



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

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**Date:** August 26, 2011  
**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 Memo for BLA

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**Recommendation**

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

1. The previously agreed to second set of two additional conformance lots remain to be manufactured. Once these lots have been manufactured please supply the following:
  - a. Release-test data
  - b. Comparability data for these conformance lots to previous production lots made before the ongoing facility and equipment changes were initiated
  - c. Stability data for all four of your conformance lots including the anti-measles titers
2. The validation of your manufacturing process remains incomplete. Please provide the following:
  - a. Final validation reports for the Phase II equipment upgrades
  - b. Final validation reports for the -----(b)(4)-----  
----- (CBER acknowledges that these reports were submitted on August 18, 2011 which was to late for the review to be completed during this review cycle)
  - c. Process robustness study data covering the outer limits of the -----  
----- (b)(4)-----.
  - d. Validation studies on bacterial growth promotion of -----(b)(4)-----  
-----.
3. The validation of your Test Methods remains incomplete in that:
  - a. The proposed --(b)(4)--- assay ((b)(4)) to test the anti-Diphtheria potency of Bivigam does not meet CFR requirements. CBER recognizes that BPC has agreed to change the testing

- method to the recommended -----(b)(4)----- assay as per the -----  
 --(b)(4)-----, but this change has not been finalized.
- b. Your ---(b)(4)--- test method needs to be validated, preferably prior to the manufacture of the second set of conformance lots. The specification for ---(b)(4)--- (with minimum and maximum limits) remains to set for the final drug product.
  - c. The -----(b)(4)----- Hepatitis A Virus -----(b)(4)----- Assay does not have an acceptable level of sensitivity for all three HAV genotypes and their subtypes.
  - d. The Particulate Matter test (SOP STP0011) performed by -----(b)(4)----- has not been validated.
  - e. The method SOPs and method validation reports related to the -----  
 -----(b)(4)----- .
  - f. Your Testing Plan and Lot Release Protocols have not been finalized.
  - g. A proposal for the testing of -----(b)(4)----- of Bivigam has not been submitted and agreed to. This would involve the validation of a -----(b)(4)----- test or similar assay.
4. The labeling and packaging for Bivigam remain to be finalized.
  5. The amount of PS80 administered in a labeled dose of Bivigam has been associated with hepatic or renal failure (Giannattasio F, et al PubMed id:12402666; Rhodes A et al, PubMed id: 8491409). Please submit a proposal to address these concerns postmarketing. Alternatively, you may consider reducing the amount of PS80 in your final formulation.
  6. Please submit a toxicological assessment on the clinical safety of glycine.

**The following comments are from the Division of Manufacturing Product Quality:**

7. According to Validation Report VP-FR-3530, “Final Report for Performance Qualification of the IGIV ----(b)(4)---- Process,” (Section 3.2.S.2.5) bioburden test results exceeded acceptance criteria at the -----(b)(4)----- steps. You refer to an investigation report (INV6001) but no mention was made of the identification of a root cause. Additionally, it appears that the corrective action was to -----(b)(4)-----  
 ----- steps which resulted in acceptable results. This type of corrective action is unacceptable and represents a deviation to your validated process. Please indicate whether this -----(b)(4)-----  
 ----- is a reprocessing step or it represents a permanent change to your validated process. In either case, you should provide necessary protocol and a summary validation report to include justification why the root cause has not been identified and no preventive action has been taken to address the bioburden deviations.
8. Please provide the following facilities and equipment information for the Biotest manufacturing site:
  - a. Validation summaries for shared and dedicated equipment.
  - b. Validation summaries including system descriptions and data for HVAC, utility systems, and cleaning systems after facility upgrade.
9. With regard to your cleaning, sanitization and sterilization of equipment used at the Biotest facility, please provide the following:
  - a. Validation protocols, summary reports and routine procedures for all equipment used in the manufacture of Bivigam. Include in your response clean and dirty hold times and containment procedures to prevent cross contamination of shared equipment.
  - b. Regarding the (b)(4) system at the Biotest facility (Section 3.2.A.1.3.3.); the bioburden specification of ----(b)(4)---- is high. Similarly, the endotoxin specification is high at ---

(b)(4)-. Both values exceed the limits of the (b)(4) used for final rinsing. Please provide your rationale for these specifications and provide data accumulated from your periodic monitoring program.

10. Please provide validation reports for the -----(b)(4)----- systems used at the Biotest facility.
11. The leachables study performed by -----(b)(4)----- for the -----(b)(4)----- used to transport -----(b)(4)----- from Biotest to ----(b)(4)---- resulted in the detection of leachables in -----(b)(4)----- analysis. You conducted a toxicological risk assessment (-----  
-----  
-----) and concluded that the ----(b)(4)---- can be used without negative impact on ----  
(b)(4)---- quality; however, this report was not included in the submission for review. Please submit the report supporting your conclusions.

**The following DMPQ questions relate to -----(b)(4)-----, the contract fill finish facility specifically for the manufacture of Bivigam:**

12. Please provide a copy of --(b)(4)-- product changeover and line clearance procedures.
13. Please provide Validation Summaries for critical process equipment and utilities at the (b)(4) site (Section 3.2.A.1.1).
14. In section 3.2.P.7 you provide the specifications for the container closure system for the final product but did not provide studies conducted to assure the integrity of the container closure system or to ensure that the vial and stopper are non-reactive with the product. Please provide container closure integrity studies as well as extractable and leachable studies in support of the container closure system.
15. The section for aseptic process simulation (Section 3.2.A.1.4) lacks sufficient narrative to allow a complete evaluation of the process. Please provide the media fill protocol for the relevant filling line, including fill volume, type of medium used, incubation parameters, interventions, growth promotion results and summary reports for media fills. Include in your response the identification of what rooms are covered by the media fills and whether any facility isolates were used during growth promotion testing.
16. Please provide validation summaries for ---(b)(4)--- filter validation.
17. Please indicate the method and procedures used to conduct 100% visual inspection of the final product at the (b)(4) site.
18. The reports submitted to support shipping validation conditions (Section 2.3.R with link to 3.2.R.4) do not provide sufficient enough information. Please provide the following:
  - a. Additional information regarding how this testing was conducted and on what material; BDS and/or final product.
  - b. The contents of the cargo hold during PQ testing. Include how the shipment will be monitored while en route and include an identification of temperature recording devices within a shipment load.
  - c. The rationale for monitoring temperature for only ---(b)(4)--- when transport of the BDS and final filled product would require a much longer cross-country trip.

- d. Data to show the BDS and product temperature range during the “----- (b)(4) -----”.
  - e. The PQ summary shows a “Cargo Hold High Temperature During Test Period” time of (b)(4). Although not stated in the report, it is assumed that the temperature range of the study would mimic the storage requirements of the ----- (b)(4) ----- °C. Please explain why the High Temperature reading did not result in a deviation.
19. Please provide validation summaries of the ----- (b)(4) ----- of materials used in the Bivigam filtration and filling process. Include a description of the (b)(4), a description of the ---- (b)(4) ---- process, ----- (b)(4) -----, biological challenge and routine monitoring procedures.
  20. Please provide validation summaries for the autoclaves used in the Bivigam ----- (b)(4) ----- process. Include a description of the autoclaves, a description of the sterilization process, loading patterns, and routine monitoring procedures.

**The following comments are from the Office of Biostatistics and Epidemiology:**

21. We have reviewed the pharmacovigilance plan (PVP) submitted with the BLA for Biotest Immune Globulin Intravenous (Human) 10%. We agree with your plan for routine pharmacovigilance activities for Bivigam as outlined in the BLA, for most anticipated AEs for IGIVs, and we note your intention to specifically report on IGIV class effects and hypotension. However, you should conduct a post-market safety study to further assess the risk of hypotension.
22. Polysorbate-80 is associated with hypotension in animal models and is present in Bivigam at levels higher than in any marketed IG product. Although there were no clinically significant cases of hypotension or other cardiac adverse events in the clinical trial for Bivigam, Nabi-7101 was too limited in size to exclude a lack of excess risk of hypotension with Bivigam compared to other IGIV treated patients. Please propose a plan for a post-market observational safety study to further assess hypotension risk in Bivigam-treated patients. Please include in your proposal the sample size to be included and a rationale for this size, as well as information that will be collected at baseline, the frequency and methods for follow-up data collection, and the information to be collected in follow-up.
23. You should also collect and analyze the spontaneously reported pharmacovigilance data to specifically examine at-risk populations which were studied in small numbers or excluded from pre-marketing safety studies (children, adolescents, pregnant or lactating women, elderly) and report these results in PAERs or PSURs.
24. Please consider revising your Pharmacovigilance plan to include submission of all spontaneously reported hypotension events as expedited reports for the first 3 years of marketing in the U.S.

**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-Onley 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 review of this BLA has proceeded smoothly from the product office perspective but has been delayed by problems at Biotest's Boca Raton facility. The sponsor planned to perform facility upgrades during the review period for this BLA and these upgrades have 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 Biotest perform 2 sets of 2 conformance lots each with one set after Phase 1 and one set after Phase 2 facility changes.

### **Review Disciplines**

CMC – Margaret Mikolajczyk, Douglas Frazier, Liza Virata, Pei Zhang (viral clearance), Lilin Zhong (co-chair), Michael Kennedy (chair); CMC reviewers have 7 CR items related to deficiencies in process validation, stability data, comparability data, and 7 CR items related to deficiencies in test methods, assay validation. The review of the viral clearance issues is complete and no unresolved issues remain in this area.

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 Biotest in July but the firm has not replied to 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

DMPQ – Rebecca Olin; The DMPQ review resulted in 6 CR items related to deficiencies in process validation, extractable leachables, shipping validation, and 9 CR items related to deficiencies at Biotests contract filler -----(b)(4)-----.

Toxicology – Evi Struble; The toxicology reviewer has 2 CR items related to issues of high levels of PS80 content in Bivigam and the lack of a submitted toxicological assessment on the clinical safety of glycine. The reviewer found based on the nonclinical toxicology data, it is recommended that the BLA be approved for the proposed indication with a post marketing surveillance requirement that the patient population be monitored for cardiovascular, renal or hepatic toxicity. There were no pre-clinical studies submitted with this BLA.

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. However, CRB will have to deal with the remaining labeling issues during the CR review cycle.

**Inspectional issues**

Inspectional issues were not present in the BLA because DMPQ waived the Preapproval Inspection of Biotest’s Boca Raton, Florida facility and the contract filler at -----(b)(4)-----  
---. These inspection waivers were determined by CBER SOPP XXX, because the Boca Raton facility was inspected by Team Bio in November 2010 (I was the product specialist on-site for this inspection) and (b)(4) was inspected by DMPQ in ---(b)(4)---, as part of a submission to Biotest’s Nabi-HB license (STN 103945/5308).

**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)----- . Bulk solution is transported to and received by -----(b)(4)----- where it is stored at --(b)(4)-- until the start of production. -----(b)(4)----- . After the product is filled it is either stored at 2-8 °C or sent for visual inspection [100% visual inspection is conducted]. The product vials are labeled and packaged and shipped to BPC for storage and final distribution.

