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FAX No: ------(b)(4)-------
To: --------(b)(4)---------
Bioclon SA de CV Instituto
Information Request: STN 125335/0
February 6, 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 are providing you with the information request we discussed on January 29, 2009. Some of the information may already be in the submission, so it is acceptable to reference the location of this information in the submission.

Please contact me by phone or email no later than COB tomorrow, February 6, 2009 with the dates when we will be receiving the outstanding information requested.

A. Container Closure System/Shipping Containers
A description of the container and closure system, and its compatibility with the biological substance should be submitted. This should include detailed information concerning the supplier, address, and the results of compatibility, toxicity and biological tests. Evidence of container and closure integrity should be provided.

B. Shipping Validation
A description of the shipping validation and data collected during the validation.

C. Water Systems – Please refer to meeting minutes dated 08 Jan 2008 and 10 Apr 2008
Please provide the following information on water purification systems for the production of water for use in manufacturing and rinsing of product contact equipment, and containers and closures:

1. A general description of the water system(s) should be submitted, including water source, major components, and a general discussion of the type of water used for each stage of processing.

2. Validation Summary
   A validation summary should be provided containing:
   - a narrative description of the validation process (or protocol) including acceptance criteria;
   - certification that installation qualification (IQ) and operational qualification (OQ) have been completed;

- the length of the validation period;
- the parameters monitored and tests performed;
- the frequency of monitoring each point of use during the validation period;
- a validation data summary; and
- an explanation of all excursions or failures, including deviation reports and results of investigations.

3. Routine Monitoring Program
   A narrative description of the routine monitoring program should be submitted, to include:
   - the tests performed;
   - the frequency of testing;
   - frequency of monitoring each point of use
   - the alert and action limits used;
   - summary of actions to be taken when limits are exceeded.

4. Cleaning
   Provide a summary of the sanitization procedures performed including the frequency and testing performed.

D. **Heating, Ventilation, and Air Conditioning Systems (HVAC) – Please refer to meeting minutes dated 08 Jan 2008**

1. A general description of the HVAC system(s) should be provided including:
   - The number and segregation of air handling units;
   - Whether air is once-through or recirculated;
   - Containment features; and
   - Air changes/hour.

2. Validation Summary
   A validation summary with the following information should be provided for the system, which contains:
   - a narrative description of the validation process (or protocol), including the acceptance criteria;
   - certification that IQ, OQ and certification of filters has been completed;
   - length of the validation period;

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- a validation data summary (validation data should include Performance Qualification data accumulated during actual processing); please break down the data into areas and sample points tested
- an explanation of all excursions or failures, including deviation reports and results of investigations.

3. Routine Monitoring Program
   A narrative description of the routine monitoring program should be provided including:
   - the tests performed and frequencies of testing for viable and nonviable particulate monitoring parameters;
   - viable and nonviable particulate action and alert limits for production operations for each manufacturing area; and
   - a summary of actions to be taken when limits are exceeded.

E. Computer Systems

This section should contain information on computer systems which control critical manufacturing processes. The developer of the system, i.e., whether in-house or contractor, should be identified. The information provided should also include a brief description of procedures for changes to the computer system. For each of these systems a list of the manufacturing steps which are computer-controlled should be provided. This section should also contain a validation summary for each of these systems, which includes:

- a narrative description of the validation process (or protocol), including acceptance criteria;
- certification that IQ and OQ have been completed;
- an explanation of the parameters monitored and tests performed;
- a validation data summary;
- an explanation of all excursions or failures; and
- deviation reports and results of investigations for all excursions or failures.

F. Equipment Validation and Cleaning – Please refer to meeting minutes

1. Validation Summary
   A validation summary should be provided containing:
   - a narrative description of the validation process (or protocol) including acceptance criteria;
   - certification that installation qualification (IQ) and operational qualification (OQ) have been completed;

   - the length of the validation period;

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- the parameters monitored and tests performed;
- an explanation of all excursions or failures, including deviation reports and results of investigations.

2. Cleaning Validation Summary
   This section should contain:
   - a brief description of the cleaning procedures and cleaning reagents;
   - a rationale for the cleaning procedures chosen which addresses their effectiveness for the residual products to be removed; and
   - a validation report describing the cleaning validation procedures for removal of product residues and cleaning agents. The report should identify the sampling and analytical methods used and address their sensitivities and specificities.

G. Cleaning Agent Validation

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.

H. Media Fills

If the product is intended to be sterile, information on all sterilization and aseptic processes (e.g., formulation through filling and sealing) should be submitted as described in the "Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" and "Guideline on Sterile Drug Products Produced by Aseptic Processing."

Please provide the following additional information:

1. Summary of the media fill validation containing:
   - Media used
   - Duration
   - 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
   - Number of vials to be filled / Actual number of vials filled – minimum and maximum
   - Volume of fill
   - Incubation duration and temperature / Number of units incubated
   - Number of units positive

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- Number of units rejected and cause
- Any smoke studies performed
- Growth promotion testing and results
- Number of personnel
- Acceptance criteria for all tests performed
- Line Speed

I. Lyophilization

A validation summary for lyophilization of the drug substance/product should be given, which includes:

- A narrative description of the validation (or protocol);
- Certification that IQ and OQ have been completed
- A validation data summary;
- Explanation of all excursions or failures; and
- Deviation reports and results of investigations of all excursions or failures.

J. Item 4 Volume 1.2 Other Products

Please provide the following information:
The applicant should indicate in which rooms the additional products will be introduced and the manufacturing steps that will take place in the room.

Any additional products that may share product contact equipment with the product in question should be indicated (dedicated vs. multi-use equipment should be delineated for each process step, in this section or other appropriate sections of the application).

K. Detailed Description

A detailed description of the fractionation, formulation, and purification should be provided. This should include a rationale for the chosen methods, and the precautions taken to assure containment and prevention of contamination or cross-contamination. In-process bioburden and endotoxin limits should be specified where appropriate.
Any reprocessing or related method should be fully validated and described. The allowable conditions for reprocessing of all or part of any batch should be described. Critical operations during which product or product contact surfaces are exposed to the environment should be described. If barrier isolator systems are used, a description of the system and the conditions of its use should be provided. Information and data on drug product filtration should be provided.

Item 15 Figure 12 shows rooms for rabbits and rats. Please indicate if these rooms are on a separate air handling system from the -----(b)(4)------ room.

The review of this submission is on-going and issues may be added, expanded upon, or modified

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as we continue to review the annual report. As stated above, you are requested to contact me by COB 2/6/09 as to the dates when you will submit your response to this information request. If you are unable to respond by tomorrow, please contact the Agency to discuss an alternate response date. When the information we requested is available, it should be submitted as an amendment to this file. .

Thank you for your assistance,

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

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