



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

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To: Rana Pratibha, MS  
Consumer Safety Officer  
Regulatory Project Management Branch  
Division of Blood Applications  
Office of Blood Research and Review  
CBER

Thru: Rick Wilson, MD, MS, JD  
Director, Division of Epidemiology,  
Office of Biostatistics and Epidemiology (OBE),  
Center for Biologics Evaluation and Research (CBER)

David B. Martin, MD, MPH  
Acting Chief, Therapeutics and Blood Safety Branch (TBSB),  
Division of Epidemiology, OBE, CBER

From: Alan C. Ou, MD, MPH  
TBSB, Division of Epidemiology, OBE, CBER

Subject: Filing Memorandum

Drug Name(s): Biotest Immune Globulin Intravenous (Human) 10% (Biotest-IGIV 10%)  
Approval Date: Pending

Application Type/Number: BLA 125389

Applicant/sponsor: Biotest Pharmaceutical Corporation (BPC)

## **Background**

OBE/DE has completed an initial review of BLA STN 125389 Biologics License Application for Biotest Immune Globulin Intravenous (Human), herein referred to as Biotest-IGIV 10%, which will be manufactured and distributed by Biotest Pharmaceutical Corporation (BPC) for treatment of primary immunodeficiency disorders (PID). The purpose of the review is to identify potential safety issues that might need to be addressed in a Pharmacovigilance Plan. Note that text in italics is verbatim from the BLA.

## **Disease**

PIDs are heritable disorders of immune system function primarily associated with single gene defects. The incidence is estimated to be 1 in 10,000 to 1 in 2,000 live births. PIDs are classified according to the types of immunologic mechanisms that are disrupted by the particular gene defect. Diseases in which lymphocyte function is affected are commonly divided into three main groups: antibody deficiencies, cellular deficiencies, and combined immunodeficiencies. Two other major classes of PIDs are defects in phagocyte function and complement deficiencies. Each of these forms of PID is characterized by some degree of increased susceptibility to infection which results in substantial morbidity and shortened life spans.<sup>1</sup>

## **Product**

Immune Globulin Intravenous (IGIV) isolated from human plasma is an important treatment modality for a majority of patients with PID. IGIV has been available in clinical practice since about 1980, but due to the cost and complexity of its purification process, only a few manufacturers provide it commercially. In contrast to other IGIV products, Biotest-IGIV 10% will not contain a sugar stabilizer. Biotest's rationale for developing this new IGIV 10% product are to: 1) develop a higher concentration that allows for reduced volume load, reduced infusion time, and reduced associated costs of administering this type of medication, and 2) supplement existing IGIV supply in the US, thereby reducing the risk of IGIV shortages that could negatively impact the management of PID. Biotest states that Biotest-IGIV 10% is expected to reduce serious bacterial infection (SBI) rates in patients with PID when compared to historically compiled infection data in subjects from the pre-IgG treatment era.<sup>2</sup>

*The Biotest-IGIV [10%] drug substance is manufactured by Biotest Pharmaceuticals Corporation (BPC) at Boca Raton, Florida from Source Plasma. The manufacturing process follows the modified Cohn-Oncley cold alcohol fractionation process which isolates the immunoglobulin fraction as a solution. The Cohn-Oncley method is a multi-step process of*

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<sup>1</sup> Bonilla FA, Geha RS. Primary immunodeficiency diseases. J Allergy Clin Immunol. 2003 Aug; 112(2):267.

<sup>2</sup> STN BL 125389, Clinical Overview, 2.5.1, p. 3.

*isolating immunoglobulins from plasma using different alcohol concentrations under specific conditions of temperature, pH, protein concentration and ionic strength at each step. Following fractionation, the -----(b)(4)-----  
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### **Filing Issues**

We see no filing issue in this original BLA submission from OBE Division of Epidemiology's perspective. The BLA submission does include a pharmacovigilance plan (PVP), but it does not follow the format in accordance with the E2E PVP guidance.

### **Review Issues**

The prelicensure clinical trials are small, and the subjects might not represent the patient population that is likely to be exposed to the product after licensure. Pharmacovigilance plans are designed to identify and describe potential serious safety risks, important missing information, or inadequately studied at-risk populations, and should include routine pharmacovigilance (i.e., compliance with applicable reporting requirements under FDA regulations) and possibly additional postmarketing safety monitoring activities.

The pharmacovigilance plan is developed by a product's sponsor and should specifically focus on detecting new safety concerns and evaluating previously identified risks. The sponsor should submit a detailed pharmacovigilance plan in accordance with the E2E PVP guidance, which can be found at:

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm129411.htm>.

### **Letter Ready Comments**

The FDA acknowledges that Biotest has submitted a pharmacovigilance plan (PVP) with the BLA application for Biotest Immune Globulin Intravenous (Human), also known as Biotest-IGIV 10%. This PVP, however, does not follow the format in accordance with FDA's E2E PVP guidance. Pharmacovigilance plans are designed to identify and describe potential serious safety risks, important missing information, or inadequately studied at-risk populations, and should include routine pharmacovigilance (i.e., compliance with applicable postmarket reporting requirements under FDA regulations) and possibly additional postmarket safety monitoring activities.

The pharmacovigilance plan is developed by a product's sponsor and should specifically focus on detecting new safety concerns and evaluating previously identified risks. The pharmacovigilance plan should be detailed and prepared in accordance with the E2E PVP guidance, which can be found at:

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm129411.htm>.