



**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: original BLA: new IGIV product

Recommendation

This original BLA submission is recommended for approval, based on the assigned topics and the firm's responses to one Complete Response letter and two separate information requests.

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 immunodeficiency, 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.

Supplement Review

Specific review assignments are listed in Appendix 1 and include process validation (-----(b)(4)-----
------(b)(4)----- validation, -----(b)(4)-----
storage) and final product stability. A table of contents for this review follows:

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Final product stability

SP-BK-3034-3 Stability Results for Study STY_00077

SP-DF-3036 Stability Results for Study STY_00030

SP-DF-3036-1 Stability Results for Study STY_00006

SP-DF-3046 Stability Results for Study STY_00011

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

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

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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.

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 was generated.

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Information Request I

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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3. -----(b)(4)-----
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Assessment: This response is acceptable.

4. *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 IgG -----(b)(4)----- by ----(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.

5. *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 with -----
----- (b)(4)-----, possibly

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.

Complete Response Letter

A CR letter was sent to Biotest on 9/1/11; the firm's response was received 10/26/11. The CMC questions posed by this reviewer or pertinent to this reviewer's assigned review areas are repeated below, with the firm's response and an assessment of it following each question.

Chemistry Manufacturing and Controls (CMC):

2. *The previously-agreed-to second set of two additional conformance lots remains 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.*

Release test results for the lots requested were provided, and are compared to results for earlier lots (Appendix 2). It is noted that Biotest appears to continue to experiment with the formulation, in that the pH of the latest two conformance lots is higher than that of the previous conformance lots. Also, -(b)(4)- titers for the pre-Phase 1 lots were not measured. Stability results, including the most recent submitted results at the time of this review, are included in the plots in Appendix 3.

Assessment: Biotest appears to have optimized the Bivigam formulation to their own satisfaction, and the stability data provided so far demonstrate that it is adequate to maintain stability of Bivigam for 24 months, though only at 2-8 °C, -----(b)(4)-----.

Nevertheless the experience of (b)(4) in validating a liquid IGIV product of similar formulation to Bivigam is instructive: that firm found that -----(b)(4)----- had a strongly deleterious effect on IgG stability, -----(b)(4)-----.

Biotest -----(b)(4)-----, but insists that they have determined in formulation studies that -----(b)(4)----- has no effect on IgG stability, not noting that they varied -----(b)(4)----- directly with ---(b)(4)---, providing a compensating stabilizing effect. However, suggestions to Biotest on this point have not been taken, so this formulation must be evaluated as it is. Additionally, the 10x increase in PS80 may be associated with hypotensive episodes, and is to be evaluated in a post-marketing study.

3. *The validation of your manufacturing process remains incomplete. Please provide the following [Items a. and b. were posed by DPQ reviewers]:*

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Lot Number	Age of Lots at Testing	Measles Potency
172-069-003	(b)(4)	(b)(4) ref CBER lot 176
172-069-004	(b)(4)	(b)(4) ref CBER lot 176
172-069-005	(b)(4)	(b)(4) ref CBER lot 176
172-069-006	(b)(4)	(b)(4) ref CBER lot 176

10. Your most recent stability data (Report SP-DF-3036-4) indicates that the Bivigam formulation is unstable in that: 1) at (b)(4) storage temperature, -----(b)(4)-----, anti-measles titer, -----(b)(4)----- all trend out of specification by 12 months, and -(b)(4)- has fallen from -----(b)(4)-----; and 2) anti-measles titer may trend out of specification by 24 months shelf-life even at 2-8 °C. In our experience, an optimized IGIV formulation will maintain the product's critical quality attributes within release-specification acceptance ranges for at least two years at (b)(4). Please comment.

Biotest agrees that Biotest-IGIV is not stable for two years at (b)(4), but points out that for the clinical trial lots, the stability-indicating attributes -----(b)(4)-----, potency, purity, total protein, (b)(4), and visual appearance were within specification at 18 months at 2-8 °C, that the anti-measles assay has a variability of approximately three-fold, and that the clinical lots had the following anti-measles titers at the given ages:

Biotest ends by reasserting that a shelf-life for Biotest-IGIV of 24 months at 2-8 °C is supported by the data, and volunteers the following -----(b)(4)-----:

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

Assessment: as long as it is understood that Biotest-IGIV cannot be stored at temperatures higher than 2-8 °C, no legitimate objection to licensure can be made on these grounds.

11. Please provide the -----(b)(4)----- data you have been accruing for Biotest-IGIV, in final- or interim-report form, with any analysis or interpretation that you have made to date.

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