

**Memorandum of Filing: BLA STN 125389/0, Immune Globulin Intravenous Human 10% (Biotest-IGIV)**

DATE: December 16, 2010

FROM: Mitchell Frost, M.D., Medical Officer, CBER/DH/CRB, HFM-392

THROUGH: Nisha Jain, Chief, CBER/DH/CRB, HFM-392

TO: The File for BLA STN 125389/0

SUBJECT: Original BLA Filing: Immune Globulin Intravenous Human 10% (Biotest-IGIV)

**APPROVED**

*By Mitchell Frost at 12:54 pm, Feb 24, 2011*

**Brief Description of BLA Submission**

This submission for an Immune Globulin Intravenous formulation from Biotest Pharmaceuticals Corporation has been submitted electronically in accordance to *Guidance for Industry: Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications*. The submission is also compliant with ICH guideline M4E, *Common Technical Document for the Registration of Pharmaceuticals for Human Use*, using appropriate numbering within the Modules. An Index provides links to the relevant sections. The submission contains the following:

<b><u>Files/Folders</u></b>	<b><u>Information</u></b>
Files	(a) Cover letter, (b) Form 356h, (c) Form 3674, (d) Reviewers Guide Module 1 for ICH CTD
Folders/ Files	<ul style="list-style-type: none"><li>• Labeling (item 2)</li><li>• Debarment Certification (item 16)*</li><li>• User fee cover sheet - Form 3397 (item 18)*</li><li>• Financial information (item 19)</li><li>• Other Table of Contents (item 20)**</li></ul> Module 2 for ICH CTD <ul style="list-style-type: none"><li>• Summary (item 3)</li></ul> Module 5 for ICH CTD <ul style="list-style-type: none"><li>• Clinical information (item 8)</li><li>• Statistical information (item 10)</li><li>• Case report tabulations (item 11)</li><li>• Case report forms (item 12)</li></ul>

\*Single document item or folder; \*\*This is item 19 instead of item 20 in *Guidance for Industry: Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications*

- ICH CTD Module 2.3 Quality Overall Summary
- ICH CTD Module 2.4 Nonclinical Overview

- ICH CTD Module 2.6 Nonclinical Written and Tabulated Summaries
- ICH CTD Module 3 Quality
- ICH CTD Module 4 Nonclinical Study Reports

The indication in the proposed package insert is “indication for the treatment of Primary Immunodeficiency Disorder (PIDD).”

Materials for Administrative/Labeling information as well as the Overviews and Summaries appear to contain the required information for review.

- **The proposed labeling (package insert) conforms to the PLR format under 21 CFR 201.57 (71 FR 3922-3997; January 24 2006), and has been provided in both annotated (in pdf) and clean (in Microsoft Word) versions. The SPL version has also been included.**
- **Financial certification and disclosure information (Form 3454) have been submitted. The applicant certifies that there have been no arrangements where the value of the compensation could have been affected by the outcome of the study. A list of Investigators for Study Nabi-7101 are included in the Financial Information folder.**
- **Under IND 13353, Applicant requests:**
  - **Waiver of pediatric assessment has been requested for patients 0 – 5 years of age.**

**Comment** Sponsor should request deferral for patients 2 – 5 years of age.

**Clinical Information**

The clinical material is located in Modules 2 (2.5, 2.7) and 5:

- Module 2 contains the Clinical Overview (2.5) and Clinical Summary (2.7)
- Module 5 consists of the following sections:

<b>Volume(s)</b>	<b>Information</b>
5.2	List of clinical studies
5.3.3	Code and Title of PK study report, if applicable.
5.3.5	Code and Title of Clinical study reports
5.3.7	Case report forms and case report tabulations
5.4	Literature references

**Comments**

1. The clinical safety and efficacy data in this application are based on trials in the treatment of PIDD patients; these trials being conducted under BB-IND 13353, with guidance from FDA.

2. The information in this BLA has been submitted in electronic format. On its face, the submission contains the required sections of a BLA, and it is legible and well organized. The definitions in the datafiles have been provided are acceptable.

**Conclusion and Recommendation**

1. This application is fileable.
2. This application triggers PREA and a waiver of pediatric patients aged <2 years of age.

**Appendix. Checking Refuse-to-file Conditions under SOPP 8404 and 21 CFR601.2: Clinical Section for BLA STN 125389/0**

**CBER's SOPP 8404 - Basis for a BLA RTF**

Administrative incompleteness of an application (i.e., clear omission of information or sections of information required).	No
Scientific incompleteness of an application (i.e., omission of critical data, information or analyses needed to evaluate safety, purity and potency or provide adequate directions for use [21 CFS 601.2]). The concept of "potency" of a biological product includes clinical evidence of effectiveness, demonstrated by adequate and well-controlled clinical trial(s) or acceptable alternative scientific methods.	No
Inadequate content, presentation, or organization of information in an application such that substantive and meaningful review is precluded (e.g., illegibility; failure to translate portions of the application into English; data tabulations (line listings) or graphical displays that are uninterpretable; failure to reference the location of individual data and records in summary reports; absence of protocols for clinical trials; omission of critical statistical analyses or the analysis of a study as planned in the protocol (as opposed to a different, post-hoc analysis); or due to technically deficient electronic submission (1).	No

**21 CFR 601.2 Requirements**

<b>A RTF decision may be made in the absence of any of the following:</b>	
<ul style="list-style-type: none"> <li>• A full description of manufacturing methods.</li> <li>• Data establishing stability of the product through the dating period.</li> <li>• Identification by lot number and submission of sample (s) representative of the product to be introduced or delivered for introduction into interstate commerce.</li> <li>• Summaries of results of tests performed on the lot(s) represented by the sample(s).</li> <li>• Specimens of the labels, enclosures, and containers, and if applicable Medication Guide, proposed to be used for the product.</li> <li>• An environmental assessment or claim for exclusion with supporting information;.</li> <li>• List of all manufacturing sites, including contract facilities.</li> </ul>	Defer to Product and OCBQ Reviewers
<ul style="list-style-type: none"> <li>• Data derived from nonclinical laboratory and clinical studies that demonstrate that the manufactured product meets prescribed standards of safety, purity and potency [The concept of "potency" of a biological product includes a demonstration of clinical potency, i.e., effectiveness].</li> </ul>	Present for clinical studies
<ul style="list-style-type: none"> <li>• Financial certification or disclosure statements, or both, for clinical investigators as required by 21 CFR Part 54.</li> </ul>	Present
<b>The following statements should be included in the application (as appropriate) with respect to the requirement to submit data derived from nonclinical laboratory and clinical studies</b>	
<ul style="list-style-type: none"> <li>• For each non-clinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in 21 CFR Part 58 or, if the study was not conducted in compliance with such regulations, a brief statement justifying the non-compliance.</li> </ul>	Defer to Nonclinical Reviewer
<ul style="list-style-type: none"> <li>• A statement with regard to each clinical investigation involving human subjects that it either was conducted in compliance with the requirements in 21 CFR Part 56, or was not subject to such requirements in accordance with 21 CFR 56.104 and 56.105 and was conducted in compliance with requirements for informed consent in 21 CFR Part 50.</li> </ul>	Included in each study report are statements on IRB review and informed consent