



Our STN: BL 125389/0

Biotest Pharmaceuticals Corporation
Attention: Matthew Vaughn
5800 Park of Commerce Blvd. NW
Boca Raton, FL 33487

Dear Mr. Vaughn:

This letter is in regard to your biologics license application (BLA) for Immune Globulin Intravenous (Human), manufactured at your Boca Raton, Florida location and submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in the amendment dated August 18, 2011 (as noted below). After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

Chemistry Manufacturing and Controls (CMC):

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)-----
----- (FDA acknowledges that these reports were submitted on August 18, 2011 which was too 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)-----.
 - e. Please conduct additional validation studies to determine -----(b)(4)----- of
representative batches 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. FDA 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 -----(b)(4)-----
----- remain to be submitted.
 - 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. 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.

5. 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.
6. 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.
7. Please provide validation reports for the -----(b)(4)----- systems used at the Biotest facility.
8. 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 (------(b)(4)-----) 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.
9. Please provide a copy of --(b)(4)-- product changeover and line clearance procedures.
10. Please provide Validation Summaries for critical process equipment and utilities at the (b)(4) site (Section 3.2.A.1.1).

11. 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.
12. 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.
13. Please provide validation summaries for ---(b)(4)--- filter validation.
14. Please indicate the method and procedures used to conduct 100% visual inspection of the final product at the (b)(4) site.
15. 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.
16. 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.

17. 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.

Pharmacology and Toxicology:

18. 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.
19. Please submit a toxicological assessment on the clinical safety of glycine.

Labeling:

20. The labeling and packaging for Bivigam remains to be finalized. We reserve comment on the proposed labeling until the application is otherwise acceptable. We may have comments when we see the proposed final labeling. Should additional information relating to the safety and effectiveness of this drug product become available before our receipt of the final printed labeling, revision of that labeling, may be required.

Office of Biostatistics and Epidemiology (OBE):

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.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in our “Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products,” dated February 2000. This document is available on the internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf> or may be requested from the Office of Communication, Outreach, and Development, at (301) 827-1800. For non-PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER’s SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants. This document also is available on the internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>, or may be requested from the Office of Communication, Outreach, and Development.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Pratibha Rana, at (301) 827-6124.

Sincerely yours,

Basil Golding, M.D.
Director
Division of Hematology
Office of Blood Research and Review

Center for Biologics
Evaluation and Research