

Memorandum

**Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality**

To: 125488/0 Crotalidae (pit viper) Immune F(ab')₂ (Equine) Injection; Anavip

Michael Kennedy, PhD, Chair, OBRR/DH/LPD/ HFM- 345

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Cc: Review Committee Members

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From: Nancy Waites, CMC Facility Reviewer, OCBQ/DMPQ/B1/HFM-675

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/B1/ HFM-675

Subject: Primary Review Memo

Indication: Management of patients with North American envenomation to include prevention of late and recurrent coagulopathies

Applicant: Instituto Bioclon, S.A. de C.V. U.S. License # 1900

Facility Sites: Instituto Bioclon, S.A. de C.V. (FEI: 3007581821), Tlalpan, Mexico

Instituto Bioclon, S.A de C.V.; (b) (4) (FEI: Not issued yet), (b) (4)

(b) (4)

Due Date: 22 Oct 2013

Recommendation: This review is currently on-going. At this time there are no issues identified to hold up approval of the application. The final decision regarding this application will be determined in the secondary review after the responses to the information requests and responses to the 483 observations issued during the pre-license inspection have been reviewed.

Summary

On 18 Mar 2013 the FDA received an original Biologics License Application (BLA) submitted electronically in eCTD. I completed my filing memo on 23 Apr 2013 and concluded the application could be filed per 21 CFR 601.2. I initiated my primary review on 26 Apr 2013 and completed it on 04 Oct 2013.

Information Request Dates:

On **08 Apr 2013** two information request letters were sent to the Applicant. One letter contained the four issues identified as possibly affecting filing determination and was given a response date of no later than 22 Apr 2013. The second letter listed the eleven review issues that did not adversely affect the filing of the submission with a response date of no later than 06 May 2013.

On **21 June 2013** a nine item information request was sent to Bioclon. The majority of the questions were in reference to the drug substance.

On **17 July 2013** a twenty-eight item information request was sent to Bioclon with a requested response date of 07 Aug 2013. The majority of the questions were regarding the drug product.

On **04 Oct 2013** I sent a five item information request to my Branch Chief for approval so it could be sent to Bioclon.

Telecon Dates:

None.

Noteworthy Aspects

The Applicant originally requested a Priority Review; however, this request was denied so the review timeline will follow the standard review timeline for PDUFA V.

The application describes the (b) (4) facility (Drug Product Manufacturing) as a multi-product facility and lists equipment as shared or dedicated. It was discovered during the pre-license inspection that the facility was not a multi-product facility since there has only been a single product, Anavip, manufactured in the building. Bioclon was verbally informed during the inspection that they were not a multi-product facility and the FDA would need to be notified when any new products were introduced into the facility after licensure. The notification would be in the form of a supplement.

(Possible) Post Marketing Commitments

None.

Review Milestones

Milestone	Due Date
First Committee Meeting	08 Apr 2013
Filing Meeting	02 May 2013
Filing Action	17 May 2013
Deficiencies Identified	31 May 2013
Internal Mid-Cycle Meeting	01 Sep 2013
Mid-Cycle Communication	17 Sep 2013
Late-Cycle Meeting	01 Dec 2013
Action Due Date	18 Mar 2014

Facilities and Inspections

There are three facilities involved in the manufacture of Anavip. The facilities are listed below along with a short description of their manufacturing responsibilities and a proposal for the need for an inspection for each facility.

Name, address, zip code, telephone number

(b) (4) (Horse Facility)
(b) (4)

Manufacturer Responsibility:

Immunization of the horses with snake(s) venom(s) and subsequent plasma collection. Additionally, horses are housed and cared for at the (b) (4) facility. Limited testing of the material is also performed at this site.

Inspection:

No inspection of this facility will be performed since it is considered an upstream process that produces a raw material for manufacturing. An inspection waiver memo is not necessary.

Name, address, zip code, telephone number

Instituto Bioclon, S.A. de C.V. (Tlalpan)
Calzada de Tlalpan 4687
Colonia Toriello Guerra
Tlalpan, Mexico D.F.
MEXICO
+(55) 56 65 4111

Manufacturer Responsibility:

Snake Venom and Drug Substance. The snake venom production, plasma fractionation process, (b) (4) of the drug substance, and storage of the drug substance occur in the Tlalpan facility. Drug substance and drug product release testing is performed here.

Inspection:

This site will need to be inspected. An inspection waiver memo was written and it was approved on 31 May 2013.

Name, address, zip code, telephone number

Instituto Bioclon, S.A de C.V; (b) (4)

(b) (4)

Manufacturer Responsibility:

The filling and Lyophilization of the drug product, Anavip, is conducted in the (b) (4) Facility. Labeling and visual inspection also take place in this facility.

Inspection:

This facility will need to be inspected. Kelly Lewis will be the lead inspector and he will be accompanied by an additional DMPQ reviewer, Nancy Waites. The inspection is scheduled for (b) (4).

Scope of Review

I have performed a review of this application per CBER SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements. I specifically review the contents for the information that falls under DMPQ responsibility for review.

Items Reviewed

The following sections are included in this BLA. I have provided a summary of information provided in the submission that is under DMPQ purview in this review memorandum. The topics of review follow the sections of the eCTD format.

1. FDA Regional Information (shared review)

- 1.1 Forms
- 1.2 Cover Letters
- 1.3 Administrative Information
- 1.4 Reference Section
- 1.6 Meetings
- 1.12 Other Correspondence (request for categorical exclusion)

2. Common Technical Document Summaries (shared review)

- 2.2 Introduction
- 2.3 Quality Overall Summary (shared review)
 - 2.3.1 Introduction
 - 2.3.S Drug Substance (shared review)
 - 2.3.S Anavip - bioclon
 - 2.3.P Drug Product (shared review)

2.3.P Anavip – vials – bioclon

2.3.A Appendices

2.3.R Regional Information (shared review)

3.0 Quality

3.2.S Drug Substance

3.2.S anavip-bioclon

3.2.S.1 General Information

3.2.S.1.3 General Properties (shared review)

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

3.2.S.2.2 Description of Manufacturing Process and Process Controls (shared review)

3.2.S.2.3 Control of Materials (shared review)

3.2.S.2.4 Control of Critical Steps and Intermediates (shared review)

3.2.S.2.5 Reference Standards or Materials (shared review)

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification (shared review)

3.2.S.4.4 Batch Analysis (shared review)

3.2.S.4.5 Justification of Specification (shared review)

3.2.S.6 Container Closure System

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusion (shared review)

3.2.P Drug Product

3.2.P Anavip – vials – bioclon

3.2.P.1 Description and Composition of the Drug Product (shared review)

3.2.P.2 Pharmaceutical Development (shared review)

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s) (shared review)

3.2.P.3.3 Description of Manufacturing Process and Process Controls (shared review)

3.2.P.3.4 Controls of Critical Steps and Intermediates (shared review)

3.2.P.3.5 Process Validation and / Evaluation (shared review)

3.2.P.4 Control of Excipient

3.2.P.4.1 Specification (shared review)

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specifications (shared review)

3.2.P.5.4 Batch Analysis (shared review)

3.2.P.5.6 Justification of Specifications (shared review)

3.2.P.7 Container Closure System

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion (shared review)

3.2.A Appendices

3.2.A.1 Facilities and Equipment

3.2.A.1 Bioclon Anavip

3.2.R Regional Information (shared review)

Amendments Reviewed

125488/0/6

125488/0/8

DMF Reviewed

None. The information that is usually contained in the DMF was included in the application.

Topics Deferred to Other Review Divisions

I have deferred review responsibilities to the Product Office or other appropriate office as outlined in SOPP 8401.4.

Review Issues and Resolution

There are no review issues identified at this time that would prevent approval.

Amendments from the Review

STN 125488/0/6 was received on 23 Apr 2013 in response to the IR sent to Bioclon on 08 Apr 2013 with the four issues that could possibly affect filing determination. I performed a high-level review and determined the information provided in that amendment was sufficient for determining the application met filing criteria. My review of the information submitted in this amendment is incorporated into this Primary Review memo.

STN 125488/0/8 was received on 07 May 2013 in response to the eleven review related issues that were sent to Bioclon on 08 Apr 2013. My review of the information submitted in this amendment is incorporated into this Primary Review memo.

STN 125488/0/14 was received on 16 July 2013 in response to the IR sent to Bioclon on 21 June 2013. This amendment was NOT reviewed during the primary review. A review of this information will be part of the secondary review memo.

STN 125488/0/16 was received on 07 Aug 2013 in response to the IR sent to Bioclon on 17 July 2013. This amendment was NOT reviewed during the primary review. A review of this information will be part of the secondary review memo.

STN 125488/0/19 was received on 26 Aug 2013. This amendment was a response to the 483 observations issued during the pre-license inspection. This amendment was NOT reviewed during the primary review. A review of this information will be part of a separate 483 response review memo.

Reviews of Amendments 6 and 8 ONLY are included in this Primary Review Memo. The remaining amendments are NOT included in this review memorandum. They will be reviewed in the Secondary Review or in a separate review memo.

Review and Comment

Module 1.0

1. FDA Regional Information (shared review)

1.1 Forms

Bioclon applied for and was approved for a waiver of application fees since the indication is for an Orphan Drug.

1.2 Cover Letters

Bioclon requested a Priority review; however this request was denied since there is already a licensed product on the market to treat pit viper envenomation.

1.3 Administrative Information

Bioclon has named Jennifer Spinella, MT (ASCP), RAC, an employee of Rare Disease Therapeutics, Inc., as their Official Agent for this application.

1.4 Reference Section

DMF (b) (4) is referenced in this submission for (b) (4)

1.6 Meetings

I reviewed the meeting minutes for 08 May 2012 Type B Pre-BLA Meeting and the notable agreements / discussions between the Agency and Bioclon recorded in the meeting minutes are the following:

1. The lyophilizer currently approved for the US licensed product Anascorp (Centruroides (Scorpion) Immune F(ab')₂ (Equine) Injection), located at the Tlalpan facility, cannot be used for the lyophilization of Anavip, the subject of this application, since the equipment can only be sanitized and it cannot be sterilized. Per 21 CFR Part 211.67(a) indicates that equipment and utensils used in the production of sterile drug products must be sterilized, not merely sanitized. The Tlalpan lyophilizer was deemed acceptable due to the medical necessity of the product and your current production throughput. We request that a sterilized unit be utilized for future lyophilization for United States production of Anavip.
2. If you plan to perform (b) (4) filling operations from (b) (4), we would expect your BLA to include data demonstrating that the procedure does not compromise the sterility of the product. You should also include data demonstrating that the bulk lot retains (b) (4) over the intended storage period.
3. FDA would expect stability studies on conformance lots rather than human PK studies to qualify the new lyophilizer.
4. FDA proposed that Bioclon perform an IQ, OQ, and PQ for the fill/finish facilities at (b) (4) and submit the results with the BLA.
5. Bioclon proposed to include only one conformance lot for review in the BLA. The additional two conformance lots will be produced while the BLA is under review. FDA stated that the proposal may be acceptable, if justified, based on Bioclon's production schedule and product inventory demands, and if data for the conformance lots manufactured during the BLA review are received in time to allow adequate time for review.

1.12 Other Correspondence (request for categorical exclusion)

The amended categorical exclusion was reviewed and was acceptable. A categorical exclusion memo was written and it was approved on 20 May 2013.

Modules 2 and 3 were reviewed together since Module 2 is a summary of the information provided in Module 3.

2. Common Technical Document Summaries (shared review)

2.2 Introduction

Module 2 contains the summaries for the Quality, Non-clinical and Clinical sections of the eCTD. Tabulated summaries have been provided where applicable.

The quality overall summary describes the Chemistry and Manufacturing Controls (CMC) for the manufacture of Anavip antivenom production process.

Manufacturers

Anavip is also known in Mexico as Antivipmyn. Immunization of the horses with snake(s) venom(s) and subsequent plasma collection are carried out at the (b) (4) facility. The snake venom production and the drug substance manufacturing are performed by the Instituto Bioclon, S.A. de C.V. in Mexico City, Mexico (Tlalpan facility). The filling and lyophilization of the drug product, Anavip, is conducted by Instituto Bioclon, S.A de C.V; (b) (4) facility).

Test Methods

Test methods and controls for plasma, drug substance and drug product are described within this section in the submission.

Reviewer Comment: This information does not fall under the purview of DMPQ. I did include the release specifications for the horse plasma and drug substance in this review memorandum for information only.

Drug Product Description

I have included this information in the Drug Product review section of this review memorandum.

Non-clinical and Clinical Studies

Three Non-clinical studies have been conducted, one acute toxicity study and two independent in vitro and in vivo animal efficacy studies.

Reviewer Comment: This information does not fall under the purview of DMPQ.

2.3 Quality Overall Summary (shared review)

2.3 Introduction

This section contained similar information as Section 2.2 Introduction

2.3.S and 3.2.S Drug Substance (shared review)

2.3.S and 3.2.S Anavip – Bioclon

2.3.S.1 and 3.2.S.1.3 General Information

This section actually contained a description of the final product and information about the lyophilized drug product and not the drug substance. The information pertaining to the drug product has been included in the drug product review section of this review memorandum.

The drug substance is the (b) (4). It is stored at (b) (4). The material is manufactured and (b) (4) at the Tlalpan facility in Mexico City.

2.3.S.2 and 3.2.S.2

2.3.S.2.1 and 3.2.S.2.1 Manufacturers

The information for the horse facility and the drug substance manufacturing facility along with their responsibilities is are listed at the beginning of this review memorandum in the Facilities and Inspection section.

2.3.S.2.2 and 3.2.S.2.2 Description of Manufacturing Process and Process Controls and

A more complete description of the manufacturing process is supplied in the application; however, the following sections of the review memorandum provide a high-level overview of the manufacturing process.

Important Note: The manufacturing process for the venom production, inoculation and bleeding of the horses, and (b) (4) bulk drug substance are currently approved under STN 125335/0 for the manufacture of Anascorp. The manufacturing process, including in-process testing, specifications, and equipment, has not changed since the licensure of Anascorp.

2.3.S.2.2.1 and 3.2.S.2.2.1 Venom Production

(b) (4) (Horse Facility)
(b) (4)

Storage

(b) (4)

Testing and Release of Snake Venom for Horse Immunization

(b) (4)

Test Methods and Specifications for Release of Venom Solution for *Crotalus durissus* and *Bothrops asper*

Characteristic	Test Method	Specification	Significance of Parameter
(b) (4)			

Venom Production Process Description

(b) (4)

2.3.S.2.2.2 and 3.2.S.2.2.2 Immunization Process and Plasma Collection

The horses are immunized according to a set schedule (reference “Immunization Process” in Section 2.3.S.2.2.1 or 3.2.S.2.2.1 in the submission) and then bled based on the results for potency and hematocrit test results.

Blood Collection and Separation

The bleeding procedure for the horses is described in the submission. (b) (4)

(b) (4)

Transportation to Talpan Facility

(b) (4)

The shipping process for the shipment of the plasma from the horse facility to Bioclon (Tlalpan) was not validated since the shipment is monitored for temperature (b) (4) during transit.

Reviewer Comment:

The review pertaining to the care of the horses, the determination to bleed the horses, bleeding procedure, will be performed by another member of the review group.

The horse plasma is considered an incoming raw material for manufacturing of the bulk drug substance. This review will focus on release specifications of the horse plasma and how Bioclon accepts it as a raw material as opposed to reviewing the inoculation of the horses and bleeding as part of the manufacturing process.

Since the horse plasma is monitored for temperature during transit and there is a time limit for transit time, the performance of a shipping validation is not necessary.

The following was added to the 21 Jun 2013 IR:

Please provide a short description for the procedure for receipt and storage of the horse plasma at the Tlalpan facility.

Instituto Bioclon, S.A. de C.V. (Tlalpan) – Drug Substance Manufacture

Important Note: The processes and testing specifications described in this section for the manufacture of (b) (4) bulk drug substance are (b) (4) to the manufacturing processes, in-process testing and release testing specifications used in the manufacture of the currently U.S. licensed product, Anascorp.

Testing and Release of Horse Plasma

(b) (4)

Test Methods and Specifications for Release of Horse Plasma

Description	Specification	Reference
(b) (4)		

Where process time is considered to be critical to quality (CtQ) or a critical process parameter (CPP), limits have been established and are reflected in the batch production record (BPR). The conformance batches were manufactured according to the latest version of the fractionation and (b) (4) bulking BPR as well as the filling, lyophilization and packaging BPR.

Where time is not critical (i.e., (b) (4)) limits have not been fully established, however the elapsed time required to accomplish processing activities are being documented and tracked in the statistical database to establish process consistency and capture random variations. Once sufficient experience at the commercial scale has been attained (approximately (b) (4) runs), then process limits can be established and added to the BPR which will then cause variations to be treated as process deviations.

Initial time limits and related critical parameters for (e.g. (b) (4)) were initially established in the smaller scale validation studies and incorporated into the BPR. In-process manufacturing controls for bioburden and endotoxin have been established for the critical points in the manufacturing process. A report of the process control work done to establish bioburden and endotoxin limits in the manufacturing process was completed.

In the Batch Production Record for the conformance batches the critical in-process control elements are documented and the specified acceptance criteria listed. For non in-process testing, such as EM action alert and action levels, the data will be statistically assessed on an ongoing basis to establish more appropriate levels if needed.






The endotoxin and bioburden testing are performed using general methods described in (b) (4) . The following steps in the manufacturing process were identified as critical steps where bioburden (specification: (b) (4)) and endotoxin (specification: (b) (4)) are monitored:

- (b) (4)

(b) (4)

(b) (4)

(b) (4)



Reviewer Comment: I reviewed the above listed diagrams and found them to be acceptable.

Instituto Bioclón, S.A. de C.V. (Tlalpan) Facility Description

Tlalpan

This section describes the Tlalpan Facility used for drug substance manufacturing and (b) (4) of the bulk drug substance. (b) (4)

Reviewer Comment: I have provided only a high-level overview of the facility since the facility, processes, manufacturing procedures, cleaning procedures, and equipment are all currently approved for use for the manufacture of the licensed U.S. drug substance for Anascorp.

The Tlalpan facility is a multi-product facility that consists of a three-story building, with the majority of the manufacturing activities taking place on (b) (4) floor (b) (4). Some cleaning and sterilization of materials, as well as packaging and labeling, is conducted on the lower floor (b) (4). The top floor (b) (4) houses the (b) (4), as well as the (b) (4).

(b) (4) A freight elevator is the primary means of moving materials between floors, while personnel use a common stairwell.

The initial fractionation of plasma for the USA is conducted in areas shared with production for Mexico. The (b) (4) for Anavip and the currently licensed Anascorp is conducted in Aseptic Area (b) (4) which is a dedicated area for product to be distributed in the USA. Mexican drug product is filled and lyophilized in Aseptic Area (b) (4) which is also located on (b) (4), but isolated from other areas.

Floor diagram – (b) (4)



Floor diagram – (b) (4)

An overview of the processing suite is included in the submission, Figure 2 (Figure 2 – Tlalpan Facility Layout (b) (4)



(b) (4)

Flow Diagrams

The following maps contain a layout of the Tlalpan facilities, and the flow of incoming and in-process materials, and personnel through each level of the facility.

Figure 4 - Incoming Materials Flow Diagram – Tlalpan Floor (b) (4)

Figure 5 - Bulk Drug Substance Flow Diagram – Tlalpan Floor (b) (4)

Figure 6 - Bulk Drug Flow Diagram – Tlalpan Floor (b) (4)

Figure 7 - Personnel Flow Diagram – Floor (b) (4)

Figure 8 - Personnel Flow Diagram – Floor (b) (4)

Reviewer Comment: I reviewed the above listed flow diagrams and found them to be acceptable.

Control of Contamination, Cross-Contamination and Containment

In the manufacturing area the floors are a (b) (4)

The equipment supports are (b) (4) to prevent moisture entrapment and microbial growth. The walls are (b) (4). The ceiling is a (b) (4) are used to minimize air movement between the (b) (4) area and the common entrance area, and the production holding area.

Sanitization fluids are brought into the area (b) (4). When an incident occurs that requires the removal of liquids (leaky

tubing or connection), the liquid is squeegeed, mopped and squeezed into a bucket and transported out of the area.

Per Bioclon, cleaning and sanitization of the production areas is conducted (b) (4) process. At the start of a manufacturing campaign, cleaning and sanitization, and environmental monitoring using settling plates are performed just prior to the start of production.

Aseptic Area (b) (4) is supplied with (b) (4)

The cleaning and sanitization of the aseptic area is conducted (b) (4). At the start of a manufacturing campaign, environmental monitoring is conducted using settling plates. Viable and non-viable monitoring is also performed during the manufacturing process.

For the (b) (4) production area the floor, walls, and ceiling are constructed of smooth and hard surfaces for ease of cleaning and sanitization. Cleaning and sanitization of the production areas is conducted (b) (4). At the start of a manufacturing campaign, cleaning and sanitization, and environmental monitoring using settling plates are performed just prior to the start of production. Air sampling for nonviable particles is also performed during production.

The cleaning process utilizes a (b) (4)

Materials such as glass containers are disinfected according to SOPs before entering the fractionation area.

Instituto Bioclon developed the cleaning validation based on microbiological determinations and implemented a program of environmental monitoring to select critical points for the monitoring of bioburden in the areas of the reception of (b) (4)

A disinfectant qualification study using sample coupons of representative surfaces and indicator microorganisms was conducted for each of the sanitizing agents used in the production areas. The study was designed to verify that the sanitizing agent concentrations, and contact times effectively sanitize the items tested. The rotation times have been set for a (b) (4) change to reduce the potential for microbial resistance.

Cleaning and sanitization of the (b) (4) area is conducted (b) (4) process. Monitoring is performed using settling plates just prior to the start of the (b) (4) process.

Equipment – Drug Substance Manufacturing Equipment

(b) (4)

The table below lists the equipment used in the manufacturing process. Equipment qualification of all the major manufacturing equipment used in the production process of Anavip Bulk Drug Substance has been conducted. This process included identifying the appropriate clean and dirty hold times for each specific piece of equipment.

Validation of the cleaning and rinsing of (b) (4) containers used to hold bulk drug product and vials was completed.

In addition, a cleaning study on the (b) (4) system was conducted to determine the appropriate swab sampling areas, and clean and dirty hold times for the unit.

Equipment Used in the Manufacturing Process and Product contact area.

Equipment	Manufacturing Step	Comments
(b) (4)		

(b) (4)

Utilities – Tlalpan Facility

List of Utilities and Services - Tlalpan Facility

- PCS-VA-005/I – Compressed Air System Installation Qualification (IQ) Report (b) (4)
- PCS-VA-014/I – Compressed Air System Operation Qualification (OQ) Report, (b) (4)
- VAL-459, Compressed Air System Performance Qualification (PQ) Report
- Statement of Compliance for Compressed Air Viable Particles Determination
- (March 29, 30, & 31, 2010)
- PCS-VA-007 – Aseptic Area (b) (4) Air Conditioning System (HVAC) Installation Qualification Protocol
- PCS-VA-007/I – Report for the Aseptic Area (b) (4) Air Conditioning System (HVAC) Installation Qualification (IQ)
- PCS-VA-013 - Protocol for the Aseptic Area (b) (4) HVAC OQ
- PCS-VA-013-I - Report for the Aseptic Area (b) (4) HVAC OQ
- PCS-VA-012 Protocol for the Aseptic Area (b) (4) HVAC Performance Qualification.
- PCS-VA-012-I - PQ Rep for Addendum to Aseptic Area (b) (4) HVAC system
- Performance Qualification (PQ) Report, code QV-PHARMA-RPQHVC-0609-R01
- PCS-VA-003, Results Report for the Performance Qualification (PQ) of the (b) (4) System

Reviewer Comment: I performed a high-level review of the above listed qualification reports since the protocols were executed for the validation of the Anascorp process. However, since Anascorp and Anavip are very similar products and the manufacturing process uses the (b) (4) these studies are applicable to Anavip and this BLA.

The following was included in the information request dated 21 Jun 2013:

4. The utility information provided in the BLA was for qualification studies performed in 2009 – 2010. Please provide the following information, since 2012, to demonstrate the facility and utilities have been run in a controlled manner and as qualified:

- a. Summary of EM data for the manufacturing rooms and aseptic area including a summary of any major deviations and their investigation. Please include acceptance criteria.
- b. Summary of testing results for the (b) (4) used in manufacturing including a summary of any deviations and their investigations. Please include acceptance criteria.

DRUG PRODUCT

2.3.P.1 and 3.2.P.1 Description and Composition of the Anavip® and 2.3.P.2.1 and 3.2.P.2.1 Pharmaceutical Development

Description and Dosage Form

Proprietary Name: Anavip®

Drug Substance: Crotalidae (pit-viper) Immune, F(ab')₂ (Equine) Injection

Dosage Form: Lyophilized, single-use vials

Route of Administration: IV

Anavip ® [Crotalidae (Pit-Viper) Immune F(ab')₂ (Equine) Injection], also known in Mexico as Antivipmyn, is a sterile, nonpyrogenic, lyophilized, polyvalent preparation of equine immune globulin F(ab)₂ fragments, manufactured from plasma of horses immunized with venom of Bothrops asper and Crotalus durissus. The product is obtained by pepsin digestion of horse plasma to remove the Fc portion of immune globulin, followed by fractionation and purification steps. The manufacturing procedures that contribute to the reduction of risk of viral transmission include pepsin digestion, ammonium sulfate precipitation/heat treatment, and nanofiltration.

Each vial contains no more than 120 milligrams of protein and will neutralize not less 780 times the LD₅₀ of Bothrops asper venom and 790 times the LD₅₀ of Crotalus durissus venom in a mouse neutralization assay.

Composition

Anavip contains not less than 85% F(ab)₂, the F(ab) content is not more than 7%, and the product contains less than 5% intact immunoglobulin. Each vial of Anavip contains 25.2 - 56.8 mg of sodium chloride (b) (4) final concentration), 18.2 - 85.8 mg of sucrose, and 16.2 - 51.8 mg of glycine as stabilizers. Trace amounts of pepsin, cresol (< 0.99 mg/vial), borates (< 1 mg/vial), and sulfates (< 1.7 mg/vial) may be present from the manufacturing process.

Type of Container and Closure

Anavip is supplied as a sterile lyophilized preparation in a single-use vial. This container closure is currently approved for the licensed Anascorp product. A description of the container and closure system, and its compatibility with the drug product is provided in the compatibility report which includes information concerning the supplier, address, and the results of compatibility, toxicity and biological tests. The compatibility of container closure is described in this review memorandum in Section 3.2.P.7. Results of the container closure integrity are included as well.

2.3.P.2.2 and 3.2.P.2.2 Drug Product

2.3.P.2.2.1 and 3.2.P.2.2.1 Formulation Development

Reviewer Comment: Information provided in this section does not fall under DMPQ review responsibilities. The section included a discussion of the study designed to evaluate the safety and immunogenicity of intravenous Antivipmyn and to characterize its pharmacokinetic profile.

2.3.P.2.2.3 and 3.2.P.2.2.3 Physicochemical and Biological Properties

This section discussed the potency assay, (b) (4), appearance, (b) (4), sulfate determination, cresol, protein content, reconstitution, safety, and pyrogen specifications.

Per Bioclon, healthy, mature rabbits are used to conduct this test. The test method is accordance to 21 CFR 610.13 and performed according to (b) (4) test method.

Reviewer Comment: Information contained within this section did not fall under DMPQ review responsibilities.

2.3.P.2.3 and 3.2.P.2.3 Manufacturing Process Development

Reviewer Comment: The information provided in this section discussed reconstitution time, which does not fall under DMPQ purview.

3.2.P.2.3.1 Shipping

A discussion of shipping of the final product occurs in this review memorandum in Section 2.3.P.2.4.1 and 3.2.P.2.3.1 and 3.2.P.2.4.1 Shipping Procedure

2.3.P.2.4 and 3.2.P.2.4 Container Closure System

See Section 3.2.P.7 for a description of the container and closure system, and its compatibility with the biological substance.

2.3.P.2.4.1 and 3.2.P.2.3.1 and 3.2.P.2.4.1 Shipping Procedure



(3.2.P.2.3.1 is the approved protocol)

Per Bioclon, this shipping procedure will be executed during winter season of 2012-2013 and a partial report will be written for BLA Submission. The procedure will be repeated during the summer season of 2013 and a final version of the report will be written.

NOTE: This procedure will be executed twice, once during winter season of 2013 and repeated during the summer season of 2013. The report will be written after the summer phase is completed.

The shipping validation of the final product used drug product that has met the QA release requirements and the release certificate of analysis will be used as a baseline for the quality parameters that will be measured for the protocol. The drug product was packaged in the intended commercial secondary and tertiary packaging (outer carton, cushioning materials and shipping carton). Each outer carton was equipped with a suitable calibrated temperature and relative humidity recording device.

The drug product was shipped using a courier service from Mexico to AnovoRx Distribution, LLC; 1710 North Shelby Oaks Drive, Suite 6; Memphis, TN 38134. Once the shipped product arrives in Tennessee, the shipping containers will be visibly checked for damage to the outer carton. (b) (4)



This set of samples will be tested as the control group. The acceptance criteria of this shipping study are that the Anavip drug product that has been shipped meets the intended commercial drug product release specifications.

Reviewer Comment: Since each shipping container will always be shipped with a temperature and humidity monitor, the contents will be monitored for the entire shipment. This is acceptable and the review is not affected due to the lack of shipping validation.

However, the following additional information has been requested on 17 Jul 2013:

In Section 2.3.P.2.4.1 and 3.2.P.2.4.1 you state that a partial shipping validation report for the shipping results of winter 2012-2013 will be submitted to the BLA. Please submit the report.

Please indicate what would happen to the shipment if there was evidence of a deviation in temperature, humidity or impact requirements.

Please provide additional information on the monitors placed on the shipping containers. Please specify how often they are calibrated and if they are on a preventive maintenance schedule.

2.3.P.2.5 and 3.2.P.2.5 Microbiological Attributes

See Section 3.2.P.7 for the Protocol PCB-CC-006 and Summary Report PCB-CC-005/I001 for a discussion of the container closure integrity tests performed to demonstrate the ability of the closure container system to maintain the (b) (4) polyvalent fabootherapeutics (Anavip) under the proper conditions -- meaning the physical, chemical, microbiological and biological properties are not affected. A (b) (4) testing were performed.

See Section 3.2.P.8 for stability data and protocol which demonstrate that the contact between the reconstituted product with the vial and the stopper does not affect the product potency as all the tested groups comply with the product specifications. In addition, the leak test evaluation shows that maintaining the integrity of the container closure keeps the vials sterile and therefore preventing the microbiological contamination.

2.3.P.2.6 and 3.2.P.2.6 Compatibility

A discussion of container closure compatibility can be found in this review memorandum in Section 3.2.P.7.4.

2.3.P.3 and 3.2.P.3 MANUFACTURER(S)

2.3.P.3.1 and 3.2.P.3.1 Manufacturer(s)

Manufacturer –(b) (4) (Drug Product)

The drug product manufacturing facility and its responsibilities are listed at the beginning of this review memorandum in the Facilities and Inspection section.

2.3.P.3.2 and 3.2.P.3.2 Batch Formula





2.3.P.3.2.1 and 3.2.P.3.2.1 Discussion

Drug Product Conformance Lots

Two conformance lots were manufactured for this application. The third conformance lot will be manufactured during the pre-license inspection.

Lot (b) (4)

(b) (4)



Details of the composition of the final product lot (b) (4) can be found in the submission in Section 3.2.R Regional Information, Executed Batch Records, Drug Product BPRs List.

Reviewer Comment: I reviewed the executed batch record for (b) (4) and found it to be
--

acceptable. No deviations were noted by Bioclon.

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

Details of the composition of the final product lot (b) (4) can be found in the submission in Section 3.2.R Regional Information, Executed Batch Records, Drug Product BPRs List.

Reviewer Comment: I reviewed the executed batch record for (b) (4) and found it to be acceptable. No deviations were noted by Bioclon.

2.3.P.3.2.2 and 3.2.P.3.2.2 Summary of Testing

The release testing for the drug product is listed in the table below.

Test Description	Specifications / Limit(s)
Appearance (Lyophilized)	(b) (4)
Appearance (Reconstituted)	Transparent liquid or slightly opalescent and colorless or slightly yellow, free of foreign particles in suspension
Identification	Meets requirements
Potency	BF: NLT 780 LD50 neutralized/vial CF: NLT 790 LD50 neutralized/vial
Purity (b) (4)	F(ab)2 NLT 85% Fab NMT 7% (b) (4)
Purity (b) (4)	(b) (4) IgG (b) (4) NMT 5%
(b) (4)	(b) (4)
Protein Content	NMT 120 mg / vial
Sulfate	NMT 1.7 mg / vial
Cresol	NMT 0.99 mg / vial
Sterility	Meets requirements

Pyrogens (Rabbit)	Meets requirements
Glycine	16.24 – 51.76 mg / vial
(b) (4)	(b) (4)
Sodium Chloride	25.19 – 56.81 mg/vial
Borates	NMT 1.0 mg/vial
Sucrose	18.16 – 85.84 mg/vial
Safety	Meets requirements
Moisture Content	(b) (4)
Reconstitution	(b) (4)
Leak Test	(b) (4)

3.2.P.3.2.3 Certificates of Analysis (CofAs) for Drug Product

Reviewer Comment: I performed a high-level review of this section and the CofAs for Lot (b) (4) provided demonstrated that all release testing met specifications.

2.3.P.3.3 and 3.2.P.3.3 Description of Manufacturing Process and Process Controls Description of Manufacturing

Receipt of (b) (4) Bulk Drug Substance from Tlalpan Facility

Receipt of the (b) (4) bulk drug substance at (b) (4) from Tlalpan is governed by SOP PNS-INS-001.

Reviewer Comment: I reviewed this SOP and found it to be acceptable. A description of the SOP is contained in this review memorandum in the section describing the final product container closure. After receipt of the bulk DS, the (b) (4) are stored in the (b) (4) until needed for manufacture. ☐

The following was included in the IR dated 17 Jul 2013:

Please describe the maximum length of storage time and the storage conditions for the drug substance once it is delivered from the Tlalpan facility to the (b) (4) facility.

Preparation of Materials and Equipment

Calibration Check



The equipment used in the manufacture of the drug product is checked to confirm all equipment instrumentation and in the manufacturing areas are calibrated. This is reviewed By QA.

Cleaning and Sanitization of Production Areas, Equipment, and Materials

Prior to the beginning of the production process, all equipment and manufacturing areas are cleaned by the appropriate production personnel. All equipment and areas are identified with a status label. Detergent / Sanitizing Agents used, date cleaned, and date item was used are recorded in the BPR. The production areas, equipment and materials used are released by QA prior to use. All appropriate labels are attached to the BPR as a record of the cleaning, sanitization, and release by QA. WFI is sampled and released by QA prior to use.

Washing and Sterilization of Materials

(b) (4)






Gowning

Personnel enter the aseptic area per SOP PNO-PBT-002: Personnel Access to Aseptic Area and SOP PNO-PBT-048: Use of Uniform for Entering the Aseptic Area. SOP PNO-PBT-002: Personnel Access to Aseptic Area provides an overview of the personnel flow for the ingress and egress of personnel into the aseptic area. Personnel are required to remove their plant uniform and don a new uniform for the aseptic area. The specific procedure for donning the sterile gowns for the aseptic area is captured in SOP PNO-PBT-048: Use of Uniform for Entering the Aseptic Area. SOPs PNO-PBT-002 and PNO-PBT-048 are included in Module 3, Section 3.2.R Regional Information; method validation; standard operating procedures: pno-pbt-002 and pno-pbt-048.

<p>Reviewer Comment: I reviewed both SOPs and found them to be acceptable. Both of the SOPs were typical procedures for gowning and SOP PNO-PBT-048 contained photographs of appropriate gowning attire and appropriate gowning process.</p>

Filling

(b) (4)



(b) (4)

Visual Inspection, Packaging and Labeling

Visual inspection is performed on 100% of the vials per established Bioclon procedures. The vials are subsequently labeled and placed into secondary packaging.

Visual examination of the vials is performed in the "Revision Area" of the (b) (4) plant using the (b) (4); the review process is carried out according to the SOP PNO-PBT-035: visual inspection of freeze-dried products. The area is classified as Class (b) (4). The labeling of the products will be done in the "Packaging Area" of the (b) (4) plant. The labeling and packaging of the product is carried out according to the SOP PNO-ACO-001: Labeling and Packaging of Final Products. The area is classified as Class (b) (4).

SOPs PNO-PBT-035 and PNO-ACO-001 are included in Module 3, Section 3.2.R Regional Information; method validation; standard operating procedures: pno-pbt-035 and pno-ac0-001.

Reviewer Comment: I reviewed SOPs PNO-PBT-035 and PNO-ACO-001 and, overall, found them to be acceptable. The following comment was included in an IR dated 11 Oct 2013:

You state that the Critical defect specification during visual inspection is (b) (4) and the Major defect specification is (b) (4). Typically, the critical defect allowance is tighter than the major defect allowance. Please provide the rationale for your specifications.

Visual Inspection

SOP PNO-PBT-035 states (b) (4). The SOP also describes the visual inspection process and defect classifications thusly:

(b) (4)

(b) (4)

Reviewer Comment: The following was included in the IR dated 04 Oct 2013:

Please provided the executed batch production records for the visual inspection and packaging and labeling of the vials filled and labeled for the conformance lots.

Please provided the executed batch production records for the visual inspection and packaging and labeling of the vials filled and labeled for the conformance lots.

Process Controls

A Filling and Lyophilization Flow Chart is provided in the submission in this section. I have recreated the flow chart into a table listing the step and the controls in place for each step.

[illegible]

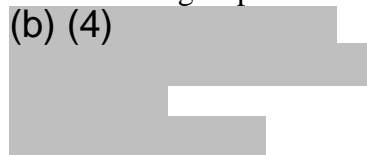
2.3.P.3.4 and 3.2.P.3.4 Control of Critical Steps and Intermediates

2.3.P.3.4.1 and 3.2.P.3.4.1 Critical Steps

In the Batch Production Record for the conformance batches, the critical process control elements were documented and the specified acceptance criteria listed. For non in-process testing, such as EM action alert and action levels, the data will be statistically assessed on an ongoing basis to establish more appropriate levels if needed.


The following steps are considered critical during the filling and lyophilization process:

(b) (4)









(b) (4)

(b) (4)



(b) (4)



More detail about the visual inspection process can be found in this review memorandum in the section that discusses the manufacturing process.


2.3.P.3.4.2 and 3.2.P.3.4.2 Stability Data

The stability data for the drug product are included in section 3.2.P.8


2.3.P.3.5 and 3.2.P.3.5 Process Validation (PV) and/or Evaluation

2.3.P.3.5.1 and 3.2.P.3.5.1 Media Fill

An aseptic process simulation, or media fill, was performed to demonstrate that growth medium exposed to (b) (4)



Media fills are scheduled to be performed every ^{(b) (4)} months. Approved batch production records are used for the media fills. It is also important to note that the media fills (b) (4)



	(b) (4)			

[REDACTED]

[REDACTED]

[REDACTED]

2.3.P.4 and 3.2.P.4 CONTROL OF EXCIPIENTS

2.3.P.4.1 and 3.2.P.4.1 Specifications

2.3.P.4.2 and 3.2.P.4.2 Analytical Procedures

2.3.P.4.2.1 and 3.2.P.4.2.1 Analytical Procedure for Glycine Content

2.3.P.4.2.2 and 3.2.P.4.2.2 Analytical Procedure for Sodium Chloride Content

2.3.P.4.2.3 3.2.P.4.2.3 Analytical Procedure for Sucrose Content

2.3.P.4.3 and 3.2.P.4.3 Validations of Analytical Procedures

2.3.P.4.3.1 and 3.2.P.4.3.1 Validation of Analytical Procedure for Glycine Content

2.3.P.4.3.2 and 3.2.P.4.3.2 Validation of Analytical Procedure for Sodium Chloride Content

2.3.P.4.3.3 and 3.2.P.4.3.3 Validation of Analytical Procedure for Sucrose Content

2.3.P.4.4 and 3.2.P.4.4 Justifications of Specifications

This section provided the justification of the specifications for the excipients listed above. This falls under the Product Office purview. I did not review this section.

Reviewer Comment: This entire section of Section 2.3.P.4 and Section 3.2.P.4 falls under the purview of the product office and includes the subsections listed above. I did not review this section.

2.3.P.5 and 3.2.P.5 CONTROL OF DRUG PRODUCT

2.3.P.5.1 and 3.2.P.5.1 Specifications

The table below lists the final release testing and specifications for Anavip.

Test Description	Specifications / Limit(s)	Test Method(s)
Appearance (Lyophilized)	(b) (4)	Visual SOP M-FQ-078
Appearance (Reconstituted)	Transparent liquid or slightly opalescent and colorless or slightly yellow, free of foreign particles in suspension	Visual SOP M-FQ-078
Identification	Meets requirements	(b) (4) - SOP M-CB-011
Potency	BF: NLT 780 LD50 neutralized/vial CF: NLT 790 LD50 neutralized/vial	SOP M-CB-016
Purity (b) (4)	F(ab) ₂ NLT 85% Fab NMT 7% (b) (4)	SOP M-CB-027
Purity (b) (4)	(b) (4) (b) (4) IgG (b) (4) (b) (4)	SOP M-CB-001
(b) (4)	(b) (4)	(b) (4)
Protein Content	NMT 120 mg / vial	(b) (4) SOP M-CB-005
Sulfate	NMT 1.7 mg / vial	(b) (4)
Cresol	NMT 0.99 mg / vial	SOP M-FQ-019
Sterility	Meets requirements	(b) (4)
Pyrogens (Rabbit)	Meets requirements	(b) (4)
Glycine	16.24 – 51.76 mg / vial	SOP M-FQ-091
(b) (4)	(b) (4)	(b) (4)
Sodium Chloride	25.19 – 56.81 mg/vial	SOP M-FQ-092
Borates	NMT 1.0 mg/vial	Instituto Bioclon
Sucrose	18.16 – 85.84 mg/vial	SOP M-FQ-093
Safety	Meets requirements	21 CFR 610.11
Moisture Content	(b) (4)	(b) (4)
Reconstitution	(b) (4)	SOP M-FQ-038
Leak Test	(b) (4)	SOP M-FQ-030

NLT – Not less than; NMT – Not more than

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

2.3.P.5.2 and 3.2.P.5.2 Analytical procedures and 2.3.P.5.3 and 3.2.P.5.3 Validation of Analytical Procedures

Reviewer Comment: The following analytical procedures listed below fall under the purview of the Product Office; therefore, I did not review them or their validation.

2.3.P.5.2.2 and 3.2.P.5.2.2 (b) (4) Test M-CB-011; 2.3.P.5.3.4 and 3.2.P.5.3.4 Validation of Analytical for (b) (4) test
2.3.P.5.2.3 and 3.2.P.5.2.3 Potency M-CB-016; 2.3.P.5.3.1 and 3.2.P.5.3.1 Validation of Analytical Procedure for Potency
2.3.P.5.2.4 and 3.2.P.5.2.4 Purity (b) (4) M-CB-027; 2.3.P.5.3.2 and 3.2.P.5.3.2 Validation of Analytical Procedure for (b) (4)
2.3.P.5.2.5 and 3.2.P.5.2.5 (b) (4) M-CB-001; 2.3.P.5.3.3 and 3.2.P.5.3.3 Validation of Analytical Procedure for (b) (4)
2.3.P.5.2.6 and 3.2.P.5.2.6 (b) (4) M-FQ-040 (b) (4)
2.3.P.5.2.7 and 3.2.P.5.2.7 Protein Content M-CB-005; 2.3.P.5.3.5 and 3.2.P.5.3.5 Validation of Analytical Procedure for Protein Content by (b) (4)
2.3.P.5.2.8 and 3.2.P.5.2.8 Sulfates M-FQ-089; 2.3.P.5.3.6 and 3.2.P.5.3.6 Validation of Analytical Procedure for Sulfate Determination
2.3.P.5.2.9 and 3.2.P.5.2.9 Cresol M-FQ-019; 2.3.P.5.3.7 and 3.2.P.5.3.7 Validation of Analytical Procedure Cresol Determination
2.3.P.5.2.12 and 3.2.P.5.2.12 Glycine SOP M-FQ-091; 2.3.P.5.3.8 and 3.2.P.5.3.8 Validation of Analytical Procedure for Glycine Content
2.3.P.5.2.13 and 3.2.P.5.2.13 (b) (4)
2.3.P.5.2.14 and 3.2.P.2.14 Sodium Chloride SOP M-FQ-092; 2.3.P.5.3.9 and 3.2.P.5.3.9 Validation of Analytical Procedure for Sodium Chloride Content
2.3.P.5.2.15 and 3.2.P.5.2.15 Borates SOP M-CB-031; 2.3.P.5.3.11 and 3.2.P.5.3.11 Validation of Analytical Procedure for Borates
2.3.P.5.2.16 and 3.2.P.5.2.16 Sucrose M-FQ-093; 2.3.P.5.3.10 and 3.2.P.5.3.10 Validation of Analytical Procedure for Sucrose Content
2.3.P.5.2.17 and 3.2.P.5.2.17 Safety M-CB-03 [21 CFR 610.11]
2.3.P.5.2.19 and 3.2.P.5.2.19 Reconstitution M-FQ-038

Reviewer Comment: The following tests listed below fall under the purview of DBSQC. I did not review them.

2.3.P.5.2.10 and 3.2.P.5.2.10 Sterility M-MB-006 (b) (4)
2.3.P.5.2.11 and 3.2.P.5.2.11 Pyrogen M-CB-014 (b) (4) Rabbit Pyrogen Testing

I did review the following tests:

2.3.P.5.2.1 and 3.2.P.5.2.1 Appearance M-FQ-078
2.3.P.5.2.18 and 3.2.P.5.2.18 Moisture Content (b) (4) Method
2.3.P.5.2.20 and 3.2.P.5.2.20 Leak Test M-FQ-030

Reviewer Comment: I did review the testing for appearance, moisture and leak testing. The appearance testing is acceptable and the moisture test is performed per (b) (4)

(b) (4) method which is acceptable. For the leak test, Bioclon described (b) (4) leak tests so it was unclear which leak test is actually used.

The following was included in the 17 Jul 2013 IR:

In sections 2.3.P.5.2.20 and 3.2.P.5.2.20 Leak Test M-FQ-030, (b) (4) methods of leak testing of the final container are described. Please indicate which leak test is used for the Anavip final product.

2.3.P.5.4 and 3.2.P.5.4 Batch analyses

Details describing the two conformance lots that were manufactured, Lot (b) (4) can be found in this review memorandum in Section 2.3.P.3.2.1 and 3.2.P.3.2.1: Discussion. Section 3.2.P.5.1 of this review memorandum lists the release testing and specifications.

The data for the release testing of the two conformance lots were provided in the submission in Section 3.2.P.5.4. All release specifications were met.

The executed batch production records (BPR) for these conformance lots are located in the submission in Section 3.2.R Regional Information, Executed Batch Records, Drug Product, Drug Product BPRs List.

Reviewer Comment: I performed a high-level review of the release test results for the conformance lots. All specifications were met. I also reviewed the executed batch production records for the two conformance lots and they were acceptable.

2.3.P.5.5 and 3.2.P.5.5 Characterization of Impurities

Reviewer Comment: This section does not fall under the purview of DMPQ thus I did not review it.

2.3.P.5.6 and 3.2.P.5.6 Justification of Specifications

The physiochemical properties of the final product are tested in part by appearance and moisture content. The specifications for these two tests are listed in Section 3.2.P.5.1 of this review memorandum.

Reviewer Comment: The appearance describes the color and appearance of the material upon visual observation and the moisture specification is listed as (b) (4) which is the same specification currently set for Anascorp. I do not have any comments.

I did not review any other justifications for testing specifications.

The following was included in the 17 Jul 2013 IR:

In section 3.2.P.5.6, sterility test, (b) (4) are referenced. Please indicate which (b) (4) test is used for sterility testing? In addition, for pyrogen testing you reference 21 CFR 613.13, which does not exist. Please clarify if this was a typographical error and you meant

to reference 610.13 (b) in addition to (b) (4)

2.3.P.6 and 3.2.P.6 Reference Standard or Materials

Reviewer Comment: This section does not fall under the purview of DMPQ, thus I did not review this section.

2.3.P.7 and 3.2.P.7 Container Closure System

2.3.P.7.1 and 3.2.P.7.1 Introduction

The general characteristics of the container closure are described in the review memorandum in Section 3.2.P.7.2. Section 3.2.P.7.3 contains a report on the evaluation of the ability of the container closure to maintain a stable environment for the drug product after the vials are exposed to extreme conditions of temperature and pressure. Testing included (b) (4) and moisture content. Section 3.2.P.7.4 provides a description of the container closure and discusses its compatibility with the drug product. The discussion includes results of compatibility, toxicity and biological tests.

The following conclusions were drawn after the studies described in the following sections were conducted:

- The components of the container closure system are compatible with the reconstituted drug product.
- The interaction between the reconstituted drug product and the container closure system does not generate toxicities as demonstrated in the animal safety testing showing that the drug product containers are not reactive, additive, or absorptive.
- The drug product maintains its efficacy, safety, purity and potency.
- The diluent used to reconstitute the product (isotonic saline solution) is not toxic.
- The container closure system maintains the polyvalent fabootherapeutic (Anavip) under the proper conditions, meaning the physical, chemical, microbiological and biological properties of the product are not affected.

3.2.P.7.2 Container Closure System general characteristics

1. Glass Vial

Type (b) (4) glass vial, 20 mL

a. Supplier

(b) (4)

2. Stopper

Grey bromobutyl rubber elastomeric closure; (b) (4)

a. Supplier

(b) (4)

(b) (4)

3. Flip Off Cap

Aluminum flip off cap; (b) (4)

a. Supplier(s)

(b) (4)

Reviewer Comment: The following was included in the 17 Jul 2013 IR:

Please specify if a bioburden and endotoxin specification exists for the incoming vials and stoppers.

3.2.P.7.3 Evaluation of the closure container system to maintain the (b) (4) polyvalent fabo therapeutics (Anavip) under the proper conditions. Protocol PCB-CC-006

Bioclon evaluated the container closure integrity, per protocol PCB-CC-006, to document the primary packaging of the final product is able to maintain the (b) (4) polyvalent fabo therapeutics (Anavip) under suitable conditions such that the physical, chemical, microbiological and biological properties are not affected.

(b) (4) and moisture content testing, using three different lots of released product, were performed under different temperature and pressure conditions to evaluate the container closure integrity.

The protocol studies described in the application applied to container closure system:

- Vial of 20 mL Type (b) (4) supplier (b) (4)
- Gray slotted rubber stopper (b) (4)
- Flip-off assembly

The protocol described the preparation of the negative and the positive test controls and the preparation of the (b) (4)

Reviewer Comment: It is unclear if the vials tested for container closure integrity were vials that were capped and crimped on the (b) (4) or if the vials were capped and

crimped via the (b) (4) process used in Tlalpan. Normally, this would be a concern since the two capping and crimping processes cannot be evaluated for equivalence; however, in this case, the (b) (4) crimped vials are integrity tested via (b) (4) each time the capping machine is set up and then (b) (4) throughout the crimping process.

Therefore, at this time I will not include the information in this review memorandum. I will include it in a subsequent review memorandum.

The protocol was confusing since I could not determine if lyophilized or (b) (4) vials were being tested. This point will need to be clarified. The data provided demonstrated that the vials could remain integral after being exposed to extreme conditions of temperature. (b) (4) and moisture testing were performed to show that the final product continued to meet specifications.

The following was included in the IR dated 04 Oct 2013:

For Section 3.2.P.7.3, please provide the following information:

Please clarify if the test vials and the control vials used in this testing protocol were stoppered and crimped using the (b) (4) equipment used in (b) (4) or the (b) (4) process used in Tlalpan.

Please clarify the following for the testing protocol:

(b) (4)

3.2.P.7.4 Study to evaluate the Compatibility and Toxicity between the container closure system and Anavip Protocol CODE: PCB-CC-005 and Report CODE: PCB-CC-005/I001

Reviewer Comment: The protocol and results for the evaluation of compatibility and toxicity between the container closure and the drug product do not fall under the purview of DMPQ, thus I did not review this information. I have provided a high-level description in this review memorandum for informational purposes only.

The container closure system evaluation demonstrated that the product contact parts of the container closure system do not interfere with the product, safety, purity, potency and efficiency.

This study consisted of the evaluation of compatibility between container-closure system (glass vial and rubber stopper) and anti-viper polyvalent fabootherapeutic (Anavip).

A study of the compatibility of the container closure system with Anavip was conducted to show:

(b) (4)



Additional information for container closure system for Anavip Supplied in Amendment 8
Description

The vial diagrams are found in SOP-IN-025: For the measurement of the type (b) (4) glass vial, and in SOP-IN-026: Performing the analysis of the rubber stopper. Bioclon provided diagrams depicting the dimensions of the vials and stoppers in the submission.

Reviewer Comment: I reviewed the two SOPs listed above and found them to be acceptable.
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(b) (4) [REDACTED]

When materials are received at (b) (4), SOP PNO-INS-001: Inspection of Orders Supplied is followed and materials are received in the warehouse and place in quarantine. At the time of receipt, the materials and their lot numbers received are confirmed to match the materials ordered and lot numbers recorded on the shipping documentation. The containers are checked for damage and have a label of identification. In addition, the lot number of the material should be properly indicated, vendor code number, quantity supplied, the material name and lot number of the product and the materials are confirmed to have an Approved status.

Reviewer Comment: I reviewed SOP PNO-INS-001 and found it to be acceptable. This is a general SOP pertaining to receipt of materials at the (b) (4) facility from the Tlalpan facility. All materials are received at the Tlalpan facility first and accepted into production use based on any applicable receipt testing performed at Tlalpan. (b) (4) orders supplies from Tlalpan and upon receipt of the order from Tlalpan, SOP PNO-INS-001 is followed.

The glass vial and rubber stopper have internal specifications that must be met 100% before the product is released for use in production. Table 1 shows the specifications and as well as the method of analysis that is performed for the glass vials. Table 2 shows the specifications and as well as the method of analysis that is performed for the rubber stoppers.

[illegible]

[illegible]

Reviewer Comment: This is very extensive testing and much more testing than we typically see at a company. The testing is acceptable.

2.3.P.8 and 3.2.P.8 Stability

2.3.P.8.1 and 3.2.P.8.1 Stability Summary and Conclusions

Five (5) clinical batches of Anavip drug product were placed on stability for up to (b) (4) months. Long-term stability studies to support the recommended conditions $25 \pm 2^\circ\text{C}$, (b) (4) while accelerated stability testing was conducted at (b) (4) RH for up to (b) (4) months. The lots were chosen to be representative of commercial drug product.

Supporting Stability Batches of Drug Product

Two more conformance batches of drug product, Lot (b) (4) and Lo (b) (4) are on stability and will be evaluated against the commercial specification. One more batch is expected to be

produce during the Pre-license Inspection and will also be place in stability and be evaluate using the commercial specifications.

The studies will be conducted per the current ICH recommendations described below. Any proposed changes to this protocol will be submitted to the agency in advance of implementation.

Stability study on conformance Lot (b) (4) was started 21 Nov 2012. Stability study on conformance Lot (b) (4) was started 27 Nov 2012. Three months data for long-term and accelerated stability were provided for the two conformance lots, (b) (4). All specifications were met.

The Stability Protocol is provided in the submission in Section 3.2.P.8.1. Per the study protocol, the finished products are analyzed as follows: Safety Test, Sterility Test (0, 12, 24 and (b) (4) months, for long period, 0 and (b) (4) months for accelerated time), appearance, (b) (4), (b) (4), (b) (4), biological potency, (b) (4), and protein components by (b) (4).

2.3.P.8.2 and 3.2.P.8.2 Post approval Stability Protocol and Stability Commitment

The intended storage conditions for Anavip drug product are ambient temperature (20 - 25 °C and ambient relative humidity). Long-term stability studies to support the recommended conditions w 25 ± 2 °C/(b) (4) while accelerated stability testing will be conducted at 40 (b) (4) RH for up to (b) (4).

A summary of the stability conditions and test points is included in the table below. All batches of drug product will be placed on stability. The studies will be conducted per the current ICH recommendations listed above. The proposed stability protocol is summarized in the following table. The protocol for stability testing can be found in Section 3.2.P.8.1.

Any proposed changes to this protocol will be submitted to the agency in advance of implementation.

Storage Conditions	Time (months)							(b) (4)
	0	3	6	9	12	18	24	
25 ± 2 °C/(b) (4)	X	Y	Y	Y	Y	Y	Y	
40 (b) (4)	(b) (4)							

X = All testing performed Y = (b) (4)

2.3.P.8.3 and 3.2.P.8.3 Stability Data

Stability Data for the conformance lots and clinical support batches can be found in section 3.2.P.8.3.


(b) (4) months data for long-term and accelerated stability were provided for the two conformance lots, (b) (4). All specifications were met.

2.3.A. and 3.2.A Appendices

3.2.A.1 Facilities and Equipment; Facilities, (b) (4) Establishment Description


Overall (b) (4) facility layout

The Toluca manufacturing facility consists of a one story building. The Filling and lyophilization for the Anavip product is performed in the Aseptic Area of the (b) (4). The main entrance of the facility is located (b) (4)

A large rectangular area is completely redacted with a solid grey block, representing the facility layout.

Aseptic Area

(b) (4)

A large rectangular area is completely redacted with a solid grey block, representing the aseptic area description.A rectangular area is completely redacted with a solid grey block.A rectangular area is completely redacted with a solid grey block.A rectangular area is completely redacted with a solid grey block.A rectangular area is completely redacted with a solid grey block.

Area Classification:

- Halls, storage, material and reagent reception and primary gowning areas are (b) (4)

- (b) (4) prior to enter to the aseptic area, crimping, sterile product and utensil reception areas are (b) (4)
- Filling and Lyophilization area is (b) (4)

Reviewer Comment: Bioclon states in the submission that the equipment is shared and the facility is a multi-product facility; however, during the pre-license inspection it was discovered that Anavip is the only product that has been filled in the facility, thus it is not a multi-product facility nor is the equipment shared. I informed Bioclon of this and told them that when they do bring in other products they will need to file a supplement.

I reviewed the floor diagram of the area related to the fill / finish of the final drug product and overall it appears to be acceptable.

Flow Diagrams

The maps containing a layout of the (b) (4) facilities, and the flow of incoming and in-process materials, and personnel through each level of the facility can be found in the submission in Section 3.2.A.1 Facilities and Equipment; Facilities, (b) (4) Establishment Description.

Figure 1 – Area Classification

Figure 2 - Incoming Materials Flow Diagram

Figure 3 - Bulk Drug Substance

Reviewer Comment: I reviewed the flow diagrams and found them to be acceptable.

Manufacturing Final Product Description

The diagrams listed below illustrate the paths for final product and personnel flow. The bulk drug substance (b) (4)

Figure 4 – Manufacturing Final Product Flow Diagram

Figure 5 – Personnel Flow Diagram

Reviewer Comment: I reviewed the flow diagrams and found them to be acceptable.

Control of Contamination, Cross-Contamination and Containment

Prior to any production activities the aseptic area is clean and sanitized. The cleaning is conducted using (b) (4). The (b) (4). The sanitizers validated for use in the sanitization of the aseptic area are: (b) (4)

Instituto Bioclon developed the cleaning validation based on microbiological determinations and implemented a program of environmental monitoring to select critical points for the monitoring of bioburden in the areas of the reception of the (b) (4)

(b) (4)

Bioclon's protocol for cleaning and sanitization of the production surfaces was based on (b) (4).

In the (b) (4) facility

During room classification and cleaning studies within the aseptic area, it was documented that the areas of manufacturing have minimum contamination on the floor, walls and ceiling. The results show that cleaning procedures are reliable, reproducible and keep the area within the established specifications.


Materials such as glass containers are disinfected according to SOPs before entering the aseptic area.

A disinfectant qualification study using sample coupons of representative surfaces and indicator microorganisms was conducted for each of the sanitizing agents used in the production areas. The study was designed to verify that the sanitizing agent concentrations, and contact times effectively sanitize the items tested. The rotation times have been set for a (b) (4) change to reduce the potential for microbial resistance. Document PMB-CC-001-I001 Validation Report for Determining Activity of Sanitants, provides details of the sanitizer qualification.


PMB-CC-001/I001 Validation Report for Determining Activity of Sanitizers Used on Room and Manufacturing Equipment Surfaces

(b) (4)

(b) (4)




(b) (4)



HVAC SYSTEM

The HVAC System in (b) (4) consists of (b) (4) air handling units (AHU). The submission provides a description of each AHU.

(b) (4)



(b) (4)



Government	Percentage
Current government	85%
Previous government	15%

Environmental Monitoring Process

Bioclon executed the following two protocols to establish routine cleaning and environmental monitoring procedures:

- PVL-CC-001: Cleaning Validation Protocol for Production Utensils Used in the Manufacturing of Fabotherapics Products
- PVL-CC-002: Environmental Monitoring Validation Protocol of Surface Production Areas

Each protocol developed alert and action levels and also determined the critical areas that needed to be monitored. Bioclon took into consideration the results of the monitoring and also the manufacturing process occurring in the area when they determined the final critical monitoring points for routine environmental monitoring. Bioclon used (b) (4) as guidance for the protocols.

[illegible]

Reviewer Comment: I reviewed the two protocols and found them to be acceptable. Bioclon demonstrated that the rooms met pre-determined area classification specifications and that the cleaning process is effective. In addition, appropriate alert and action levels were established.

Points to be routinely monitored were selected based on data analysis of the monitoring results and a consideration for the manufacturing process occurring in the area.

The following was included in the 17 Jul 2013 IR:

You state the following in the description of the EM qualification of the (b) (4) facility: “It is important to mention that the floor plan above corresponds to the plan that will be effective after (b) (4) ...” Please indicate when the (b) (4) is scheduled to occur.

Equipment (b) (4) (Drug Product)

Equipment qualification of all the major manufacturing equipment used in the production process of Anavip Drug Product has been conducted. This qualification includes the Installation, Operation and Performance qualification of each equipment process.

Reviewer Comment: The following was included in the 17 Jul 2013 IR:

Cleaning validation studies were only provided for the lyophilizer. Please provide cleaning validation studies for all major product contact equipment used in the manufacture of the drug product.

The table below lists the major equipment used in the filling and lyophilization of the final product.

Major equipment Located in the Production Area in (b) (4)

(b) (4)						

(b) (4)						

(b) (4)

Reviewer Comment: The following was included in the IR dated 17 Jul 2013:

You provided a list of major equipment used in the manufacture of the drug product and indicated which equipment is shared or dedicated. Please provide a list of the other products manufactured in the facility.

Equipment Description and Qualification

Autoclave

(b) (4)

