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To: -------(b)(4)-------
Bioclon SA de CV Instituto
Information Request: STN 125335/0
March 25, 2009

The Center for Biologics Evaluation and Research is continuing to review your biologics license application for Centruroides (Scorpion) Immune F(ab)2 Intravenous (Equine) submitted on January 21, 2009. We have the following requests:

General comment about amendment STN 125335/0/4, your February 19, 1009 submission in response to the January 29, 2009 and follow-up February 6, 2009 information request: As part of your response, Bioclon has referenced information in the original BLA in Volume 2 Page X. Volume 2 does not exist in the original application. The TOC for the original application lists volumes 1.1 through volume 1.23.

Manufacturer

1. FDA Registration numbers for Bioclon Tlalpan and Bioclon -------(b)(4)-------are not listed in the submission. Please provide these registration numbers.

Floor Diagrams

1. Floor diagrams for both (b)(4) and Talapan include rooms in their diagrams for rabbits and rats. These rooms were not mentioned in the floor diagram narrative of the BLA. Please provide information on all adjacent areas not used in the manufacture of the product. Include information of how cross contamination with adjacent areas is prevented.

2. In volume 1.2 Page 16/028, Bioclon states that Aseptic Area ----------(b)(4)----------(b)(4)----------Aseptic Area -------(b)(4)----------are both located on Floor (b)(4). Bioclon states that Aseptic Area (b)(4) is isolated from the other areas. Please provide additional information as to how Aseptic Area (b)(4) is isolated from the other areas.

Information provided by NW & RF Date: 03/24/09 Transmitted by DLC Date 3/25/09 6

Number of pages (including cover sheet) _1____

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3. Tlalpan Facility Floor Diagram – Floor(b)(4) In the narrative of the BLA, Bioclon states the -------(b)(4)----------area is maintained as Class ----(b)(4)------. Figure 10 depicts the -------(b)(4)-------area as Class ---(b)(4)-----. Please indicate the correct room classification for this area.

4. Tlalpan Facility Floor Diagram Figures 13-17 These are flow diagrams depicting the flow of materials, bulk drug substance and bulk drug product, and personnel. There is no narrative to go along with these diagrams and some of the diagrams have more than one color arrow on the same diagram. Please provide a detailed descriptive narrative to explain these diagrams.

Other Products

1. Please provide additional detailed information on area changeover between the different products. This includes both equipment and areas. Bioclon states that each manufacturing area of the facility is cleaned and sanitized after use. More detailed information is needed on the cleaning process (manual or automatic) and the cleaning validation of the area and equipment. This includes detailed location of monitoring areas along with the type of monitoring, a discussion of how the monitoring locations were chosen, and reference SOPs followed.

Filters

1. In volume 1.2 page 42/054, Bioclon provides a list of different filters used throughout the manufacturing process. Please include the filter validation and compatibility testing performed for each type of filter. Please provide cleaning validation and storage validation for the ---(b)(4)-----. filters. Please indicate if the filters are single use, dedicated, or shared.

2. On page 63/75 of volume 1.2, Bioclon states reprocessing is not performed during any of the production steps, however, in numerous places in the BPR it states that if a filter is clogged, ----------(b)(4)-----. . Please provide the validation to show ---(b)(4)----------.

Lyophilizer

1. Please provide the cleaning and sterilization validation for the lyophilizer. Please provide a detailed description of the cleaning procedure and reference SOPs used. Include a rationale for the cleaning process used and any tests performed. Include acceptance criteria and a discussion of any deviations or investigations that were performed during the validation.

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1. A cleaning and sanitization validation report was provided in Bioclon's response to the first AI; however, the response was not complete. Please provide a rationale for the cleaning acceptance criteria, along with an explanation for the justification of the established alert and action limits.

2. Please indicate how the cleaning validation for the equipment covered multiple products. The validation reports referenced Lot numbers that were used, but there was no indication if this was considered the worst case product or how they chose to use those lots to represent all materials manufactured in the facility in shared equipment.

Water

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

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

1. In the BPR it states to use ---(b)(4)-----. during the fill. These systems were not discussed in the submission. Please provide the validation and routine monitoring for these systems.

Vials

1. In Volume 1.2 page 46/058, Bioclon states the vials are ----------(b)(4)----------.

    a. Please provide the cleaning validation for the vials and include particulate removal studies. In reviewing the batch production record, the BPR states that the vials are ----------(b)(4)----------. Please provide the cleaning validation of the ----------(b)(4)----------. The description should reference SOPs used and list the acceptance criteria used in the validation. For all validations, please include a discussion of any deviations or investigations that were performed during the validation.

    b. Please provide the equipment validation for the ----(b)(4)----- washer. This would include a detailed description of the loads validated along with a list of

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acceptance criteria and a discussion of any deviations or investigations performed. This was not included in the original submission.

Stoppers

1. In volume 1.2 page 46/058, Bioclon states that the stoppers are washed in -----(b)(4)---- stopper washer ----------(b)(4)----------.

    a. Please provide the cleaning validation ----------(b)(4)---------- validation for the stoppers. Please provide the ---------(b)(4)------ validation for the stoppers. Please provide a detailed description of the autoclave validation for the stoppers. Please provide the equipment validation for the ------(b)(4)------ washer since this was not included in the original submission.

Filling

1. Bioclon states the vials are filled with ----------(b)(4)----------. Please provide a more detailed and accurate description of the filling process. Please indicate the room classification the vials are filled under. Please include a description of your routine monitoring and a discussion of where and when the monitoring takes place and the rationale for this. In the batch production record there is a sentence that describes the cleaning of the filling syringe. Please provide the cleaning validation and sterilization for the filling syringe. Please indicate if these syringes are dedicated or shared. Please provide a detailed description of the cleaning procedure. Please provide the validation for the filling machine along with cleaning validation.

Leak testing and visual inspection –

1. ----------(b)(4)----------. Please provide detailed information on the leak test and its validation. Please provide more detailed information on how the visual inspection is performed and how personnel are trained to perform the visual inspection. Please describe in detail the types of defects that are considered critical, major and minor defects and what the alert and action levels are for each category of defect. Please provide a detailed description of what would happen if vials fail visual inspection. Reference SOPs used in both processes.

2. In volume 1.2 page 62/074 the chart for drug product test methods and specification lists a Leak Test SOP M-FQ-030. Please provide the validation for this test.

Autoclave

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1. In Volume 1.2 page 64/076, not enough information is provided in the application to determine if the autoclave has been validated appropriately. Please provide a description of the loads that were validated in the autoclave along with the parameters validated. Please provide the name and SOP number of the autoclave SOP used in production. Please provide a rationale for the placement of the biological indicators within the load during validation. Please indicate if thermocouples were used during the validation and indicate their placement within the autoclave and loads along with a rationale for their placement. Please provide a list of the acceptance criteria for the autoclave validation. Please provide a discussion of any deviations or investigations that occurred during the validation. Please provide the testing to verify the D values of the biological indicators used in the validation studies.

Dry Heat Oven

1. In volume 1.2 page 64/076 not enough information was provided in the application to determine if the dry heat oven was validated appropriately. Please provide the acceptance criteria for the validation. Please provide a description of the ------(b)(4)----- studies performed and the results. Please provide the ------(b)(4)-------- studies performed. Please provide a description of the loads validated in the oven. Please indicate where the ------(b)(4)------- vials were placed and the rationale for their placement. Please indicate if thermocouples were used during the validation and where they were placed within the oven and loads along with the rationale for their placement. Please provide a discussion of any deviations and investigations that occurred during the validation.

HVAC

1. In Table 1, Page 3/43 of the amendment, please define "Ambient" % Relative humidity. Does this mean there is no humidity control in the aseptic area? Table 3 page 8/48 of the amendment states that the room classification is under static conditions. Please provide the qualification of the environment of the rooms under dynamic conditions. Figure 4, page 9/049 of the amendment is a floor plan that depicts the sample locations listed in Table 3. Please provide a detailed written narrative of where EM samples are taken and provide a rationale for those sample locations. Please provide the results of the EM monitoring during validation of the rooms during HVAC validation. Please discuss any deviation and investigations that occurred during HVAC validation.

2. In the first Additional Information request, Bioclon was asked to provide a summary of actions that are taken if any alert or action levels are exceeded during environmental monitoring. Bioclon's response was the "----------(b)(4)----------." This response lacks sufficient detailed information. Please provide a more detailed description of actions that are taken when an alert or action level is exceeded. Please reference SOPs used and indicate if the organisms are identified.

3. Please provide a detailed description of your environmental monitoring procedures.

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4. Table 4, page 12/052 of the amendment, provides Action limits, but no alert levels. Please provide action and alert levels as requested in the first Additional Information request.

5. Please provide the rationale for the action limit for the Class (b)(4) Sterile Area viable count which is listed as -----(b)(4)----. Please explain why this action limit is ------(b)(4)----------. Please provide the dimensions of the settling plates used during EM and please indicate if these plates have been qualified for use in the EM program. Please provide detailed information on the conditions the EM plates are incubated under such as time and temperature and when the plates are checked for growth.

6. In the first Additional Information request, Bioclon was asked for more detailed information on the IQ, OQ, and PQ for the HVAC validation. Bioclon provided a brief description of the HVAC system, but there was no mention of an IQ, OQ or PQ. The original submission stated that the HVAC was not validated using the conventional approach, however the system was tested and is maintained to perform as intended by monitoring and testing each component of the HVAC system to verify its performance during the production process. No further information has been provided. Please provide detailed information on how the HVAC was validated.

Media Fill

In our Type C Meeting with Bioclon, Bioclon agreed to follow the following guidance documents - "Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" and "Guidance for Industry : Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice" The first guidance describes the type of information and data that should be included in the BLA and the second guidance describes the procedures and practices that will help enable a sterile drug manufacturing facility to meet CGMP.

1. The information discussed in these two guidance documents that Bioclon agreed to follow was only partially provided, and in some cases not provided, in Bioclon's response. Please refer to the original Additional Information request and submit the information requested. The following are some examples where information was requested and either not provided or only partially provided. This is not an all inclusive list of deficiencies.

    - The microbiological monitoring program used during routine production and media fills should be described.

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- The parameters used for production filling and for media fills (e.g., line speed, fill volume, number of containers filled, or duration of fill) should be compared.
- Interventions - description of intervention, duration of intervention, and number of interventions
- Rationale for the "worst case" conditions chosen
- Environmental monitoring to be performed (step, duration, location)/Results of EM this includes not only room monitoring, but also personnel monitoring
- Number of vials to be filled/Actual number of vials filled – minimum and maximum
- Any smoke studies performed
- Growth promotion testing & results
- Number of personnel

2. Please provide a detailed description of how the media fill differs from actual filling process and provide an explanation for the differences.

CMC

1. Please submit a list of deviations that occurred during the production of the conformance batches (lots ----------(b)(4)----------). For each deviation, please provide the date the deviation occurred, a brief description, and what lot was affected.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission. Please submit this information as an amendment to this file no later than April 1, 2009. Please do not send an advance copy of the response by email unless requested to do so by FDA. If you anticipate you will not be able to respond by this date, please contact the Agency immediately. The action due date for this file is July 24, 2009.

Thank you for your assistance,

Debbie Cordaro
Regulatory Project Manager
FDA/CBER/DBA/OBRR/RPMB