

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

Edward Thompson, RPM, OBRR/DBA/RPMB/ HFM- 380

Cc: Review Committee Members

Michael Brony, OCBQ/DCM/APLB, Labeling, Promotional Materials

Robert Fisher, PhD, OBRR/DH/LPD, CMC, Product

Mitchell Frost, MD, OBRR/DH/CRB, Clinical

Erica Giordano, OCBQ/DMPQ/PRB, Other, Quality Control

Ravi Goud, MD, OBE/DE/AEB, Epidemiology

Xue Lin, PhD, OBE/DB/TEB, Biostatistics

Iftexhar Mahmood, MD, OBRR/DH, Clinical Pharmacology

Erin McDowell, OCBQ/DIS/BMB, BIMO

Evi Struble, PhD, OBRR/DH/LPD, Pharm/Tox

Maria Virata-Theimer, OBRR/DH/LPD, CMC, Product

Yonggang Wang, PhD, OBRR/DH/LPD, CMC, Product

Lilin Zhong, OBRR/DH/LPD, CMC, Product

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

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

Subject: Filing 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) México

Due Date: 02 May 2013

Recommendation: This application can be filed.

Summary

On 18 Mar 2013 the FDA received an original Biologics License Application (BLA) submitted electronically in eCTD. I initiated this filing memo review on 22 Mar 2013 and completed it on 23 Apr 2013. I conclude that, with the receipt of Amendment 6, STN 125488/0/6, this application can be filed per 21 CFR 601.2.

On 05 Apr 2013 I forwarded a list of four issues to the RPM which I identified as possibly affecting filing determination and eleven issues that were just review related issues. The review related issues would not adversely affect the filing of the submission; however the information was needed in order to perform a thorough review. The RPM sent two letters to the Applicant on 08 Apr 2013; one letter contained the possible filing issues with a response date of no later than 22 Apr 2013; the second letter listed the review issues with a response date of no later than 06 May 2013.

The original application along with Amendment 6 appears to contain sufficient information in accord with CBER SOPP 8404 ver. 3 "Refusal to File Procedures for Biologic License Applications" to recommend filing of the application.

An amendment to the application was received on 23 Apr 2013 in response to a request made from CBER for information pertaining to the qualification of the filling line and the depyrogenation tunnel at the (b) (4) facility. The methods, procedures, and validation documentation provided in this submission, under DMPQ review purview, appear satisfactory to conclude that the submission meets filing criteria. Therefore, I find the submission acceptable for filing.

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.

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, and the manufacturing, filling, lyophilization and packaging of finished product are conducted in the Tlalpan facility. Drug substance and drug product release testing is performed here.

Inspection:

This site will need to be inspected. TeamBio is scheduled to perform an inspection at the Tlalpan facility September 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.

Inspection:

This facility will need to be inspected.

In regards to the Pre-License Inspections, the following issues will need to be resolved:

1. The Mid-Cycle time point of the application is in August and TeamBio is currently scheduled to perform a biennial inspection in September. Can we work with TeamBio to get the inspections done? Could TeamBio perform an inspection at both facilities, or possibly, the currently licensed facility and DMPQ performs an inspection at the (b) (4) facility?
2. Is it possible to waive the Tlalpan inspection altogether since (b) (4) this product, Anavip, and the product Bioclon currently manufactures for the U.S., Anascorp, (b) (4) I will discuss this with the Product Office to obtain their opinion on this matter. We will keep in mind that the last inspection occurred at the Tlalpan facility in 2011, thus this may not be a possibility.

Scope of Review

I have performed a very high-level, preliminary review of this original BLA to identify missing information that could affect DMPQ's ability to recommend filing of the application. I only reviewed the submission to ascertain if information was included, I did not review the contents of the information for completeness or acceptability.

Review

I evaluated the application per SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements: The chart in Appendix 1 captures my review of the sections in red font.

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. The sections in black font in the attached chart fall under the review responsibilities of other review divisions who are included in the Review Committee Members.

Review Issues and Resolution

On 05 Apr 2013 I forwarded a list of four issues to the RPM which I identified as possibly affecting filing determination and eleven issues that were just review related issues. The review related issues would not adversely affect the filing of the submission; however the information was needed in order to perform a thorough review. The RPM sent two letters to the Applicant on 08 Apr 2013; one letter contained the possible filing issues with a response date of no later than 22 Apr 2013; the second letter listed the review issues with a response date of no later than 06 May 2013.

On 23 Apr 2013 the FDA received Amendment 6 that responded to the items identified as possibly affecting DMPQ's ability to recommend filing of the submission. I reviewed the

information provided on a high level to determine acceptability for filing. I did not perform an in-depth review of the information itself. I have concluded that the information is acceptable for filing.

Amendments from the Review

STN 125488/0/6

Review Issues

The issues identified as possibly affecting DMPQ's ability to file the submission are listed in the first part of the list of identified issues. The remaining issues identified are review issues only, meaning that the information will be needed to perform a review of the submission; however, they do not have an impact on the determination of filing.

The following request for information pertains to issues identified that may affect filing:

Module 1 Contents

1. Please note that the (b) (4) facility is required to have its own FEI number. If you have not already applied for one, please do so now. If you have already applied for one, please provide the date you applied for the FEI number.

Instituto Bioclon Response (Amendment 6):

Instituto Bioclon applied for a DUNS number which is required for the registration of an Establishment. An application for a FEI number for (b) (4) facility will be done once the DUNS number is obtained.

FDA Response:

This is acceptable for filing.

Module 3 Contents: Drug Product Equipment

1. Please provide a description of the depyrogenation tunnel and the filling line used in the (b) (4) facility.
2. Please provide *summaries* of the equipment qualification for the depyrogenation tunnel and the filling line used in the (b) (4) facility. A more complete review of the equipment qualification can be performed on inspection.

Instituto Bioclon Response for questions 1 and 2 (Amendment 6):

A description of the depyrogenation tunnel and the filling line used in the (b) (4) facility is locations is provided in Module 3.2.A.1 Facility and Equipment-Equipment-(b) (4) Facility: summary- for-filling-equipment and summary-for-depyro-equipment.

FDA Response:

The information provided for the filling line and the depyrogenation tunnel appears to be acceptable for filing.

3. The brief, high-level description of the filling process seemed to indicate that some sort of (b) (4) Please provide information on the (b) (4) Please provide a description of the equipment along with a *summary* of the executed performance qualification.

Instituto Bioclon Response (Amendment 6):

Information on the (b) (4) along with a summary of the executed performance qualification is provided in Module 3.2.A.1 Facility and Equipment-Equipment-(b) (4) Facility: summary-for-the (b) (4) t.

FDA Response:

This information provided for the (b) (4) appears to be acceptable for filing.

The following request for information pertains to review issues only. Note: This information was not submitted with Amendment 6. It will be submitted at a later date and a more complete review will be captured in a review memorandum.

Module 1 Contents:

1. Please amend your request for a categorical exclusion. The request was made under the correct exclusion, 21 CFR 25.31 (c); however, the wording accompanying the request was incorrect.
2. The following hyperlinks appear to be broken:
 - a. Section 3.2.S.2.4 has a hyperlink to Section 3.2.R Executed Batch Records
 - b. Section 3.2.S.2.5 has a link to 3.2.S.4.4 Batch Analysis

Module 2 Contents:

3. It is unclear if all applicable facility and equipment information is included in the submission. A list of equipment and utilities was supplied for the Tlalpan facility; however only a list of utilities was included in the submission for the (b) (4) facility. Please provide a list of all major equipment used in the (b) (4) facility for the fill finish of the Anavip drug product and indicate if the equipment is shared or dedicated to Anavip.

Module 3 Contents: Drug Substance

4. The (b) (4) bulk drug substance is shipped to (b) (4) for final fill and finish. Please provide the shipping validation for shipping of (b) (4) bulk drug substance from Tlalpan to (b) (4) Please include a description of the packing and shipping procedures.

**Module 3 Contents: Drug Product
Container Closure**

5. Please provide additional information on the stoppers and vials used as the container closure for the final drug product such as line drawings with measurements indicated. Please provide the acceptance specifications for the materials. Please provide a description for the process for the receipt of these materials. Is any testing conducted prior to release into production? Please provide a brief description of raw material qualification performed for these materials.

Process

6. Please confirm the manufacture of the bulk drug substance will only occur in the Tlalpan facility and the filling and lyophilization will only occur in the (b) (4) facility.
7. Please provide a description of the receipt process of the bulk drug substance at (b) (4) Please indicate where the material is stored and under what conditions.
8. Please describe the process for transferring the bulk drug substance to the filling machine; specifically, describe the container for the BDS and how it is connected to the filling machine. For example, is the BDS in a tank and then an aseptic or sterile connection is made from the tank to the filling machine?
9. Please provide a more detailed description of the types of gowning used and of the gowning process prior to entrance into the aseptic filling area.
10. Please clarify if a (b) (4) 
this is not included in the media simulations, please provide the rationale for not including this step.
11. Please clarify where labeling of the vials will occur. Please describe the labeling process and the vial visual inspection process.