



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

To: To File (BLA STN 125488/0)

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

Product: Crotalidae (pit viper) Immune F(ab')₂ (Equine) Injection
Trade name: Anavip[®] (US)

Subject: Review Memo: original BLA, assigned CMC topics – Stability Section

Recommendation

This original BLA is recommended for an approval, based upon evaluation of assigned topics, with the following Post Market Commitments (PMCs):

1. Bioclon commits to provide stability updates for the conformance lots (b) (4) (a lot initiated during the pre-licensure inspection) annually as a PMC Annual Report. The final stability report will be submitted as a PMC Final Study Report within 3 months of the final time point.
2. Bioclon commits to submitting interim stability results for each conformance lot as PMC updates within 4 weeks after QC review/approval.
3. 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 final study report will be submitted within 3 months after completion of the study.

Executive Summary

Three materials were tested for their stabilities in this stability study, i.e., (b) (4) (b) (4) Anavip Bulk Product, and 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) was proposed. A dating period of (b) (4) is recommended with the following PMC concept: The next three bulk lots should be placed under stability studies in order to evaluate (b) (4) parameter using the current validated protocol.
- 3) For **Final Drug Product** stored at $25 \pm 2^\circ\text{C}$ (b) (4) Relative Humidity condition, a dating period of (b) (4) months was proposed. A dating period of **24 months** is recommended at this moment, with the possibility of being extended based upon evaluation of pending interim stability results.

Background Information

Pit viper envenomation is an Orphan disease, affecting less than 8,000 patients in the U.S. each year. Currently, there is only one FDA approved antivenom indicated for this disease in the market, i.e., CroFab[®]. Instituto Bioclon S.A. de C.V., Tlalpan, Mexico is now submitting an original Biologics License Application (BLA) to support the safe and effective use of Anavip[®] for the treatment of this disease.

Bioclon is an authorized manufacturer of Anascorp (License no. 1860), a Centruroides (Scorpion) Immune F(ab')₂ (Equine) product. The Anavip (b) (4) process is almost identical to the Anascorp (b) (4), therein the Anascorp information was cross-referenced in this submission. Both Anascorp and Anavip is a lyophilized product administrated intravenously. The dating period for Anascorp is 24 months at $25 \pm 2^\circ\text{C}$, and the proposed one for Anavip is (b) (4) months with the same storage condition.

Robert W. Fisher, Ph.D., Staff Scientist, CBER/DH, was consulted during this review.

CMC Review Summary

This review encompasses the stability section from the original BLA submission, which was received on 16 March, 2013. Updates of stability testing were received on 30 Sept, 2013 (125488/0.25), 20 Nov, 2013 (125488/0.30), and 08 Jan, 2014 (125488/0.34), respectively.

1. Stability Study Concept and Methods:

The purpose of this study is to provide guidance for assessing the proposed storage conditions and establishing the shelf life, without sacrificing the specified product's potency, purity and quality. Three types of materials are included in this stability study:

a) (b) (4)

c) Drug Product (Final Container Product) – Anavip is stored in clear glass vials (b) (4) with gray rubber stopper, formula (b) (4) using a 20 mm green flip off assembly, code (b) (4). The lyophilized drug product is. Five clinical lots and three conformance lots placed long-term stability study (25 ± 2 °C/(b) (4) relative humidity), sampled at 0,3,6,9,12,18,24,(b) (4) months. Three conformance lots are also being placed for accelerated stability study (25 ± 2 °C/(b) (4) relative humidity), sampled at (b) (4) months. The following test parameters are included (also see Appendix 1):

- Appearance (Lyophilized, (b) (4) power)
- (b) (4)
- Humidity (b) (4)
- (b) (4)
- Biological potency ($BF \geq 780$; $CF \geq 790$ LD50Neut/Vial)
- Safety (meets (b) (4) and 21 CFR 610.11)
- Sterility (meets (b) (4))
- Identification ((b) (4))
- Purity by (b) (4)
- Purity by (b) (4)

2. Results

a) (b) (4)

Table 1. (b) (4).

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

(b) (4)

(b) (4)

c) Final product: In long term stability studies, all the data up to (b) (4) months from five clinical lots were provided, as well as the results for certain assays at (b) (4) months (Table 3 and Figure 3). The results from clinical lots were met and supported a dating period of (b) (4) months. The stability studies performed using conformance lots are under way – data up to 12 months for two conformance lots, and 3 months for the third lot were provided (Table 4 and Figure 3). The data from the third conformance lot was not included in statistical analysis since only data from two time-points were available (0 and 3 months). The conformance lots reflect the current performance; therefore the data from both clinical lot and conformance lot were pooled in the statistical analysis. All results were met. But the biological potency assay for CF has a lower initial value and deeper slope. Per ICH Q1E guidance, the dating period was determined by the crossing time between 95% conformance interval and acceptance criteria, the available data indicated a dating period of about 24 months.

In accelerated studies, all results passed as of (b) (4) months. The deeper slope for CF in comparison with the one for BF is consistent with the result from the real-time stability data.

Table 3. Final Container Batches.

Batches	Lot No.	Starting date	Ending date	Tm (°C)	Status	Comments
Lot 1 (○)	P-6A-06	(b) (4)	(b) (4)	25 °C	(b) (4) months	Complete
Lot 2 (▽)	P-7D-10	(b) (4)	(b) (4)	25 °C	(b) (4) months	No enough samples for (b) (4) mo. point
Lot 3 (□)	P-8E-02-A	(b) (4)	(b) (4)	25 °C	(b) (4) months	No data for Fab (b) (4) mo. point

Lot 4 (◇)	P-8E-02-D	(b) (4)	(b) (4)	25 °C	(b) (4) months	No data for (b) (4) humidity, Fab (b) (4) mo. point
Lot 5 (△)	P-8F-04-C	(b) (4)	(b) (4)	25 °C	(b) (4) months	No data for (b) (4) Humidity, Fab (b) (4) mo.)

Table 4. Conformance batches.

Batches	Lot No.	Starting date	Ending date	Tm (°C)	Status	Comments
Lot 1 (●)	(b) (4)	(b) (4)	(b) (4)	25 °C	12 months	Ongoing
				(b) (4) °C	(b) (4) months	Completed
Lot 2 (◇)	(b) (4)	(b) (4)		25 °C	12 months	Ongoing
				(b) (4) °C	(b) (4) months	Completed
Lot 3 (■)	(b) (4)	(b) (4)	(b) (4)	25 °C	3 months	ongoing
				(b) (4) °C	(b) (4) months	ongoing

Figure 4. Anavip Final Product Long Term Stability Data (Five Clinical lots and three conformance lots. (The inner and outer dotted lines are 95% CLs for the regression line and for the individual points; the dotted blue line indicated the limit of specification; the solid red line indicated the supported shelf life).

(b) (4)

(b) (4)

Reviewer's comments: Conformance lots reflect the most recent manufacturing process. According to above analysis, a dating period of 24 months is recommended with the possibility of being extended based upon the pending data from conformance lots. Please note that the final product was filled at (b) (4) g/vial and there is no set limit for the biological (b) (4) in bulk product prior to filling. In order to guarantee a dating period of (b) (4) months, the set limit should be determine and kept as a set level. The request of it will be dealt with by Dr. Robert Fisher, Process Validation

Reviewer. The real-time data from conformance will be requested and a PMC item is generated for this purpose.

3. Summary of information requests and responses other than stability updates.

- 1) Please submit a comparison of the following hold (or pre-use storage) times incurred during manufacture of your clinical and conformance lots: (b) (4)

Bioclon's Response on 20-Nov-2013: Figure below shows the Bulk storage time (b) (4) prior to the filing and lyophilization process of the clinical and conformance lots. Most of the lots were hold less than (b) (4). Third conformance lot (b) (4) was hold up to (b) (4) days in order to perform it in a pre-license inspection

(b) (4)

Appendix 1. (b) (4) Drug Product Acceptance Specifications (from 3.2.P.5.1.)

Test Description	Test Method(s)	Specifications / Limit(s)
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	BF: NLT 780 LD ₅₀ neutralized/vial CF: NLT 790 LD ₅₀ neutralized/vial
Purity (b) (4)	SOP M-CB-027	F(ab) ₂ NLT 85% Fab NMT 7% (b) (4)
Purity (b) (4)	SOP M-CB-001	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 0.99 mg / vial
Sterility	(b) (4)	Meets requirements
Pyrogens	(b) (4)	Meets requirements
Glycine	SOP M-FQ-091	16.2 – 51.8 mg / vial
(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	(b) (4)
Leak Test	SOP M-FQ-030	(b) (4)

NLT – Not less than; NMT – Not more than

CF – Crotalus Durissus (b) (4) BF - Bothrops Asper (b) (4)