**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: File, BL STN 125389/0

From: Rebecca Olin, OCBQ/DMPQ/MRB2, HFM-676

Through: Chiang Syin, Ph.D., Chief, OCBQ/DMPQ/MRB2, HFM-676

Subject: **Review Memo** Biotest Pharmaceuticals Corporation (License #1792) BLA: For the manufacture of a new intravenous 10% human immune globulin (Biotest-IGIV) for the treatment of Primary Immune Deficiency Disorders.

**Action Due: September 3, 2011**

## Recommended Action

A Complete Response Letter will be issued to the firm.

## Product

Immune Globulin Intravenous Human 10% (Biotest-IGIV)

## Summary

Biotest submitted this BLA in support of the manufacture of Immune Globulin Intravenous Human 10% (Biotest-IGIV) at the Boca Raton, FL facility, and sterile filtration and filling of the final product at ----------(b)(4)----------.

Biotest is submitting this BLA based on a two phase submission approach where Phase I entails the initial submission of two conformance lots produced after facility, process, and manufacturing equipment upgrades followed by Phase 2 where a second set of conformance lots will be produced after additional facility and utility upgrades. Biotest and FDA agreed that an amendment to the BLA could be submitted approximately 4 months after the initial BLA submission. This 2+2 strategy was recommended by FDA and was based on the fact that Biotest's IGIV product is not a novel product and its manufacture uses well-characterized equipment, processes and excipients.

-----(b)(4)------- facility was recently approved under BL STN 103945/5308 as an additional drug product contract manufacturer for sterile filtration and filling of Biotest's Nabi-HB product. The formulation and filling of Biotest-IGIV at ----------(b)(4)----------. The narrative provided for (b)(4) in the submission did not address the differences in manufacture between Nabi-HB AND Biotest-IGIV.

However, Biotest has only completed the first phase of facility improvements to date. The changes included ----------

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

Upgrades are being implemented currently after which the second set of conformance lots will be manufactured and submitted in an amendment to the BLA. These changes include: ----------(b)(4)----------.

On May 9, 2011 Amendment 9 was submitted to the BLA notifying CBER that Biotest was experiencing problems with the new ----------(b)(4)---------- and that they anticipated another -(b)(4)- delay before manufacturing could resume.

**CR Questions**

1. 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)---------- and ----------(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.

2. 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.

3. 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 Biotest-IGIV. 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.

4. Please provide validation reports for the ---------(b)(4)---------- and the (b)(4) systems used at the Biotest facility.

5. The leachables study performed by --------(b)(4)---------- for the ----(b)(4)----- used to ----------(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.

**The following questions relate to ----------(b)(4)----------, the contract fill finish facility specifically for the manufacture of Biotest-IGIV.**

6. Please provide a copy of -(b)(4)- product changeover and line clearance procedures.

7. Please provide Validation Summaries for critical process equipment and utilities at the -(b)(4)- site (Section 3.2.A.1.1).

8. 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.

9. 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.

10. Please provide validation summaries for ---(b)(4)--- filter validation.

11. Please indicate the method and procedures used to conduct 100% visual inspection of the final product at the -(b)(4)- site.

12. The reports submitted to support shipping validation conditions (Section 2.3.R with link to 3.2.R.4) do not provide enough information for review. 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.

13. Please provide validation summaries of the -----(b)(4)-------- of materials used in the Biotest-IGIV 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.

14. Please provide validation summaries for the autoclaves used in the Biotest-IGIV ------(b)(4)---------- process. Include a description of the autoclaves, a description of the sterilization process, loading patterns, and routine monitoring procedures.

## REVIEW NARRATIVE

### Product Information

Biotest-IGIV is a ready-for-use sterile 10% (100 mg/mL) protein solution for intravenous infusion containing highly purified and concentrated human immunoglobulin G (IgG) antibodies. The product is supplied in 50 and 100 mL (b)(4) clear ----(b)(4)---- glass vials with gray ----(b)(4)---- rubber stoppers and aluminum seals with plastic flip off caps. All containers and materials used in processing are latex free. Biotest-IGIV is indicated for the treatment of Primary Immune Deficiency Disorders associated with defects in humoral immunity such as X-linked agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

**Manufacturing Overview**

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

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

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

**Bioburden and Endotoxin**

The following is a list of steps where bioburden and endotoxin testing is conducted during BDS manufacture along with the specifications for that step:

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

----------(b)(4)----------
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5 pages redacted (b)(4)

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

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

----------**(b)(4)**----------

----------(b)(4)---
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----------(b)(4)----------
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----------(b)(4)----------
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## DRUG PRODUCT

-------(b)(4)--------, the contract filler for Biotest-IGIV is located in ------(b)(4)--------. Biotest-IGIV will be sterile filtered and filled in Building (b)(4) which is comprised of ----------(b)(4)----------.

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

**Utilities**

Critical utilities, equipment and systems used to support Biotest-IGIV in Building (b)(4) include the following:

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

----------(b)(4)----------:

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

Only a system description and preventive maintenance schedule were provided. No validation data was provided. **See CR #7, 13 & 14.**

**Container Closure System**

Biotest-IGIV will be filled in 50mL and 100mL vials. The 50 mL vial is a --------(b)(4)--------- clear glass serum bottle ----------(b)(4)----------. These vials are manufactured by ----------(b)(4)----------. The 100 mL vial is a ---------(b)(4)---------- clear (b)(4) vial also ----------(b)(4)----------. The vials are manufactured by ----------(b)(4)----------. The stopper is a 20 mm finish serum stopper, ----(b)(4)---- rubber formulation ----------(b)(4)--------- with ----------(b)(4)----------. Both the 50 and 100 mL vials use the same stopper. The stoppers are manufactured by ----------(b)(4)----------. The seals are 20 mm finish, aluminum seal with a white plastic flip-off cap, manufactured by ----------(b)(4)----------. No container closure integrity studies are referenced. Also lacking are extractables and leachables studies for the vials and stoppers. **See CR #8.**

**Aseptic Process Validation**

A brief overview of how media fills are conducted was provided. No discussion of actual media fills and their results was provided. **See CR #9.**

**Sterile Filtration**

Final sterile filtration is conducted using ----------(b)(4)---------- validation was provided. **See CR #10.**

**Visual Inspection**

A 100% visual inspection is conducted on final filled product but the submission does not provide any further information including what method of inspection is used. **See CR #11.**

**Shipping Validation**

Two reports were provided in the submission that appear to be non-specific studies conducted by (b)(4) for an undefined shipping container referred to as CR3079. The first report is an IQ/OQ report in which empty chamber studies were conducted at ----------(b)(4)----------. Hot and cold spots were identified but without a description of what is being tested and evaluation of the data is not possible. The PQ report explains that temperature data will be gathered from the cargo hold of loaded trucks during temperature controlled shipments but does not mention what the trucks are loaded with, the location of temperature monitoring devices, product loading patterns or 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. **See CR #12.**

**History**

Review Initiated: November 19, 2010
Review Completed: August 19, 2011
Telecon Date(s): None