



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

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**To:** To File (BLA STN 125389/0)  
**From:** Douglas J. Frazier, Biologist, CBER/DH/LPD/HFM-345  
**Through:** Dorothy Scott, MD, Chief, CBER/DH/LPD/HFM-345  
**CC:** Pratibha Rana, RPM, HFM-380  
**Applicant:** Biotest Pharmaceuticals Corporation  
**Product:** Immune Globulin Intravenous (Human)  
Trade name: Bivigam  
**Subject:** Midcycle Review: original BLA: new IGIV product

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**Recommendation**

This original BLA submission is recommended for the following Information Requests:

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2. -----  
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4. ----- (b)(4) -----  
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5. Please submit any further final-product stability data that has become available.

6. Please assay --(b)(4)-- titers in retained samples of Bivigam lots that were used in the clinical and stability studies. Please submit those results as well as information on the initial --(b)(4)-- titers, the ages of the lots, the storage conditions for these lots, and the storage conditions in which these clinical samples were kept.

## **Background Summary**

Biotest-IGIV 10% is a ready-for-use, sterile solution containing highly purified and concentrated human IgG antibodies. It is prepared from plasma donated by healthy qualified plasma donors. The plasma is processed using a modified Cohn/Oncley cold-alcohol fractionation process with two added viral reduction steps (solvent/detergent incubation and 35-nm ---(b)(4)--- filtration). Biotest-IGIV 10% contains  $100 \pm 10$  mg/mL protein, of which at least 96% is Human Immunoglobulin, is formulated in 100-140 mM sodium chloride, 200-290 mM glycine, and 0.15 – 0.25% polysorbate 80, pH 4.0 – 4.6, without preservatives. 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. “----- (b)(4)-----are latex free.”

Biotest-IGIV 10% is indicated for the treatment of PIDD associated with defects in humoral immunity. These include, but are not limited to, congenital X-linked a gammaglobulinemia, common variable immuno-deficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Biotest-IGIV is manufactured at Biotest Pharmaceuticals Corporation, 5800 Park of Commerce Blvd., N.W., Boca Raton, FL 33487. Filling into final container is performed at -----(b)(4)-----.

Biotest Pharmaceutical Corporation (BPC) was founded on 04 Dec 2007 after the purchase of the former Nabi Biopharmaceuticals Plasma Therapeutics manufacturing facility in Boca Raton, FL by Biotest AG of Dreieich, Germany. Biotest acquired full rights to Nabi-HB® as well as a number of INDs and preclinical assets. One of the assets acquired was an ongoing clinical trial for an IGIV therapy: Investigational New Drug Application 13353, submitted 13 Apr 2007; Protocol Nabi-7101, “*Open Label, Phase III Safety, Efficacy, and Pharmacokinetic Study of Nabi-IGIV 10% Immune Globulin Intravenous-Human in Subjects with Primary Immune Deficiency Disorders (PIDD).*” Biotest completed the clinical study for the IGIV product on 24 Jul 2009.

Biotest states that it has completed the first phase of a 2-phase plan to improve the IgG manufacturing facility. In the first phase (Jan 2009 through Dec 2009), significant changes to the facility and manufacturing equipment included: -----

----- (b)(4)----- . In February 2010, Biotest manufactured the first 2 conformance (i.e., Phase 1 comparability) lots. These lots were manufactured at the anticipated commercial scale via the intended commercial process, were placed on stability, and release-tested.

## **Supplement Review Summary**

Specific review assignments are listed in Appendix 1 and include process validation (----- (b)(4)-----) and final product stability.

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## Final product stability

The four clinical lots and lots filled in the 100 mL configuration for stability studies (see Table 2.3.S.7-1, above) were tested for stability to support an initial drug product shelf life of up to 24 months at 2 - 8°C and ultimately up to -----(b)(4)----- . The protocol includes testing after storage in an inverted position at 3, 6, 9, 12, 18, 24, ----(b)(4)---- at 2 - 8°C. -----  
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