



**Questions from the Applicant:**

**Clinical, Chemistry, Manufacturing and Controls (CMC)**

**Applicant Question: 1.4.1 Regarding CR letter item 15**

Please set appropriate upper and lower limits -----(b)(4)-----  
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You indicate in your May 1, 2009, response that -----(b)(4)-----  
-----; this  
typically involves manufacturing one conformance lot for each condition.

**Discussion Points:**

----- (b)(4) -----  
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----- (b)(4) -----  
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----- (b)(4) -----  
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Does the Agency agree or have any comment on this?

**FDA Response to Question 1.4.1:**

The Agency finds your proposal to -----(b)(4)-----  
----- plasma scale acceptable. However, please clarify if you are -----  
----- (b)(4) -----  
-----.

**Applicant Question: 1.4.2 Regarding CR letter item 82 [sic]**

Please submit and implement plasma screening procedures, such as those described in 9CFR113.53, 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, provided that the detection assays are sufficiently sensitive for pool testing.

**Discussion Points**

Beyond the current pooled plasma testing (enclosed in -(b)(4)-immune Plasma Specifications) we do not think that further testing is warranted especially since we have validated several orthogonal approaches of viral reduction.

Please let us know if you agree.

**FDA Response to Applicant Question 1.4.2:**

The Agency does not agree with your approach. Ensuring the safety of a plasma-based product requires a multi-tiered approach, including proper vaccination strategies, plasma screening, and validated viral clearance methods.

**Applicant Question: 1.4.3 Regarding Observation Point #2 of 483 Comments**

*Process Validation was not completed. Several examples were given and deficiencies described.*

**Discussion Points**

*We have proposed to perform Process Validation in compliance with a Process Validation Protocol. At the November 19, 2009, Type C meeting teleconference Bioclon presented an outline of their concept of Process Validation for Anascorp. We also noted that we would submit to the Agency the Process Validation Protocol we would follow along with some documentation of the work being done thus far. Enclosed is the Process Validation Protocol and data generated for the pepsin digestion step -----(b)(4)-----  
-----.*

- a. *Does the Agency think this protocol is sufficient to allow the performance and completion of the validation process for Anascorp manufacturing?*
- b. *Is the example of the data presented sufficiently detailed for the parameters presented and a good example of what to do for all other parameters of the manufacturing process?*
- c. *Does the Agency have any other comments?*

**FDA Response to Applicant Question 1.4.3:**

- a. FDA has the following comments/questions about the protocol:

Please indicate what data you used to base the validation intervals for the Critical Process Parameters of your conformance lots.

Will the process you are validating involve mixing different batches of concentrates prior to formulation? If so, how is this addressed in the validation plan?

Please indicate if the values listed in Table 3 Target Operating Parameters and Acceptable Ranges Determined for -----(b)(4)----- (page 4 of “Examples of Data Generated”) will be incorporated into the batch record and used during the manufacture of the conformance lots.

On page 15 of 44, the manufacture of Anascorp ends with the terminal Sterile Filtration step. Please note that the filling and lyophilization processes will also need to be validated and this information included in the BLA.

On page 31 of 44, the list of steps where critical process parameters will be determined ends with -----(b)(4)----- . Please include the critical process parameters for the final sterile filtration and fill and provide validation data for these manufacturing steps.

The protocol should have a section where it notes that all of the equipment, utilities, facility, etc., qualification (I/O/PQ as applicable) has been performed prior to the process validation being performed.

Please comment on when the batch records for the validation lots (lots used for process validation) may become available for review?

- b. Yes, this is acceptable.
- c. This is not an all-inclusive list of questions or comments. Additional questions and comments may arise after reviewing the submission in its entirety. Manufacturing process validation is only a part of manufacturing under CGMPs.

Please note that mixing studies must be performed for the tank to establish the time and speed required to consistently obtain complete dissolution and homogeneity of the content. Therefore, instructions such as “----- (b)(4) -----” should not be used in lieu of defined mixing parameters. Also, please ensure the instructions in the batch record are quantitatively defined for all steps

Please indicate why -----(b)(4)----- was not considered a critical process parameter for -----(b)(4)----- .

All hold times will need to be validated as well as time intervals for each manufacturing step.

Please note that in addition to filter cleaning and storage procedures, the filter qualification should also include leachables and extractables, studies, if applicable

Please explain the filtration process where filters of -----(b)(4)----- size are used. Please clarify if one of the filters is used in the process or if all the filters are used. The filters are listed in numerous process steps in the validation, for example, page 13/44 Preparation of -(b)(4)- step.

For the “Preparation of -(b)(4)-” step (page 13 of 44), please comment on why the mixing step is being performed -----(b)(4)----- .

On page 15 of 44, Section XIV Nanofiltration, the sentence that starts “---(b)(4)-----” is incomplete. Please revise this sentence to make it complete. Please clarify if -----(b)(4)----- are being used in this step.

On page 15 of 44, Section XV Terminal Sterile Filtration, please describe in more detail how the filter integrity test is being performed on the -(b)(4)- filters used. In addition, please provide the name of the manufacturer of the filters and provide a description of how the specification of greater than -(b)(4)- was established for the filter integrity test.

On page 30 of 44, Section I Formulation, the list of critical process parameters does not list mixing speed or time. Will a mixing qualification be performed for the mixing of the excipients?

On page 33 of 44, Section 2 -----(b)(4)-----, please describe how an -----(b)(4)-----  
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**Clinical**

**Applicant Question: Regarding CR letter item 77:**

*In the 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, though September 23, 2006, a span of 16 months, together with a Statistical Report covering the period of 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.*

**Discussion Point**

*After discussion with the FDA during the November 19, 2009 teleconference, the Agency suggested in order to evaluate the safety data for the package insert, an integrated safety update would be need. They indicated that it would be best to update all safety data with a cut-off date of June 2009.*

*After review and further consideration, we suggest that we provide the Agency with the following safety information to support an up-to-date report containing all new data through June 2009, along with comparisons/integration of all other studies safety data.*

*We will prepare a new study report with a single set of analysis for study AL-03/07 containing all data from August 08 to June 09. This would comprise approximately 836 patients (554 patients in BLA submission plus approximately 282 patients from June 08 to June 09). We will update and prepare safety tables and listings for this dataset.*

- *Comparison of this data with critical safety tables for all other studies which will comprise approximately an additional 109 patients.*

*We propose to update the following tables from the ISS. Please see the enclosed Tables, 5.3.1.a and 5.3.1.b. We also propose to update Table 5.3.2. a listing of "Adverse Events Reported in > 1% Patients, by Frequency" and create another table for "Adverse Events Reported in >5% of Patients, by Frequency".*

*We wish to discuss this proposal with the Agency and obtain feedback on its suitability.*

**FDA Response to Applicant Question 1.4.4:**

During the teleconference of November 18, 2009, FDA acknowledged that it would take time for Bioclon to organize data for safety update for studies AL-03/07 and for the integrated summary of safety and tentatively agreed upon Bioclon's proposed date for data cutoff as being June 2009. However, FDA subsequently determined that it is not reasonable to set a cutoff date ahead of knowing Bioclon's timeline for responding to the complete response (CR) Letter. Thus, FDA included in the minutes to the aforementioned teleconference this Post-Meeting Comment:

- If the date of resubmission is delayed, the cutoff date for the integrated safety report must be adjusted to no more than 90 days prior to resubmission.

Should Bioclon have difficulty in meeting this cutoff, please explain in detail your needs in organizing the additional safety data for resubmission in response to the CR Letter, and how that will impact the time frame for data cutoff.

Question 1.4.4 asks for feedback on comparison of data from AL-03/07 (836 patients) with critical safety tables for all other studies (109 patients), including:

- An adverse event summary table (Table 5.3.1.a)
- An adverse event frequency table to show individual items and subject ID, as well as intensity and relatedness of the events (Table 5.3.1.b)
- Updated listing of adverse events reported in >1% of patients, by frequency (Table 5.3.2) in >5% of patients, by frequency (new table)

Although these tables are acceptable, you should provide analysis of the data with respect to product exposure (actual dose and dose per body weight, etc.), concomitant medication use, and patient characteristics (age, sex, race, etc.), and if there has been a formulation change, you should identify the data with respect to formulation as well.

The safety data are not to be confined to adverse event frequencies, but also include vital signs, physical examination, clinical laboratory findings, and any other results from pertinent investigations or observations.

Please submit listings of deaths, serious adverse events, study withdrawals from adverse events, and interruption/dose reduction for product administration, as well as pertinent case report forms.

The above list is not meant to be all-inclusive. Please provide any post-marketing safety data from countries in which the product is licensed, if available.

Please include in your submission all data listing in SAS transport files (.xpt format).