



Meeting Response Memorandum

Our Reference: CRMTS #8670
STN 125389/0/45

Division of Blood Applications

TODAY'S DATE: September 5, 2012 **PAGES:** 4

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SUBJECT: FDA Response to Sponsor Questions

PRODUCT: Immune Globulin Intravenous (Human)

We completed our review of your information package for Immune Globulin Intravenous (Human) and are providing the following responses to the questions you posed in the package. Although we continue to reserve September 10, 2012, 3:30pm-5:00pm for a face-to-face meeting with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us as soon as possible so that we may clear the meeting time. Alternatively, if you have questions regarding specific responses or advice, please inform us so that the appropriate members of the review team can provide clarification during the reserved meeting time.

THANK YOU

Questions from Sponsor:

Chemistry, Manufacturing and Controls (CMC)

CR item 1:

The validation of your Test Methods remains incomplete in that a proposal for the testing of (b)(4) (b)(4) of Bivigam has not been agreed to and finalized. This would involve the validation of a (b)(4) test or similar assay.

Sponsor Question 1:

Is the updated validation plan and test method modifications described for the (b)(4) (b)(4) assay at (b)(4) acceptable as provided? If not, what specific changes need to be made?

FDA Response to Question 1:

As discussed in our teleconference of August 23, 2012 your current validation plan is acceptable. We agreed that you may use FDA supplied (b)(4) standard as an interim benchmark for low (b)(4) to develop your own in house (b)(4) standard, which should be formulated similar to your Bivigam product with a comparable level of activity to the FDA supplied (b)(4) material. It is the agency expectation that your validated assay should include the use of the new NIBSC standard and that you will set your interim release criteria based on the testing data of your manufactured Bivigam lots using your validated assay.

Sponsor Question 2:

Does this lot release protocol and specifications fulfill the FDA's requirements for Bivigam? If not, what are the specific requirements to finalize the lot release protocol?

FDA Response to Question 2:

Your lot release protocol appears to be acceptable however the final decision will be made by DPQ/OCBQ and PRB/DMPQ/OCBQ during the next review cycle.

Sponsor Question 3:

Biotest would like to understand in more detail the FDA's methodology for performing (b)(4) lot release on existing products? What standards are the FDA using?

FDA Response to Question 3:

As part of our discussion during and our follow up to the teleconference of August 23, 2012, the Division of Hematology has supplied your firm with our current assay protocol, some samples of benchmark material with low (b)(4), and as much technical advise as possible.

CR Item 2:

The viral clearance studies performed to support the adventitious agent removal/inactivation capabilities of your manufacturing process are inadequate as the assays used have not been fully validated. In order to complete the validation of your (b)(4) Assay, you must complete bridging studies between the (b)(4) format and the (b)(4) format for SinV and SV40 viruses.

Sponsor Question 4:

Does FDA agree with this approach?

FDA Response to Question 4:

The approach is considered acceptable by the agency.

CR Item 3:

Your reported bioburden results in your cleaning validation report exceeded the revised acceptance limit of (b)(4) for (b)(4). Please provide additional validation studies for the (b)(4) to support that your cleaning procedures are capable of reducing bioburden to meet the acceptance limit.

Sponsor Question 5:

Does FDA agree with this approach?

FDA Response to Question 5:

Revalidation for all (b)(4) is not necessary. Please complete your investigation of the single failure, perform additional runs post CAPA for this (b)(4) as appropriate, and submit the information for review.

CR Item 4:

We noted that the (b)(4) solution interfered with your (b)(4) testing performed for the (b)(4) cleaning validation, and prevented you from demonstrating the ability of your cleaning process to remove product residual. Please perform residual protein analysis on (b)(4) post-cleaning rinse samples with appropriate acceptance criteria, and submit the data for review.

Sponsor Question 6:

Does FDA agree with this approach?

FDA Response to Question 6:

Please recall that this issue was originally agreed to be a PMC. Since there were other issues requiring a complete response, this issue was added to the list of CR questions. Therefore, implementation of the residual protein analysis assay will be sufficient, provided you meet acceptance criteria.

Sponsor Question 7:

Biotest requests the FDA confirm that there are no other pending issues to prevent the approval of Bivigam.

FDA Response to Question 7:

To our current knowledge, there are no additional issues pending. We will notify you if any new issues arise from review of your responses to the CR letter.

END.