Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To:	File for 125335
From:	Robert Fisher, Staff Fellow, CBER/OBRR/DH/LPD, HFM-345
Through:	Michael Kennedy, Team Lead, CBER/OBRR/DH/LPD, HFM-345
CC:	Dorothy Scott, Chief, CBER/OBRR/DH/LPD, HFM-345
Product:	Centruroides (Scorpion) Immune $F(ab')_2$ (Equine) Injection "Anascorp"
Subject:	Final CMC review for STN 125335/0, Centruroides (Scorpion) Immune $F(ab')_2$ (Equine) Injection, "Anascorp"

Recommendation:

Approval with the following post-marketing commitments:

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

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

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

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

Executive Summary:

In February 2011, the original BLA for Anascorp was transferred to Rare Disease Therapeutics, Inc. (RDT) from Instituto Bioclon and a response to the Agency's 23 June 2009 Complete Response Letter received. RDT/Bioclon performed process validation as described in the 15 July 2010 telecon held

between the sponsor and the Agency. The process improvements, process validation, and in-process controls were found to be adequate and sufficient for licensure. Four PMCs were requested in order to tighten specifications and formalize discussions related to equine plasma testing; RDT agreed to these changes in an amendment received 13 July 2011.

Background:

1. STN 125335/0 is an original BLA submission for *Centruroides* (Scorpion) Immune $F(ab)_2$ (Equine) Injection.
    a. The final drug product is a lyophilized equine $F(ab')_2$ concentrate produced from the plasma of horses immunized with venom extracted from 4 species of North American scorpions: *Centruroides limpidus limpidus*, *Centruroides noxius noxius*, *Centruroides limpidus tecomanus*, and *Centruroides suffusus suffusus*.
    b. Phase II and III studies were performed under IND--(b)(4)--
2. I was responsible for reviewing Chemistry, Manufacturing, and Controls section of this submission (Volumes 1.2 to 1.4), with the exception of viral clearance validation, raw materials, stability, specifications, and assay validation.
3. A response to the 88-item complete response (CR) letter was received in February 2011.
    a. Most (CR items 1-59) CR items were CMC in nature and were issued and reviewed by the product office and DMPQ. CR items 82-88 were related to animal husbandry issues and were reviewed by the Division of Veterinary Services consult by Dr. Beren.
        i. The justification for PMC 4 is outlined in Dr. Beren's memo. ----------(b)(4)----------.
    b. The product office CR items can be broadly grouped into 1) lack of adequate process validation, 2) lack of adequate in-process control data, 3) lack of adequate documentation in the master batch record (or batch production record, BPR)
        i. Process validation is reviewed in section 5 below. Briefly, 3 pilot scale lots were produced followed by 3 scale-up validation lots and 3 conformance lots. The latter 6 lots were produced at full production scale.
        ii. Additional in-process controls were implemented throughout the manufacturing procedure. This included ----------(b)(4)----------. For details see figure 1.
        iii. Over the course of this review, Bioclon has submitted three versions of their BPR. Revision A was in place during the initial review and was found to be an inadequate description of the manufacturing process.
            1. CR item 3 specifically pointed out deficiencies in the Revision A BPR. As a result Bioclon submitted a revision (Revision B) in their February 2011 CR response. This BPR contains additional detail, including mixing start and stop times, process limits, and verification signature fields. Notably ----------(b)(4)----------.

2. Conformance lots were manufactured with BPR Revision C. Changes from revision “B” were editorial in nature.

4. Manufacturing process (based on BPR Revision C, valid from February 2011-February 2013):
   a. Note that Bioclon has indicated (response to CR items 11d and 26) that ----------(b)(4)----------.
   b. Venom Production
      i. ----------
      ii. ----------.
      iii. ----------.
      iv. ----------.
      v. ----------.
      vi. ----------.
      vii. ----------.
   c. Plasma Collection
      i. Animal husbandry issues including immunizations and bleeding procedures were reviewed in a consult by Dr. Joel Beren, D.V.M.
         1. ----------.
         2. ----------.
         3. ----------.
      ii. ----------.
      iii. ----------.
      iv. ----------.
      v. ----------.
      vi. ----------.
      vii. ----------.
      viii. ----------.
   d. ----------

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e. ----------

i. ----------.

ii. ----------.

iii. ----------

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iv. ----------.

v. ----------.

vi. ----------.

vii. ----------.

viii. ----------.

f. ----------.

i. ----------.

5. Process Validation:
   a. No process validation was provided in the original submission, as the sponsor indicated in STN 125335/0.10.
      i. While Bioclon *appeared* to follow a process that produced product in a consistent manner (as evidenced by bulk and final release testing of 10+ years of product for the Mexican and other markets), no studies were performed to demonstrate robustness. In addition, in-process controls were inadequate to ensure control of the manufacturing process. No studies were performed to examine mixing times and speeds, ----------(b)(4)----------.
      ii. The original prelicensure inspection held during April 2009 resulted in several 483 items directly attributable to the lack of process validation. This included issues with the master batch record.
      iii. These deficiencies were discussed with the sponsor during the original prelicensure inspection, and were included in the CR letter issued in June 2009.
   b. Several telecons were held with the sponsor to address the CMC issues, both from the prelicensure inspection as well as from the CR letter.
      i. A telecon to address CRMTS 7259 was held 19 November 2009, after the Agency submitted responses to the firm on 17 November 2009.
         1. Bioclon proposed setting a specification for cresol (CR item 81) that would reflect the concentration of -(b)(4)- and cresol in the product; the Agency agreed with this proposal, and indicated that the specification should be based on data from manufacturing experience with this product. Bioclon also proposed the use of a ----------(b)(4)---------- (CR item 26). The Agency did not find this acceptable since process validation for nanofiltration had been found inadequate, and Bioclon was informed that the process should be validated such that the filters would be appropriately sized as to avert clogging. After reviewing the Agency's responses, Bioclon had additional questions on the use of RO/DI water testing and use of WFI in their manufacturing process (CR items 50, 51, and 52). ----------(b)(4)----------. Bioclon was informed that after a high-level review of the process validation included in the meeting pre-read materials, the Agency found the

proposal reasonable. The Agency requested that revised batch records, additional information on mixing steps, and validation for each hold step be submitted.

ii. Another Type C meeting (CRMTS 7330) was scheduled for 21 January 2010 to discuss Bioclon's proposed responses to the CR letter.

1. During the internal pre-meeting on 08 January 2010, significant information gaps were identified. The sponsor was made aware of the deficiencies and agreed to postpone the meeting the meeting until additional information was submitted and reviewed. On 25 February 2010, the sponsor notified the Agency that they could not provide an estimate on when the meeting materials might be expected; therefore the CMRTS 7330 meeting was canceled with the expectation that when the information was available, a new meeting request would be generated.

iii. On 07 May 2010, the Agency received a request for a Type C meeting from the sponsor including pre-read materials. An internal meeting was held on 7 July 2010, and the Agency's responses provided to the sponsor on 12 July 2010. The telecon with the sponsor was held on 15 July 2010, and the meeting minutes provided to them on 13 August 2010.

1. The Agency acknowledged that Bioclon had made progress in addressing the issues identified in the CR letter, and provided advice in terms of specific deficiencies in the master batch record. They were also advised to perform process validation/engineering runs prior to their conformance lots, and to ensure that the production scale was adequate to validate their manufacturing procedure. It was also suggested that --------(b)(4)------- plasma (if available) be used during the PV/engineering runs to conserve this resource. A resubmission (including responses to the CR items) was anticipated to be submitted in February 2011, with a September 2010 cutoff for clinical data.

c. Bioclon subsequently ran 3 small scale lots (----------(b)(4)----------) prior to their full scale lots. See **Error! Reference source not found.**.

i. Critical process parameters were established based on historical data and a design of experiments (DoE) analysis, per validation protocol I-PVP-ID-001 (Appendix A).

ii. All three lots met the pre-established acceptance criteria. No deviations were reported.

d. Bioclon then ran (b)(4) scale-up (SUV) batches with Batch Production Record (BPR) Revision "B" at full commercial scale ranging from (b)(4) of starting ------(b)(4)------ plasma.

i. Scale-up verification data was contained in PTP-ID-1000/FDA/01, dated January 2011 (Appendix B).

ii. Lot ---(b)(4)-- was manufactured from (b)(4) batches of concentrate, each manufactured with (b)(4) of plasma (-(b)(4)-, initiated 31 August 2010 and -(b)(4)-, initiated 03 September 2010). Lot -(b)(4)- was manufactured from a (b)(4) starting plasma volume (initiated on 7 September 2010), and lot --(b)(4)- was manufactured from one (b)(4) starting plasma volume (initiated on 10 September 2010). See table 2.

iii. Note that one SUV lot (---(b)(4)--) was manufactured from concentrates obtained from -(b)(4)- runs. ----------(b)(4)----------.

1. ----------

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

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

iv. All three scale-up lots met acceptance criteria, including in-process control and release testing.

v. Three deviations were reported during the SUV lot production runs.

1. Deviation 10-020 reported a failure of the -(b)(4)- pump ----------(b)(4)----------. A maintenance order was generated and the equipment repaired. The incident was noted in the BPR, and the root cause was lack of maintenance on the pump. The corrective action was to repair the pump. Preventative actions included placing the --(b)(4)--- pumps on an (b)(4) maintenance program.
2. Deviation 10-024 reported a power failure during the (b)(4)filtration of lot -(b)(4)-. The operator isolated product in the (b)(4) system by ----------(b)(4)----------. The incident was noted in the BPR. The emergency power system provided backup power within several minutes of the outage, and product samples were analyzed and determined not to have been affected. Root cause was power interruption from the mains, and corrective actions included product testing (as described above). Preventative action included verification of backup power availability.
3. Deviation 10-032 was triggered by QA/QC personnel when recurrent documentation issues were noted with lots being produced under BPR Revision “B”. A list of errors found was included in the deviation report. The corrective action was to follow SOP P-AC-205 for management and control of incidents, and personnel were retrained on Good Documentation Practices, Good Manufacturing Practices, and a request to change control to modify the BPR to make it less confusing for the operators.

e. Three conformance lots were generated in 2011. Two were being manufactured during the June 2011 prelicensure inspection, and one (lot (b)(4)) was manufactured in March 2011. These lots will be the first Anascorp lots introducted into the U.S. market.

6. Revalidation intervals for the manufacturing process should not exceed --(b)(4)- (per I-PVP-ID-001).

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