



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

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**Date:** April 20, 2012

**To:** To File (STN 125389/0)

**From:** Michael C. Kennedy, Ph.D., LPD/DH/OBRR, HFM-345 By Michael C. Kennedy at 3:38 pm, Apr 24, 2012

**Through:** Dorothy E. Scott, M.D., Chief, LPD/DH/OBRR, HFM-345 By Mahmood Farshid at 5:15 pm, Apr 24, 2012

**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 September 1, 2011

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**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. Your Testing Plan and Lot Release Protocols have not been finalized.
  - b. 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 demonstrate experimentally that virus would be detected at the theoretical limit of detection in a (b)(4) format when the assay is used for the following viruses: HIV, PRV, BVDV, SinV, and SV40.

3. (b)(4)

4. You have not included in your 100% visual inspection program for Biotest IGIV, as previously requested, a complete description of the defect set used to qualify (b)(4) inspectors for Biotest IGIV final product, nor have you submitted all validation data supporting (b)(4) 100 % visual inspection program for this product. Please submit both a complete description of the defect set, and all supportive validation data.
5. Cleaning validation is not adequate in that:
  - a. Your use of a (b)(4) cleaning validation limit of (b)(4) is not appropriate for cleaning validation for equipment utilized in downstream process steps (b)(4), as use of this criterion would allow carryover of residual cleaning agents. Please reevaluate use of this cleaning validation acceptance criterion, select a criterion that would not allow for significant carryover of cleaning agent, and submit validation data demonstrating that you can meet the new acceptance criterion.
  - b. Your cleaning validation acceptance criteria do not reflect cleaning process capability, as actual values observed during validation were well below set acceptance criteria. Please evaluate actual data obtained during cleaning validation studies, and set cleaning validation acceptance criteria that reflect your process capabilities.
  - c. Your use of a family approach to cleaning validation allows for introduction of equipment that has not yet been evaluated for cleanability, in that you do not perform at least one cleaning validation run for each equipment within each family. Please perform at least one cleaning validation run for the following equipment: (b)(4) (b)(4), and certain miscellaneous equipment ( (b)(4) (b)(4) etc.) and submit the results of these runs for review.
6. You have not performed a bulk drug product shipping validation study that utilizes actual shipper, containers, and modes of transportation normally employed to transport product. Please perform the study and submit the results for review.
7. The toxicology assessment of the (b)(4) does not contain an assessment of the potential human exposure to the leachables from the (b)(4). Please submit a toxicological assessment that includes a worst case scenario exposure of human subjects to these compounds and demonstrates that, even at these exposures, appropriate safety factors are in place to ensure safety of all subjects.

## **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) (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 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 produce their Nabi-HB product 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 this review cycle there are a number of issues which could be resolved by post-marketing commitment 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 high (b)(4) would not be released represented an issue that would not allow approval of this BLA to move forward. Additionally, it came to light only weeks before the action due date that much of the information regarding the viral clearance studies supplied in the BLA was in fact incorrect. Therefore, the review of this BLA will require the issuance of a second Complete Response Letter as there are several CMC and facility related issues which remain to be resolved.

### **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 study and met the requirement recommended 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 reviewer has 1 CR item related to issues of toxicological assessment for the extractable/leachables studies performed by BPC.

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) (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.

**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)

Biotest-IGIV bulk drug substance is manufactured from source plasma following a modified Cohn-Oncley 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)

(b)(4)

**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.