DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125488/0 **BLA APPROVAL**

Instituto Bioclon, S.A. de C.V.
Attention: Walter Garcia Ubbelohde, MD
Amores No. 1304
Colonia del Valle
Mexico City, Distrito Federal
Mexico

Dear Dr. Garcia Ubbelohde:

We have approved your biologics license application for Crotalidae Immune F(ab')$_2$ (Equine) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Crotalidae Immune F(ab')$_2$ (Equine) under your existing Department of Health and Human Services U.S. License No. 1900. Crotalidae Immune F(ab')$_2$ (Equine) is indicated for management of adult and pediatric patients with North American rattlesnake envenomation.

Under this authorization, you are approved to manufacture Crotalidae Immune F(ab')$_2$ (Equine) drug substance at the Instituto Bioclon, S.A de C.V. facility in (b) (4) Mexico and drug product at Instituto Bioclon, S.A de C.V; (b) (4) , Mexico. You may label your product with the proprietary name Anavip and you will market it in 20 mL vials as a sterile lyophilized powder

We did not refer your application to the Food and Drug Administration Blood Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefited from an advisory committee discussion.

The dating period for Crotalidae Immune F(ab')$_2$ (Equine) shall be 24 months from the date of manufacture when stored at 25 ± 2 °C/(b) (4) relative humidity conditions. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product in accordance with 21 CFR 610.50. Following the final sterile filtration, no reprocessing/ reworking is allowed without prior approval from the Agency.

Please submit final container samples of the product together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the

manufacturing, testing, packaging or labeling of Crotalidae Immune F(ab')$_2$ (Equine), or in the manufacturing facilities.

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to this BLA at the time of use (prior to marketing) and include implementation information on FDA Form 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Information on submitting SPL files using eLIST may be found in the guidance for industry titled, "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertisement and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 [21 CFR 601.12(f)(4)].

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims [21 CFR 202.1(e)(6)].

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. You should submit postmarketing adverse experience reports and distribution reports to the Office of Biostatistics and Epidemiology, at following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave
WO71-G112
Silver Spring, MD 20993-0002

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the biological product for this indication has an orphan drug designation, you are exempt from this requirement.

AGREED UPON POSTMARKETING COMMITMENTS

We acknowledge your written commitments as described in your letter dated April 21, 2015 as outlined below:

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

1. Instituto Bioclon, S.A. de C.V. (Bioclon) commits to (b) (4) the final study reports will be submitted as a BLA supplement by May 31, 2018 using data obtained with Anavip (b) (4) production lots.

2. Bioclon commits to provide the test method standard operating procedures (SOPs), validation protocols, and 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) as a BLA supplement by January 29, 2016.

3. Bioclon commits to (b) (4) using data obtained with Anavip (b) (4) production lots. The (b) (4) the final study report will be submitted as a BLA supplement by May 31, 2018.

4. Bioclon commits to perform a study to evaluate (b) (4) and to perform bioburden and endotoxin testing (b) (4) . Final testing (b) (4) will be done and the results will be compared with the product manufactured using the (b) (4) . The "Postmarketing Study Commitment – Final Study Report" will be submitted by November 30, 2015.

5. Bioclon commits to complete the validations of (b) (4) . Bioclon will provide the "Postmarketing Study Commitment – Final Validation Report" to CBER by August 31, 2015.

6. Bioclon commits to provide the (b) (4) and the final study report will be submitted as a BLA supplement by May 31, 2018.

7. Bioclon commits to provide stability updates for the conformance lots (b) (4) (a lot initiated during the pre-license inspection) annually in the PMC Annual Report. The final stability report will be submitted as a "Postmarketing Study Commitment – Final Study Report" by September 28, 2018.

8. Bioclon commits to submitting interim stability results for each conformance lot as "Postmarketing Study Commitment – Status Update" by September 30, 2016.

9. Bioclon commits to place the next three bulk lots on full stability study with at least the following parameters being monitored: (b) (4) by using the validated method (code PVM-ID-013). The "Postmarketing Study Commitment – Final Study Report" will be submitted by August 31, 2017.

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA, STN BL 125488. Please refer to the sequential number for each commitment and the submission number as shown in this letter.

Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Commitment – Status Update**
- **Postmarketing Study Commitment – Final Study Report**
- **Supplement contains Postmarketing Study Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a "**Postmarketing Study Commitment – Status Update**." The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-506B PMC; and,
- summarize any data collected or issues with fulfilling the non-506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Study Commitment – Final Study Report** or **Supplement contains Postmarketing Study Commitment – Final Study Report**.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Sincerely,

Jay S. Epstein, MD
Director
Office of Blood Research and Review
Center for Biologics
Evaluation and Research

Enclosure