



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research**

Date: July 31, 2012

To: To File (STN 125389/0)

From: Michael C. Kennedy, Ph.D., LPD/DH/OBRR, HFM-345

Through: Dorothy E. Scott, M.D., Chief, LPD/DH/OBRR, HFM-345

CC: Pratibha Rana, RPM, CBER/DBA, HFM-370

Applicant: Biotest Pharmaceuticals Corp. (BPC)

Product: Immune Globulin Intravenous (Human)
Trade name: BiviGam®

Subject: Chairs Final Review - Biotest Complete Response to the CR Letter of April 26, 2012

Recommendation

This BLA submission is recommended for a Complete Response Letter with the following Items:

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.
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.
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.
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.

Background Summary

This Original Biologics License Application (BLA) submission from Biotest Pharmaceuticals Corporation (BPC) was submitted on November 3, 2010 and is for a new intravenous 10% human immune globulin with the proposed trade name, “Bivigam™” and is indicated for the treatment of Primary Immune Deficiency Disorders. Bivigam is a sterile 10% protein solution formulated in (b)(4) mM glycine, (b)(4) mM NaCl, and (b)(4) polysorbate 80 at pH 4.0-4.6, without any sugar stabilizer, or albumin. Bivigam is manufactured from US Source Plasma (----(b)(4)-----) by a modified Cohn-Oncley cold alcohol fractionation process and with two added viral inactivation steps - solvent/detergent treatment (Triton X-100/tri-n-butyl phosphate) and nanofiltration (35 nm filter). The manufacture, in-process testing, and the majority of the final product release testing, are performed at the BPC Boca Raton, FL facility. Filling into final container vials is performed under contract at -----(b)(4)----- . The proposed shelf life of Bivigam is 24 months, stored at 2-8 °C.

The sponsor planned to perform facility upgrades during the initial review period for this BLA and these upgrades caused a number of delays – local building permit issues substantially slowed plant construction, the sponsor had to scrap scheduled conformance runs in order to -----(b)(4)----- , equipment failures forced the sponsor to re-validate their newly installed -----(b)(4)----- . These facility upgrade issues were discussed with the agency during pre-BLA meetings and because the upgrade was planned to be performed in 2 phases CBER required that BPC perform 2 sets of 2 conformance lots each with one set after Phase 1 and one set after Phase 2 facility changes. Because of these facility related delays the firm could not complete the manufacture of the second set of conformance lots which resulted in a 24 item CR Letter being sent to BPC on September 1, 2011. The sponsor responded to the CR letter on October 26, 2011 and because of the large number of CR issues a six month review clock was granted for the second review cycle. At the conclusion of the second review cycle there were a number of issues which could have been resolved by post-marketing commitments but the DMPQ reviewer (Destry Sullivan) had several items that could not be resolved by PMC. The product office felt the BPC lack of an in place ----(b)(4)----- Test in order to provide adequate assurances that product with ----(b)(4)----- would not be released represented an issue that would not allow approval of this BLA to move forward. Additionally, the viral clearance studies remain incomplete as bridging studies for several viruses still need to be submitted. So a second CR Letter containing 7 unresolved issues was sent to the sponsor on April 26, 2012. The sponsor responded to this Complete Response Letter on June 6, 2012, and because the issues were somewhat limited the sponsor requested that it be classified as a Class I review and given a 2 month review cycle which was granted. However, the review of this latest response found that it contained some problematic deficiencies which could not be resolved during the allowed review time and will require the issuance of a third Complete Response Letter.

Review Disciplines

CMC – Margaret Norton, Douglas Frazier, Liza Virata, Pei Zhang (viral clearance), Lilin Zhong (co-chair), Michael Kennedy (chair); CMC reviewers have 2 CR items related to test methods and assay validation. BPC has not yet provided a validated -----(b)(4)----- Test method which it could use to monitor the ----(b)(4)----- levels of Bivigam. The earlier review of the viral clearance was thought to be complete but later conflicting information supplied by the sponsor has re-opened this issue. There also remain some lesser issues related to deficiencies in process validation, extractable/leachables testing, and follow-up clinical studies which will be the subject of----- (b)(4)----- .

DMPQ – Rebecca Olin was the DMPQ reviewer for the first review cycle and contributed 14 items to the first CR letter. The complete response from BPC was reviewed initially by Pete Amin but transferred in

March, 2012 to Destry Sullivan whose review found unresolved issues related to the validation of equipment, cleaning methods, shipping, and visual inspection.

BIMO – Lillian Ortega; The results of Bioresearch Monitoring inspections of four clinical sites did not reveal problems that impact the data submitted in the application. The BIMO review is complete and no unresolved issues remain in this area.

Statistical – Jessica Kim; the statistical review found that Bivigam met the primary efficacy and safety objectives of their submitted studies and met the requirement recommended by the FDA: by demonstration of one sided upper 99% upper confidence limit for the rate of SBIs per person-year is less than 1 for efficacy and one-sided 95% upper confidence limit for the proportion of infusions with one or more temporally associated AEs is less than 40%. The statistical review is complete and no unresolved issues remain in this area.

OBE – Craig Zinderman, Scott Winecki; The OBE review determined that the supplied clinical study identified no new safety signals and the sponsor's plan for routine pharmacovigilance activities including specifically monitoring and reporting on IGIV class effects was acceptable. However, OBE agreed with the Toxicology recommendation that the sponsor should conduct a post-market safety study to further assess the risk of hypotension.

APLB – Alpita Popat; the APLB review found the proprietary name Bivigam to be acceptable and proposed numerous changes to the packaging, labeling, and PI. These revisions were supplied to BPC and the firm has not accepted and implemented these revisions.

PK – Harold Boxenbaum; the PK review is complete with the finding that submitted studies were acceptable and no unresolved issues remain in this area

Toxicology – Evi Struble; The toxicology review is complete with the finding that submitted studies were acceptable and no unresolved issues remain in this area. The primary Toxicology issue was that the high levels of PS80 found in the product possibly represent a risk of hypotension and this issue will be addressed via a post-marketing study requirement.

Clinical – Mitch Frost; The clinical review found that sponsor had successfully met the clinical endpoints for safety and efficacy but agreed with the toxicology review that the high levels of PS80 found in the product possibly represent a risk of hypotension. The reviewer recommended that Bivigam be approved for the proposed indication and that the issue of potential hypotension due to PS80 be addressed via a post-marketing study requirement.

Inspectional issues

Inspectional issues were not present in the BLA because under SOPP 8410 DMPQ determined that a preapproval inspection was not needed since the facility was the subject of a Team Bio cGMP inspection in November 2010 which was designated VAI. However, there was a DMPQ preapproval inspection of the contract filler (b)(4) since this firm had no prior CBER inspection history (it had been previously inspected by CDER). This PAI was conducted by Rebecca Olin and Grace Deneke of DMPQ on -----
----(b)(4)----- under another supplement (STN 103945/5308) which requested the use of (b)(4) as the contract filler for BPC's licensed Hepatitis B Immune Globulin product (Nabi-HB[®]). The PAI resulted in a 10 item 483 which was responded to appropriately by the sponsor and (b)(4) received approval to fill Nabi-HB on June 9, 2011.

Two Team Bio inspections have taken place at the Biotest Boca Raton facility since this BLA has been filed. Both inspections were classified VAI but contained several 483 citations which were similar to the review issues with cleaning validation and process validation.

Manufacturing Overview

The following manufacturers are involved in the production of Biotest-IGIV:

Site	Responsibility
Biotest Pharmaceuticals Corporation 5800 Park of Commerce Blvd, NW Boca Raton, FL 33487	----- (b)(4) ----- ----- ----- (b)(4) ----- -----
----- (b)(4) ----- ----- ----- (b)(4) -----	----- ----- (b)(4) ----- -----

Biotest-IGIV bulk drug substance is manufactured from source plasma following a modified Cohn-Onclay cold alcohol fractionation process with three added viral reduction steps. After fractionation, the ----- (b)(4) ----- undergoes virus inactivation/removal, further purification and formulation into bulk drug substance. BDS production is an ---- (b)(4) ---- step manufacturing process which is briefly identified as following:

[(b)(4)]

Final drug product sterile filtration and fill is conducted at -----

----- (b)(4) -----
-----, After filling the product is either stored at 2-8 °C or sent for visual inspection. A 100% visual inspection is conducted but the submission does not indicate what method of inspection is used. Vials are labeled and packaged and sent to BPC for storage and final distribution.

Recommendation

BPC has a number of outstanding issues to complete before approval of this BLA could be recommended as such a Complete Response Letter should be sent to the sponsor.