58

We asked you to provide a comparison of the procedure performed during your routine media fills and the procedure that actually occurs during the aseptic filling process (February 6, 2009). Your February 19, 2009, Response stated that the two processes are similar and you provided an executed media fill batch record to illustrate this statement. You did not include a written narrative. A comparison of the manufacturing batch production record (MBPR) submitted in the original BLA with the media fill batch production record (FBPR) submitted in the amendment raised the following concerns regarding equivalency:

- (a) The MBPR references SOP P-PB-031 (Preparation and washing of vials in the -(b)(4)-) and SOP P-PB-015 (Operation of the Dry Heat Oven Type --(b)(4)--), but the FBPR does not reference these SOPs.
- (b) The MBPR references SOP P-PB-054, but the FBPR does not.
- (c) The MBPR provides instructions on the washing of the filling syringe, but the FBPR does not. The MBPR references room release, environmental monitoring prior to room release, inspecting vials -----
------(b)(4)-----
---. These steps are not mentioned in the FBPR.
- (d) The FBPR references SOP P-PB-029 for how to perform the filling operation while the MBPR references P-PB-056 for the filling operation.
- (e) The MBPR references entering materials into the fill area -----
------(b)(4)-----
------. This entry process is not mentioned in the FBPR.
- (f) Neither the MBPR nor the FBPR record the actual number of vials filled for the media fills. The FBPR records “theoretical volume” and a “no. of theoretical pieces,” but you did not record actual fill volume and actual number filled. You recorded the number of vials incubated, but not the number filled.
- (g) Please provide additional information describing how the media fill and the actual aseptic fill are similar. In areas that are not similar, please provide the justification for their applicability and/or acceptability.

Bioclon Response 58(a)

The Filling and Lyophilization BPR is being revised with the new format as with the provided examples. The corrections for this observation will be included in the latest

revision and will be used for the conformance batches. A brief comment is that the SOP listed above should have been “13 instead of “31”.

Bioclon Response 58 (b)

During the review of both BPRs, SOP P-PB-054 is for the operation of the -(b)(4)- washer machine and Bioclon currently uses the -(b)(4)- washer machine for both applications (production and media fill), hence the SOP reference has been removed from the Media fill and aseptic filling process BPRs.

Bioclon Response 58 (c)

The BPRs (Production Filling and Lyophilization and the Media Fill BPR) have been reviewed and are being revised to accommodate these changes for the conformance and on-going production process. The instruction sets are similar for both BPRs which will utilize the following format.

Bioclon Response 58 (d)

SOP P-PB-029 is correct and SOP-PB-056 will be revised so the two documents are equivalent.

Bioclon Response 58 (e)

Both BPRs were reviewed and are being revised to provide similar instructions both

Bioclon Response 58 (f)

Both BPRs were reviewed and are being revised to provide similar instructions for both BPRs.

Bioclon Response 58 (g)

SSR and Rational (study design) to be included in the Media Fill BPR.

FDA Response

The responses for CR #58 (a) – (g) are acceptable.

CR # 59

Regarding your sterility testing, please indicate if you performed any type of Bacteriostasis / Fungistasis testing to show that a negative sterility test result for the bulk drug substance and the bulk drug product is accurate.

Bioclon Response

------(b)(4)----- testing is performed to show that a negative sterility test result for the bulk drug substance and drug product is accurate.

Attachment

- PVA-AC-001 – Closed System Sterility Test Validation Protocol for the -----(b)(4)-
----- Method

- *PVA-AC-001/I001 – Validation Report for the Sterility Test Using the -----
-(b)(4)----- Method*

FDA Response

I reviewed both documents listed above and found them to be acceptable.

FDA Review

The first document listed was the unexecuted protocol and the second report listed was the report from the executed protocol. The product tested was Alacramyn Lyophilized End product /5 mL Diluent which is acceptable since Anascorp is the US version of Alacramyn. It is the same product manufactured under the same conditions with the same formulation except Alacramyn is for the Mexican market and Anascorp is for the US market. The protocol procedure follows -----(b)(4)----- and -----
------(b)(4)------. Bioclon used appropriate ATCC strains to ensure that the product did not inhibit growth of bacteria or fungi.

------(b)(4)-----
-----.

These results lead to the conclusion that the sterility test under a closed system under the conditions of the test is appropriate for the analyzed product. The test guarantees that microorganisms such as: aerobic bacteria, yeasts and fungi will grow in the (b)(4) incubation period.