Memorandum

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

To: **File:** STN 125335/0 Centruroides (Scorpion) Immune F(ab)2 Intravenous (Equine)

Instituto Bioclon, S.A. de C.V. (License No. 1813)

From: Nancy Waites, Facility Reviewer, MRB1/DMPQ/OCBQ/HFM-675

Subject: Review of Biologics License Application submitted on 21 Jan 2009 and received 22 Jan 2009.

Through: Carolyn Renshaw, Branch Chief /MRB1/DMPQ/OCBQ/HFM-675

Cc: Deborah Cordaro, RPM, OBRR/DBA/RPMB/HFM-380
Robert Fisher, Ph.D.,Chair, OBRR/DH/LPD/HFM-345

Conclusion: I recommend a Complete Response Letter to be sent to the company.

The following review is based on the information provided in the original BLA and two additional information requests. The first additional information request was sent to the US Agent on 06 Feb 2009 and the second additional information request was sent to the US Agent on 25 Mar 2009. Responses to these information requests were submitted under STN 125335/0/4 and STN 125335/0/15 respectively.

Review of the original application and amendments was difficult since the responses provided by Bioclon were not necessarily applicable to the conformance lots contained in the BLA. For example, Bioclon provided information regarding the use of sterile (b)(4) during the manufacture of Anascorp that was unclear and contradictory. Please see review for full details; however, I was unable to determine if (b)(4) water was used during the production of the conformance lots. In some areas of the BLA, Bioclon stated (b)(4) water was used, but in the batch production records, there was no documentation that (b)(4) water was used during the manufacturing process. During the PLI, it was discovered that sterile (b)(4) water had not been used up to that point during manufacture of Anascorp, and actually had never been used. A second example of lack of clarity for the information submitted to the BLA, when asked, Bioclon provided general information for equipment qualification procedures and assurances that equipment qualification had been performed and all specifications were met (STN 125335/0/4 and STN 125335/0/15).

The original BLA had little or no information about the qualification or validation of equipment and utilities. During the inspection, it was discovered that no equipment qualification or utility validation had been performed at the time the conformance lots were manufactured. The information Bioclon had provided in their response was so general in nature that we were unable to determine when the qualification / validation occurred. It was not until we were at the site that we discovered it had not occurred at all.

It was difficult for me to clearly understand which information within the application and amendments applied to the conformance lots contained within the submission and which information was either something that Bioclon would implement in the future (i.e. use of (b)(4) water) or if the information applied to processes that occurred after the conformance lots were manufactured (i.e. equipment qualification).

The FDA had at least two Type C meetings (08 Jan 2008 and 10 Apr 2008) with Bioclon where we specifically stated what type of information needed to be submitted to the BLA. In some instances, Bioclon did not submit the information at all without any explanation for the omission. For example, in the 10 April 2008 meeting, FDA stated that hold time validation of the purified water collected in a secondary container used in production needed to be submitted to the BLA. This information was never submitted to the BLA. FDA also stated that with regard to a retrospective validation of the water system a review of past test results will not be sufficient. Bioclon submitted information to the BLA stating that they had performed a retrospective validation by a data review and all specifications were met.

During these telecons, Bioclon proposed to follow the following guidance documents:

- Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice
- Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products

Bioclon did not submit all information as put forth in these guidance documents which resulted in a submission that was difficult to review and several rounds of additional information requests.

A pre-license inspection was performed 21-24 April 2009 and a thirty-three item 483 was issued to Bioclon.

After review of the information in the original BLA and the amendments submitted in response to the two additional information requests along with the inspection, there is still an inadequate amount of detail provided for DMPQ to be able to make an informed decision about this application.

I recommend a CR letter.

Please include the following items in the CR letter:

1. In general, the information provided is not sufficiently detailed and descriptive to permit a comprehensive review. Please note that only applicable information should be included within an application and any information based on future proposals should not be included. The information should be presented in a coherent and cohesive manner and include dates, data, specifications / action levels, acceptance criteria, rationales for specifications / action levels and acceptance criteria, and copies of approved protocols with accurate summaries of results. Please amend your application accordingly.

2. The FDA had at least two Type C meetings (08 Jan 2008 and 10 Apr 2008) with Bioclon where we specifically stated what type of information needed to be submitted to the BLA. In addition, Bioclon proposed to follow these guidance documents:
    - Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice
    - Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products

Bioclon did not submit all information as put forth in these guidance documents and as specified in the Type C meetings. This would include, but is not limited to, providing validation data for hold time for water used in production that is held in secondary containers, and providing information on container/closure integrity testing such as CCI testing results and CCI validation and summary results. Please review all meeting minutes, guidance documents, and additional information requests and provide all information as requested. If information is not available for a requested item, please state that no information is available for the requested item. The information submitted must be detailed, concise, and coherent. Please submit the information even if you already believe the information is contained in the BLA or the amendments. The information as provided in the original BLA and amendments is not in a detailed, concise, coherent manner which would allow for a timely and accurate review of the submission and to be able to come to an informed conclusion and recommendation on adequacy.

3. Please provide the registration number for your Tlalpan facility.

4. All outstanding inspectional observations listed on the FDA Form 483 must be resolved. For example, Bioclon's response to FDA Form 483 Item #1 is unacceptable. An acceptable inspection of your facilities is required prior to licensure.

5. CMC information provided to the BLA should be applicable to the conformance lots. If there have been process improvements since the manufacture of the conformance lots, please provided detailed descriptions of these improvements including their date(s) of implementation.

6. Process validation should be completed. This includes, but is not limited to, time limits for holding of production water in secondary containers, aseptic processing, room environment qualification under dynamic conditions, and cleaning of the vials and stoppers including ----------(b)(4)---------- reduction validation. Please provide detailed descriptions and data summaries.

7. Equipment qualification on all major manufacturing equipment used in the production of Anascorp should be completed. Please provide detailed descriptions and data summaries. This includes, but is not limited to, cleaning validation with appropriate clean and dirty hold times. Please provide information on all equipment qualification and cleaning validation even if it was previously included in the original BLA and/or amendments in order to facilitate a cohesive review of the material.

8. Utility qualification for all utilities used in the production of Anascorp must be completed. Please submit detailed descriptions and data from these qualifications. This includes, but is not limited to water, compressed gas, and the HVAC system. Please provide information on all utility qualification and validation even if it was previously included in the original BLA and/or amendments in order to facilitate a cohesive review of the material.

9. Please provide your finalized approved shipping validation protocol along with a detailed summary of the executed protocol and data.

10. In the Additional Information Request dated 06 Feb 2009, you were asked to provide additional information for the container closure system. You provided a partial response.

    a. Please provide the finalized approved protocol for the container closure system assessment along with a detailed summary of the executed protocol and data to support your conclusions.
    b. As part of your response you reference a stopper extractable ----------(b)(4)------ test report performed by (b)(4). Please provide a rationale for how the extractable studies for the stoppers, as performed by (b)(4), apply to your product.
    c. Validation of container closure integrity testing was not provided as requested.
    d. Bioclon states that leak testing is performed per the ----------(b)(4)----------. Please provide an explanation how the leak test as performed per the ----------(b)(4)---------- is equivalent to microbial or dye ingress leak testing. Please provide evidence of validation of the container closure integrity test.

11. In-process specifications or action levels should be set based in part on process validation and equipment qualification. Examples include---(b)(4)----------

-----(b)(4)----levels of intermediates after each critical processing step and the allowable failure rate for the number of vials not passing specifications after washing or depyrogenation. The specifications and/or action levels and results must be captured in the applicable batch production record. Please provide a justification for your in-process specifications and/or action levels.

12. A final specification or action level should be established for the total number of filled drug product vials that may be rejected during final visual inspection before a lot must be held and a determination is made to discard the entire lot. Please submit this specification or action level.

13. The information in the original application and amendments appear contradictory or lacking in accuracy.

    a. The narrative provided by Bioclon in the BLA for the room classifications do not match the room classifications described in the HVAC validation summary such that ----------(b)(4)---------- in the narrative; however, in the HVAC validation summary both of these sample points are described as -----(b)(4)--. Please explain.
    b. In the BLA narrative, the cleaning procedure only describes the vials being placed and washed in the (b)(4) washing machine; however, the actual vial washing procedure starts out with -------(b)(4)-------- of the vials prior to placement into the (b)(4) washer.

    Please review the application and amendments and address any contradictions and confirm the written narratives accurately reflect the actual data obtained and the procedures as they are actually performed.

14. In your response, dated 06 April 2009, to our request for additional information for filter compatibility testing, you stated that the information provided by --(b)(4)-- was used to determine the compatibility of the filter with the product. Additionally, you stated you have used the filters for --(b)(4)-- for the same process and the finished product has been compliant with the quality specifications. Please provide the justification of the applicability of the information obtained by --(b)(4)-- to your product. Please provide the approved protocol used and the summary of the report that was written to document that the --(b)(4)-- filters are acceptable for use without performing compatibility testing.

15. In your response, dated 06 April 2009, you state that if a filter becomes blocked while in use, ----------(b)(4)----------. Please note that this practice is unacceptable. Developmental studies should be performed to determine the adequate filter size to prevent clogging. Process validation of filtration should demonstrate that the filters are adequately sized to perform the function required without clogging. If any filter becomes clogged or if the time to

filter increases during the manufacture of the drug substance or final drug product, this will be considered a deviation requiring an investigation.

16. Please provide additional information on your equipment cleaning validation and sanitization qualification such as information on swab recovery studies and a clear, detailed description of the cleaning process used for equipment cleaning validation and how it is applicable to the actual cleaning procedure used during manufacturing. You provided a small diagram in an amendment depicting the swab sample areas for a ----------(b)(4)----------, but no narrative descriptions or justifications of the sample areas were provided. Please provide this information.

17. For routine environmental monitoring of manufacturing and aseptic areas, you provided a rationale for the chosen sampling points based on criticality of manufacturing steps. Please explain how the number of locations to sample was determined and indicate if data produced during room classifications were incorporated into determining the sample locations. Please provide an explanation if data from room classification qualification and HVAC validation was not used to help determine sample locations.

18. You state that representative analyses of (b)(4) water used in the manufacture of the final product were included in the original application. You also stated that the (b)(4) water was tested and met (b)(4) Sterile (b)(4) specifications and representative analyses of the (b)(4) were included in the application. However, you only submitted copies of test data for "-(b)(4)- water"; no testing was included for Sterile (b)(4). Additionally, (b)(4) water was not used in the manufacture of the conformance lots. Please comment.

19. You state in your original application that Sterile (b)(4) water is aseptically transferred into production equipment at the time of use. No data was provided in the submission to show that this process can be performed aseptically. In fact, as determined during the inspection, (b)(4) water was not used during the manufacture of the conformance lots so this step has never been performed. Please comment.

20. You state in your submission (19 Feb 2009) that a copy of the RO/DI system validation report is included in Appendix 1. A copy of this report was not included. Please provide a copy of this validation report.

21. You provided a list of sample ports and a list of specifications for each port during the validation of the RO/DI system. It appears some ports may have two different specifications for microbial limits (WFI and Purified Water). Please provide a rationale for the two different specifications and provide the justification for the use of two different specifications for the same sample port.

22. Please provide data to support conclusions obtained in the water system validation report and the HVAC system validation report. Also, please reference the

meeting minutes dated 10 April 2009 in which CBER / DMPQ states that a retrospective data review for the water system may not be an acceptable validation of the system. Please provide a justification for performing only a retrospective data review for validation of the water system.

23. In the original submission, Page 32/44, you state that the differential pressure between each room is ---(b)(4)--- monitored. In the amendment (19 Feb 2009), page 2/42, you state that it is a -(b)(4)- observation. This information appears to be contradictory. Please clarify how differential pressure is monitored between adjacent manufacturing rooms.

24. In your amendment (19 Feb 2009), four tables were used to summarize the HVAC system and air-flow characteristics of the controlled manufacturing areas used for production of Anascorp drug product. Table 3, page 48 of the amendment states that the room classification is under static conditions. The Sterile Area – ----------(b)(4)---------- listed as a Class (b)(4) area under static conditions with a differential pressure of ---------(b)(4)-------. The Sterile Area (----------(b)(4)----------) is listed as Class (b)(4) under static conditions with a differential pressure of ------(b)(4)------. Please provide an explanation how cross contamination is prevented between the Class ----------(b)(4)----------, and the Class (b)(4) area since they are located within the same room without any physical separation or differing differential pressures. Table 3 also indicates 6 additional locations that are classified, however the differential pressure and room numbers are not provided for these locations. Please provide this information. Please note that FDA recommends classification of the rooms based on dynamic conditions.

25. Please clarify if environmental monitoring is performed during dynamic or static conditions.

26. You were requested to submit additional information on the HVAC system as per the information request dated 25 March 2009. Your response, dated 06 April 2009, included summaries of typical results obtained during three separate drug product manufacturing runs. The acceptability of the data provided in the tables cannot be discerned because the sample points are identified in the diagrams with numbers and the results are identified with a description. Personnel monitoring results are provided in three tables. It appears the monitoring was for three different batches; however, only one set of results is provided. It is not clear if only one person was monitored or if these tables are the results of all personnel monitored during the fill. We were unable to determine if all sample points were monitored. You provided acceptance criteria for Class (b)(4) and Class (b)(4) areas; however it appears Sample (b)(4) in located in a Class (b)(4) area. Please clarify this information and provide a response in a detailed, concise, and coherent manner to allow for a timely and accurate review of the submission.

27. You were asked to submit data for the validation and monitoring of the compressed air system in the 25 March 2009 information request. You stated, 06 April 2009, you did not validate the system; however it is monitored for ----------(b)(4)----------. You did not provide any information detailing the specifications for ----------(b)(4)----------. No data were provided to show routine system monitoring. Please provide this information in a detailed, concise, and coherent manner to allow for a timely and accurate review of the submission.

28. You were asked to provide a comparison of the procedure performed during your routine media fills and the procedure that actually occurs during the aseptic filling process (06 Feb 2009). You stated, 19 Feb 2009, that the two processes are similar and you provided an executed media fill batch record to illustrate this statement. No written narrative was included. A comparison of the manufacturing batch production record (MBPR) submitted in the original BLA with the media fill batch production record (FBPR) submitted in the amendment raised the following concerns regarding equivalency:

    - The MBPR references SOP P-PB-031 (Preparation and washing of vials in the (b)(4)) and SOP P-PB-015 (Operation of the Dry Heath Oven ----------(b)(4)-----), but the FBPR does not references these SOPs.
    - The MBPR references SOP P-PB-054, but the FBPR does not.
    - The MBPR provides instructions on the washing of the filling syringe, but the FBPR does not. The MBPR references room release, Environmental monitoring prior to room release, inspecting vials ----------(b)(4)----------, etc. These steps are not mentioned in the FBPR.
    - The FBPR references SOP P-PB-029 for how to perform the filling operation while the MBPR references P-PB-056 for the filling operation.
    - The MBPR references entering materials into the fill area ----------(b)(4)----------. This entry process is not mentioned in the FBPR.

Neither the MBPR nor the FBPR record the actual number of vials filled for the media fills. The FBPR records a “theoretical volume” and a “no. of theoretical pieces”, but actual fill volume and actual number filled are not recorded. The number of vials incubated is recorded, but not the number filled.

Please provide additional information describing how the media fill and the actual aseptic fill are similar. In areas that are not similar, please provide the justification for their applicability and/or acceptability.

29. Regarding your sterility testing, please indicate if any type of Bacteriostasis / Fungistasis testing was performed to show that a negative sterility test result for the bulk drug substance and the bulk drug product is accurate.

30. You have not established in-process ----------(b)(4)---------- levels. Please establish and submit these levels.

Review and Comments

Anascorp, Antivenin *Centruroides* (Scorpion) Equine Immune $F(ab)_2$ contains *Centruroides* scorpion venom-specific binding fragments, enzymatically derived from equine antiscorpion immunoglobulin. The antibodies are obtained from horses that have been (b)(4)immunized with venom of C *noxius, Cl. limpidus, Ct. tecomanus, and Cs.suffusus.* The antibodies are then cleaved by pepsin to form $F(ab)_2$ fragments. The $F(ab)_2$ content is at least 85% and Fab content is no more than 7%. The protein content and IgG specification limits are each not more than (NMT) 5%, and the product specification for --(b)(4)-- is not more than (b)(4). The material binds and neutralizes venom toxins, facilitating redistribution away from target tissues and elimination from the body. Anascorp is a sterile preparation presented as a lyophilized powder in a 10 mL vial. The product is manufactured by Instituto Bioclon, S.A. de C.V. in Mexico City, Mexico.

Manufacturers

a. Manufacturer - Tlalpan (Scorpion Venom and Anascorp® Drug Product)
The scorpion venom production, plasma fractionation process, and the manufacturing, filling, lyophilization and packaging of finished product are conducted in the Tlalpan facility.

Address: Instituto Bioclon, S.A. de C.V. (Tlalpan), Calzada de Tlalpan 4687 Colonia Toriello Guerra, Tlalpan, Mexico D.F., MEXICO

b. Manufacturer - ----------(b)(4)----------
Immunization of the horses with scorpion venom and subsequent plasma collection are carried out at the ----------(b)(4)---------- facility. Additionally, horses are housed and cared for at the (b)(4) facility.

Address: Instituto Bioclon, S.A. de C.V. ----------(b)(4)----------

c. Distributor: Rare Disease Therapeutics, Inc. (RDT)
Rare Disease Therapeutics will distribute Anascorp® drug product in the United States. RDT will also be responsible for collecting adverse event and product complaint data.

Facility Overview

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

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Tlalpan
The Tlalpan facility consists of a three-story building, with the majority of the manufacturing activities taking place on the ground 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)----------. 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. Filling and lyophilization for the USA are 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 plans and workflow descriptions are included in STN 125335/0, STN 125335/0/4, and STN 125335/0/15. I reviewed the floor plans and the general descriptions provided by Bioclon and based on the information provided, they are acceptable.

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

Per Bioclon, 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.

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

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

Aseptic Area (b)(4)
Aseptic Area (b)(4) is the sterile suite where filling and lyophilization of drug product is conducted for the USA market.

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

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

The cleaning and sanitization of the aseptic area are conducted ----------(b)(4)----------. Shared equipment is cleaned and sanitized prior to start new production. At the start of a manufacturing campaign, environmental monitoring is conducted using settling plates. In addition, viable particle counts are collected ----------(b)(4)----------.

During the PLI that was performed 21-24 April 2009, it was determined that humidity was not monitored or controlled. Air flow pattern studies such as smoke studies were not performed. This was captured on the FDA Form 483 that was issued to the company.

Floor (b)(4)
Per Bioclon, Floor (b)(4) of the Tlalpan facility houses the -------(b)(4)------- and the Quality Control Laboratory. The ----(b)(4)---- area is maintained as Class (b)(4) with a Class -------(b)(4)----------.

Per Bioclon, cleaning and sanitization of the ----(b)(4)---- area is conducted ----------(b)(4)----------. Monitoring is performed using settling plates ----------(b)(4)----------.

Bioclon did not provide any information on the cleaning and sanitization of the -------(b)(4)---- unit. I am unable to determine if the cleaning process has been validated or if the equipment, which is multi-product equipment, is cleaned appropriately.

Other Products
Bioclon manufactures other products within the same facility using the same equipment and rooms as the US product. The only time the US product is segregated is during the ----------(b)(4)---------- steps. The original BLA did not provide information on the equipment that was shared. Bioclon only stated that the rooms were cleaned between campaigns. In STN 125335/0/4, Bioclon provides a list of equipment that was used in the equipment cleaning validation studies. It is unclear if this is the only shared equipment or if this was just the shared equipment they used for cleaning validation. The equipment listed was the following: ----------(b)(4)----------.

The additional products that Bioclon manufactures within the same facility are listed below. Per Bioclon, each of the antivenin F(ab)2 products are manufactured in shared areas. This experimental product is manufactured on a campaign basis, and is thus not manufactured concurrently to Anascorp. These sections of the facility are cleaned and sanitized between each batch of drug product.

- Black Widow Antivenom, Analatro™

Analatro™, Antivenin Latrodectus (Black Widow) Equine Immune F(ab)2, is an experimental drug product being studied in Phase 3 clinical trials for the treatment of black widow envenomation under BB-IND (b)(4). This experimental product is manufactured on a campaign basis, and is thus not manufactured concurrently to Anascorp.

- Snake Antivenom, Anavip®

Antivipmyn, Antivenin Crotalidae (Pit Viper) Equine Immune $F(ab)_2$ is an investigational drug product under BB-IND -(b)(4)-. Antivipmyn is being studied in Phase 3 clinical trials for the treatment of Pit Viper envenomation.

- Snake Antivenom, Antivipmyn Tri®

Antivipmyn Tri, Antivenin Polyvalent Equine Immune F(ab)2 is an investigational drug product in the United States, and is approved for marketing in Mexico.

- Snake Antivenom, Coramyn®

Coralmyn, Antivenin Micrurus (Coral Snake) Polyvalent Equine Immune $F(ab)_2$, is a drug product that is approved for marketing in Mexico.

- Snake Antivenom, Mricamyn®

Africamyn, Antivenin (African Snake) Polyvalent Equine Immune F(ab)2, is an investigational drug product.

At the time of the manufacture of the conformance lots, cleaning validation for the equipment and facility had not been completed. During the pre-license inspection, it was discovered that sanitization agents were not appropriately qualified.

Bioclon provided summary information for the cleaning validation of a ----------(b)(4)---------- in their amendments. The information included a justification for the ----------(b)(4)----------. **Bioclon did not include swab recovery studies so I am unable to determine if the results from the swab testing are accurate. They did not include cleaning validation information on other equipment that was used such as ----(b)(4)---- and lyophilizer. A clear description of the cleaning procedure was not provided in the submission so I was unable to determine if the cleaning process was manual or automatic. A small diagram was supplied depicting the swab sample areas, but no narrative descriptions or justifications of the sample areas were provided.**

The cleaning processes are -(b)(4)- cleaning procedures as determined during the PLI.

Based on the information provided in the submission, I am unable to determine if the cleaning validation was performed appropriately.

Changeover Procedure

Per Bioclon, cleaning of the production areas are done ----------(b)(4)---------- as described in SOP P-PB-016 for the cleaning and sanitization of the production areas. The SOP describes also the preparation of the cleaning and sanitizing solutions to be use in the cleaning and sanitization process. The cleaning of the production area is done ----------(b)(4)----------.

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

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Monitoring and justification of the location chosen
The environmental monitoring (air sampling and settling plates) is done according to SOP P-MB-021. The intention of choosing the locations described in the diagram in the submission is to capture data from the dirtiest areas and monitoring them after cleaning.

This changeover procedure appears to be acceptable; however, Bioclon did not provide any information for the specifications for room monitoring after cleaning so I am unable to determine if the manufacturing areas can be cleaned on a consistent basis. Bioclon provided a justification for the monitoring locations; however, I am unable to determine if the monitoring locations are based on data from prior validation studies.

Production Process

Venom Production

The Anascorp F(ab) is produced by the horse in response to envenomation with scorpion venom. The venom is obtained by extraction from several species of scorpions that are indigenous to the Southwestern United States and Mexico. The venom is extracted from the glands, purified, and sterilized before being characterized and stored for use in subsequent operations.

A description of the venom production is included in STN 125335/0 the under Section C Methods of Manufacturing and Packaging. ----------
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----------(b)(4)-------

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Bioclon describes the scorpion glands purchased from Mexican suppliers. A list of reagents used to process the scorpion glands and extract the venom for use in subsequent steps is provided in Table 1 of STN 125335/0. Per Bioclon, each reagent is purchased from qualified suppliers and meets predefined quality specifications.

Plasma Collection

Bioclon provides a description of the horse immunization and subsequent bleeding procedures in STN 125335/0. ----------
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----------(b)(4)----------

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

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Plasma Fractionation

This is the first processing step in the production of the drug substance. Per Bioclon, each reagent is purchased from qualified suppliers and meets predefined quality specifications. A description of the reagents used for scorpion venom production and the associated quality standards are included in STN 125335/0.

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

No process validation information or data were included in the original application. During the PLI, it was determined that process validation had not occurred up to the date of the inspection. Bioclon will need to submit process validation protocols and data. The description of the bulk formulation states that -(b)(4)- water was used in bulk formulation. Later in the submission, Bioclon states that (b)(4) water is used for final formulation. This information is contradictory. Bioclon clarified, during the PLI, that no (b)(4) was used in the manufacture of the conformance lots. (b)(4) water must be used for final formulation of the product.

Container Closure System/Shipping Containers

Packaging Components

Per Bioclon, the following packaging components are used in the drug product filling and lyophilization process. Each component is purchased from qualified suppliers and meets predefined quality specifications.

Drug Product Container-Closure System

Component	Description	Supplier
Vial	10 mL Type (b)(4) glass	---(b)(4)---
Stopper	---(b)(4)---; gray butyl rubber ----------(b)(4)----------	----------(b)(4)----------
Cap	20 mm flip-off	---(b)(4)---

During the manufacture of the conformance lots, the stoppers were ----------(b)(4)----------. In the future, Bioclon will purchase stoppers that are ----------(b)(4)------. However, at the time of the conformance lot were manufactured, the cleaning validation of the vials and stoppers was not performed. Process validation for the ----(b)(4)---- of the stoppers had not been performed.

Bioclon was asked to supply a description of the container and closure system, and its compatibility with the biological substance. This should include detailed information concerning the supplier, address, and the results of the compatibility, toxicity and biological tests. Evidence of container closure integrity should also be supplied. Bioclon

responded in STN 125335/0/4 and stated that detailed information was supplied in the original BLA and reference letters for the DMFs for the vials, stoppers, and caps were included in the original submission. The detailed information in the original BLA referenced by Bioclon's response is contained in the above chart. The only cross-reference letter contained in the original BLA is for the (b)(4) Stoppers. The information provided from (b)(4) for the stoppers was for extractables testing ---------(b)(4)----------; however **Bioclon did not include a rationale for how the extractable studies, as performed, applied to their product. There was no information on leachables of the stoppers. Data for leachable/extractable studies on the glass vials was not provided.** Per Bioclon, a study is being conducted to assess the effect of the container-closure system (glass vial and rubber stopper) on the quality and biological safety of Anascorp®. The study is scheduled to begin on March 2, 2009 and will be completed in four weeks. **A copy of a draft protocol was included in the response. I did not review the protocol since it was an unapproved, draft protocol. Bioclon did not provide any information on container/closure integrity testing such as CCI testing results and CCI validation and summary results as requested.**

Bioclon did not supply a sufficient amount of information for me to be able to determine if the container closures are acceptable.

Shipping Validation
No information was included in the original BLA describing shipping validation. Bioclon was requested to provide the information on the shipping validation. Bioclon stated that a shipping study is being conducted using Anascorp drug product and packaging that is representative of the intended marketed product. This study is scheduled to start approximately March 2, 2009 and will be completed by mid-June, 2009. **A draft shipping protocol was provided in the response, but I did not review it since it was a draft**.

I am unable to determine if shipping validation is acceptable at this time. Bioclon will need to submit a final protocol for review since we do not accept draft protocols.

Equipment
Through reading the information provided in the BLA and reading the translated Master Batch Production Record, the following is a list of equipment that I think is used in the manufacturing process:

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

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

During the PLI, it was discovered that no equipment qualification or cleaning validation had been performed for any of the manufacturing equipment, or laboratory equipment. We did review some equipment qualification and cleaning validation during the PLI and it was found to be unacceptable. This was captured in the 483 that was issued.

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

c. Process

i. Preparation of Components

Each of the container-closure components is prepared as described in the following paragraphs. ----------
----
----------(b)(4)----------
----------.

There is no specification for how many vials can be defective (cracked, broken, contaminated) before an investigation is opened up.

Vials

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

----------.

The final rinse of the vials must be (b)(4) water. There is no in-process specification for the number of vials that need to pass the QC visual inspection after washing before the lot is discarded and an investigation is opened up.

This description of the vial cleaning in the BLA, only mentions that the vials are placed in the -(b)(4)- washer; however, after reading the batch production record, I find that the vials are ----(b)(4)--------- prior to placing them in the -(b)(4)- washer. Bioclon was asked to provide detailed information on the ----------(b)(4)---- of the vials prior to placing them in the -(b)(4)- washer. This information was not provided. Very little information was provided for the ----------(b)(4)---------- cleaning validation of the vials so I am unable to determine if the cleaning of the vials is acceptable and is consistently performed.

Stoppers

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

---.

Per Bioclon, the autoclave and sterilization cycle have been validated for the intended use, and are periodically requalified for use. **During the PLI, a small sample of autoclave load validations were reviewed and found to be unacceptable. This was captured in the issued 483. At the time the conformance lots were manufactured, the autoclave and sterilization cycles had not been validated.**

Endotoxin reduction studies have not been performed. Cleaning validation has not been performed. Final rinse of the stoppers must be done with (b)(4) water. Bioclon did not provide any information at all on the --(b)(4)-- stopper washer, as requested in Additional Information Request dated 25 March 2009. During the manufacture of the conformance lots, Bioclon applied --(b)(4)-- to the stoppers and autoclaved the stoppers themselves. Bioclon did not provide information on the validation of the sterilization and -----(b)(4)----- of the stoppers as requested in Additional Information Request dated 25 March 2009.

Caps

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

-----.

Filling

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

Bioclon was asked to provide additional information on the filling process.

Per Bioclon, Product filling is done in accordance with SOP P-PB-029, "Standard Operating Procedure for Aseptic Filling of Injectable Products in the --------(b)(4)---------" in which it is indicated that the flask, the stoppers and the flip-off caps are prepared and sterilized before use. The filling area must be clean and sanitized and approved by quality control, complying with the parameters established for the aseptic area. The same is true for the lyophilizer. The operating personnel must be trained and skilled in the regulations to working this area.

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

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

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

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

Description of the Environmental monitoring.

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

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

<u>The ---(b)(4)---------- filling of the vials was observed during the PLI. The observations were captured in the 483 that was issued.</u>

Lyophilization

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

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

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

----------.

The lyophilizer was not qualified at the time the conformance lots were manufactured. During the inspection, the qualification of the lyophilizer was reviewed. The qualification was not acceptable and was included in the issued 483.

Application of Crimp Caps
The drug product vials ----------(b)(4)----------. Aluminum crimp caps are applied ----(b)(4)----.
Leak testing and visual inspection are performed on 100% of the vials per established Bioclon procedures. The vials are subsequently labeled and placed into secondary packaging.

Leak Testing
Bioclon was asked to provide additional detailed information on the leak testing specifically, how it was performed and to provide detailed information about the validation of the leak test. **Bioclon stated that the leak test was not validated.** The test was described by Bioclon as performed in accordance with ----------(b)(4)---------- (general analysis method) described in the ----------(b)(4)----------. The ---(b)(4)--- test is done as follows: ----------(b)(4)----------
----------.

Bioclon did not provide an adequate amount of information for me to determine the acceptability of this leak test. Bioclon must detail how performing the leak test per the ----------(b)(4)---------- is equivalent to microbial or dye ingress leak testing.

Visual Inspection of Final Drug Product Vials
One hundred percent visual inspection is performed in accordance with the “Standard Operating Procedure for Visual Inspection of Fabotherapic Products" P-PF-062. ----------
----------(b)(4)----------
----------.

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

----------.

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

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

---.

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

----------.

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

Bioclon does not have a specification for the number of vials that can be defective which would trigger the batch being held to determine if the entire lot needed to be discarded.

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

----------. I did not review these since the Veterinary Consult on this submission reviewed this information.

Plasma Fractionation (Drug Substance)

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

---.

Per Bioclon, for the final drug product, the specifications for Anascorp® are intended to ensure the physical, chemical, and biological quality of the drug product. Release tests and specifications are summarized in Table 9 of the submission. I reviewed the test specification for sterility ----(b)(4)---- of the bulk drug substance. The bulk drug substance is considered sterile and the sterility test is performed per ---(b)(4)---. ----------
---

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

---.

Process Validation Data
------(b)(4)------ Lyophilizer

Per Bioclon, currently, the facility produces antivenin products solely for the market in Mexico and the clinical trials in the United States and Mexico. The existing process was used to produce the initial materials for US clinical trials. ----------
---

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

---.

<u>During the PLI, the qualification of the lyophilizer was reviewed. The deficiencies noted, as recorded in the EIR, during the inspection were the following:</u>

<u>Deficiencies with the PQ:</u>

- **<u>Data was not provided on the temperature distribution study for the thermocouple location</u>**

- **No explanation was provided as to the location of the thermocouple in the shelf (middle, rear, front)**
- **Data not provided on results of residual moisture, microbial samples, or solution testing**
- **Comparison of placebo to product was not completed**
- **Determination of hot and cold spots in lyophilizer was not provided**

--(b)(4)-- Autoclave
Per Bioclon, the --(b)(4)-- Autoclave has been validated for a variety of loads that are representative of those used to prepare materials for production. In addition to temperature mapping studies, media and biological indicators were placed in a distribution of locations throughout the autoclave during each run, and subsequently examined to demonstrate an appropriate Sterility Assurance Level (SAL) after autoclaving. Using ----------(b)(4)---------- as the test organism, an ----------(b)(4)----------.

Bioclon was asked to provide additional information on the autoclave validation. Bioclon provided a list of loads that were validated along with data and acceptance criteria. As stated in the submission, these are the acceptance criteria for autoclave load validation:

Acceptance Criteria

1. ----------(b)(4)----------.
2. ----------(b)(4)----------.
3. ----------(b)(4)----------.
4. ----------(b)(4)----------.
5. ----------(b)(4)----------.

Deviations Occurring During Validation
There were no deviations during the validation.

Autoclave load validation was reviewed during the inspection and was found to be unacceptable. The issues are captured in the issued 483.

In Bioclon's narrative submitted to the BLA, they specifically state there are acceptance criteria for F_o and for the biological indicator; however, the 483 that was issued during the inspection stated the following in regards to autoclave load validation:

c. **Acceptance criteria did not include a specification that the biological indicators were negative after testing.**
d. **Acceptance criteria did not include a specification for F_0.**

Bioclon did not provide BI placement map or TC placement map, BI validation, etc. There is no certification that IQ/ OQ has taken place, as requested.

(b)(4) Dry Heat Oven

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

Bioclon was asked to provide additional information for the validation of the dry heat oven.

Bioclon provided two sets of acceptance criteria that were used. One set of criteria for -------(b)(4)-------. A second set of criteria was provided for (b)(4). **Bioclon did not provide a rationale for the differing sets of acceptance criteria.**

ACCEPTANCE CRITERIA FOR DRY HEAT DEPYROGENATION

• ----------(b)(4)----------.
• ----------(b)(4)----------.
• ----------(b)(4)----------.

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

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

Description of the Load Patterns of -(b)(4)- Oven (Depyrogenation), Placement of Biological Indicators, and Placement of Thermocouples

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

----------:

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

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

ACCEPTANCE CRITERIA FOR DRY HEAT DEPYROGENATION

• ----------(b)(4)----------.

• ----------(b)(4)----------.

BIOLOGICAL CHALLENGE TEST (Sterilization Cycles with Dry Heat)

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

Description of the Load Patterns of -(b)(4)- Oven Sterilization.

The table included in the submission shows the results of the Validation of the Load Pattern where the minimum F_H is shown in each of the cycles run to determine lethality, which complies with the Acceptance Criteria of an F_H -----(b)(4)-----.

Conclusions:

----------(b)(4)----------. It is concluded that it is compliant with the acceptance criteria and it demonstrated that the equipment effectively complies with the process performed.

Redact 1 page (b)(4)

the completeness of the information supplied in this submission or subsequent amendments.

Disinfectant Effectiveness Studies
Bioclon did not provide detailed enough information in the original BLA to determine the acceptability of the disinfectant effectiveness studies. Bioclon was asked to provide the following information:

Please provide an explanation as to how the process used during the cleaning agent validation is equivalent to the actual cleaning procedure used in your facility and for your equipment. Please indicate which organisms were used in the validation of the cleaning agent and if any of the organisms were environmental isolates

Bioclon responded with a very general outline of the testing procedure and listed the ATCC organisms used and provided the data results. Bioclon did not use a spore former as one of the test organisms.

I was still unable to determine how the studies were performed so the studies were reviewed during the inspection. The studies were determined to be unacceptable and the issues are captured in the issued 483. During the PLI, it was noted that the testing was not complete. The organisms were not applied to representative materials and equivalent process techniques were not used in the testing of the agents. No rationale was provided for the ATCC organisms used nor was actual EM isolates used for the study.

Utilities
Water System

Based on the information provided in the BLA, I am unable to determine if the water system has been qualified appropriately or what the routine monitoring of the system entails. I am unclear as to which type of water is used in which step since the written narrative does not match the batch production record. ----------(b)(4)---------- Routine monitoring data was not submitted to the BLA as requested.

Use of (b)(4) and (b)(4) Water
Per Bioclon, the reverse osmosis/deionized (RO/DI) water produced by the Tlalpan facility is used for ----------(b)(4)----------. The water system is described below in more detail. RO/DI water produced at Tlalpan consistently meets the ----------(b)(4)---------- water requirements.

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

Bioclon only included copies of the test data for --(b)(4)-- water". There was no testing included for sterile WFI water.

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

RODI Water Produced at Tlalpan

Per Bioclon, the water production system at Instituto Bioclon is a Reverse Osmosis (RO) ----------(b)(4)----------.

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

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

During the PLI, Bioclon was issued a 483 and one of the items listed in the 483 states that WFI water should be used for stoppers and vials and other product contact materials.

Routine Maintenance and Operation
The water production system at Instituto Bioclon is a Reverse Osmosis (RO) ----------
---
----------(b)(4)----------

---------.

The effectiveness of each of the maintenance, cleaning, and sanitization steps is verified through routine monitoring of the water produced by the RO/DI system. The chemical and microbial limit specifications for the RO/DI water are presented in Tables 4 and 5 of the submission. In addition to the microbial limits presented in Table 5, all samples must be absent of pathogenic organisms.

System Validation
Per Bioclon, the Tlalpan FODI system was retrospectively validated using data from water produced in 2005 and 2006. A copy of the validation report is included in Appendix 1. **A copy of this validation report was not included in the submission; therefore I could not review it.**

Per Bioclon, the retrospective validation examined the chemical and microbiological characteristics of the RODI water produced over a -(b)(4)- period. During this time, the system was maintained and operated according to approved Instituto Bioclon procedures, which are to be used during routine production of Anascorp.

Table 6 is included in the amendment and lists the specifications for RODI Water System Validation. The specifications follow the (b)(4) specifications for RODI water; however, Bioclon has two specifications for microbial limits. One meets the purified water specification of -------(b)(4)-------- and the second microbial specification is for WFI water – ---------(b)(4)--------. Table 7 lists the validation sampling locations and frequency of the RODI system. **Bioclon does not provide a rationale for either the ports sampled or the frequency of the sampling. It is not clear which microbial specification the ports were expected to meet – WFI or Purified Water.**

Per Bioclon, the validation results indicated that the (b)(4) water system produced water that met the requirements for (b)(4) Purified Water over a -(b)(4)- period. ----------
----------(b)(4)----------
----------. As this was a retrospective validation, no deviations occurred.

No raw data was provided in the submission so I could not verify this statement. Refer to meeting minutes dated 10 April 2009 where DMPQ states that a retrospective data review will not be acceptable for validation.

Sterile Water for Injection (WFI)

Bioclon then adds the following Section C in their submission for sterile water for injection. Bioclon states that the sterile water for injection to be used will be purchased from -----(b)(4)----. Earlier in the submission, Bioclon stated that (b)(4) water is used and it is purchased from ---------(b)(4)---------. **The information is contradictory**. In the first information request, Bioclon was asked to provide additional information detailing which steps in the manufacturing process WFI water is used. Bioclon's response was that the information is provided in the original BLA. When questioned as to the exact steps in the batch production record used WFI water, Bioclon provided the steps within the batch production record where sterile WFI is used (STN 125335/0/15). Bioclon stated in their response that WFI water had been used in the listed steps. Bioclon also stated that sample certificates of analysis for the sterile WFI were attached. **The C of As were not included in the submission.** Bioclon then provides a brief description of the WFI system at -----(b)(4)----- and a description of the validation of that system. **This information is not applicable to this submission.**

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

HVAC

A general description of the air handling units was provided. ----------(b)(4)----------.

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

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

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

Location of AHUs

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

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

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

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

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

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

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

<u>In the original submission, Page 32/44, Bioclon states that the differential pressure between each room is -----(b)(4)----- monitored. In the amendment, page 2/42 states that it is a --(b)(4)-- observation. This information appears to be contradictory.</u>

The following tables within the amendment summarize the HVAC system and air-flow characteristics of the controlled manufacturing areas used for production of Anascorp drug product.

Table 1 listed an overview of the classified areas used for Anascorp Manufacturing and it listed Rooms ----------(b)(4)--------. Although not specifically stated, this appears to be the Aseptic Area (b)(4) and its support areas. The chart supplies room dimensions, number of air changes per hour airflow (ft^3/ min) room temperature, percent relative humidity (ambient), and differential pressure. Table 2 is entitled Overview of Air Characteristics in Areas Used for Anascorp Drug Product Manufacturing, but it appears to be a chart describing the HEPA filters used in the areas listed in Table 1.

Figure 1 depicts the Room Classifications for Floor (b)(4) of the Tlalpan Manufacturing Areas. Figure 2 depicts the air system classification zones in Aseptin Area (b)(4).

Table 3 is a Summary of Room Classifications and Differential Pressures and it is tied together with Figure 4 Locations used for Air Monitoring in the Tlalpan Manufacturing Areas (Floor (b)(4)).

Table 3, page 48 of the amendment states that the room classification is under static conditions. The Sterile Area – filling ---------(b)(4)------------ is listed as a Class (b)(4) area under static conditions with a differential pressure of --------(b)(4)--------. The Sterile Area ---------(b)(4)------------ is listed as Class -(b)(4)- under static conditions with a differential pressure of ----------(b)(4)----------.

<u>Please explain how cross contamination is prevented between the Class (b)(4) area and the Class (b)(4) area that are located within the same room and have the same differential pressure. Table 3 also indicates 6 additional locations that are classified, however the differential pressure and room numbers are not provided for these locations. Please provide this information.</u>

Figure 4 is a floor plan that depicts the sample locations listed in Table 3. Bioclon, when requested, provided a justification for the sample points monitored. **<u>I am unable to determine if these points are worse case areas based on qualification data. I would agree with Bioclon that they are critical areas (------------------------(b)(4)---------------------), but I am unclear if there should be additional sample points based on cleaning and room classification data.</u>**

Figure 5 depicts the locations of the HEPA filters and returns in the ---(b)(4)--- room. **<u>There is no written description of this figure included in the submission.</u>**

4. Air Monitoring (Viable and Non-Viable Particles)

a. **Static Monitoring**

Routine static air monitoring in the classified areas consists of analyzing the levels of viable and non-viable particles on an ongoing basis. --(b)(4)---.

<u>Per Table 4, monitoring is performed during periods of manufacturing is taking place, yet in the body of the submission they state monitoring is during static conditions. Bioclon states that if an action limit is passed then QA will be notified</u>

and appropriate steps will be taken to clean and sanitize the area. Do not mention that an investigation will be opened or to what level any microbes will be identified.

Bioclon was requested to provide additional information on the HVAC system.

Bioclon stated that an IQ and OQ were completed and all specifications were met. Per Bioclon, a conventional performance qualification was not performed on the HVAC system, however a smoke test to verify laminar flow in critical areas was conducted with satisfactory results. Routine testing of the system to assure the quality of the air produced by the system is conducted -------(b)(4)------- as follows.

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

In addition to this testing, the pressures and air flows for air supply ducts and returns are balanced to ensure the correct distribution of air and differential pressure in each of the controlled areas. Typical results obtained during three separate drug product manufacturing runs are summarized in tables within the submission.

I am unable to determine the acceptability of the data provided in the tables since the sample points are identified in the diagrams with numbers and the results are identified with a description. Personnel monitoring results are provided in three tables. It appears the monitoring was for three different batches; however, only one set of results is provided. I am unsure if only one person was monitored or if these tables are the results of all personnel monitored during the fill. The sample points meet specifications, but I am unable to determine if all appropriate personnel were monitored. I am unable to determine if all sample points were monitored. Bioclon provided acceptance criteria for Class (b)(4) and Class (b)(4) areas; however it appears Sample 3 in located in a Class (b)(4) area. During the PLI, a 483 item was for the observation that air flow studies (i.e. smoke studies) had not been performed under dynamic conditions. The smoke studies that Bioclon mentions in the BLA were only smoke studies performed by the filter vendor. It was also noted during the PLI and was captured in the issued 483 that environmental monitoring of the personnel was not performed appropriately.

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

----------. **----------(b)(4)----------.**

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

Media Fills
No information was provided in the original submission describing the media fills. Bioclon was requested to provide this information.

The media fill process is done according to Instituto Bioclon SOP P-PB-029, and is designed to simulate the routine production process of aseptic filling and lyophilization.

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

----------.

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

----------.

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

----------.

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

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

Redact 1 page (b)(4)

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

The narrative for the room classifications provided by Bioclon in the BLA, do not match the room classifications described in the HVAC validation information provided to the application. For example, ----------(b)(4)----------; however, in the HVAC information provided to the BLA both of these sample points are described as Class (b)(4).

During the PLI, some observations were recorded in the issued 483 with respect to personnel monitoring and acceptability of the plates used in EM.

Particle Count
Nonviable particle counts are measured during the filling process. **Bioclon did not provide specifications for nonviable particulate counts.**

Smoke Test.
The smoke test is performed as part of the --(b)(4)-- testing for requalification of the aseptic area. However, no smoke test is done, either during production or media fill process.

As stated before, these smoke tests are performed by the filter vendor and actual air flow studies under dynamic conditions have not been performed.

Growth Promotion Results

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

----------.

During the PLI, it was noted that the positive controls do not actually represent the plates that are used during EM. Please see issued 483.

Description of how the media fill differs from actual filling process
The media fill study is a close simulation of the aseptic manufacturing operations as described above with the exception of ----------
----
----------(b)(4)----------

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

I compared the manufacturing batch production record (MBPR) submitted in the original BLA with the media fill batch production record (FBPR) submitted in the amendment and I was unable to determine if the two fills are equivalent.

- **The MBPR references SOP P-PB-031 (Preparation and washing of vials in the -(b)(4)-) and SOP P-PB-015 (Operation of the Dry Heath Oven Type ---(b)(4)--), the FBPR does not references these SOPs at all.**
- **The MBPR references SOP P-PB-054, but the FBPR does not.**
- **The MBPR discusses the washing of the filling syringe, but the FBPR doesn't even mention this step. The MBPR references room release, Environmental monitoring prior to room release, inspecting vials ----------(b)(4)----------, etc. None of these steps are mentioned in the FBPR.**
- **The FBPR references SOP P-PB-029 for how to perform the fill while the MBPR references P-PB-056 for the filling operation.**
- **The MBPR references entering materials into the fill area ----------(b)(4)----------. This entry process is not mentioned in the FBPR.**

Neither the MBPR nor the FBPR record the actual number of vials filled. The FBPR records a "theoretical volume" and a "no. of theoretical pieces", but actual fill volume and actual number filled are not recorded. The number of vials incubated is recorded, but not the number filled.

Reference Standards
I did not review this section since it is a Product Office issue.

Specifications/Analytical Methods
Sterility testing is performed per ---(b)(4)---. The remaining testing is the responsibility of the Product Office.

Stability/Expiration Dating
Specifications
The stability specifications for Anascorp drug substance are listed in Table 22 of the submission. The stability specifications for Anascorp drug product are listed in Table 14 of the submission. The key attributes are appearance, potency, purity ----------(b)(4)----------, sterility, safety, and moisture content. In each case, the stability specifications are identical to the release specifications for Anascorp drug product. Sterility is performed per -(b)(4)-. The data for sterility met the specification of "meets requirements".

Bulk Drug Substance
Registrational Stability Studies
Protocol and Test Methods
----------(b)(4)----------.

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

Anascorp Drug Product
Registrational Stability
Protocol and Test Methods
Three lots of Anascorp drug product were placed on stability according to current ICH guidelines for registrational stability studies (ICH QIA (R2): Stability Testing of New Substances and Products). The lots were chosen to be representative of commercial drug product. A summary of the registrational stability protocol is included in Table 13 of the submission, and details on the stability batches are included in Table 14 of the submission.

The intended storage conditions for Anascorp drug product are ambient temperature (20 - 25°C and ambient relative humidity). Long-term stability studies to support the recommended conditions are 25 (b)(4) °C/---(b)(4)---, while accelerated stability testing was conducted at 40 (b)(4) °C/----------(b)(4)----------.

The physicochemical tests performed for the registrational stability studies are appearance (lyophilized product), (b)(4), moisture content, potency, purity --------(b)(4)----------, and identification (b)(4). At selected time points, safety and sterility are also performed on Anascorp drug product.

A significant change to the analysis of (b)(4) Assay data was instituted for the analysis of the primary stability batches. ----------(b)(4)----------

----------.

Supporting Stability Studies
Supporting stability studies were conducted on material made with the ----------(b)(4)---------- and provide long-term data in support of the primary (registration) stability studies.

The intended storage conditions for Anascorp drug product are ambient temperature (20 - 25°C and ambient relative humidity). Long-term stability studies to support the recommended conditions w 25 (b)(4) °C/---(b)(4)---, while accelerated stability testing was conducted at 40 (b)(4) °C/----------(b)(4)----------. A summary of the stability conditions and test points is included in **Table** 15 of the submission.

The physicochemical tests performed for the registrational stability studies are appearance (lyophilized product), (b)(4), moisture content, potency, purity ----------(b)(4)------, and identification -(b)(4)-. At selected time points, safety and sterility are also performed on Anascorp drug product.

Impurities Profile
I did not review this section since it is a Product Office issue; however, I did note that **Bioclon does not have an in-process specification for ----------(b)(4)----------.**

On 25 June 2009, we received an amendment to the BLA (STN 125335/0/25) which was an executed batch production record for Lot (b)(4) (in Spanish) and the Certificate of Analysis for the same lot (fill date 21 April 2009). This information had originally been submitted with Bioclon's 483 responses; however, I had told them to submit it as am amendment to the BLA since the 483 response was not an appropriate avenue for this new information. This lot of material was manufactured while the FDA was performing the Pre-License Inspection in April 2009. I reviewed the executed batch records submitted in this amendment and find that they are **not supportive** of Bioclon's statement that this manufactured lot continues to illustrate Bioclon's ability to manufacture acceptable product since release testing of the material was acceptable. Bioclon used the Batch Production Record that the Agency had previously found to be unacceptable due to the lack of detail (see FDA Form 483). At the time this lot was manufactured, Bioclon had not appropriately remedied the 483 observations that were issued to the firm during the pre-license inspection; therefore, this information provided by Bioclon does not illustrate Bioclon's ability to manufacture product under GMPs. The same concerns that were raised for the conformance lots submitted to the BLA still apply to this lot ---(b)(4)--- i.e. no process validation, inadequate aseptic filling technique, insufficient information to determine if the equipment is acceptably qualified, etc.