DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

Official Meeting Summary

Meeting ID #:	CRMTS #7259
Application type and number:	BLA 125335/0
Product name:	Centruroides (Scorpion) Immune F(ab)2 Intravenous (Equine)
Firm:	Instituto Bioclon, S.A. de C.V.
Meeting type:	Type C
Meeting category:	BLA, Other
Meeting date & time:	November 19, 2009, 11:00 a.m. – 11:45 a.m.
Meeting format:	Teleconference
Meeting Chair/Leader:	Robert Fisher, Ph.D.
Meeting Recorder:	Debbie Cordaro

FDA Attendees:

Basil Golding, M.D., Director, Division of Hematology, OBRR
Nancy Waites, Biologist, Division of Manufacturing and Product Quality, OCBQ
Lori Peters, Consumer Safety Officer, Division of Manufacturing and Product Quality, OCBQ
Robert Fisher, Ph.D., Staff Fellow, Division of Hematology, OBRR
Dorothy Scott, M.D., Chief, Laboratory of Plasma Derivatives, Division of Hematology, OBRR
Michael Kennedy, Ph.D., Team Lead, Division of Hematology, OBRR
Debbie Cordaro, Regulatory Project Manager, Division of Blood Applications, OBRR

Instituto Bioclon, S.A. de C.V. (Bioclon) Attendees:

Juan Lopez de Silanes, President, Instituto Bioclon, S.A. de C.V.
Rita Mancilla Nava, Plant Manager, Instituto Bioclon, S.A. de C.V.
Jorge F. Paniagua, Ph.D., Vice President, Instituto Bioclon, S.A. de C.V.
Walter Garcia Ubbelohde, M.D., Medical Director, Instituto Bioclon, S.A. de C.V.
Araceli Olguin, Manager, Research & Development
Milton Ellis, President, Rare Disease Therapeutics, Inc.
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Background and Objectives:

On January 21, 2009, Instituto Bioclon, S.A. de C.V. (Bioclon) submitted an original biologics license application (BLA) for the use of Centruroides (Scorpion) Immune $F(ab)_2$ Intravenous (Equine) in the treatment of clinically important signs of scorpion envenomation. On July 23, 2009, FDA issued a complete response (CR) letter. On September 15, 2009, the firm submitted a meeting request, including meeting materials, (attachment 1) to discuss four Chemistry, Manufacturing and Controls (CMC) items in the letter.

FDA sent proposed responses to the CMC questions to the firm on November 17, 2009 (attachment 2). After reviewing the proposed responses, Bioclon notified FDA that they decided to limit the agenda for this meeting to questions 2 and 3 (attachment 3). At FDA's request, on November 17, 2009, Bioclon submitted a brief outline of their concept of process validation (attachment 4).

Discussion:
Bioclon noted they submitted their concept of process validation as requested by the Agency. By the end of the month, Bioclon expects to complete a process validation protocol that they will submit to FDA. Also, they expect to complete a tech transfer procedure to the Tlalpan facility by November 30, 2009. The firm anticipates requesting a meeting with the Agency, for the week of January 18, 2010, to discuss the tech transfer.

When asked if the firm intends to request a meeting to discuss additional CMC issues in the CR letter, Bioclon stated further discussion is needed regarding items 15 and 82 of the CR letter.

Chemistry, Manufacturing and Controls (CMC)

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.*

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

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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 because Bioclon did not provide a protocol or data in the original submission to support their assertion that the RO/DI water met stated specifications. The firm did not provide an explicit justification 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 letter items 51 and 52 as part of the information 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 ----------(b)(4)----------.

Additional discussion:
Bioclon stated that they asked specifically about the RO/DI validation because they understood the information the Agency was requesting for HVAC in the original CR letter. After the discussion, Bioclon also understood that a retrospective validation of the RO/DI system is still necessary even if the company is ----------(b)(4)----------.

With regard to HVAC issues, Bioclon confirmed that they added the relevant humidity controls FDA requested, although they did not submit details in this submission. The firm performed a prospective validation of the humidity controls, but they omitted this information from this submission.

Applicant Question 3:
[Regarding Item 50]
----------*(b)(4)*----------.

Discussion Points:

----------*(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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Additional Discussion:

Bioclon acknowledged they did not submit the WFI documents. When asked if after Bioclon shows they included the WFI information in the batch record, and confirms WFI ----------(b)(4)----------, they would need to validate the RO/DI, FDA responded they would still need to perform a validation even though it is retrospective. FDA is looking for how the firm plans to document what they do, including change control, SOPPs, and P&ID drawings (any changes to RO/DI system) that will be caught in the P&ID. While Bioclon states they performed a retrospective validation, FDA reminded Bioclon to include acceptance criteria, and documentation of situations where the criteria were not met. The documentation of the investigation of these situations should completely describe the event and the corrective action taken.

FDA asked about the data demonstrating the use of -(b)(4)-. When FDA asked how the firm ----------(b)(4)----------, Bioclon responded they will use a process tank filled with ---
----------(b)(4)----------
---------- will provide process validation demonstrating the washing is performed aseptically, and include hold times, and the multiple transfers to validate the process.

Final discussion:

Bioclon stated that they were no longer considering the proposed -------(b)(4)----------, and noted that they have several years of experience using the current system without problems. ----------
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----------(b)(4)----------

FDA performed a high level review of the firm's concept of process validation and it appears reasonable. The issue of RO/DI was addressed in the outline submitted. FDA clarified that the firm should submit batch records, the number of mixing steps, and a validation of each hold step. Bioclon agreed to submit more detail in the future and indicated they would submit a draft protocol for process validation by the end of November. They informed FDA that their plans were to run process validation lots in mid-to-late January and requested feedback from the Agency prior to January 18, 2010. FDA suggested Bioclon submit an updated batch record for future discussions. Bioclon responded that it was a work in progress but they were willing to provide a copy. FDA reiterated that the batch records should include allowable ranges for hold times, mixing speeds, in-process testing sample details and any other pertinent information.

Decisions made and/or agreements reached:
The firm will provide information as discussed during this meeting.

Issues requiring further discussion:
None.

Action items:
The firm will respond to the CR letter.

Attachments/Handouts:

1. Meeting materials submitted 17-SEP-2009 L# 473020 STN 125335/0/29
2. FDA's proposed responses sent to the firm November 17, 2009.
3. Response from Firm regarding draft responses. Telecon 17-NOV-2009
4. Outline of process validate submitted by Bioclon Telecon 17-NOV-2009

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