



FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: 3/8/14

From: Michael C. Kennedy, Ph.D.; CBER/OBRR/DH/LPD; HFM-345;

To: File for STN# 125488/0

Through: Dorothy Scott, M.D.; CBER/OBRR/DH/LPD; HFM-345;

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

Subject: Final review memo –Anavip BLA: Assay Validation Studies

Product: Anavip Crotalidae (Pit-Viper) Immune F(ab')₂ (Equine)
Injection

Submission Date: March 16, 2013

Manufacturer: Instituto Bioclon

RECOMMENDATIONS:

This submission is recommended for approval with the following Post Marketing Commitments:

1. Bioclon commits to complete the validations of (b) (4) and to provide the final validation report to CBER by April 30, 2014.
2. Bioclon commits to provide the (b) (4) and the final study report will be submitted as a BLA supplement within 3 months of completion of the study.

Please note that even though this BLA is recommended for approval the approval will not take place because of a compliance hold due to inspectional issues at the Tlalpan facility.

BACKGROUND SUMMARY:

This submission is an original BLA was received March 16, 2013 for the manufacture of Antivenin, Anavip Crotalidae (Pit-Viper) Immune F(ab')₂ (Equine) [ANAVIP®]. The areas of this submission under my review were limited to the analytical methods, primarily aspects of assay validation. This submission contained acceptable level of design, execution, and documentation for the validation of important analytical methods used for final product release, in process testing, and some product specific clinical immuno-based assays.

REVIEW SUMMARY:

This submission contained the following validation protocols and final reports:

1. Final Report #PVM-CC-008 “Validation of the Analytical Method for Determining Potency (Neutralized LD50/vial) for ANAVIP Finished Product”
2. Report # IPVM-ID-004 “Protocol for Validating the Analytical Method for Determining Protein Composition in Fabotherapeutic Products by (b) (4) [REDACTED]”
3. SOP # M-CB-027 “Analytical Method for determination of Protein content by (b) (4) [REDACTED]”
4. Report # PVM-ID-008 “Protocol for Validating the Analytical Method for Determining (b) (4) IgG (b) (4) [REDACTED] for Fabotherapeutics”
5. SOP # M-CB-001 “Analytical Method for Separating Protein by (b) (4) [REDACTED]”
6. Final Report # PVM-ID-011 “Validation of the (b) (4) [REDACTED] Analytical Method for Determining Sulfates in (b) (4) [REDACTED] Finished Product”
7. SOP # M-FQ-056 “Analytical Method for the Determining Sulfates in Finished Product”
8. Final Report #: PVM-ID-009 “Protocol for Validating the Analytical Method for Determining Cresol in Fabotherapeutics Finished Product”
9. SOP # M-FQ-019 “Analytical Method for Determining Cresol in Fabotherapics”
10. Validation Protocol # PVM-ID-003 “Protocol for Validating the Analytical Method for Determining Total Protein in (b) (4) [REDACTED] Fabotherapeutics Finished Product by the (b) (4) [REDACTED]”

11. SOP# M-CB-005 “Analytical Method for the Determining Total Protein in (b) (4) Finished Product by the (b) (4)”
12. Final report #IVM.074 “Validation Protocol and Report for the Determination of Sucrose (Analytical Method)”
13. Final Report #PVM-ID-014 “ Analytical Method Validation Protocol for the Determination of Identity for the Final Product ANAVIP® by (b) (4)
14. Final Report # PVM-ID-006 “VALIDATION OF THE ANALYTICAL METHOD BY (b) (4) TO DETERMINE VENOM OF PIT VIPERS IN HUMAN PLASMA”.
15. Final Report PVM-ID-005 “Validating the Analytical Method for Quantifying F(ab)₂ in Human Plasma by (b) (4)”.
16. SOP M-CB-001 “SOP for the Development of Immunization Schemes”

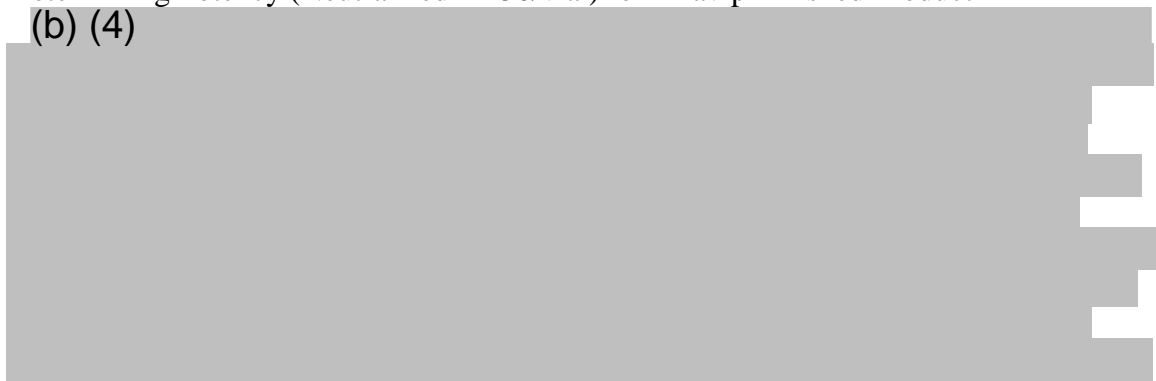
Additionally, ANAVIP® release testing uses the following compendial analytical methods:

1. Sulfate - (b) (4)
2. Glycine - (b) (4)
3. (b) (4) - (b) (4)
4. Sodium Chloride - (b) (4)
5. Borates - (b) (4)
6. Moisture Content - (b) (4)
7. Pyrogens - (b) (4)
8. Sterility - (b) (4)
9. General Safety (21 CFR 610.11)

Review of assay validations:

Potency Assay: Final Report # PMV-CC-008 “Validation of the Analytical Method for Determining Potency (Neutralized LD50/vial) for Anavip Finished Product”

(b) (4)



(b) (4)

Purity Assay: Report # PVM-ID-008 “Protocol for Validating the Analytical Method for Determining (b) (4) IgG (b) (4) for Fabotherapeutics”; SOP # M-CB-001 “Analytical Method for Separating Protein by (b) (4)

This assay is used for (b) (4) release testing for final product.

(b) (4)

Total Protein: Validation Protocol # PVM-ID-003 “Protocol for Validating the Analytical Method for Determining Total Protein in (b) (4) Fabotherapeutics Finished Product by the (b) (4)”; SOP# M-CB-005 “Analytical Method for the Determining Total Protein in (b) (4) Finished Product by the (b) (4)

This assay is used for determining total protein in (b) (4) (b) (4) final product. (b) (4)

Molecular Integrity: Report # IPV-M-ID-004 “Protocol for Validating the Analytical Method for Determining Protein Composition in Fabotherapeutic Products by (b) (4)”; Final Report # M-CB-027 “Analytical Method for determination of Protein content by (b) (4)”; SOP (P-ID-043) for the integration of

(b) (4)

Excipients: Sucrose Final report #IVM.074 “Validation Protocol and Report for the Determination of Sucrose (Analytical Method)”

This validation protocol covers the method of determination of sucrose content by (b) (4).

Contaminates: Sulfates Final Report # PVM-ID-011 “Validation of the (b) (4) Analytical Method for Determining Sulfates in (b) (4) Finished Product”; SOP # M-FQ-056 “Analytical Method for the Determining Sulfates in Finished Product”

This assay is used for determining total sulfates in (b) (4) final product. (b) (4)

Contaminates: Cresol Protocol #: PVM-ID-009 “Protocol for Validating the Analytical Method for Determining Cresol in Fabootherapeutics Finished Product”; SOP # M-FQ-019 “Analytical Method for Determining Cresol in Fabootherapeutics”

This assay is used for determining residual Cresol in the final product. This method determines Cresol levels by (b) (4)

- (b) (4)

Identity Testing: Final Report #PVM-ID-014 “Analytical Method Validation Protocol for the Determination of Identity for the Final Product ANTIVIPMYN® by (b) (4)

The parameters that were evaluated through the validation of the test method were the following:

- a) Linearity and Precision of the System.
- b) Accuracy, Linearity and Repeatability of the method.
- c) Intermediate Precision of the method.
- d) Long term stability of sample at (b) (4)
- e) Lower Limit of Quantification evaluation.
- f) Higher Limit of Quantification evaluation.
- g) Method Sensitivity.

The analytical method for the determination of identity for the Anavip final product was found to be suitable and reliable for the purpose established since:

- a) The components of the formulation do not present an analytical response.
- b) The variation of the response in the samples is acceptable
- c) The method is capable of determining the identity of Antivipmyn in presence of Anascorp or in the presence of Aracmyn.
- d) The identity in samples of Anavip final product meets the linearity and reproducibility requirements in dilutions of the product from (b) (4)
- e) The results of the determination of identity are comparable for different batches, different analysts, and performing assays on different days.
- f) The analytical signal is stable from (b) (4)

A complete copy of this validation protocol is provided in the attached Validation appendix in order to provide a representative example of how the Sponsor conducts and documents this type of study.

Clinical Testing: Venom Detection Final Report PVM-ID-006 “VALIDATING THE ANALYTICAL METHOD FOR DETERMINING (b) (4) SNAKE VENOM IN HUMAN PLASMA BY (b) (4)”

(b) (4)

The parameters that were evaluated through the validation of the test method were the following:

- 1) Linearity and Precision of the System.

- 2) Recovery of the venom.
- 3) Accuracy, Linearity and Repeatability of the method.
- 4) Intermediate Precision of the method.
- 5) Short term stability of samples on (b) (4).
- 6) Short term stability of sample under (b) (4) cycles.
- 7) Long term stability of sample at (b) (4).
- 8) Low Quantification Limit evaluation.
- 9) High Quantification Limit evaluation.
- 10) Selectivity.

Clinical Testing: Drug Product Detection Final Report PVM-ID-005 “Validating the Analytical Method for Quantifying F(ab)₂ in Human Plasma by (b) (4)

The parameters that were evaluated through the validation of the test method were the following:

- 1) Linearity and Precision of the System.
- 2) Recovery of the venom.
- 3) Accuracy, Linearity and Repeatability of the method.
- 4) Intermediate Precision of the method.
- 5) Short term stability of samples on (b) (4).
- 6) Short term stability of sample under (b) (4) cycles.
- 7) Long term stability of sample at (b) (4).
- 8) Low Quantification Limit evaluation.
- 9) High Quantification Limit evaluation.
- 10) Selectivity.

Information Requests sent to the Company:

The following IR was sent to the company on August 22, 2013:

1. Please provide the CoAs for the Snake venom (Bothrops asper) Lot: (b) (4) and Snake venom (Crotalus durissus) Lot: (b) (4), used in your potency assay validation. Please provide details on the stability program for these 2 snake venom lots and the (b) (4) Lot (b) (4) standard.
2. Please add a minimum (b) (4) Please provide modified SOPs and validation protocol.

Bioclon supplied the requested CoAs and informed CBER that the venoms were currently

not under a stability program. The sponsor agreed to immediately implement a stability program and provided a stability protocol which was found to be acceptable. The sponsor also agreed to (b) (4)

as a PMC since it would require (b) (4)

CONCLUSIONS:

All assay validations were appropriately designed and executed with all acceptance criteria being met. While the level of validation in some instances was minimal it was deemed adequate for a small manufacturing concern and associated testing laboratory.