Summary Basis for Regulatory Action

Date: 06 May 2015

From: Michael C. Kennedy, Chair of the Review Committee

BLA/ STN#: STN 125488/0

Applicant Name: Instituto Bioclon

Date of Submission: 18 March 2013

PDUFA Goal Date: 6 May 2015

Proprietary Name/ Established Name: Anavip/ Crotalidae Immune $F(ab')_2$ (Equine)
Indication: Management of adult and pediatric patients with North American rattlesnake envenomation

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Jay S. Epstein, M.D., _____
□ **I concur with the summary review.**
□ **I concur with the summary review and include a separate review to add further analysis.**
□ **I do not concur with the summary review and include a separate review.**

Offices Signatory Authority: Mary Malarkey, _____
□ **I concur with the summary review.**
□ **I concur with the summary review and include a separate review to add further analysis.**
□ **I do not concur with the summary review and include a separate review.**

Material Reviewed/ Consulted Specific documentation used in developing the SBRA Reviewer Name – Document(s) Date
Biomonitoring Review: Erin McDowell
Clinical Review: Mitchell Frost, Nisha Jain, Charles Maplethorpe
Clinical Pharmacology Review: Iftekhar Mahmood
CMC Review: John Dennis (consult), Robert Fisher, Maria Luisa Virata, Yonggang Wang, Michael Kennedy, Lilin Zhong
Epidemiology: Ravi Goud
Facilities (DMPQ): Nancy Waites
Labeling (APLB): Michael Brony
Lot Release/Testing plan: Erica Giordano, Karen Campbell, Joseph Quander, III

Pharmacology/ Toxicology Review: Evi Struble
RPM: Edward Thompson
Statistical Review: Mary Lin, Renee Rees

1. Introduction

Anavip [Crotalidae Immune F(ab')$_2$ (Equine)] is a lyophilized equine F(ab')$_2$ product indicated for the treatment of envenomation from North American rattlesnakes. Anavip is licensed to Instituto Bioclon, S.A. de C.V. ("Bioclon") at their facilities in Tlalpan, Mexico, D.F., and Mexico D.F, with the equine plasma obtained from Bioclon's horse ranch in The manufacturing facilities have been inspected by the Agency, most recently by Team Biologics in (b) (4).

The manufacturing process is based on repeated immunization of horses with a mixture of venoms from two Crotalidae species *Bothrops asper* and *Crotalus durissus*. The equine plasma is digested with pepsin, then precipitated with ammonium sulfate to purify the resulting F(ab')$_2$ contaminants, intact immunoglobulins, (b) (4). The pepsin digest and ammonium sulfate/heat treatment, steps early in the manufacturing process, contribute to viral inactivation. Nanofiltration is used to reduce the level of any viral contaminants that may persist. Additional levels of viral safety are provided by monitoring the health of donor horses, vaccinating horses against known epizootic diseases, and using procedures to screen plasma for adventitious agents.

Anavip is formulated with sucrose, glycine, , and sodium chloride. Trace amounts of pepsin, sulfates and cresol may be present in the product. The product is lyophilized in 20 mL glass vials, and has an expiry period of 2 years from the date of manufacture when stored at room temperature. The initial recommended dose is 10 vials, each reconstituted in 10 mL of 0.9% Sodium Chloride and then combined and further diluted in 0.9% Sodium Chloride to yield 250 mL of solution for infusion.

2. Background

The original BLA from Bioclon was received on March 16, 2013 requesting licensure of Anavip [Crotalidae Immune F(ab')$_2$ (Equine)]. Clinical studies to support licensure were conducted under IND 11275. Some of the studies to support licensure of Anavip were performed with Antivipmyn, an antivenin which has comparable source, manufacturing and composition as Anavip. (Noteworthy differences include (b) (4)

3. Chemistry, Manufacturing and Controls (CMC)

a) Product Quality

Equine plasma used in the production of Anavip is sourced from the production herd maintained at Bioclon's facility in Horses in the herd are identified by , and are vaccinated against Rabies, Western Equine Encephalitis (WEE), Eastern Equine Encephalitis (EEE), Venezuelan Equine Encephalitis (VEE), West Nile Virus (WNV), Influenza, Tetanus,

and Rhinopneumonitis. Food and water are monitored for contaminants under a quality assurance program; food is from qualified vendors. Bioclon conducts physical examinations on individual horses once per [redacted]

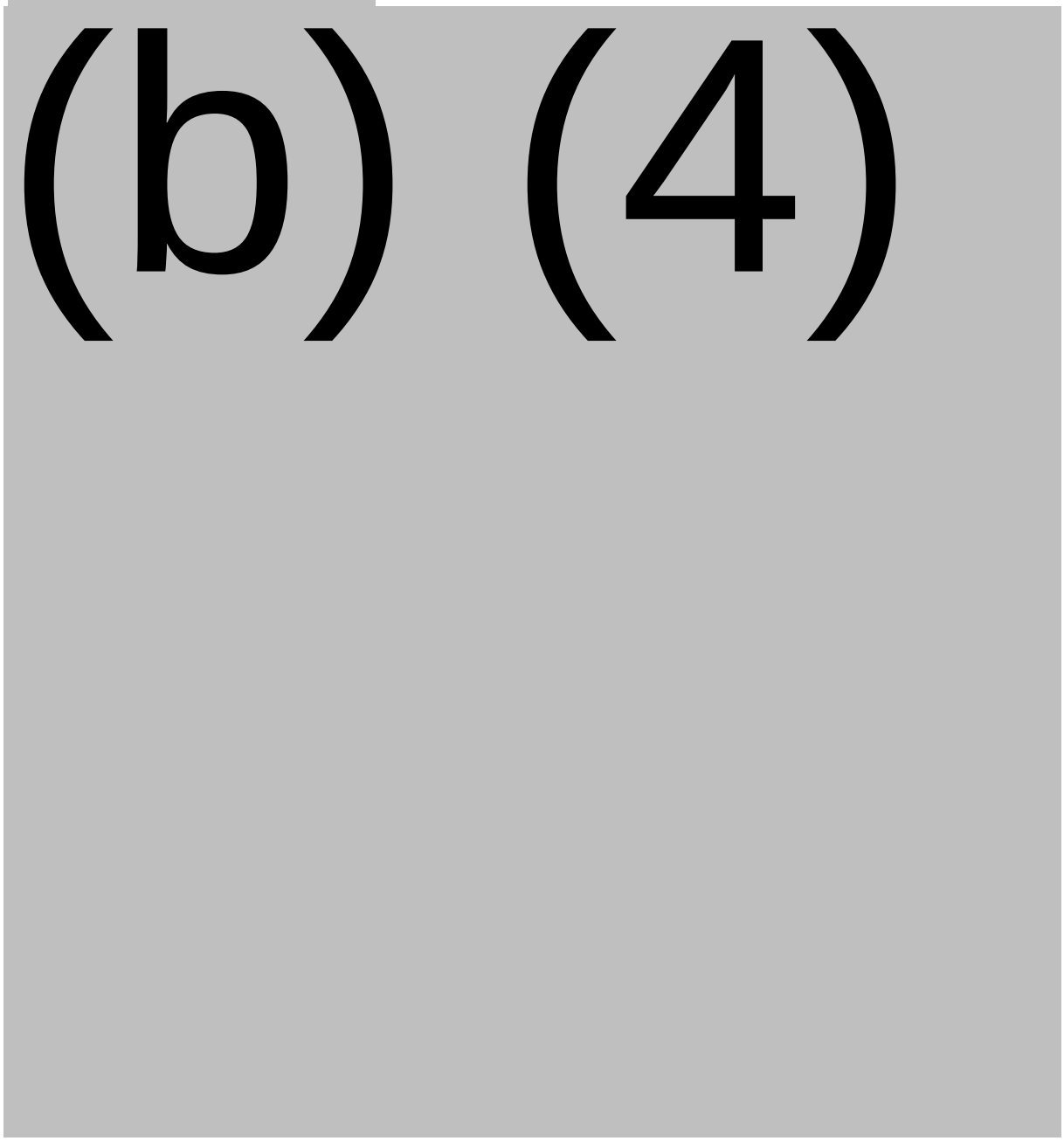
One challenge was to convince Bioclon that vaccinations were an important safety component to guard against viruses of known epizootic potential. Another challenge was to convey the importance of having a multi-tiered approach to protect against adventitious agents.

While Bioclon agreed to vaccinate the production herd against rabies (as well as VEE, WEE, and EEE as recommended by our veterinary staff), they remained hesitant to conduct screening on the equine plasma using the cytotoxicity assay. The rationale behind plasma testing (as described in 9 CFR 113.53(c) is to preclude the introduction of adventitious agents into the manufacturing facility and production stream. This test is based on screening plasma for overt cytotoxicity in cell culture, followed by immunofluorescence testing for known equine agents. FDA's experience is that this test has been useful and informative for screening equine plasma. Bioclon has committed to performing cytotoxicity testing as described in 9 CFR 113.53(c) on the equine plasma to preclude introduction of potentially contaminated lots into the manufacturing stream.

Other veterinary concerns included the aggressive bleed schedule in the absence of active monitoring of the health status of the donor horse. RBCs are separated from plasma, and then returned to the horse approximately [redacted] later. No data weres provided on the viability of the RBC, therefore Bioclon was asked to monitor the hematocrit levels of the donor horses and exclude any that were becoming anemic. Bioclon modified their donor horse testing scheme to accommodate this testing, and provided data to suggest that their bleeding procedures do not appear to lead to anemia at a [redacted] frequency in the donor herd.

Plasma obtained from the horses is tested for [redacted] using validated assays. It is transported and stored under appropriately validated conditions. In-process controls and release testing are performed at appropriate points in the manufacturing process to ensure control over the procedure. All raw materials used in the production of Anavip are from appropriately qualified vendors, quarantined on receipt, tested and released to production by QA personnel.

(b) (4)



Manufacture

Anavip is a sterile preparation of pit viper venom-specific $F(ab')_2$ binding fragments, presented as a lyophilized powder in a 20 mL vial. The drug substance is manufactured by Instituto Bioclon, S.A. de C.V. in Mexico and the drug product is is manufactured by Instituto Bioclon, S.A de C.V; Mexico. Anavip [Crotalidae Immune $F(ab')_2$ (Equine)] has venom-specific binding fragments, enzymatically derived from equine anti-pit viper venom immunoglobulin. The

antibodies are obtained from horses that have been hyperimmunized with the venoms of Crotalid species *Bothrops asper* and *Crotalus durissus.*

The antibodies are then cleaved by pepsin to form $F(ab')_2$ fragments. The $F(ab')_2$ content is at least 85% and Fab content is no more than 7%. Intact immunoglobulin is less than 5%. The product has a high specific activity, with a minimum of 780 LD_{50} (mouse) neutralizing units/vial for B. asper and a minimum of (b) (4) LD_{50} (mouse) neutralizing units/vial for C. durissus and a maximum protein content of 120 mg/vial.

Venom production.

Bioclon purchases *Bothrops asper* and *Crotalus durissus* pit viper venoms from commercial sources for use in their analytical assays, as well as for use in immunizing the donor horses.

Horse immunization and plasma collection.

Horses are vaccinated and boosted with a mixture of the venoms of Crotalid species *Bothrops asper* and *Crotalus durissus*.

Bulk, filling, and lyophilization process

(b) (4)

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5 pages determined to be not releasable: (b)(4)

(b) (4)

Bioclon provided the extractables and testing results performed by along with Bioclon's test results for testing the compatibility of the container closure system with the Anavip product. The quality attributes tested during this study were those that would reflect any change resulting from the interaction between the product and the container-closure system. The quality attributes evaluated were as follows:
(b) (4)
All specifications were the final release specifications of the product during routine manufacturing.

Bioclon has provided adequate information to determine the acceptability of their container closure system.

b) CBER Lot Release

Bioclon performs final container testing on all lots of Anavip; the tests performed by Bioclon were validated and are adequate to assure the safety and potency of the product. Release specifications are provided in the Table below. For post approval lot release, the applicant will submit samples and a lot release protocol for each lot. Routine lot release is performed according to the Laboratory Quality Product Testing Plan developed by CBER.

Anavip release specifications

Test Description	Test Method(s)	Specifications / Limit(s)[1]
Appearance (Lyophilized)	Visual SOP M-FQ-078	(b) (4)
Appearance (Reconstituted)	Visual SOP M-FQ-078	Yellow-green, opalescent liquid
Identification	(b) (4) SOP M-CB-011	Meets requirements
Potency	SOP M-CB-016	(b) (4)
Purity ( )	SOP M-CB-010	$F(ab')_2$ NLT 85% Fab NMT 7% (b) (4)
Purity ( )	SOP M-CB-001	(b) (4) IgG NMT 5%
(b) (4)	(b) (4)	(b) (4)
Protein Content	SOP M-CB-005	NMT 120 mg / vial
Sulfate	(b) (4)	NMT 1.7 mg / vial
Cresol	SOP M-FQ-019	NMT .99 mg / vial
Sterility	(b) (4)	Meets requirements
Pyrogens	(b) (4) 21 CFR 610.13	Meets requirements
Glycine	Instituto Bioclon	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sodium Chloride	SOP M-FQ-092	25.2 – 56.8 mg/vial
Borates	Instituto Bioclon	NMT 1.0 mg/vial
Sucrose	SOP M-FQ-093	18.2 – 85.8 mg/vial
Safety	21 CFR 610.11	Meets requirements
Moisture Content	(b) (4)	(b) (4)
Reconstitution	SOP M-FQ-038	
Leak Test	SOP M-FQ-030	
Pepsin	(b) (4)	≤160 ng/vial

[1] NLT – Not less than; NMT – Not more than

Stability:
Stability (including) Three materials were tested for their stabilities in this stability study, i.e., , Anavip Bulk Product, Anavip Drug Product.

The dating period of each material was evaluated based on the data from five clinical lots and three conformance lots, and summarized as follows:

1. (b) (4)

2. For **Bulk Product** stored at (b) (4), a dating period of (b) (4) **months** was proposed. A dating period of (b) (4) months is recommended with the following PMC recommendation: The next three bulk lots should be placed under stability studies in order to evaluate parameter using the current validated protocol.

3. For **Final Drug Product** stored at 25 ± 2 °C Relative Humidity condition, a dating period of months was proposed. A dating period of **24 months** is recommended at this time, with the possibility of being extended based upon evaluation of pending interim stability results.

Control of Adventitious Agents:

As described above, a multi-tiered approach is used to control adventitious agents. First, equine donor herd health is monitored and appropriate vaccinations used to reduce risk from known epizootic threats. Second, Bioclon has committed to performing cytotoxicity testing as described in 9 CFR 113.53(c) on the equine plasma to preclude introduction of potentially contaminated lots into the manufacturing stream. Finally, the manufacturing process has been validated to include both viral inactivation and removal procedures as described below.

The manufacturing process for Anavip has three steps that were validated for viral reduction or removal: 1) pepsin digestion, 2) ammonium sulfate precipitation/heat treatment, and 3) nanofiltration with filters. Viral clearance/reduction was validated by a contract research organization

(b) (4) . The degree of viral inactivation/removal was considered to be adequate.

c) Facilities review/inspection

The facilities involved in the manufacture of Crotalidae Immune F(ab)'$_2$ (Equine) (Anavip) are listed in the table below. The activities performed and the inspectional histories of the facilities are included in the table below.

Manufacturing Facilities for Anavip

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/Justification
Drug Product Manufacturing Facility				
Instituto Bioclon, S.A de C.V; [redacted] México	(b) (4)	(b) (4)	Pre-License Inspection	(b) (4)
Drug Substance Manufacturing Facility				
Instituto Bioclon, S.A. de C.V. (Tlalpan) Calzada de Tlalpan 4687 Colonia Toriello Guerra Tlalpan, Mexico D.F. MEXICO	3007581821	811974559	Waived	Team Biologics Inspections January 13-23, 2014, resulted in an issuance of a Warning Letter. A follow-up inspection occurred November 10-20, 2014 and was classified as VAI.

A pre-license inspection of Instituto Bioclon, S.A de C.V; [redacted] was conducted by CBER DMPQ on [redacted] for the filling, lyophilization, labeling and visual inspection of the drug product, Anavip.

At the end of the inspection CBER issued a Form FDA 483 with two observations. Deficiencies included improper aseptic technique observed during the (b) (4) filling and uncontrolled forms used for release testing of the drug product. The firm responded to the observations on August 26, 2013 and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

A routine Team Biologics inspection was performed at the Tlalapan facility January 14-23, 2014, and resulted in a 31 item FDA-483 being issued. This inspection was classified Official Action Indicated and a Warning Letter was issued to the firm on April 16, 2014. CBER worked with the firm to address the issues and a follow up Team Biologics inspection in November 2014 was classified as Voluntary Action Indicated. The compliance issues halted the review clock for this BLA for almost 11 months. An acceptable complete response was received on March 6, 2015

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable.

d) Environmental assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

One GLP nonclinical toxicology study was included with the Anavip BLA. Study 1299-001 evaluated acute toxicology following intravenous administration of Crotalidae Immune $F(ab')_2$ (Equine) (Anavip) in adult rats. Groups of 5 male and 5 female 6-week old (b) (4) rats were exposed to vehicle or test article at 500, 2000, and 5000 mg/kg for up to 60 minutes via the tail vein. The animals were observed for 14 days, then sacrificed and necropsied; however no histopathology was performed. 4 deaths were observed; 2 males in the 2000 mg/kg dose group and 2 males in the 5000 mg/kg dose group. Major irritation was observed at the injection site at all doses, and included tissue necrosis and tail shedding. NOAEL for systemic toxicity was determined by the sponsor to be 500 mg/kg, with no safe dose for local toxicity. These results were confounded by highly variable plasma concentrations of the test article. Due to the high concentration (180 mg/kg) and high viscosity of the test article, the intended systemic exposure was not

achieved. Due to lack of consistent exposure in each group no conclusions should be drawn as to the safety and NOAEL of Anavip. Thus, the NOAEL determination by the sponsor is not considered valid and may not be used to support labeling claims for Anavip.

5. Clinical Pharmacology

Study Title: A Phase I biosafety and pharmacokinetics study of Anavip in healthy subjects.

Fourteen healthy subjects were enrolled in this pharmacokinetic study. There were seven males and seven females in the study (between 19 to 23 years and 54.5 to 83.0 kg body weight). Healthy volunteers received Antivipmyn (an antivenin which has comparable manufacturing and composition as Anavip).
Antivipmyn (one vial = 81.9 mg) was administered intravenously over 30 minutes on Day 1 and again on Day 21. Blood samples for the pharmacokinetic study were collected from all subjects at time 0, 5, 10, 20, 30, 45 minutes, at 1, 2, 4, 24 hours, and on days 3, 5, 7, 9, 11, and 21. The last sample (day 21) was drawn prior to administration of the second dose of the drug. $F(ab')_2$ concentrations were measured in human plasma by (b) (4) . A 2-compartment model (infusion) was used to describe the concentration-time data for the estimation of pharmacokinetic parameters. Mean clearance, half-life, and volume of distribution at steady state were 22 ± 7 mL/hour, 133 ± 53 hours, and 3.3 ± 0.9 liters, respectively.

The pharmacokinetics of Anavip indicate that the drug has a low clearance, small volume of distribution, and long half-life. The study provides the pharmacokinetic assessment after the first dose and no pharmacokinetic assessment was made after the second dose.

6. Clinical/ Statistical

a) Clinical Program

To support a proposed indication of management of coagulopathy in patients with North American pit viper envenomation, data from a healthy volunteer PK study and two randomized, controlled, open-label, clinical trials were submitted.

In the PK study, among 14 healthy volunteers who received a single vial of Anavip intravenously (IV), the mean elimination half- life was 133 hours.

The phase 2 trial (AN03/02) was designed as a randomized, controlled, multicenter, open-label study. Twelve subjects aged 18-70 years were randomized in a 1:1 ratio to receive either Anavip or the licensed product, CroFab, as an active control. The subjects were dosed until initial control was achieved, followed by maintenance doses. Initial control was considered to be achieved if the leading edge of local injury was not

progressing more than 1 inch/hour and platelet count, fibrinogen level, PT and PTT were either in or returning to the normal range. Maintenance dosing was initiated 6 hours after the last dose required to achieve initial control and was continued every 6 hours for 3 doses.

All patients in both treatment groups achieved initial control of local injury and coagulopathy following treatment.

In the CroFab arm, at the end of maintenance dosing, 5 of 6 subjects had platelet counts above 150,000/mm^3, and all 6 had fibrinogen levels above 150 mg/dL. However, during the follow-up phase, 2 subjects showed laboratory findings of recurrent coagulopathy with platelets below 150,000/mm^3 and fibrinogen levels below 150 mg/dL leading to inpatient management with administration of additional CroFab doses (one subject received an additional 6 doses (12 vials) and one subject received an additional 4 doses (8 vials).

In the Anavip arm, at the end of maintenance dosing, 5 of 6 subjects had platelet counts above 150,000/mm^3. One subject's platelets were 114,000/mm^3 and were trending upward and all 6 had fibrinogen levels above 150 mg/dL. During the follow-up phase, 5 of 6 subjects had platelet counts above 150,000/mm^3, with no downward trend; one subject's platelet count was 127,000/mm^3 on follow-up Day 1, reached 160,000/mm^3 on Day 4 and continued trending upward. All 6 subjects in the Anavip group had fibrinogen levels above 150 mg/dL during the follow-up phase. None in the Anavip group required rehospitalization or retreatment with Anavip.

The clinical outcomes of this study provided preliminary evidence of the effectiveness of Anavip on management of coagulopathy in subjects with North American pit viper envenomation.

In the phase 3 (YA07/02) randomized, controlled, double-blind, multi-center study, two Anavip regimens were compared along with CroFab, at 16 sites in the U.S. A total of 123 subjects aged 2-80 years with signs and symptoms of envenomation were randomized (1:1:1) into three groups:

- Group 1: Anavip with Anavip maintenance therapy (N = 41)
- Group 2: Anavip with Placebo (normal saline) maintenance therapy (N = 41)
- Group 3: CroFab with CroFab maintenance therapy (N = 41)

One subject in Group 2 and one subject in Group 3 did not receive the study drug. The number of subjects who dropped out and the reasons for dropping out are summarized in the following table:

Subject Disposition

Reason for Dropout	Group 1	Group 2	Group 3
Lost to follow-up	2	5	2
Consent withdrawn	1		1
Did not meet entry criteria		1	
Investigator judgment			1
Death	1		
Number of Subjects Completing Study	37	35	37

The primary objective of this trial was to confirm the effectiveness of Anavip in management of coagulopathy. The study had an in-hospital Acute Treatment Phase that included screening and baseline assessments, initial and maintenance dosing, and an outpatient Follow-up Phase that included 4 follow-up visits on Days 5, 8, 15 and 22.

Initial dosing consisted of sequential intravenous doses infused to achieve initial control. If initial control of envenomation was not achieved, treatment was repeated until initial control was attained. Maintenance dosing (4 vials of Anavip; placebo [normal saline], or 2 vials of CroFab) was initiated 6 hours after the start of the last dose required to achieve initial control, and continued every 6 hours for 3 doses. The Follow-up Phase began immediately after the third maintenance dose. Patients returned to the clinical site on Days 5, 8, and 15 for scheduled follow-up visits. Patients with ongoing signs of envenomation received 4 vials of Anavip or 2 vials of CroFab. Dosing was continued as needed until the patient was stabilized.

The primary efficacy endpoint was a reduction in the proportion of subjects experiencing a coagulopathic effect as measured on Study Day 5 or 8. Patients were assessed as experiencing a coagulopathic effect if on either Study Day 5 (±1 day) or 8 (±1 day) they had either absolute platelet levels < 150,000/mm^3 or absolute fibrinogen levels <150 mg/dL; or experienced clinical coagulopathy between end of maintenance dosing and Study Day 5 requiring additional antivenom doses.

The comparison of outcome proportions between treatment groups was tested using an exact logistic regression model with terms for treatment and region. (Please refer to the statistician's more detailed analyses below).

Comparisons of the proportion of subjects experiencing a coagulopathic effect for the two levels of Anavip versus CroFab were performed in the following order: Anavip with Anavip maintenance dose versus CroFab; then Anavip with placebo maintenance dose

versus CroFab. The efficacy analysis did not meet, but trended toward, the pre-specified statistically defined superiority criterion. However, the numbers of subjects showing pre-specified criteria for coagulopathic effect were 10.3% and 5.3% in treatment Groups 1 and 2 respectively, compared to 29.7% in Group 3.

FDA conducted a post-hoc analysis to assess the outcomes of the subjects who presented with or without baseline coagulopathy in the three treatment groups. Using pre-specified criteria for coagulopathy, Group 1 (Anavip/Anavip) had the highest percentage of baseline coagulopathic subjects among the three groups; 41.5% compared to 17.5% and 32.5% for Group 2 (Anavip/Placebo) and Group 3 (CroFab/CroFab), respectively. In this analysis only 18% of the subjects with baseline coagulopathy in Group 1 continued to remain coagulopathic at Days 5 or 8 compared to 58% of subjects in Group 3.

Thirty-three percent (33%) of all baseline coagulopathic subjects continued to experience coagulopathy on either Day 5 or 8, compared to only 6% of subjects who were non-coagulopathic at baseline. Only 10% of the Group 1 subjects (Anavip/Anavip) experienced coagulopathy at Day 5 or 8 compared to 30% of subjects in Group 3 (CroFab/CroFab). An exact logistic regression analysis adjusting for baseline coagulopathy and region was conducted post hoc and showed that treatment effect for both Groups 1 and 2 were statistically significantly different than for Group 3. These analyses provide supportive evidence of the efficacy of Anavip.

Modification of the Indication

FDA performed an additional post-hoc exploratory analysis of clinical outcomes by the type of snake envenomation that resulted in a more narrowed indication than was initially sought. The number of subjects and the type of snake envenomation is shown in the following table:

Number of Subjects by Type of Snake Envenomation

Type of Snake Envenomation	Number of Subjects
Rattlesnake species	57
Copperhead	21
Unknown	43
Water Moccasin/Cottonmouth	1

A review of the outcomes of the components of the primary endpoint prespecified criteria, (i.e. platelet count or fibrinogen level) by snakebite type showed that the majority of subjects who were envenomated by copperhead snakes (N=21) did not exhibit significant coagulopathic effects by the prespecified criteria as compared to the majority of subjects who were envenomated by rattlesnakes (N=57). However, formal statistical analysis could not be performed on the data due to the large number of subjects in which the snake type was unknown (N=43). Therefore, FDA concluded that the results of the phase 3 trial could only measure a significant response of Anavip to envenomation by rattlesnakes. FDA decided that the indication should reflect this limitation, and modified the the indication to “management of adult and pediatric patients with North American

rattlesnake envenomation," rather than the broader indication for treatment of crotalid envenomation.

Twenty-four percent (21/86) of patients studied in clinical trials were 16 years of age or younger (6 patients were 2 years of age to 5 years of age, 15 patients ranged from at least 5 years of age to 16 years of age). None of the pediatric patients in the phase 3 study experienced a recurrent coagulopathic effect. All adverse reactions in the pediatric patients were non-serious. The most frequent adverse reactions among pediatric patients were nausea and vomiting, itching, and fever. Thus, the safety and efficacy in the pediatric population was not different from the adults.

Statistician Review and Comments

The sponsor reported that the primary comparison between Anavip/Anavip and CroFab/ CroFab was not statistically significant (two-sided p-value=0.06, odds ratio (OR) =0.275 and 95% CI: 0.058, 1.048). Though the comparison between Anavip/Placebo and CroFab/CroFab is nominally statistically significant (OR=0.135, p-value=0.01), a pre-specified hierarchical testing strategy prevents formally performing this test since the primary comparison between Anavip/Anavip and CroFab/ CroFab is not statistically significant.

Though the sponsor pre-specified the primary analysis to be on the intent-to-treat (ITT) population, the sponsor's actual primary efficacy analysis is a complete case analysis which excludes from the ITT population seven subjects who do not have any primary efficacy data. Although it would be preferable for the primary analysis to be on the ITT population, the sponsor did not pre-specify a primary missing data imputation method, the seven subjects excluded did not have any follow-up data beyond baseline, as a result, the complete case analysis is regarded as the primary analysis in this review and the ITT analyses with various imputation methods are treated as supportive evidence.

Post-hoc analysis with no imputation for missing data identifies baseline coagulopathy as a highly significant prognostic factor (OR=7.397, p-value=0.006) and when the primary efficacy analysis is adjusted for this factor, the primary comparison between Anavip/Anavip and CroFab/CroFab is statistically significant (OR=0.184; 95% CI: 0.033, 0.794; p-value=0.02).

Post-hoc ITT analyses using baseline observation carried forward (BOCF) and multiple imputation (MI) for the missing cases show that the primary comparison between Anavip/Anavip and CroFab/CroFab is statistically significant for showing a difference. Additionally, when imputing the missing cases as all successes or as all failures, and correcting for baseline coagulopathy, the primary comparison between Anavip/Anavip and CroFab/ CroFab was statistically significant. These ITT analyses were considered supportive of efficacy of Anavip.

In summary, although the primary study results do not seem to provide evidence strong enough to support a superiority claim of Anavip over CroFab on management of coagulopathy in patients with North American crotalid envenomation, post hoc analyses are supportive of efficacy of Anavip on management of adult and pediatric patients with North American rattlesnake envenomation. It was not possible to perform formal statistical analyses by snake subtype due to the large number of subjects (43) in which the snake type was unknown.

Bioresearch Monitoring

Three Bioresearch Monitoring (BIMO) inspections of clinical investigators were conducted in support of BLA STN 125488/0. The inspections revealed the investigational product accountability and disposition records were not clearly documented at one site.

The BIMO branch requested three clinical investigator inspections on May 22, 2013 covering one clinical study in support of the BLA. Information from the BLA was compared to source documents during the inspections. The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The BIMO inspection assignments included specific questions for the following clinical study: A Comparison of Anavip [Crotalinae (pit viper) equine immune F(ab)2] and CroFab (Crotalidae Polyvalent Immune Fab, ovine) in the Treatment of Patients with Crotalinae Envenomation: A Randomized, Prospective, Blinded, Controlled, Comparative, Multicenter Study (Protocol No. YA-C-02).

Site #	Study Site	Location	Form FDA 483 Issued	Inspection Final Classification
10	Loma Linda University Adventist Health Sciences Center	Loma Linda, California	No	NAI
16	Banner Good Samaritan Medical Center	Phoenix, Arizona	No	NAI
20	St. Joseph's Regional Health Center	Bryan, Texas	Yes	VAI

b) Pediatrics

Anavip was granted orphan product designation on 29 January 2004 for "the treatment of Crotalid envenomation requiring medical attention." Due to the orphan product designation, PREA requirements do not apply.

c) Other Special Populations

No other special populations were studied or are under consideration for studies with Anavip.

d) Overall Comparability Analysis

There are no additional concerns related to CMC, preclinical and clinical disciplines.

7. Safety

CMC

The excipients and impurities found in Anavip (glycine, sucrose, sodium chloride, borates, sulfates, and cresol) are commonly found in IGIV products, with the exception of cresol and borates. Cresol, when used at the dose typically found in an infusion of Anavip, has been associated with myalgia, elevated creatine kinase activity, and malignant hyperthermia. Myalgias were reported with Anavip and Alacramyn at a low rate (1.7%), but were not necessarily treatment related. However, other products (insulin, insulin analogs, growth hormone preparations) that contain cresol include the following warning, which is recommended to be included in the Anavip labeling: "Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient." A toxicity evaluation for borates was submitted by the sponsor and included an EMEA report entitled "Summary Report on Boric Acid and Borates" as well a peer-reviewed manuscript ("Boric acid single dose pharmacokinetics after intravenous administration to man", Arch Toxicol (1984) 55: 64-67.). The maximal exposure of boron from the EMEA document is considered safe in humans at 39 mg/day, which exceeds the maximal exposure from Anavip.

Clinical

A total of 86 patients were treated with Anavip, ranging from 2 to 80 years old. The patient population was comprised of 60 males and 26 females. Patients were monitored for signs and symptoms of adverse reactions, including acute hypersensitivity reactions and serum sickness. Follow-up interviews were conducted at 5, 8, 15 and 22 days after treatment to assess symptoms of ongoing venom effect, serum sickness, and any other adverse reactions.

The most common adverse reactions observed in more than 2 percent of patients in the clinical trials for Anavip were: pruritus, nausea, rash, arthralgia, peripheral edema, erythema, headache, myalgia, pain in extremity, and vomiting.

The table below shows the adverse reactions occurring in patients across all clinical trials for Anavip. Seventy six percent (65/86) of patients receiving Anavip reported at least one adverse reaction.

Incidence of Adverse Reactions in Clinical Studies of Anavip by Body System

	Anavip [N=86] n (%)
Patients Reporting at Least One Adverse Event	65 (76%)
Skin and subcutaneous tissue disorders	47 (55%)
Pruritus	37 (43%)
Rash	10 (12%)
Blister	4 (5%)
Erythema	3 (4%)
Gastrointestinal disorders	28 (33%)
Nausea	20 (23%)
Vomiting	5 (6%)
Musculoskeletal and connective tissue disorders	19 (22%)
Arthralgia	9 (11%)
Myalgia	6 (7.0%)
Pain in extremity	5 (6%)
General disorders and administration site conditions	21 (24%)
Edema peripheral	7 (8%)
Chills	3 (4%)
Pyrexia	4 (5%)
Nervous system disorders	12 (14%)
Headache	5 (6%)
Psychiatric disorders	4 (5%)
Anxiety	2 (2%)
Insomnia	2 (2%)
Metabolism and nutrition disorders	4 (5%)
Dehydration	2 (2%)
Respiratory, thoracic and mediastinal disorders	5 (6%)
Dyspnea	1 (1%)
Blood and lymphatic system disorders	2 (2%)
Thrombocytopenia	1 (1%)

A total of nine subjects, including six (14.0%) subjects in Group 1, one (2.7%) subject in Group 2, and two (4.9%) subjects in Group 3 experienced at least one SAE. Most SAEs were assessed as severe and not related to study drug. The only treatment-related SAE was severe swelling in Group 1 considered possibly related to study drug. Serum sickness was not reported in the clinical trials.

In conclusion, the safety profile of the Anavip was acceptable. Overall, the data supports the safety of Anavip for management of coagulopathy in patients with North American rattlesnake envenomation.

8. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee (BPAC). The product is not a new molecular entity per section 918 of FDAAA, nor did the review committee identify any issues requiring presentation to BPAC.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this BLA.

10. Labeling

Proprietary name: The proprietary name suggested by the sponsor (Anavip) was initially reviewed by the Advertising and Labeling Branch (APLB) on June 13, 2013 and was found to be acceptable. APLB provided a re-evaluation of the proprietary name within 90 days of the PDUFA deadline (December 16, 2013).

Physician labeling: The final Anavip package insert is PLR compliant.

Package insert, carton and container labeling: No additional problems were identified with regard to content and format.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The primary regulatory issues involved in the review of Anavip were related to the phase 3 pivotal clinical study which was designed to show superiority, but failed to do so by predetermined statistical analysis. Post-hoc analyses were supportive of the efficacy of Anavip. Bioclon has adequately demonstrated the safety and efficacy of Anavip. The review committee therefore recommends approval of this biologics license application.

b) Risk/ Benefit Assessment

Most AEs associated with administration of Anavip were mild or moderate in nature. The most frequently reported AEs were pruritus and nausea. Many of the other reported AEs (e.g. bruising, bleeding) are expected sequelae of rattlesnake envenomation and are listed in the package insert.

Allergic reactions, anaphylaxis, serum sickness and hypersensitivity reactions, are well-characterized and recognized serious AEs associated with heterologous immune globulins. These reactions occur at a lower rate than the already FDA-approved crotaline antivenin, Crofab, but statistical comparisons of rates of AEs cannot be made. Routine pharmacovigilance is sufficient to monitor continued safety concerns.

Cresol is used as a preservative during manufacturing steps and is present in Anavip at no more than 0.99 mg/vial. At the highest dose of 24 vials the patient exposure would be 23.8 mg, or, for a 70 kg individual, 0.34 mg/kg. No-observed-effect levels (NOEL) in life-time exposure studies in rats and mice were 38 and 28 times higher, respectively, than the highest exposure from Anavip. Thus, the use of cresol in Anavip is not likely to pose a toxicity risk to patients.

However, cresol content in Anavip is potentially higher in some lots than levels expected in another antivenom product from the same company. [redacted]. The AE and association with cresol is conveyed in the product insert; and this AE would be difficult to evaluate because of the association of crotalid envenomation with rhabdomyolysis and the compartment syndrome.

Data submitted by the sponsor as part of the application, available published medical literature, and data collected by CBER for similar products identified no new safety concerns.

	Conditions	Action Plan
Identified Risks	Hypersensitivity reactions (e.g. serum sickness, anaphylaxis)	• Routine pharmacovigilance • AEs are mentioned in the warnings and precautions portion of the proposed product insert
Potential Risks	Myalgias due to Cresol	• Routine pharmacovigilance • AE is mentioned in the warnings and precautions portion of the proposed product insert
Missing Information	Children less than 2 years old	• Routine pharmacovigilance

Since the product is effective in treating life-threatening snake bites and the safety profile is indicative of relatively low risk, the benefit of this product clearly outweighs the risk.

c) Recommendation for Post-marketing Activities

Based on the review of the pre-licensure safety data and the sponsor's PVP, OBE/DE recommends routine pharmacovigilance: adverse event reporting in accordance with 21 CFR 600.80

No safety issues have been identified that would warrant a Risk Evaluation and Mitigation Strategy (REMS) or a new Postmarketing Requirement (PMR).

POSTMARKETING COMMITMENTS

CMC

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

4. Bioclon commits to perform a study to evaluate (b) (4) and to perform bioburden and endotoxin (b) (4) [redacted]. 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 [redacted]. Bioclon will provide the "Postmarketing Study Commitment – Final Validation Report" to CBER by August 31, 2015.

6. Bioclon commits to provide [redacted] 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 [redacted] (a lot initiated during the pre-license inspection) annually in the PMC Annual Report. The final stability report will be submitted as a "Post Marketing Study Commitment - Final Study Report" by September 28, 2018.

8. Bioclon commits to submit interim stability results for each conformance lot as "Post Marketing 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: [redacted] by using the validated method (code PVM-ID-013). The "Postmarketing Study Commitment – Final Study Report" will be submitted by August 31, 2017.

The information to fulfill these PMCs will be submitted as a Postmarketing Commitment Submission/Final Study Report to CBER.