Memorandum

Date: 10 July 2009

To: File for STN 125335/0

From: Robert Fisher, Staff Fellow, CBER/OBRR/DH/LPD, HFM-345

Through: Dorothy Scott, Chief, CBER/OBRR/DH/LPD, HFM-345

Subject: CMC complete review, STN 125335/0, Instituto Bioclon *Centruoides* (Scorpion) Immune $F(ab)_2$ Intravenous (Equine)

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1. Executive summary
    a. A complete review of STN 125335/0 has been performed, and specific deficiencies identified in the CMC section of the submission. These include (but are not limited to) inadequate animal husbandry procedures, inadequate testing of source equine plasma, lack of process validation, lack of hold time validations, and inadequate in-process controls.
2. Recommended action:
    a. Communicate the following complete response to the sponsor:
        i. ANIMAL HUSBANDRY
            1. Please verify that you will utilize plasma screening procedures, such as those described in 9 CFR 113.53, to preclude introduction of adventitious agents into your manufacturing stream. This may be done on the plasma pool in lieu of testing individual plasma units.
            2. In the absence of adequate data to validate cleaning and sterilization for the needle and tubing set used in bleeding your donor herd, a new sterile disposable hypodermic needle and sterile disposable IV collection set should be used for each bleed.
            3. Given the excessive bleed volumes and aggressive bleeding schedule, it is very strongly recommended that the hematocrit of donor horses be measured and documented prior to each bleed and one day post. Animals with hematocrits below 25% should not be bled and hematocrits should not drop below 18% post bleed. This information should be amended to the veterinary records for each horse.
            4. You should use unique container identification, such that ----------(b)(4)----------
            5. Please establish a quality assurance certification program to include ------(b)(4)------, and water. The water source for your donor animals should be monitored to ensure sufficient quality; an annual report from the municipal water supplier may be sufficient if contaminants such as toxic organic compounds e.g. herbicides and pesticides in use in the region are monitored.

6. Please verify that your SOP P-SA-029 establishes adequate withdrawal times for each therapeutic used for treatment of your donor herd.
7. We acknowledge your response of 01 May 2009 that indicates horses will be immunized against ----------(b)(4)----------. Please verify that lots of your product designated for the U.S. market will be manufactured using plasma from vaccinated horses.

ii. CHEMISTRY, MANUFACTURING, AND CONTROLS

1. Your conformance lots should be manufactured on the scale that you intend to market in the United States.
2. Your document control procedures should include adequate revisioning procedures. The revision "A" batch records included in your submission of 4 June 2009 (STN 125335/0.23) appear to precede the batch records in place during the prelicensure inspection.
3. Ensure that your batch record captures all relevant aspects of the manufacturing process. For example, for steps where a mixing time is specified a start and stop time should be recorded; for steps where multiple mixing procedures are performed each one should be documented as executed.
4. The list of reagents used in your manufacturing process is incomplete. For example, ----------(b)(4)---------- ---------- but is not included in the list of reagents specified in your BLA. Please prepare and submit a comprehensive list of reagents including the supplier, purpose, quality standard, and certificate of analysis. This list should include excipients as well as materials used to formulate buffers.
5. Your process narrative is not in agreement with your batch record. Please revise your process narrative and resubmit.
6. You should establish sufficient in-process controls to demonstrate that you have a controlled manufacturing process. These additional controls should include bioburden and endotoxin determinations, protein concentration, and protein recovery and/or yield.
7. You should validate the mixing times and speeds used in your manufacturing process. For example, you should have data to demonstrate that ----------(b)(4)---------- at a certain speed for a given amount of time achieves adequate mixing. This type of validation should be performed for each mixing step in your manufacturing process. Note that it is highly recommended that ----------(b)(4)---------- ----------
8. You should establish minimum and maximum process times for each stage, including ----------(b)(4)---------- ----------(b)(4)---------- ----------. These times should be based on your manufacturing

experience with this product and should be set in such a manner that any unusually short (or long) process times would be noticed as a deviation from the normal process. For example, ----------(b)(4)----------. Robustness should be demonstrated for a minimum and maximum -(b)(4)- time. Likewise, your ----(b)(4)---- step should be performed for a validated, defined amount of time.

9. For steps involving pH changes, the rate of addition of acid or base should be controlled to minimize the formation of high pH gradients. The total amounts of acid or base added should be measured and fall within a pre-determined volume. In general, any step where material is added to the process stream should be controlled with regard to the rate of introduction.
10. Regarding filtration steps:
    a. For all filtration steps in the batch record, please indicate the number and types of filters used.
    b. For steps where filters are rinsed before use, please specify a time, flow rate, and volume for the rinsing solution.
    c. Note that filtration steps should be controlled with regard to pressure and/or flow rates.
    d. If you experience filter clogs during --------(b)(4)----------, you should evaluate the appropriateness of your filtration procedure and/or filter materials.
11. The batch record should include instructions for the preparation of all reagents (for example, ----------(b)(4)----------).
12. Please provide a list of hold times for all buffers used in the manufacturing process.
13. Please set appropriate upper and lower limits on the amount of plasma used in the fractionation process, ----------(b)(4)----------. You indicate in your 01 May 2009 response that -(b)(4)----------. Please provide data to demonstrate that lots manufactured with ------(b)(4)----------; this would typically involve manufacturing one conformance lot for each condition.
14. Please provide data validating the cleaning, sterilization, and depyrogenation of the -(b)(4)- containers used for collection of horse blood.
15. Prolonged storage times of intermediates at -(b)(4)- may adversely impact product stability and dating period due to proteolytic

enzyme activity and increased bioburden. You will need to validate the hold times used for storing the process intermediates and bulk product. This validation should include bioburden, endotoxin, molecular integrity, potency, and other parameters as appropriate.

16. Please submit a cleaning/sanitization study for the -(b)(4)-- system. Include details on how you will determine the maximum number of uses of the ------(b)(4)-----.
17. Please describe how many lots require additional -------(b)(4)-------
    ----------.
18. Please establish a ramping rate for all flow rate changes involved in the -(b)(4)- process.
19. Please expand upon your answer #31 in STN 125335/0.22, where the ----------(b)(4)----------
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20. With regard to formulation, your process should be controlled to the point where you are able to use a consistent procedure for formulation. If -(b)(4)- of your runs require a ---(b)(4)--- procedure at the formulation step while -(b)(4)- do not, this indicates a fundamental difference in the manufacture of these lots.
21. Your formulation procedure is not adequately described in the master batch record; please specify what volume of (b)(4) is used to dissolve the excipients, what mixing method is used to dissolve the excipients, and the mixing conditions for blending the excipient solution with the product concentrates. Note that these mixing conditions should be validated with an appropriate mixing study.
22. Please note that if you intend to ----------(b)(4)----------
    ----------, you would have to validate this process and demonstrate that it does not impact product stability or quality.
23. For the nanofiltration step, please establish specifications for ramp times during pressure changes
24. Please verify that in the event of a nanofilter clog or a post-filtration integrity test failure, the affected lot of product will be discarded.
25. Please explain why no deviation was recorded in the executed batch record for the event observed on 24 April 2009 where the air hose attached to the nanofiltration pressure tank was forcibly ejected.

3. Summary:
    a. STN 125335/0 is an original BLA submission for *Centruroides* (Scorpion) Immune $F(ab)_2$ Intravenous (Equine)

i. The final drug product is a lyophilized $F(ab')_2$ 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*.
ii. Phase II and III studies were performed under IND -(b)(4)-

b. 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.
c. A CMC information request was submitted to Bioclon prior to midcycle; see my CMC midcycle memo dated 15 April 2009 uploaded to the EDR.
    i. Responses were submitted in STN 125335/0.22, received 01 May 2009.
    ii. This response was reviewed and taken into consideration for my review of the manufacturing process.
d. A prelicensure inspection was held on the Tlalpan and ----(b)(4)---- facilities in April 2009 and numerous 483 observations issued.
    i. The sponsor replied to the 483 observations on 4 June 2009; however many of the remedial steps were scheduled to take place in June/July 2009.
        1. In general, the responses to the 483 items were acceptable; however they will have to be confirmed on a follow-up inspection.
    ii. The master batch record has been updated, and it appears that "new" conformance lots are being generated without sufficient validation.
    iii. A copy of the executed batch record for Lot ---(b)(4)-- (produced during the inspection) was submitted on 24 June 2009 in STN 125335/0.25. Notably, an incident observed during nanofiltration where an air hose was blown off the pressure tank (as described in the EIR) was not captured as a deviation.
e. Process Validation:
    i. No process validation was performed, as indicated in STN 125335/0.10.
    ii. The following are listed as process controls:
        ----------(b)(4)----------

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    iii. In-process control samples are taken according to the following chart:

[--(b)(4)--]

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

f. STN 125335/0.23 received on 12 June 2009 provided a revised batch record (DM-CB-008 revision A, DM-PR-001 revision A, DM-PB-001 revision A, and DA-PB-002 revision A) based on some of the comments and 483 observations issued during the April 2009 pre-license inspection. This review is based on the original batch record (DM-CB-008 revision E, DM-PR-001 revision A, DM-PB-001 revision F, and DA-PB-002, revision A). Please note that the document codes and revisions are not typographical errors; there appears to be overlap in their document control procedures. ----------(b)(4)----------.

g. The process summary provided in the CMC midcycle memo was based on the process narrative provided in the original BLA submission (STN 125335/0). It became clear during the inspection that the process narrative is not in agreement with the master batch record; therefore my review is based on the batch record contained in STN 125335/0..

h. Manufacturing process:
   1. Venom Production
      ----------(b)(4)----------

8 (Eight) Pages Found to be Non-Releasable: (b)(4)