DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Meeting Response Memorandum

Our Reference: CRMTS #7259
Ref #STN 125335/0

Division of Blood Applications

TODAY'S DATE: November 17, 2009 **PAGES:** 5

TO: ----------(b)(4)--------
c/o --------(b)(4)--------
Instituto Bioclon, S.A. de C.V.
email: ---------(b)(4)----------

FROM: Debbie Cordaro
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OBRR
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SUBJECT: Summary of FDA Internal Meeting

PRODUCT: Centruroides (Scorpion) Immune F(ab)2 Intravenous (Equine)

We have completed our review of your information package for Centruroides (Scorpion) Immune F(ab)2 Intravenous (Equine) and are providing the following responses to the questions you posed in the package. Although we continue to reserve November 19, 2009 11:00 am–12:30 pm for a telecom with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us as soon as possible so that the meeting time may be cleared. Alternatively, if you have questions regarding specific responses or advice, please inform us so that the appropriate members of the review team can provide clarification during the reserved meeting time.

THANK YOU

General Comments

With regards to applicant actions following receipt of a complete response letter, according to 21 CFR 601.3(b)(1) the applicant will "resubmit the application or supplement, addressing all deficiencies identified in the complete response letter". The Agency would like to verify that Bioclon understands that the review process will commence once all items noted in the complete response letter of 23 July 2009 are addressed.

Questions from the Applicant:

Chemistry, Manufacturing and Controls (CMC)

Applicant Question 1: _Regarding Item 81

Please set a separate specification for --(b)(4)-- to reflect the amount present in the final formulation.

Discussion Points:

The current test method for --(b)(4)-- is conducted according to the --(b)(4)--. This test method is indicated for use for both to cresol and --(b)(4)--, and does not discriminate between the two compounds. In our response to the Agency dated June 17,2009 (included in Attachment 2), we provided typical values for --(b)(4)-- plus cresol in Anascorp finished product lots, as well as calculations showing the theoretical maximum amount of each compound in the finished product based on dilution during processing. These data showed that the maximum value for the combination of cresol and -(b)(4)- is --(b)(4)-----, considerably below the cresol level in Humalog (Insulin Lispro Recombinant) and well below a level that would be expected to pose a safety risk for either compound. Based on these calculations and analytical results, we believe that a release specification for Anascorp drug product should specify a maximum limit for the combination of --(b)(4)-- and cresol, and we are proposing to set this specification based on the previously conducted analysis of finished product lots.

We wish to discuss this proposal with the Agency and obtain feedback on its suitability.

FDA Response to Question 1:

The Agency accepts that a maximum limit for the combination of *(b)(4)* and creosol may be set. The release specification should be set based on data obtained from your manufacturing experience with this product.

Applicant Question 2: Regarding Item 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.

Discussion Points:

We believe that the previously submitted retrospective validation, including data review, of the RO/DI system is appropriate since:

- *The system is routinely tested against(b)(4)standards for Purified Water, and has consistently met the requirements since being installed.*

- *The RO/DI water produced by the system is used ----------(b)(4)----------. Sterile Water for Injection (WFI) purchased from an approved supplier (----(b)(4)-------) and tested before use is used for -----(b)(4)----------.*

We wish to verify that FDA agrees with this approach, and to obtain additional input from the Agency regarding the RO/DI water system validation.

FDA Response to Question 2:

The Agency can neither agree nor disagree with this approach since no protocol or data were provided in the original submission to support your assertion that the RO/DI water met stated specifications. No explicit justification was provided as to the rationale for the acceptability of using water from a system that is not validated for manufacture of a commercial product. Final RO/DI water test results are not the sole criterion used to determine appropriate validation. In addition to final testing, the Agency looks at IQ, OQ, and PQ along with preventive maintenance schedules, P&IDs, and change control to determine if a system is appropriately validated. Please reference CR # 51 and 52 as part of the information that we need to determine if your system is appropriately validated. As it currently stands, that information supplied by Bioclon in the original application is insufficient to determine the state of validation and control of the RO/DI system.

In addition, the Agency will not recognize the statement repeatedly made by Bioclon that RO/DI ----------(b)(4)----------.

Applicant Question 3: Regarding Item 50

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

Discussion Points: ----------*(b)(4)*----------

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

----------*(b)(4)*----------
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FDA Response to Question 3:

The Agency cannot comment on the reason for the apparent discrepancy since the Agency has never seen documented evidence for the ----------
----------(b)(4)----------
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Sponsor Question 4: Regarding Item 26:

Please verify that in the event of a nanofilter clog or a postfiltration integrity test failure, the affected lot of product will be discarded. If you propose reprocessing, you should submit an SOP and prospective validation plan.

Discussion Points:

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

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We wish to obtain FDA's feedback on the proposed plan ----------*(b)(4)*--------.

FDA Response to Question 4:

This is not acceptable. Please reference #11d in the CR letter in which the Agency states, "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." ----------(b)(4)---------- cannot substitute for adequate process validation; Bioclon must validate their manufacturing process such that filters are appropriately sized and will not clog.