



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

To: BLA STN 125488/0 File

From: Maria L. Virata-Theimer, Ph.D., Chemist, LPD/DH/OBRR, HFM-345

Through: Michael C. Kennedy, Ph.D., Team Leader, LPD/DH/OBRR, HFM-345

CC: Edward M. Thompson, RPM, DBA/OBRR, HFM-380

Applicant: Instituto Bioclon, S.A. de C.V., Mexico City, Mexico

Product: *Crotalidae* (Pit Viper) Immune F(ab')₂ (Equine) Injection
Proposed Trade Name: Anavip[®]

Subject: CMC Review: Original BLA – Raw Materials, Product Specifications,
Adventitious Agents Testing

Recommendation

Approval, with the following Postmarketing Commitments (PMCs) as agreed upon by the sponsor on 27-FEB-14:

1. Instituto Bioclon, S.A. de C.V. (Bioclon) commits to (b) (4) [REDACTED] Anavip production lot. The (b) (4) [REDACTED] and the final study reports will be submitted as a BLA supplement within 3 months of the completion of the studies.
2. 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) as a BLA supplement within one year after approval.
3. Bioclon commits to (b) (4) [REDACTED] Anavip production lot. (b) (4) [REDACTED] and the final study report will be submitted as a BLA supplement within 3 months of completion of the study.

Executive Summary

My Discipline Review memorandum covers specific assigned CMC sections of the original Biologics License Application (BLA) submission from Instituto Bioclon, S.A. de C.V. (Mexico City, Mexico), through Rare Disease Therapeutics, Inc. (Franklin, TN), for their *Crotalidae* (Pit Viper) Immune F(ab')₂ (Equine) Injection product, "Anavip". The CMC sections I reviewed were: Raw Materials, Product Specifications, and Adventitious Agents Testing. The sponsor submitted representative certificates of analyses of their raw materials and provided clarifications to my questions about their raw material suppliers. I found most of their proposed drug substance and drug product specifications for Anavip to be acceptable, since most of these were based on the specifications of Anascorp[®], another Bioclon equine F(ab')₂ product (BLA STN 125335/0, approved 4-AUG-11) which is manufactured similarly to Anavip. However, I found that the (b) (4)

(b) (4)
i.e., up to (b) (4). While these issues were not substantive enough to delay approval of this BLA, I requested PMCs from the sponsor to (b) (4)

(b) (4). Other reviewers, Drs. Michael Kennedy and Evi Struble, also requested PMCs from the sponsor (b) (4), respectively (see their respective Discipline review memos). The sponsor agreed to do all these abovementioned PMCs (see BLA STN 125488/0.41, dated 27-FEB-14).

With regards to testing their equine plasma for adventitious agents, the sponsor currently has a (b) (4) test in place, but lacks the follow-up tests recommended by 9 CFR §113.53 (c)(6) for the detection of cytopathogenic and/or hemadsorbing agents (as prescribed in 9 CFR §113.46) and the detection of extraneous viruses by the fluorescent antibody technique (as prescribed in 9 CFR §113.47). In response to our Information Request (IR) sent on 18-APR-13, Bioclon said that they arranged to have an external testing laboratory, (b) (4), create the additional adventitious agents test methods for them. The sponsor agreed to our PMC request to provide the test method SOPs, validation protocols and validation study reports for the additional tests within one year after BLA approval (see BLA STN 125488/0.41, dated 27-FEB-14).

Background Summary

FDA CBER received on 18-MAR-13 this Original BLA submission (dated 15-MAR-13) from Instituto Bioclon, S.A. de C.V. (Mexico City, Mexico), through Rare Disease Therapeutics, Inc.(RDT)(Franklin, TN), for their *Crotalidae* (Pit Viper) Immune F(ab')₂ (Equine) Injection product with the proposed trade name, "Anavip". Anavip is a lyophilized equine F(ab')₂ product indicated for the treatment of patients with North American crotalid (pit viper) envenomation, regardless of severity, including the prevention of late or recurrent coagulopathies. This product and indication were granted an Orphan Drug Designation.

Michael Kennedy, Ph.D. of LPD/DH/OBRR, HFM-345 is the chair of this BLA submission. My Discipline review focused on the following CMC issues: Product Specifications, Raw Materials, and Adventitious Agents Testing. Dr. Kennedy reviewed most of the Analytical Methods, except for the tests for sterility and pyrogens, which were reviewed by Hyesuk Kong, Ph.D. of LMIVTS/DBSQC/OCBQ, HFM-407.

Supplement Review Summary

Anavip is obtained by the pepsin digestion of equine plasma enriched with anti-crotalid immunoglobulin (IgG) to remove the Fc portion of the IgG followed by fractionation and purification steps. The equine plasma starting material comes from horses that have been immunized with a mixture of pit viper venoms from two species, *Bothrops asper* and *Crotalus durissus*. Anavip is manufactured at the Bioclon facility in Tlalpan, Mexico using the same manufacturing process in the production of *Centruroides* (Scorpion) Immune F(ab')₂ (Equine) Injection, Anascorp[®], an antivenom product made by RDT/Bioclon for scorpion envenomation that was approved by the FDA on 4-AUG-11 (BLA STN 125335/0).

The Anavip final product is supplied as a sterile, nonpyrogenic, purified, lyophilized powder in a 20 mL vial with not more than 120 mg total protein and not less than the 780 mouse LD₅₀ neutralizing units for *Bothrops asper* and 790 mouse LD₅₀ neutralizing units for *Crotalus durissus*. Like Anascorp, Anavip is also formulated with sucrose, glycine, (b) (4) and sodium chloride. Trace amounts of pepsin, sulfates and cresol may be present in the product. The proposed specifications for Anavip's raw materials, drug substance and final drug product can be found in the tables below in Sections I and II and are listed side-by-side with the currently approved specifications of Anascorp for comparison.

I. Raw Materials

A. Equine Plasma

The equine plasma used in the manufacture of Anavip is collected from a horse production herd that Bioclon maintains at their (b) (4). Details on the source of animals, animal husbandry procedures (adventitious agent screening and quarantine procedures), routine care and maintenance of the horse production herd, water and food monitoring, treatment of certain diseases/conditions, etc. were provided in Section 3.2.S.2.3.1 Animal Husbandry.

The equine plasma is tested prior to further manufacturing for (b) (4) and adventitious agents/(b) (4). Table 1 below lists the proposed specifications of equine plasma for Anavip compared to those currently approved for Anascorp.

Table 1: Proposed Specifications for Equine Plasma for Anavip vs. Anascorp

Test	Reference	Anavip Specification/Limit	Anascorp Specification/Limit
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(b) (4)

(b) (4)

Adventitious Agents/(b) (4)	9 CFR 113.53(c)	No toxicity	
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NLT = not less than; NMT = not more than

Reviewer's Comments: John U. Dennis, DVM of DVS/OM/CBER, HFM-22, reviewed the animal husbandry procedures, routine care and maintenance of the horse production herd (see his Discipline Review Memo).

B. Venoms

The horses at (b) (4) are injected with a mixture of pit viper venoms, specifically from *Bothrops asper* and *Crotalus durissus*, to elicit IgG antibodies directed against the venoms. According to Section 3.2.S.2.2.1 Venom Production, the two venoms come in (b) (4)

[REDACTED]

*Reviewer's Comments: B. asper and C. durissus are both South American pit viper species. The Certificates of Analysis (CoA) of the snake venoms were requested from the sponsor in the 18-APR-13 IR. The sponsor provided representative CoAs of each venom type from the supplier, (b) (4), on 6-MAY-13 in BLA Amendment 7 (dated 2-MAY-13, received on 3-MAY-13)(see Responses to the IR section below). In addition, an IR was sent by Dr. Kennedy on 22-AUG-13 to request CoAs of specific snake venom lots (Lot (b) (4) for *B. asper* and Lot (b) (4) for *C. durissus*) that were used in the (b) (4) assay validation. These CoAs were provided in BLA Amendment 21 (dated 5-SEP-13, received on 6-SEP-13).*

C. Reagents

Table 2 below lists the chemical reagents used in the different production steps of Anavip (see also Table 1 in Section 3.2.S.2.3 Control of Materials). Representative CoAs from each supplier/manufacturer for the following manufacturing process reagents were also provided in Section 3.2.S.2.3: (b) (4)

Table 2: Reagents used in the Production of Anavip

Reagent Name	Supplier	Purpose	Quality Standard
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(b)

(4)

(b) (4)

Table 4: Proposed Drug Product (DP) Specifications of Anavip vs. DP Specifications of Anascorp

Test	Test Method/SOP No.	Anavip Specification/Limit	Anascorp Specification/Limit
Appearance (Lyophilized)	Visual SOP-FQ-078	(b) (4)	(b) (4)
Appearance (Reconstituted)	Visual SOP-FQ-078	Yellow-green, opalescent liquid	(b) (4)
Identification	(b) (4) SOP M-CB-011	Meets requirements	Meets requirements
Potency	SOP-M-CB-016	<i>Bothrops asper</i> : NLT 780 LD ₅₀ neutralized/vial <i>Crotalus durissus</i> : NLT 790 LD ₅₀ neutralized/vial	NLT 150 LD ₅₀ neutralized/vial
Purity (b) (4)	SOP-M-CB-027	F(ab) ₂ NLT 85% Fab NMT 7% (b) (4)	(using SOP M-CB-010) F(ab) ₂ NLT 85% Fab NMT 7% (b) (4)
Purity (b) (4)	SOP-M-CB-001	(b) (4) IgG NMT 5%	(b) (4) IgG NMT 5%
(b) (4)	(b) (4) Bioclon SOP M-FQ-040	(b) (4)	(b) (4)
Protein Content	(b) (4) SOP-M-CB-005	NMT 120 mg/vial	NMT 120 mg/vial
Sulfate	(b) (4)	NMT 1.7 mg/vial	NMT 1.7 mg/vial
Cresol	SOP M-FQ-019	NMT 0.99 mg/vial	NMT 0.41 mg/vial
Sterility	(b) (4)	Meets requirements	Meets requirements
Pyrogens	(b) (4)	Meets requirements	Meets requirements
Glycine	SOP M-FQ-091	16.2-51.8 mg/vial	6.6-94.9 mg/vial
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium Chloride	SOP M-FQ-092	25.2-56.8 mg/vial	45-80 mg/vial
Borates	Instituto Bioclon	NMT 1.0 mg/vial	NMT 1.0 mg/vial
Sucrose	SOP M-FQ-093	18.2-85.8 mg/vial	4.3-38.3 mg/vial
Safety	21 CFR 610.11 Bioclon SOP M-CB-003	Meets requirements	Meets requirements
Moisture Content	(b) (4)	(b) (4)	(b) (4)
Reconstitution	SOP M-FQ-038	(b) (4)	(b) (4)
Leak Test	SOP M-FQ-030	(b) (4)	(b) (4)
Residual Pepsin	(b) (4)	(b) (4)	(b) (4)

NLT = not less than; NMT = not more than

Reviewer's Comments: (1) Several specifications are similar for both Anavip and Anascorp, which appear to be acceptable. However, some specifications appear to be set quite high or have rather wide ranges (b) (4), particularly for (b) (4).

An IR was sent to the sponsor on 18-APR-13 (b) (4) lots. In their IR response, the sponsor agreed to

(b) (4) as requested (see BLA Amendment 7, received on 6-MAY-13, and Responses to IR section below, see also BLA Amendment 41, dated 27-FEB-14, received on 28-FEB-14).

(2) In the original BLA submission, the sponsor did not set a specification for residual pepsin in the final product, therefore, this was also requested in the 18-APR-13 IR. In their IR response, they proposed a residual pepsin limit of (b) (4) based on (b) (4) test results of (b) (4) Anavip lots (see Responses to IR section below) and chose to set the limit as the resulting (b) (4). I found this proposed maximum limit to be set quite high (see my additional comments in the Responses to IR section below). Anascorp has a residual pepsin limit of (b) (4), which was set based on the data of only (b) (4) lots and is also the (b) (4).

(3) The cresol specification in the Anavip final product was also set ~2.5X higher than that of Anascorp. It should be noted that according to the Anavip draft package insert, an initial dose of 10 vials is to be administered to the patient, and up to a total of 24 vials may be injected within the first 18 hours as needed. The Pharm/Tox reviewer, Dr. Evi Struble, sent an IR to the sponsor on 22-AUG-13 to request a justification for this specification and a toxicologic assessment of cresol at the amounts present in Anavip, because there are safety concerns regarding cresol and similar compounds that have been associated with adverse events such as myalgias. Dr. Struble later requested the sponsor to (b) (4) (see BLA Amendment 41)

(4) As mentioned previously, *B. asper* and *C. durissus* are both South American pit viper species. Dr. Kennedy sent an IR on 22-AUG-13 to the sponsor to request that they (b) (4). The sponsor's responses to this particular item are in BLA Amendments 21 (dated 5-SEP-13, received 6-SEP-13) and 26 (dated 3-OCT-13, received 4-OCT-13). Amendment 26 contained a draft (b) (4) test validation protocol which included (b) (4), however, the sponsor did not provide any (b) (4). According to their IR response in Amendment 21, (b) (4) as recommended by FDA. The sponsor also said that they expect to complete their validation study of the (b) (4) by end of March 2014. A PMC was requested for the sponsor to submit the final validation study report by 30-APR-14. Bioclon agreed to do this PMC on 27-FEB-14 (see BLA Amendment 41).

III. Adventitious Agents Testing

In Section 3.2.A.2 Adventitious Agents Safety Evaluation, Bioclon stated that they have implemented a release testing of all horse plasma used in the production of Anavip for adventitious agents (b) (4) according to 9 CFR 113.53(c). They provided a copy of the study report (Report No. 15276), (b) (4) Determination in of (b) (4), which was done specifically on antiscorpion horse hyperimmune plasma lot (b) (4), that was used for Anascorp production (dated 23-MAR-12). The study was performed by an external testing laboratory, (b) (4). According to the sponsor, they submitted the results of the Anascorp study was because it is a product similar to Anavip.

Reviewer's Comments: Their current method SOP for (b) (4) testing of adventitious agents in horse plasma lacks the follow-up tests recommended in 9 CFR §113.53 (c)(6) for the detection of cytopathogenic and/or hemadsorbing agents (as prescribed in 9 CFR §113.46) and the detection of

extraneous viruses by the fluorescent antibody technique (as prescribed in 9 CFR §113.47). An IR was sent to request for the method SOPs and method validation study reports for these additional tests, if available (see Responses to 18-APR-13 Information Request below).

IV. Responses to 18-APR-13 Information Request

After initial review, an IR was sent to Bioclon on 18-APR-13. The sponsor responded on 6-MAY-13 with the following information contained in BLA Amendment 7 (dated 2-MAY-13):

- 1. Please provide representative Certificates of Analysis (CoA) from each supplier/manufacture for the following manufacturing process reagents: (b) (4), sodium chloride, (b) (4). If different grades of sodium chloride are used for each process step, please provide the CoA for each type.**

CoAs for the abovementioned manufacturing process reagents were provided in Module 3, Section 3.2.S.2.3 Control of Raw Materials.

- 2. There were a few CoAs you submitted that were listed as being from (b) (4). Please confirm whether this is a typographical error and that the correct manufacturer's name should be "(b) (4)".**

Bioclon confirmed that the correct manufacturer's name should be "(b) (4)".

- 3. There were some discrepancies regarding the names of the suppliers/manufacturers you listed in Table 1: List of Reagents used in the Production of Anavip (Section 3.2.S.2.3 Control of Materials) vs. the names on the actual representative CoAs you provided. For instance, you indicated that your supplier for several reagents is (b) (4) and yet the representative CoAs you submitted are from (b) (4). For other reagents, you listed (b) (4) as the supplier, however, the CoAs were again from (b) (4). There were also CoAs listed as being (b) (4)", but the corresponding supplier on your table is (b) (4). Please clarify the following:**

- a. why several CoAs were from (b) (4) and not the listed supplier/manufacture**

Bioclon said that they have several approved suppliers (distributors) that can deliver the raw materials, e.g., (b) (4). All suppliers are approved by their QA Department. (b) (4) is a supplier that can also provide raw materials as other suppliers. Bioclon also submitted representative CoAs from (b) (4) in Amendment 7.

- b. what is the relationship between (b) (4)**

(b) (4) are suppliers for Bioclon (b) (4) is a chemical reagent manufacturer in (b) (4)

- c. what is the relationship between (b) (4)**

(b) (4) is the chemical reagent manufacturer (b) (4) is the supplier.

- d. what is the relationship between "(b) (4)"**

(b) (4) are both manufacturers and sell the raw materials to Bioclon's suppliers.

4. **Please provide a representative CoA from your (b) (4) supplier of the (b) (4) snake venoms (if available).**

Representative CoAs from (b) (4) were provided for each venom type in Module 3, Section 3.2.S.2.3 Control of Raw Materials.

5. **Your proposed (b) (4) [redacted] which indicate to us that you do not have good control of your manufacturing process. The (b) (4) [redacted] to reflect the capacity of the manufacturing process. Please commit to (b) (4) [redacted] production lots of Anavip and/or identically manufactured products with different specificities.**

Bioclon committed to (b) (4) [redacted] production lots of Anavip and/or identically manufactured products with different specificities.

Reviewer's Comment: Bioclon formally sent their agreement to do these PMCs (along with (b) (4) in BLA Amendment 41.

6. **Please establish a (b) (4) [redacted] in the Anavip final product based on data of Anavip lots tested by a validated (b) (4) [redacted]. Please include the statistical analysis report from testing a sufficient number of Anavip final product lots to support your (b) (4) [redacted].**

Bioclon agreed to establish a (b) (4) [redacted] as requested above. A statistical analysis report from testing (b) (4) [redacted] Anavip final product lots to support the (b) (4) [redacted] was provided in Section 3.2.R Regional Information/Method Validation Package/Analytical Test Methods (see (b) (4) [redacted]-specs-dp.pdf).

(b) (4) [redacted]

(2) *There appears to be typographical errors in the statistical report. The sponsor stated twice that (b) (4) [redacted] lots were tested when actually only (b) (4) [redacted] lots were tested.*

(3) *Bioclon formally sent their agreement to do this PMC in BLA Amendment 41.*

(b) (4)

7. Your current method SOP for (b) (4) testing of adventitious agents in horse plasma lacks the follow-up tests recommended in 9 CFR §113.53 (c)(6) for the detection of cytopathogenic and/or hemadsorbing agents (as prescribed in 9 CFR §113.46) and the detection of extraneous viruses by the fluorescent antibody technique (as prescribed in 9 CFR §113.47). Please provide your method SOPs and method validation study reports for these additional tests, if available.

Bioclon did not test for 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) and did not intend to routinely perform them due to the problematic and the long period of time that takes to obtain the necessary standard virus to perform such tests. The standard virus is not available in Mexico.

Because of FDA's recommendation, Bioclon said they will work with an external testing laboratory, (b) (4) to create the necessary SOPs to test for the additional testing listed above. They also stated that the process for (b) (4) to perform the testing listed above takes at (b) (4) and the work to test and validate the work will take (b) (4). Bioclon committed to provide the SOPs and validation work (protocol and report) in 9 months.

(b) (4)

Reviewer's Comment: Bioclon formally sent their agreement to provide all these supporting documents as a PMC (see BLA Amendment 41).

APPENDIX

Supporting documents in the Original BLA submission that were reviewed:

1. Section 3.2.S.2.2 Description of Manufacturing Process and Process Controls: 3.2.S.2.2.1 Venom Production
2. Section 3.2.S.2.3 Control of Materials
3. Section 3.2.S.4 Control of Drug Substance: 3.2.S.4.1 Specification
4. Section 3.2.P.4 Control of Excipients: 3.2.P.4.1 Specifications
5. Section 3.2.P.5 Control of Drug Product: 2.3.P.5.1 Specifications
6. Section 3.2.R Regional Information
7. Section 3.2.A.2 Adventitious Agents Safety Evaluation
8. PVM-CC-009: Protocol for the validation process of the analytical test method for the determination of pepsin traces in fabotherapeutics (Anascorp) by (b) (4) assay (dated July 2012)

Supporting documents in BLA Amendment 7 that were reviewed:

9. Response to FDA Information Request Dated 18-APR-13
10. Section 3.2.S.2.3 Control of Materials – revised version, contains additional representative CoAs
11. Letter from (b) (4) to Bioclon regarding additional virus testing (dated 25-APR-13)
12. Statistical Analysis to Establish (b) (4) in Anavip Final Product (approved 22-APR-13)

Supporting documents in BLA Amendment 21 that were reviewed:

13. Response to FDA Information Request Dated 22-AUG-13
14. Certificates of Analysis for *C. durissus* venom lot (b) (4) (dated 20-MAY-11) and *B. asper* venom lot (b) (4) (dated 02-NOV-10)

Supporting documents in BLA Amendment 26 that were reviewed:

15. Draft Potency SOP: Analytical Method Validation Protocol to Determine the Potency (b) (4) Polyvalent Fabotherapeutics (Anavip) Finished Product (FP) (Code: PVM-ID-0XX)

Supporting documents in BLA Amendment 41 that were reviewed:

16. Response to FDA Information Request Dated 25-FEB-14 – contains CMC PMCs agreed upon by sponsor on 27-FEB-14