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

Date: July 13, 2009

To: To File (BLA STN 125335/0)

From: Douglas J. Frazier, Biologist, HFM-345

Through: Dorothy Scott, MD, LPD Chief, HFM-345

CC: Debra Cordaro, RPM, HFM-370

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

Product: Centruroides (Scorpion) Immune $F(ab)_2$ Intravenous (Equine)
Trade name: Anascorp® (US), Alacramyn® (Mexico)

Subject: Final Review, original BLA, assigned CMC topics

Recommendation

This original BLA is recommended for the following Complete Response Letter queries:

- Please provide representative Certificates of Analysis from each supplier/manufacturer for the following processing reagents: ----------(b)(4)----------, cresol, pepsin, ammonium sulfate, ----------(b)(4)----------, glycine, sucrose, and sterile sodium chloride solution (ISS).

- Please revise your final-product release specifications for glycine and sucrose to include minimum acceptable limits as well as maximum ones, preferably based on representative data from routine production lots, and resubmit the complete, revised list of specifications.

- Please devise a specification for residual pepsin in final product Anascorp, and provide an assay validation and standard operating procedure (SOP) for pepsin measurement.

- Please provide an update to your final-product stability studies, when additional data is available.

Background Summary

Instituto Bioclon S.A. de C.V. (Bioclon), Calzada de Tlalpan 4687,Colonia Torriello Guerra, C.P. 14050 Tlalpan Mexico D.F. is submitting an original Biologics Licence Application (BLA) containing Chemistry, Manufacturing and Control data, Pre-clinical data and Clinical data to support the safe and

effective use of Anascorp®, Centruroides (Scorpion) Immune $F(ab)_2$ Intravenous (Equine) (i.e., of the product type historically known as antivenom or antivenin), for the treatment of patients with clinically important signs of scorpion envenomation. The IND under which clinical data were obtained is BB-IND -(b)(4)-. Bioclon has not been licensed in the US for any other products.

Anascorp is a sterile preparation of scorpion venom-specific binding fragments, presented as a lyophilized powder in a 10 mL vial, and contains $F(ab)_2$ fragments of (b)(4)immune equine IgG that is obtained from horses immunized with the venom of the Mexican scorpion species *C. noxius*, *C.l. limpidus*, *C.l. tecomanus*, and *C.s. suffusus*. The $F(ab)_2$ fragments are generated by pepsin digestion of (b)(4)immune equine IgG, and the Anascorp product is to contain at least 85% of $F(ab)_2$ fragments, with Fab-fragment content of not more than 7%. Each vial of Anascorp drug product contains $\geq$150 LD_{50} neutralizing units.

Supplement Review Summary

This review encompasses the following assigned sections from the BLA submission, which are reviewed in turn, below:

Item 4 (CMC):
- A. Description and Characterization of the Biological Substance/Product
- C. Methods of Manufacturing and Packaging
- E. Process Controls
- F. Reference Standards & Certificates of Analysis
- Appendix 9: Analytical Test Methods

Item 6 (Human Pharmacokinetic & Bioavailability)
Section 16.1.10: documentation of interlaboratory standardization methods etc.
- Report on…(b)(4) type immunoassay for…horse anti-$F(ab')_2$ …in human plasma (1.6 p. 226)
- Analytical method[:]…(b)(4) Immunoassay for anti-Horse $F(ab')_2$ in human plasma (1.6 p. 278)

A. Description and Characterization of the Biological Substance/Product

1. Description

a. Names: Anascorp® (US), Alacramyn® (Mexico)

b. Active Biological Component: $F(ab)_2$ fragments, derived from (b)(4)immune equine serum, with a minimum level of binding/neutralizing activity ($\geq$150 LD_{50} neutralizing units/vial) against the venom of four particular varieties of Centruroides scorpions (i.e., *C. noxius*, *C.l. limpidus*, *C.l. tecomanus*, and *C.s. suffusus*).

2. Characterization

a. Physicochemical Characterization (Biological Specifications) – tests include potency, ----------(b)(4)---------- purity by -----(b)(4)-------, $F(ab)_2$ content by (b)(4), total protein, General Safety, etc. For a complete list of tests performed, see bulk and final product acceptance specifications, Appendix 1.

b. Biological Activity Potency – Each vial of Anascorp drug product is to contain $\geq$150 LD_{50} neutralizing units, as measured by ----------(b)(4)----------.

C. Methods of Manufacturing and Packaging

1. Venom Production

a. Raw Materials – ----------(b)(4)---------- The identification criteria for venom glands are transcribed below:

Centruroides species	-(b)(4)-	-(b)(4)-	---(b)(4)---	--(b)(4)--	------(b)(4)------
C. limpidus limpidus	-(b)(4)-	-(b)(4)-	(b)(4)	(b)(4)	(b)(4)-
C. noxius noxius	-(b)(4)-	-(b)(4)-	(b)(4)	(b)(4)-	(b)(4)
C. limpidus telomancus	-(b)(4)-	---(b)(4)---	(b)(4)	(b)(4)-	(b)(4)
C. suffusus suffusus	-(b)(4)--	---(b)(4)---	(b)(4)	--(b)(4)-	(b)(4)

Reviewer's comments –Bioclon has not actually determined the extent of cross-reactivity between these venoms and that of US scorpions, as suggested in previous communications. However, the number of species used to generate the (b)(4)immune serum appears to be sufficient to produce an antivenom product that consistently produces the desired clinical effect. While another antivenom product, CroFab, was assayed in vitro *to determine its ability to neutralize a number of venoms produced by related snake species, and in fact may be used to treat such envenomations, Anascorp is indicated only for a single US scorpion species. Accordingly, it may be assumed that adequate cross-reactivity against US scorpion species has been demonstrated per the results of the clinical trial.*

b. Reagents – the following reagents are used to extract venom from scorpion venom glands for use in subsequent steps: ----------(b)(4)----------

c. Process – ----(b)(4)-----:

----------(b)(4)----------

d. Testing and Release – ----------(b)(4)----------.

2. Plasma Collection

a. Raw Materials – ----------(b)(4)----------

----------(b)(4)----------.

Reviewer's comments: what (b)(4) test method is used to determine titer in horse plasma donations? This question was raised by another reviewer in the IR dated April 14, 2009, question 29.

b. Reagents – ----------(b)(4)----------.

3. Plasma Fractionation

a. Reagents – fractionation reagents are listed below:

Reagent	(b)(4)	-----(b)(4)----
Cresol	---(b)(4)---	(b)(4)
Pepsin --------(b)(4)----------	---(b)(4)---	(b)(4) ---(b)(4)---
Ammonium sulfate	---(b)(4)---	(b)(4)
Sodium hydrochloride	---(b)(4)---	(b)(4)
---(b)(4)---	-----(b)(4)-----	(b)(4)
Glycine	--------(b)(4)--------	(b)(4)
Sucrose	---(b)(4)---	(b)(4)
(b)(4) sodium chloride ---------(b)(4)-------	---(b)(4)---	(b)(4)
---(b)(4)---	---(b)(4)---	(b)(4)
(b)(4)	---(b)(4)---	(b)(4)

Reviewer's comments: CBER generally prefers the use of USP/NF-grade excipients in final product. There is a National Formulary monograph on --(b)(4)--. ACS-grade chemicals may be less pure in general than USP-grade. An information request item has been generated.

b. Auxiliary Materials – these are all filter types and materials:

- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------
- ----------(b)(4)----------

Reviewer's comments – These filter types should all be qualified as part of the process steps they are used for.

c. Process – See Appendix 2 for process flow.

Reviewer's comments -- ----------*(b)(4)*----------.

d. Bulk Drug Solution

----------(b)(4)----------.

Reviewer's comments -- So how is this sterile bulk ---------(b)(4)--------- sampled for testing? This point may be addressed when the pre-license inspection is repeated.

4. Drug Product Filling and Lyophilization

a. Packaging Components – Vials: 10 mL Type (b)(4) glass, from ----------(b)(4)----------; Stopper: -----(b)(4)----, gray butyl rubber, ----------(b)(4)----------; Cap: 20 mm flip-off, from ----------(b)(4)----------.

Reviewer's comment -- "----------(b)(4)----------. Also, final-product glass vials are washed with ---(b)(4)--water (Vol 1/3, p. 46); the water should have a specification for maximum endotoxin, or else a Water-for-Injection system should be added and put to use.

b. Equipment – the machinery used in the filling line is not described in detail, but these details can be ascertained during the pre-license inspection. The lyophilizer itself is ----------(b)(4)----------.

c. Process – Bioclon states that "the existing process was used to produce the initial materials for US clinical trials. ----------(b)(4)----------:

-----(b)(4)-----

Reviewer's comments -- do final product vials contain a partial vacuum, or are they backfilled with a sterile gas, e.g., nitrogen? If they do contain a vacuum, then 100% spark-testing should be done. This point should be addressed during inspection or by DMPQ reviewers.

More involved scrutiny must be done of: chamber cleaning, ---(b)(4)---, and loading; temperature and moisture mapping; PLC control of cycles including cycle setpoints and temperature ramping rates; routine monitoring of shelf temperature, chamber pressure, and elapsed time; etc.

5. Flow Charts – see Appendix 2 for overall scheme – full flow charts not included in this memo.
   a. Scorpion Venom Production
   b. Immunization Scheme
   c. Plasma Fractionation (Drug Substance)
   d. Filling and Product Lyophilization (Drug Product)

E. Process Controls
1. Description of Control Checks
   a. Scorpion Venom Production – the following test methods and acceptance specifications are presented (CMC Vol. 1/3, Table 11):

----(b)(4)-----

   b. Immunization – ----------(b)(4)----------.

2. In-Process and Final Controls
   a. Specifications with Justification – ----------(b)(4)----------.

   Reviewer's comments – the requirement for in-process quality specifications is being addressed by the committee chairperson and DMPQ reviewers.

Identification ---------- ----------(b)(4)----------.

Glycine & Sucrose: since these formulation-excipients function as stabilizers, their specifications should include lower limits as well as upper ones. A CR letter question has been devised.

   Reviewer's comments - There is no final-container specification for pepsin: should there be a pepsin test for final product, or can we accept the reported validation result that less ----------(b)(4)--------

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Final Product – the intended storage conditions for Anascorp product are “ambient temperature (20 – 25 °C and ambient relative humidity)”. Bioclon states that stability data at this temperature are available through 12 months (“no significant changes…after up to nine months of storage” at 25 °C and 40 °C), but that stability samples will be monitored for --(b)(4)--, and the results reported in subsequent regulatory filings as they become available. Acceptance parameters include the following:

- Appearance (----------(b)(4)----------)
- Identification by (b)(4) (meets requirements)
- Potency (NLT 150 LD50 neutralized/vial)
- Purity by (b)(4) ($F(ab)_2$ FIO, Fab FIO, ---------(b)(4)----------)
- -------(b)(4)------
- Sterility (meets (b)(4))
- Safety (meets (b)(4)/21 CFR 610.11)
- Moisture content ((b)(4))

Results all passed as of 12 months, for both real-time and accelerated storage conditions (see plots, Appendices 4 & 5), as did historical data (Appendix 6).

Labeling: general comment –

The PI states that each vial of lyophilized product as supplied contains not more than 5% protein – this statement is in error, since the quantity "5%" only has meaning for mixtures and solutions of one thing in another, "5% w/w" or "5% w/v". Obviously the intention is to signify that the total load of horse protein is not more than a certain amount, but it should be stated in a way that makes scientific sense, e.g., a five-ml vial contains not more than 250 mg of equine serum proteins. This minor error can be addressed when review of the package insert is done, as the BLA approaches approval.

Appendix 1. Drug Substance and Drug Product Acceptance Specifications

------(b)(4)------

Drug Product Test Methods and Specifications (Item 4, Vol. 1, Table 12)		
Specification	Test Method	Limits
Appearance (lyophilized)	Visual SOP M-FQ-078	---------- ----------(b)(4)---------- ----------
Appearance (reconstituted)	Visual SOP M-FQ-078	----------(b)(4)----------
Identification ((b)(4))[1]	SOP M-CB-011	Meets requirements
Potency[2]	SOP M-CB-016	NLT 150 LD_{50} neutralized/vial
Purity ((b)(4))	SOP M-CB-010	$F(ab)_2$: NLT 85% Fab: NMT 7% ----------(b)(4)---------- ----------(b)(4)----------
Purity (--(b)(4)--)	SOP M-CB-001	----------(b)(4)---------- IgG: NMT 5%
(b)(4)	--(b)(4)--	--(b)(4)--
Protein Content ((b)(4))	SOP M-CB-005	--(b)(4)--
Sulfate	----(b)(4)---	--(b)(4)--
Cresol	SOP M-FQ-019	--(b)(4)--
Sterility	--(b)(4)--	Meets requirements
Pyrogens	--(b)(4)--	Meets requirements
Glycine	--(b)(4)--	-----(b)(4)-----
(b)(4)	--(b)(4)--	--------(b)(4)--------
Sodium Chloride	--(b)(4)--	45 – 80 mg/vial
Borates	--(b)(4)--	-----(b)(4)-----
Sucrose	Instituto Bioclon	-----(b)(4)-----
Safety	21 CFR 610.11	Meets requirements
Moisture content	----(b)(4)----	--(b)(4)--
Reconstitution	SOP M-FQ-038	-----(b)(4)-----
Leak test	SOP M-FQ-030	--(b)(4)--

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

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

5 pages redacted (b)(4)