



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

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: Final Review, first review cycle: original BLA: new IGIV product

Recommendation

This original BLA submission is recommended for the following Complete Response Letter questions:

1. An additional two conformance lots remain to be completed; please provide the following:
 - An update on their manufacture;
 - Release-test data, including lot release protocols;
 - A comparison of these conformance lots with previous production lots made before the ongoing facility and equipment changes were initiated;
 - -----(b)(4)-----
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2. Please provide final summary validation reports for the following process steps/equipment:
 - -----(b)(4)-----;
 - -----(b)(4)-----.
3. Please conduct additional validation studies to determine the following:
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----- (b)(4) -----
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 - ----- (b)(4) -----
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4. Please provide any additional available stability data for lots -----(b)(4)-----, particularly the anti-measles titers.

In addition, Biotest has made a post-marketing commitment that will need to be included in the eventual approval letter:

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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 ± 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: at -----

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----- 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 (-----
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and final product stability.

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SP-DF-3036-4 DATA TABLE FOR IGIV LOT ---(b)(4)--- (2-8°C) SP-DF-3036-4

-(b)(4).

All lots met the drug product release criteria for the stability-indicating parameters after storage for up to 24 months at 2 - 8°C, with the exception of lots -----(b)(4)-----, which failed visual appearance. Biotest notes that all lots but these two were formulated with a -----(b)(4)----- . To date, with the exception of the one vial in which --(b)(4)-- particulates were observed at the 18-month stability interval for lot -----(b)(4)----- particulates have not been observed in the lots manufactured using the -----(b)(4)----- . BPC states their belief that the particles observed in this vial were either “transient or at the sub-visible borderline” because particles have not been observed in this vial in the subsequent visual inspections. All lots met the drug-product release criteria for the stability-indicating parameters after -----(b)(4)----- .

-(b)(4).

Biotest concludes that an initial shelf life of 24 months for the drug product when stored at 2 - 8°C is warranted. This presumption is to be confirmed in the ongoing stability studies for the conformance lots, which will be continued during BLA review and are to be filed to the BLA when they are available.

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Assessment: the clinical and stability lots were not tested for potency; the conformance lots were tested for potency but so far only have data up to three months. Data from all lots were pooled and assessed for stability (see plots, Appendix 5); all data generated support a two-year dating period at 2-8 C only, but potency has not been assessed with a sufficient track record to confirm that it remains above the lower limit during Bivigam’s shelf-life. The conformance-lot potency data that has been generated so far appears to indicate, albeit with a low level of assurance, that potency may be falling rapidly. Accordingly, additional stability data is crucial to support approval of this product. An IR is generated.

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Information Requests

CBER sent information requests on April 7 and 8, 2010 that were responded to on May 9, 2010. The questions are followed by Biotest’s responses and CBER’s assessments:

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

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

Biotest responds: "Section 3.2.P.8 of the BLA has been updated to include the additional final product stability data that have become available."

Assessment: the two lots for which potency data were obtained (lot nos. -----**(b)(4)**-----
----) have been tested through 9-12 months at both 2-8 °C **(b)(4)**-. The data are plotted in Attachment 6. While significant -----**(b)(4)**----- were not observed, within 12-24 months two of four potency trends -----
-----**(b)(4)**------. The magnitudes of the trends correlate with ---**(b)(4)**---. Additional values at 12, 18, and possibly 24 months (the presumed target expiry) appear to be necessary to adequately characterize the stability profile of Bivigam.

Action: send a CR letter comment requesting any additional stability data generated since the last submission, and noting that a full 24 months stability data set at 2-8 °C may be necessary on the two lots for which potency was measured.

3. *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.*

Biotest responds: “--(b)(4)-- titers have been assayed in retained samples of Biotest-IGIV lots that were used in the clinical and stability studies. All lots and samples were maintained under storage conditions of 2-8°C. The initial clinical and stability lots were not assayed for --(b)(4)-- titers at the time of lot release because --(b)(4)-- potency was not a product release criteria for Biotest-IGIV at that time; however, the lots used in the clinical study and the conformance lots were tested following manufacture of the conformance lots as part of the comparability study (FR-2010-05) conducted to support the BLA. These data, as well as the data from testing completed in response to the Agency’s question, are provided in Table 6.1...All samples tested meet the release criteria --(b)(4)-- for --(b)(4)-- potency.”

Assessment: the data cannot be used for a comparison of the quality of the clinical and conformance lots because either 1) different units of measurement are reported for each data set or 2) because in the case of --(b)(4)--, no testing was done of the clinical material. The question was asked because 1) one of the four clinical lots (lot no. 172-069-003) was formulated -----
------(b)(4)-----

having an effect on stability; 2) because Biotest has been upgrading some of its production equipment during the past several years, so that a biochemical comparison of clinical and conformance lots appeared to be in order; and 3) because insufficient stability data regarding product potency has yet been generated.

Action: comparability of clinical lots and conformance lots can only be based on initial (time zero) potency data, not on relative stability during the shelf life. Stability will need to be determined directly from data generated *de novo* on the two conformance lots.

IT IS NOTED that Biotest has added an ------(b)(4)----- to the manufacturing line, and has had difficulties achieving consistent process control using it. Since the manufacturing upgrades are ongoing while the firm seeks licensure for this new IGIV product, a complete revalidation of the affected process steps must necessarily be done to support this BLA.

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