



FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

To: File for BLA STN# 125488/0

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Through: Michael C. Kennedy, Ph.D., Team Leader, CBER/OBRR/DHRR/LPD

Cc: Edward Thompson, RPM, CBER/OBRR/DBA/LRPM/HFM-380

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

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

Subject: Amendment to Final Memo: Original BLA/Stability section

RECOMMENDATIONS:

The recommendation for approval of this original BLA remains unchanged, with the following revised PMCs:

1. Bioclon agrees to provide stability updates for the conformance lots (b) (4) (b) (4) (a lot initiated during the pre-licensure inspection) annually in the PMC Annual Report. The final stability report will be submitted as a PMC Final Study Report by September 28, 2018.
2. Bioclon agrees to submit interim stability results for each conformance lot as PMC updates by September 30, 2016.
3. Bioclon agrees 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 by August 31, 2017.

REVIEW SUMMARY:

This amendment was made to reflect the most recent update of the long term stability and accelerated stability studies for the final product. The recommended 24 months shelf life for the final product remains unchanged when stored at 25C ± 2 °C (b) (4) RH.

1. Statistical approach: Analysis of Covariance (ANCOVA) was used to determine if the data from individual batch could be pooled across lots per ICH Q1A (R2) guidance. Briefly, one of the three models, 1) common-intercept-common-slope (CICS), 2) separate-intercept-common-slope (SICS), or 3) separate-intercepts-separate-slopes (SISS), will be selected

based on the quality of intercepts and slopes tested at a significance level of (b) (4). For CICS or SICS models, the expiry date will be calculated based on the pooled data; for SISS model, the expiry date will be calculated based on the worst lot scenario. The expiry date will be predicted as the maximum storage period within which the 95% confidence interval (CI) for the lot remains within the specification range.

- i. For potency assay, due to the intrinsic relatively high variation of mouse-based potency assay, the trending line, rather than 95% CI, will be used in the determination of expiry date.
- ii. When the predicted expiry date is shorter than the actual time stability data, the trending line will be used in the determination of expiry date.

2. Long-term stability studies

An update to the long term stability studies for three conformance lots was requested and received on April 10, 2015 (STN 125562.050). The update includes up to 24 months data for Lot (b) (4) and up to 18 months data for Lot (b) (4).

2.1 Results:

a) Biological Potency CF \geq 790 LD50Neut/Vial

A SISS model was applied, and each of (b) (4) lots was assessed individually (table 1 and Figure 1):

- i. For all lots, except lot (b) (4) the 95% CI curve crossed with the set specification at an earlier time-point than the current tested time, indicating that the 95% CI may not predict the actual shelf life accurately. In this regard, the trending line was used in prediction of expiry dates for individual lot (this similar rule has been successfully applied in other products as well when mouse-based potency assay was used, such as, H-BAT).
- ii. A 23 month expiry date was predicted for this parameter, based on the worst case scenario of lot (b) (4)

b) Biological Potency BF \geq 780 LD50Neut/Vial

A SISS model was applied, and each lot was assessed individually (Table 2 and Figure 2).

- i. For (b) (4), the predict shelf life is (b) (4) and (b) (4) months using either 95% CI or trending line strategy (Table 2 and Figure 2). Please note that the actual stability data for (b) (4) month met the set specification indicating that this parameter is relatively stable than statistically predicated.
- ii. For all other lots the predicted shelf life was above (b) (4) months.
- iii. A (b) (4) months expiry date was predicted for this parameter.

c) (b) (4)

- i. A SISS model was predicted due to a negative slope for lots (b) (4) and positive slopes for all other lots. Since all slopes are nearly close to "0", a SICS model with common slope was deemed to be more appropriate in this analysis (Table3).
- ii. A shelf life of (b) (4) months was predicated for this parameter using pooled data (Figure 3).

d) Humidity (b) (4)

A SICS model was predicted and supported a (b) (4) months expiry date for this parameter using pooled data (Figure 4).

e) (b) (4)

f) F(ab)'2 (NLT 85%)

A SISS model was predicted, and each lot was assessed separately (Table 6 and Figure 6).

i. A shelf life of (b) (4) months was predicated for this parameter based on the worst case scenario of lot (b) (4) .

g) F(ab) (NMT 7%)

A SICS model was predicted, and the pooled data indicated (b) (4) of shelf life associated with this parameter (Figure 7).

i. F(ab) was not tested for lot (b) (4) but it less likely impacts the trending analysis.

h) (b) (4)

A SISS model was predicted, and each lot was assessed separately (Table 8 and Figure 8). No limit of this parameter was noticed.

i) (b) (4)

3. ACCELERATED STABILITY STUDIES:

An update to the accelerated stability studies for three conformance lots was requested and received on April 17, 2015 (STN 125562.050). Three conformance lots were placed at (b) (4) RH for up to (b) (4) months in this stress condition. All tested results met with the set specifications (Figure 10). The data were plotted and none of the parameters predicate a failure within studied (b) (4) months [Parameter of F(ab) was not analyzed since only one or two time-points results were provided for each lot].

- i. Biological potency for CF is close to fail at (b) (4) months, consistent with the predicted limitation of this parameter in long term stability program.

4. CONCLUSION:

The most recent conformance lot, (b) (4), manufactured during pre-licensure inspection represents the worst case scenario in all tested parameters, such as, the Biological Potency for CF, F(ab)'2, (b) (4) predicted a shelf life of 23, (b) (4) and 20.5 months respectively (table below). However since 18 months data has been available for this lot, it appears to be plausible to have an initial shelf life of 24 months for this product. Sponsor committed to provide update to the current real-time stability data in a PMC format. Sponsor may request for extension of the shelf life thereafter.

| Parameters | Lower limit (Months) | Worst scenario (Batch No.) |
|-----------------------|----------------------|----------------------------|
| Biological Potency BF | (b) (4) | None |
| Biological Potency CF | 23 | (b) (4) |
| (b) (4) | (b) (4) | None |
| Humidity | (b) (4) | None |
| (b) (4) | (b) (4) | None |
| F(ab)'2 | (b) (4) | (b) (4) |
| F(ab) | (b) (4) | None |
| (b) (4) | (b) (4) | None |
| (b) (4) | 20.5 | (b) (4) |

