DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Our STN: BL 125335/0

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

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

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

This letter is in regard to your biologics license application (BLA) for Centruroides (Scorpion) Immune F(ab)2 Intravenous (Equine), submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all submissions you have made relating to this BLA. After our complete review, we have concluded that we cannot grant final approval due to the deficiencies outlined below.

CMC:

1. You should manufacture your conformance lots on the scale that you intend to market them in the United States.

2. Your document control procedures should include adequate revisioning procedures. The revision "A" batch records included in your submission of June 4, 2009, (STN 125335/0.23) appear to precede the batch records in place during the pre-licensure inspection.

3. Your batch record does not capture all relevant aspects of the manufacturing process. For example, for steps in which you specify a mixing time, you should record a start and stop time; and, for steps in which you perform multiple mixing procedures, you should document each one as executed. Please submit a revised batch record containing missing limits for critical time ranges, volumes, and other appropriate details, as well as appropriate signatures to document critical executed steps.

4. The list of reagents used in your manufacturing process is incomplete. For example, you ----------(b)(4)---------- but you did not include it in the list of reagents specified in your BLA. Please prepare and submit a comprehensive list of reagents including the supplier, purpose, quality standard, and certificate of analysis. This list should include excipients as well as materials used to formulate buffers.

5. The information in the original application and amendments appear contradictory or inaccurate.

    a. The narrative in the BLA for the room classifications does 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 comment.

    b. In the BLA narrative, the cleaning procedure only describes the vials 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 comment.

    c. Your process narrative is not in agreement with your batch record. 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.

6. You should complete process validation. 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)---------- validation. Please provide detailed descriptions and data summaries.

7. Please establish sufficient in-process controls to demonstrate that you have a controlled manufacturing process. For example, in-process specifications or action levels should be set based in part on process validation and equipment qualification. Specific examples include ----------(b)(4)---------- 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.

8. Please submit a validation of the mixing times and speeds you use in your manufacturing process. For example, you should have data to demonstrate that the agitation of your ---(b)(4)--- solution at a certain speed for a given amount of time achieves adequate mixing. You should perform this type of validation for each mixing step in your manufacturing process. Note that we highly recommended you replace (b)(4) mixing (----------(b)(4)----------) with mechanical stirring where possible (i.e., use of a mechanical mixer, stir bar, or equivalent.)

9. Please establish minimum and maximum process times for each stage, ----------(b)(4)----------. These times should be based on your manufacturing experience with this product and you should set them in such a manner that any unusually short or long

process times are noted as deviations from the normal process. For example, if your pepsin digest target time is -(b)(4)-, you should have data to demonstrate that -(b)(4)- is sufficient to ensure your desired level of digestion. You should demonstrate robustness for a minimum and maximum digest time. Likewise, you should perform your ---(b)(4)---- step for a validated, defined amount of time.

10. For steps involving pH changes, you should control the rate of addition of acid or base to minimize the formation of high pH gradients. You should measure the total amounts of acid or base added, and ensure that they fall within a predetermined volume. In general, you should control any step where material is added to the process stream with regard to the rate of introduction. Please revise the relevant SOPs and your master batch record to include these additional controls.

11. Regarding filtration steps:

    a. For all filtration steps in the batch record, please indicate the number and types of filters used.

    b. For steps where you rinse filters before use, please specify a time, flow rate, and volume for the rinsing solution.

    c. Note that you should control filtration steps with regard to pressure and/or flow rates. Please specify validated pressure and/or flow rates for filtration steps in your master batch record.

    d. In your April 6, 2009, response, 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, we will consider this a deviation requiring an investigation.

12. In your April 6, 2009, response to our request for additional information for filter compatibility testing, you stated that you used the information provided by --(b)(4)-- to determine the compatibility of the filter with the product. Additionally, you stated you used the filters for --(b)(4)-- for the same process and the finished product was compliant with the quality specifications. Please justify why information obtained by --(b)(4)-- is applicable to your product. Please provide the approved protocol you used and the summary of the report written to document that the ---(b)(4)--- filters are acceptable for use without performing compatibility testing.

13. Please revise your batch record to include instructions for the preparation of all reagents (for example, ----------(b)(4)----------).

14. Please provide a list of hold times for all buffers used in the manufacturing process.

15. Please set appropriate upper and lower limits on the number of concentrates mixed to yield a lot of bulk product. You should set limits based on the volume or weight of plasma instead of ----------(b)(4)----------. You indicate in your May 1, 2009, response that ----------(b)(4)----------. Please provide data to demonstrate that ----------(b)(4)----------; this typically involves manufacturing one conformance lot for each condition.

16. Please provide data validating the cleaning, sterilization, and depyrogenation of the –(b)(4)- containers used for collecting horse blood.

17. Please submit data for hold-time validation of all intermediate hold times. The validation data should include bioburden, endotoxin, molecular integrity, potency, and other parameters as appropriate.

18. Please submit a cleaning/sanitization study for the -(b)(4)- system. Include details about how you will determine the maximum number of uses of the (b)(4) membrane.

19. Please provide data from your 3 most recent production years on the proportion of lots ----------(b)(4)----------.

20. Please establish a ----------(b)(4)----------.

21. Please expand upon your answer #31 in STN 125335/0.22, in which you list the hold times of the ----------(b)(4)----------?

22. You should control your formulation process to the point where you are able to use a consistent procedure for formulation. If (b)(4) of your runs require a concentration procedure at the formulation step and (b)(4) do not, this indicates a fundamental difference in the manufacture of these lots. Please revise your batch record to reflect a consistent formulation process.

23. Your formulation procedure is not adequately described in the master batch record. Please specify what volume of –(b)(4)- is used to dissolve the excipients, what mixing method is used to dissolve the excipients, and the mixing conditions for blending the excipient solution with the product concentrates. Please submit a mixing study to validate that your formulated product is homogeneous.

24. You should control your filtration process to the point where ----(b)(4)---- formulated product should not be necessary. If you experience filter clogging at this step of your

manufacturing process, you should reevaluate the filtration conditions, including the numbers and types of filters used. Please note that if you ----------(b)(4)----------, you must validate the process and demonstrate that it does not impact product stability or quality. Please submit a validation for this procedure.

25. For the nanofiltration step, please establish specifications for ----------(b)(4)----------. Reflect the specifications in the revised batch record.

26. Please verify that in the event of a nanofilter clog or a post-filtration integrity test failure, the affected lot of product will be discarded. If you propose reprocessing, you should submit an SOP and prospective validation plan.

27. Please explain why you did not record a deviation in the executed batch record for the event observed on April 24, 2009, in which the air hose attached to the nanofiltration pressure tank was forcibly ejected.

28. Please complete the small-scale validation studies of the nanofiltration step with the consideration of mimicking the full-scale manufacturing process. If there is an unavoidable difference, please justify it and verify that the difference does not compromise the validity of small-scale studies. The validation studies should include the clearance of enveloped viruses and non-enveloped viruses, for example, XMuLV, PRV and PPV. You should monitor critical parameters related to the full scale manufacturing process during the validation studies. You should use these parameters, ----------(b)(4)----------, to define your small-scale viral validation studies.

29. Please note that filter integrity is an essential in-process control and that you must compare the performance of the filter used in your viral validation studies to that of the filters you use in your full-scale production. Please note that Bioclon was informed in the CMC pre-BLA meeting on January 8, 2008, that with regard to non-enveloped viruses (for example, PPV), "testing results must be provided to assess removal of small viruses." Also note that ICH guidance Q5A indicates "viral clearance characterization studies should be performed with nonspecific model viruses with differing properties." Please submit data to validate the capacity of your manufacturing process to remove small, non-enveloped viruses.

30. You should submit additional viral clearance data, including kinetic studies, where appropriate, and robustness studies. Orthogonal approaches should be used for viral clearance; i.e., steps to remove virus as well as steps to inactivate virus. For inactivation steps, kinetic data are critical because virus inactivation does not follow simple first-order kinetics. You should evaluate robustness in your validation studies. You should include critical parameters, such as ----------(b)(4)----------, in the robustness evaluation. You should confirm virus reduction by these manufacturing processes under worst-case conditions. Please provide kinetic data on inactivation of your model viruses such as ----------(b)(4)---------- for the pepsin

digestion step, or any other step of the manufacturing process for which you wish to claim inactivation.

31. Please submit data to characterize each of the virus preparations for spiking used in your validation studies, for example, the state of aggregation and the infectivity of virus stocks. You should include "hold" samples of spiking virus in the experiments for calculation of the virus reduction. You should provide data on the storage and stability of the virus stocks used for the spiking experiments. In addition, please provide validation data on analytical procedures in order to assure that the assays will reproducibly determine the titers of virus stocks. The critical parameters for these analytical procedures include the determination of accuracy, precision, specificity, linearity and range for your virus assays. Please submit Standard Operating Procedures (SOPs) pertaining to virus preparation, storage, cell culture cultivation and propagation for these assays.

32. Please revise your viral clearance tables to remove clearance values less than 1 log because we do not consider this amount of reduction significant and you should not use values less than 1 log for calculation of total clearance.

33. Please provide representative Certificates of Analysis from each supplier/manufacturer for the following processing reagents: ----------(b)(4)----------, cresol, pepsin, ammonium sulfate, ----------(b)(4)----------, glycine, sucrose, and sterile sodium chloride solution (ISS).

34. Please revise your final-product release specifications for glycine and sucrose to include minimum and maximum acceptable limits, preferably based on representative data from routine production lots, and resubmit the complete, revised list of specifications.

35. Please devise a specification for residual pepsin in final product Anascorp, and provide an assay validation and standard operating procedure (SOP) for pepsin measurement.

36. Please provide an update to your final-product stability studies when additional data is available.

37. The facilities and process information is not sufficiently detailed and descriptive to permit a comprehensive review. Please note that you should include only applicable information within an application and you should not include any information based on future proposals. You should present the information 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.

38. The FDA held two Type C meetings (January 8, 2008, and April 10, 2008) with your firm in which we specifically stated what type of information you needed to submit to the BLA. You proposed to follow these guidance documents:

    a. Guidance for Industry Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice

    b. Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products

    You did not submit all information as put forth in these guidance documents and as specified in the Type C meetings. This includes, 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 presented in a detailed, concise, coherent manner that allows for a timely and accurate review of the submission. We are unable to come to an informed conclusion and recommendation on adequacy given the information you previously provided.

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

40. You must resolve all outstanding inspectional observations listed on FDA Form 483. For example, Bioclon's response to FDA Form 483 Item #1 is unacceptable. An acceptable inspection of your facilities is required prior to licensure.

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

42. You should complete equipment qualification on all major manufacturing equipment used in the production of Anascorp. 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.

43. 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.

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

45. In the Additional Information Request dated February 6, 2009, we asked you 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. In your response you reference a stopper extractable and ---(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. You state 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.

46. You should establish a final specification or action level 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.

47. 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 ---------- ---(b)(4)----------, but no narrative descriptions or justifications of the sample areas. Please provide this information.

48. You provided a rationale for the chosen sampling points based on criticality of manufacturing steps for routine environmental monitoring of manufacturing and aseptic areas. 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.

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

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

51. You state in your February 19, 2009, submission 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.

52. 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.

53. 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 April 10, 2009, in which CBER/DMPQ stated 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.

54. On page 32 of 44 of the original submission you state that the differential pressure between each room is -----(b)(4)---- monitored. On page 2 of 42 of the February 19, 2009, amendment 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.

55. In your February 19, 2009, amendment, you presented four tables to summarize the HVAC system and air-flow characteristics of the controlled manufacturing areas used for production of Anascorp drug product. Table 3 on page 48 of the amendment states that the room classification is under static conditions. The Sterile Area – ----------(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)------. Please explain how you prevent cross contamination between the Class ----------(b)(4)----------, and the Class (b)(4) area if they are located within the same room without any physical separation or differing differential

pressures. Table 3 also indicates six additional locations that are classified; however, you did not provide the differential pressure and room numbers for these locations. Please provide this information. Please note that we recommend you classify the rooms based on dynamic conditions.

56. Please clarify if you perform routine environmental monitoring during dynamic or static conditions.

57. We requested that you submit additional information on the HVAC system in our March 25, 2009, information request. Your April 6, 2009, response included summaries of typical results obtained during three separate drug product manufacturing runs. We cannot discern the acceptability of the data provided in the tables because the sample points are identified in the diagrams with numbers and the results are identified with a description. You provided personnel monitoring results 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 you monitored all sample points. You provided acceptance criteria for Class (b)(4) and Class (b)(4) areas; however, it appears Sample (b)(4) is located in a Class (b)(4) area. Please clarify this information and provide a response in a detailed, concise, and coherent manner.

58. We asked you to provide a comparison of the procedure performed during your routine media fills and the procedure that actually occurs during the aseptic filling process (February 6, 2009). Your February 19, 2009, response stated that the two processes are similar and you provided an executed media fill batch record to illustrate this statement. You did not include a written narrative. 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:

    a. 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 Heat Oven ----------(b)(4)----------), but the FBPR does not reference these SOPs.

    b. The MBPR references SOP P-PB-054, but the FBPR does not.

    c. 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.

    d. 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.

    e. The MBPR references entering materials into the fill area ----------

-----(b)(4)----------. This entry process is not mentioned in the FBPR.

f. 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 you did not record actual fill volume and actual number filled. You recorded the number of vials incubated, but not the number filled.

g. 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.

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

Clinical:

60. We note that your study reports in the Clinical Section (Item 8) of this BLA do not bear signatures of the responsible parties. For instance, the pages for "Signature of Sponsor's Responsible Medical Officer" have the wording "not applicable." Please submit signed clinical study reports or documentation that "a responsible medical officer" was responsible for each clinical study report.

61. Please address the lack of adequate dose-ranging studies in establishing the proposed dose (3 initial vials, with repeat at 30- to 60-minute intervals up to 5 vials; more if envenomation is severe) in the draft package insert. You should have a systematic approach to dosing based on pharmacokinetics, body mass, and the use of concomitant medications in the clinical development program for the product. Please also address the lack of GCP documentation for your human PK data.

62. In all the clinical studies presented, subject follow-up after discharge is based on telephone interview and not in-person visits or laboratory tests. In pediatric patients, the information from phone contact would likely be second-hand and this adds to the uncertainty about the accuracy of the follow-up safety data. Please address the impreciseness of such data collection, particularly with reference to the inability to confirm a diagnosis for serum sickness in at least 10 subjects in AL-03/07.

63. The use of antihistamines or corticosteroids is not specifically prohibited in the protocol of most clinical studies and there may be other confounding concomitant medications such as benzodiazepines and narcotics. Please address how you can adequately evaluate safety in the presence of these mitigating or confounding factors.

64. In several of the clinical studies, including the pivotal trial (AL-02/03), you use the decline in serum venom levels by a binding assay after Anascorp treatment as an endpoint for efficacy. Please address the issue that in the absence of assay validation to

detect active venom when antivenom is present the venom levels in Anascorp-treated subjects would be un-interpretable.

65. In some clinical studies, including AL-02/03 and AL-03/07, the study report states that the maximum protein content of the Anascorp used was (b)(4). This differs from the specifications for release. Please confirm that the same formulation was used for your clinical studies as the one proposed for marketing.

Study AL-02/03:

66. The primary efficacy endpoint was to demonstrate resolution of clinically important systemic signs of scorpion envenomation within four hours for patients treated with Anascorp. The "Severity Evaluation" document in the study protocol's Appendix 1 does not grade severity and only lists "clinically important systemic signs of scorpion envenomation" under components of (1) respiratory compromise and (2) pathological agitation.

    a. As indicated in this protocol, judgment of the resolution of the clinical signs was left to the Investigator's discretion. Clinical signs are non-specific for envenomation and not entirely objective and there is considerable confounding by concomitant medication(s), especially in the case of "pathologic agitation." In 3 of the 7 placebo-treated subjects, the Investigator provided an assignment for resolution at 4 hours different from what the systemic signs would have dictated. Please address the validity in the evaluation of primary endpoint in this study.

    b. The signs of "respiratory compromise" were observed in 3 subjects (2 in Anascorp arm and 1 in placebo arm) and subsided within 2 hours. Its components, "upper respiratory compromise," "other respiratory compromise," and "pulse oximeter <90%," are not informative because the degree of compromise or the actual pulse oximeter reading are not known. The observed "other respiratory compromise" in this study is described as "respiratory acidosis" without actual data presented to substantiate severity. Thus, we cannot verify any of the "respiratory compromise" signs from the information submitted. Please address the fact that because all signs of "respiratory compromise" in the 3 study subjects subsided within 2 hours of treatment no effectiveness can be inferred for Anascorp in the treatment of "respiratory compromise." Efficacy, if established, is primarily driven by the data on "pathological agitation."

    c. For the treatment of a serious and life-threatening condition, the product should demonstrate effect on mortality or major morbidities. You did not demonstrate efficacy in AL-02/03 on "respiratory compromise" or any life-threatening manifestations of scorpion envenomation because this study does not seem to have enrolled the most severe cases of scorpion envenomation to demonstrate success in reducing mortality or major morbidity. Please be advised that you need to conduct a study on subjects with more serious manifestations if your product claim includes treatment of a serious and life-threatening condition.

67. In the original submission of this protocol to BB-IND (b)(4), you proposed a sample size of at least 12 subjects to discern a significant difference between treatments assuming expected success proportions of 0.85 for the Anascorp treatment and 0.10 for the comparator group. The finalized study protocol for AL-02/03 does not pre-specify a hypothesis for a given difference in success rate between treatment arms. However, the Statistical Analysis Plan dated September 22, 2005, states that the product will be declared superior to placebo if the difference in success rates is 0.2 or greater. An appropriate hypothesis should be based on the lower bound of the 95% confidence interval for the difference in success rates between treatment arms. If the endpoint is vague and the venom toxicities exhibited by the subjects under study are not life-threatening, such as agitation in the absence of respiratory or other serious manifestations, there should be a much bigger difference in order to be certain of a meaningful therapeutic benefit. Please address:

    a. The inconsistencies in your assumptions of treatment effect; and

    b. Why a difference of 0.2 can be regarded as clinically meaningful, considering your assertion that Anascorp is indicated for the treatment of a serious and life-threatening condition when a placebo success rate is estimated to be 0.1.

68. The placebo is said to be lyophilized material to be reconstituted with normal saline, but the finalized protocol dated November 30, 2003, states it is normal saline (page 7 of protocol, BLA vol. 1.8, page 194). Please provide detailed information on the nature of the placebo.

69. Please address the imbalance between treatment arms in:

    a. The subjects' age (and hence maturity and body mass);

    b. The time between scorpion sting and administration of test product; and

    c. The median dose of midazolam sedation administered prior to study enrollment.

70. Two of the subjects had no detectable venom in serum at any time during the study (one in each treatment arm) and two other subjects did not have serum venom assayed (both in Anascorp arm). Thus, there were only 11 subjects with documented envenomation in this study (5 in Anascorp arm and 6 in placebo arm). Please reanalyze your data for subjects with documented envenomation.

71. Please address the fact that the serum antivenom assay is a binding assay for equine F(ab')2 and may not necessarily be demonstrating serum activity in neutralizing scorpion venom.

Studies AL-03/06, AL-02/04, AL-02/05, and AL-02/06:

72. In AL-03/06, a study based on chart review of patients with scorpion sting but not antivenom treatment, approximately 30% of "envenomated" subjects showed some form of respiratory compromise. It appears to confirm, as in the pivotal trial (AL-02/03), that scorpion envenomation in young children is predominated by neuromuscular toxicity as manifested by "pathological agitation." There were no deaths or serious adverse events using standard of care and it is not clear how "respiratory compromise" contributes to morbidity, which appears to be readily reversible with supportive care. Please address the potential role of antivenom in scorpion envenomation as being primarily in the shortening of the neuromuscular effects of envenomation or reduction in the use of concomitant medications, rather than providing benefit on mortality or irreversible morbidity.

73. Although you consider the open-label studies, AL-02/04, AL-02/05, and AL-02/06, as "controlled," using the natural history study, AL-03/06, as historic control, we cannot consider this appropriate because:

    a. AL-03/06 was completed (July 2007) after completion of these three "controlled" trials (October 2006); and

    b. The protocols for these "controlled" studies were finalized before AL-03/06 was initiated.

    Please address the lack of pre-specified hypotheses-testing in these "controlled" studies, which were intended to incorporate the historic data from AL-03/06 as "control" to establish efficacy.

Study AL-99/02:

74. Please address the reconstitution of Anascorp in AL-99/02 (in 5 mL normal saline) as being different from that in the pivotal trial, AL-02/03 (10 mL saline, section 9.4.2 of study report), or the proposed use in the draft package insert for this BLA submission (5 mL sterile water).

75. Please address the fact that the adverse event reporting in AL-99/02 is defined by relatedness to Anascorp treatment, making the database incomplete because of non-reporting of events deemed "not related."

76. Please note that since the comparator to Anascorp (Birex) is not a licensed product in the U.S., AL-99/02 is not adequate to support efficacy of Anascorp in scorpion envenomation.

Study AL-03/07:

77. In this BLA submission, you did not provide an up-to-date study report of AL-03/07. Although you included an interim report covering the period May 23, 2005, through September 23, 2006, a span of 16 months, together with a Statistical Report covering the period up to June 2008, an additional 21 months, there should be one up-to-date interim study report covering the entire period up to at least June 2008, so that the information and dataset in the Statistical Report can be reconciled with the submitted study report data. In addition, the dataset was submitted piecemeal in relation to periods between May 2005 and June 2008. Please submit an up-to-date study report that contains all the appropriate documentation together with a complete dataset for evaluation. A "Statistical Report" alone will not fulfill regulatory requirements.

78. Please address the lack of clinical laboratory testing to evaluate safety in AL-03/07.

Biostatistics:

79. In the original protocol of study AL 02/03 (IND --(b)(4)--), you determined the sample size of 12 with a 2:1 ratio by assuming 85% success rates in the Anascorp-treated group and 10% in the placebo group. However, in the final protocol the allocation ratio becomes 1:1 and the sample size remains the same. The trial ends up with 15 patients with an almost 1:1 ratio (8 vs. 7). You did not justify the new allocation ratio together with the sample size. Please comment.

Preclinical/Toxicology:

80. Based on the batch data submitted with amendment 0.24, Appendix 2, in which the measured amount of cresol is --(b)(4)-- and your calculations on the "theoretical maximum level of cresol" are --(b)(4)--, please revise the specification for cresol downward from --(b)(4)--.

81. Please set a separate specification for --(b)(4)--to reflect the amount present in the final formulation.

Animal Husbandry:

82. Please submit and implement plasma screening procedures, such as those described in 9 CFR 113.53, to preclude introduction of adventitious agents into your manufacturing stream. You may do this on the plasma pool in lieu of testing individual plasma units.

83. In the absence of adequate data to validate cleaning and sterilization for the needle and tubing set used in bleeding your donor herd, you should ----------(b)(4)----------. Please implement this change and submit a revised SOPP.

84. Given the excessive bleed volumes and aggressive bleeding schedule, we very strongly

recommend that you measure and document the hematocrit of donor horses prior to each bleed and 2-3 days post-bleed. You should not bleed animals with hematocrits below 25% should and hematocrits should not drop below 18% post-bleed. This information should be amended to the veterinary records for each horse.

85. You should use unique container identification, such that containers from the ----(b)(4)---------- in the master batch record. Please submit an SOP to reflect a revised numbering system or method that differentiates -----(b)(4)----------

86. Please establish a quality assurance certification program to include hay, pelleted feed, and water. You should monitor the water source for your donor animals to ensure sufficient quality; an annual report from the municipal water supplier may be sufficient if contaminants, such as toxic organic compounds (e.g., herbicides and pesticides), in use in the region are monitored. Please submit your certification program and relevant data.

87. Please verify that your SOP P-SA-029 establishes adequate withdrawal times for each therapeutic used for treatment of your donor herd. Please submit the revised SOPP to reflect these times.

88. We acknowledge your response of May 1, 2009, that indicates you will immunize horses against ----------(b)(4)----------. Please verify that you will manufacture lots of your product designated for the U.S. market using plasma from vaccinated horses. You should provide immunization protocols to include doses, immunization frequency, and deferral times for horses after immunizations. We will verify immunization records on inspection.

Labeling:

89. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in our "Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products," dated February 2000. This document is available on the internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf or may be requested from the Office of Communication, Outreach, and Development, at (301) 827-1800. For non-PDUFA products, please contact the regulatory

project manager. For details, please also follow the instructions described in CBER's SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants. This document also is available on the internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm, or may be requested from the Office of Communication, Outreach, and Development at the above telephone number.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Debra Cordaro, at (301) 827-6157.

Sincerely yours,

Basil Golding, M.D.
Director
Division of Hematology
Office of Blood Research and Review
Center for Biologics
Evaluation and Research