FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

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

To: File for STN# 125335/0

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

Cc: Kelly R. Lewis, RPM, CBER/OBRR/DBA/LRPM/HFM-380
Debbie Cordaro, RPM, CBER/OBRR/DBA/LRPM/HFM-380

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

Product: Centruroides (Scorpion) Immune $F(ab)_2$ Intravenous (Equine)

Submission Date: November 11, 2008

Manufacturer: Instituto Bioclon

RECOMMENDATIONS:

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. While many other parts of the submission were found to be insufficient to allow a recommendation for approval the sections reviewed by me were adequate and appropriately validated. However, all the laboratory facilities and aspects of laboratory operations (training for laboratory personnel performing testing, data collection, etc.) will need to be followed up on inspection in order to assure that they meet the necessary standards.

BACKGROUND SUMMARY:

This submission is an original BLA was received January 22, 2009 for the manufacture of Antivenin, *Centruroides* (Scorpion) Equine Immune F(ab)2 [ANASCORP®]. The areas of this submission under my review were limited to the analytical methods, primarily aspects of assay validation.

REVIEW SUMMARY:

This submission contained the following validation protocols and final reports:

1. Final Report # IVPMA-002 “Validation of the Analytical Method for Determining Potency (Neutralized LD50/vial) for Alacramyn Finished Product”

2. Report # IPVM-ID-004 “Protocol for Validating the Analytical Method for Determining Protein Composition in Fabotherapeutic Products by -----(b)(4)----------”

3. SOP # M-CB-027 “Analytical Method for determination of Protein content by --------(b)(4)----------”

4. Report # PVM-ID-008 “Protocol for Validating the Analytical Method for Determining Albumin, IgG and IgG(T) by ----------(b)(4)---------- for Fabotherapeutics”

5. SOP # M-CB-001 “Analytical Method for Separating Protein by ----(b)(4)----------”

6. Final Report # PVM-ID-011 “Validation of the -----(b)(4)---- Analytical Method for Determining Sulfates in -------(b)(4)-------- 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)---------- Fabotherapeutics Finished Product by the -------(b)(4)------”

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 ALACRAMYN® by -------(b)(4)----------”

14. Final Report # PVM10-001 “VALIDATION OF THE ANALYTICAL METHOD

BY --------------(b)(4)------------ TO DETERMINE VENOM OF SCORPION Centruroides 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, ANASCORP® release testing uses the following compendial analytical methods:

1. Sulfate - ---(b)(4)---
2. Glycine - ----(b)(4)----
3. --------(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)

<u>Review of assay validations:</u>

Potency Assay: Final Report # IVPMA-002 “Validation of the Analytical Method for Determining Potency (Neutralized LD50/vial) for Alacramyn Finished Product” -- -- -- -- ----------------------------(b)(4)-- -- -- -- -- -- -- -- --- In this reviewer opinion the potency assay was demonstrated to be reliably accurate and reproducible to be used as a primary release testing method.

Purity Assay: Report # PVM-ID-008 “Protocol for Validating the Analytical Method for Determining Albumin, IgG and IgG(T) by ----------(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.

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Total Protein: Validation Protocol # PVM-ID-003 "Protocol for Validating the Analytical Method for Determining Total Protein ----------(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)---------- final product. ----------(b)(4)----------

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Molecular Integrity: Report # IPVM-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 the ----------(b)(4)----------

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

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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.
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Contaminates: Cresol Protocol #: PVM-ID-009 "Protocol for Validating the Analytical Method for Determining Cresol in Fabotherapeutics Finished Product"; SOP # M-FQ-019 "Analytical Method for Determining Cresol in Fabotherapics"
This assay is used for determining residual Cresol in the final product. This method determines Cresol levels by ----------(b)(4)----------

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Identity Testing: Final Report #PVM-ID-014 "Analytical Method Validation Protocol for the Determination of Identity for the Final Product ALACRAMYN® 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 Sesitivity.

The analytical method for the determination of identity for the Anascorp 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 Anascorp® in presence of Antivipmyn® or in the presence of Aracmyn®.
d) The identity in samples of Anascorp® 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 ----------(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 # PVM10-001 "VALIDATION OF THE ANALYTICAL METHOD BY ----------(b)(4)---------- TO DETERMINE VENOM OF SCORPION Centruroides IN HUMAN PLASMA"

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

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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 ----(b)(4)-----.
6) Short term stability of sample under freezing - unfreezing cycles.
7) Long term stability of sample at --(b)(4)---.
8) Low Quantification Limit evaluation.
9) High Quantification Limit evaluation.
10) Selectivity.

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: Drug Product Detection Final Report PVM-ID-005 "Validating the Analytical Method for Quantifying $F(ab)_2$ in Human Plasma by ----(b)(4)----------
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----------(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.

Information Requests sent to the Company:

The following IR was sent to the company on April 8, 2009:

1. Please provide the assay SOP (SOP M-CB-011), the assay validation protocol, and the assay validation final report, for your (b)(4) based Identity testing.

2. Please provide the assay SOP, assay validation protocol, and the validation final report, for your Sucrose determination test.

The company responded to the IR by providing the following:

- Final report #IVM.074 "Validation Protocol and Report for the Determination of Sucrose (Analytical Method)";
- Final Report #PVM-ID-014 " Analytical Method Validation Protocol for the Determination of Identity for the Final Product ALACRAMYN® by ----------(b)(4)------
- Final Report # PVM10-001 "VALIDATION OF THE ANALYTICAL METHOD BY ----------(b)(4)---------- TO DETERMINE VENOM OF SCORPION Centruroides IN HUMAN PLASMA".
- Final Report PVM-ID-005 "Validating the Analytical Method for Quantifying $F(ab)_2$ in Human Plasma by ----------(b)(4)----------"

The response contained sufficient information to allow a complete review of the analytical methods validation.

CONCLUSIONS:

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

The laboratory facility and aspects of laboratory operations (training for laboratory personnel performing testing, data collection, etc.) will need to be followed up on inspection in order to assure that they are adequate.

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