



Official Meeting Summary

Meeting ID #: CRMTS #8670
Application type and number: STN 125389/0
Product name: Immune Globulin Intravenous (Human)
Sponsor: Biotest Pharmaceuticals Corporation (Biotest)
Meeting type: Type A
Meeting category: Other
Meeting date & time: September 10, 2012, 3:30 p.m. - 5:00 p.m.
Meeting format: Face-to-face
Meeting Chair/Leader: Michael Kennedy, Ph.D.
Meeting Recorder: Pratibha Rana, M.S.

FDA Attendees:

Howard Chazin, M.D., Deputy Director for Medical Affairs, OBRR/DH
Mitchell Frost, M.D., Medical Officer, OBRR/DH/CRB
Dorothy Scott, M.D., Chief, OBRR/DH/LPD
Mikhail V. Ovanesov, Ph.D., Visiting Scientist, OBRR/DH/LH
Michael Kennedy, Ph.D., Biologist, OBRR/DH/LPD
Pratibha Rana, M.S., Regulatory Project Manager, OBRR/DBA

Biotest Attendees:

Gary Ingenito, M.D., Ph.D., Vice President, Clinical and Regulatory Affairs
Jordan Siegel, CEO, Biotest Pharmaceuticals Corporation
Herman Keuper, Ph.D., Vice President, Manufacturing and Engineering
Janice Smith, Vice President, Quality Operations and Materials Management
Eckhard Flechsig, Ph.D., Director, Global Research Bioanalysis
Matthias Germer, Ph.D., Senior Director, Research Plasma Proteins

Background and Objectives:

Biotest submitted a meeting request on August 23, 2012 to discuss the Complete Response letter dated August 6, 2012. The pre-meeting materials were submitted on August 23, 2012.

FDA provided its proposed responses to the Sponsor's questions on September 5, 2012. After reviewing the proposed responses, the Sponsor notified FDA on September 6, 2012 of its decision to proceed with the agenda as planned.

Questions from the 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)----- 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)----- 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.

Additional Discussion:

FDA reiterated that Biotest's current validation plan is acceptable. FDA recommended an initial alert level limit based on manufacturing capabilities but prefers it to be below the (b)(4) sample provided by CBER as (b)(4) represents an IGIV sample with a low level of ---(b)(4)-----, which is regarded as being reasonably safe.

FDA advised Biotest that they should establish an initial alert limit, validate their test, evaluate process parameters for the licensed product, then develop a retest algorithm with a lower alert limit. FDA also notified Biotest that there will be postmarketing commitments regarding the retest algorithm.

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.

Additional Discussion:

FDA notified again the final decision will be made by DPQ/OCBQ and PRB/DMPQ/OCBQ.

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 in 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.

Additional Discussion:

This question was not discussed during this meeting.

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.

Additional Discussion:

FDA stated that any other issues and missing data will be resolved by postmarketing commitments.

CR Item 3:

Your reported bioburden results in your cleaning validation report exceeded the revised acceptance limit of -----(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.

Additional Discussion:

Biotest informed FDA that they will submit all bioburden and cleaning validation data from all ---(b)(4)---.

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

Additional Discussion:

This question was not discussed during this meeting.

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.

Additional Discussion:

FDA requested Biotest submit revised dates for the clinical postmarketing commitments in the complete response submission. FDA stated that the complete response submission will have a two month review clock. Biotest notified FDA of their intention to submit their response by early October.

Action items:

None.

Attachments:

None.

END