

## LATE CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** Thursday, November 21, 2013 at 2 p.m. to 4 p.m.

**Meeting Location:** Woodmont Office Complex I  
Conference Room 1  
1401 Rockville Pike  
Rockville, MD 20852

**Application Number:** STN 125488/0

**Product Name:** Crotalidae Immune F(ab')<sub>2</sub> Equine Injection

**Indication:** Management of patients with pit viper envenomation and prevention of late or recurrent coagulopathies

**Applicant Name:** Instituto Bioclon S.A. de C.V.

### INTRODUCTION

The purpose of this Late Cycle meeting (LCM) is to share information, to discuss substantive review issues identified to date, and to communicate our objectives for the remainder of the review cycle. This application has not yet been fully reviewed by the signatory authority, division director or chairperson; therefore, the meeting will not address the final regulatory decision for the application. We are sharing this information to promote collaborative and successful discussion.

Please be advised that any new information submitted before the LCM that had not been requested by the Agency will not be addressed during the meeting. Furthermore, during the meeting, we may request the submission of additional information, as necessary, to address identified issues. Our planned review timelines for any requested additional information will be communicated to you during the meeting.

**SUBSTANTIVE ISSUES TO BE DISCUSSED AT THE LATE CYCLE MEETING:**

**CHEMISTRY, MANUFACTURING AND CONTROLS:**

1. Please commit to (b) (4) [REDACTED]  
(b) (4) [REDACTED] production lots of Anavip and/or identically manufactured products with different specificities.
2. Per pharmacology/toxicology concerns regarding possible worst case scenario cresol exposure to patients (b) (4) [REDACTED]
3. Bioclon does not have critical reagents for their potency assay (snake venom standards and internal positive control) on an ongoing stability program.
4. Bioclon has agreed to (b) (4) [REDACTED] but the validation will not be completed until the end of March 2014 so this will need to be a PMC.
5. Bioclon has not provided any (b) (4) [REDACTED]
6. The stability data suggest that they need shorten the dating period for both drug substance and drug product.

**FACILITIES AND EQUIPMENT:**

7. No substantive issues at this time and no PMCs at this time.

**NON-CLINICAL PHARMACOLOGY/TOXICOLOGY:**

8. Worst case scenario exposure calculations raise concerns regarding possible exposures to cresol that are higher than other approved products. At these amounts there is potential for adverse reactions due to cresol such as generalized myalgias. (b) (4) [REDACTED]

**CLINICAL PHARMACOLOGY:**

9. There are no substantive review issues at this time.

**CLINICAL:**

10. The pre-specified primary endpoint for superiority over CroFab with regard to prevention of recurrent coagulopathy was not met with statistical significance. Additional assessment of efficacy parameters is ongoing.

**BIORESEARCH MONITORING:**

11. There are no substantive review issues at this time.

**PHARMACOVIGILANCE:**

12. There are no substantive review issues at this time.

**REMS OR OTHER RISK MANAGEMENT ACTIONS:**

13. No issues were identified that would require a *Risk Evaluation and Mitigation Strategy* (REMS).

**LABELING:**

14. APLB will perform a secondary review of the proprietary name within 90 days of the Action Due Date.
15. Recommendations to the *Prescribing Information* and the vial and carton labels will be provided as part of the labeling review.

**ADVISORY COMMITTEE MEETING:**

16. Presentation of the BLA at the Blood Products Advisory Committee meeting is not planned.

**PMR/PMC:**

17. Bioclon commits to (b) (4) [REDACTED] production lots of Anavip and/or identically manufactured products with different specificities.
18. Bioclon commits to provide the test method standard operating procedures (SOPs), method validation protocols, and method validation study reports (including all test results) for the detection of cytopathogenic and/or hemadsorbing agents (as described in 9 CFR 113.46) and the detection of extraneous viruses by the fluorescent antibody technique (as described in 9 CFR 113.47).

19. Bioclon commits to (b) (4) product lots of Anavip and/or identically manufactured products with different specificities.
20. Bioclon commits to (b) (4) in the final drug product and performing the appropriate process validation to support the necessary manufacturing changes related to the (b) (4).
21. Instituto Bioclon commits to completing the validation of their (b) (4) and providing CBER the final validation report by April 30, 2014.
22. Bioclon commits to provide stability updates for the conformance lots manufactured in support of STN 125488/0 (lots (b) (4) plus one lot to be initiated during the pre-licensure inspection). These updates will be submitted annually as a PMC Annual report, and the final stability report will be submitted as a PMC Final Study report within 3 months of the final time-point.

**OUTSTANDING INFORMATION REQUESTS:**

23. On November 7, 2013, the pending information request sent by the agency to the applicant is one. An information request was sent to Instituto Bioclon on November 6, 2013. Instituto Bioclon acknowledged receipt of this request. The response is expected on November 21, 2013.

LCM AGENDA

1. Introductory Comments – 5 minutes (RPM/Chair)  
Welcome, Introductions, Meeting guidelines, Objectives of the Meeting
2. Discussion of Substantive Review Issues – 55 minutes (Review Committee)
  - a. Substantive issues
  - b. Outstanding information requests
3. Post-marketing commitments and risk management – 10 minutes (CMC Reviewer)
4. Questions from Instituto Bioclon – 10 minutes
5. Wrap up and Action Items – 10 minutes