



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

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**To:** STN: 125389.0

**From:** Lilin Zhong, M.S., LPD, DH, OBRR, HFM-345  
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**Applicant:** Biotest Pharmaceuticals Corporation (BPC)

**Product:** Immune Globulin Intravenous (Human), 10% Liquid (Biotest-IGIV)  
Proposed Trade name: BIVIGAM

**Subject:** Final Review (Viral Validation)

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**Recommendation**

Approval

**Background Summary**

The original BLA was submitted by Biotest Pharmaceuticals Corporation (BPC) on 03-NOV-2010 for the product of Immune Globulin Intravenous (Human), 10% Liquid (BIVIGAM). Viral safety data are included in the application to support the approval. The data are obtained from the following studies: 1) Plasma screening; 2) Analytical assay validation (serological testing for antibodies and antigen and NAT testing); and 3) Manufacturing procedures that are intended for virus clearance.

Human Source Plasma (SP) for the production of BIVIGAM is obtained from FDA-licensed plasma collection centers in the United States. All plasma is serological tested for anti-HIV and anti-HCV antibodies as well as HBsAg, NAT tested for HAV, HBV, HCV, HIV and Parvovirus B19. The B19 DNA limit for the manufacturing plasma pools is set as less than or equal to  $10^4$  IU/mL.

Three manufacturing steps are designed specifically to contribute to the overall viral safety of the product:

- 1) Precipitation and Removal of Fraction III including Depth Filtration;
- 2) S/D treatment by TNBP/Triton X-100;
- 3) 35 nm virus filtration.

--(b)(4)-- treatment is embedded in both S/D treatment step and Nanofiltration step.

**CMC Review - Viral Safety**

**1. Materials used for the viral validation study**

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**FDA Information Request (April 07, 2011):** Since the viral validation studies were done at different locations by Biotest or -----(b)(4)-----, please submit a summary to indicate the LRF values of all viruses tested at each location and the differences, if any, in the testing methods.

**Sponsor's Response (May 09, 2011):** Viral validation studies were conducted at two separate locations, yet there is no two studies done at two locations for the same virus validation studies (Table below):

**Labs for Virus Validation Studies**

Laboratory	--(b)(4)--	Biotest Virus Validation Lab
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Virus	HIV, WNV, BPV	BVDV, PRV, SinV, PPV, MEV, SV40
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Reviewer's comments: Sponsor's response is acceptable.

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**Table 5. Proposed Viral Reduction**

Virus type Family	Virus Removal/Inactivation (log <sub>10</sub> )								
	Enveloped viruses					Non-enveloped viruses			
	Retro	Flavi			Herpes	Picorna	Parvo		Polyoma
Step/Virus	HIV	BVDV	SinV	WNV	PRV	MEV	BPV	PPV	SV40
Precipitation and Removal of Fraction III and Depth Filtration	--	1.87*	--	--	--	5.29	--	4.00	2.00*
TNBP/Triton X-100 Treatment	> 4.43	> 5.04	> 7.11	(b)(4)	> 4.01	--	--	--	--
35 nm Virus Filtration	> 5.19	> 4.88	--	--	> 4.64	<1.0	6.18	< 1.0	> 5.02
Total Clearance	> 9.62	> 11.79	> 7.11	(b)(4)	> 8.65	5.29	6.18	4.00	> 7.02

\* without depth filtration -- not done values below 1 log<sub>10</sub> are considered as insignificant and are not used for total clearance;

HIV, human immunodeficiency virus; BVDV, Bovine viral diarrhea virus, model virus for HCV; SinV, Sindbis virus, model virus for HCV; WNV, West Nile virus; PRV, Pseudorabies virus, model virus for herpes viruses and Hepatitis B virus; MEV, model virus for hepatitis A virus; BPV, Bovine parvovirus, model virus for human Parvo B19V; PPV, Porcine parvo virus, model virus for human Parvo B19; SV40, Simian virus 40, model virus for highly resistant non enveloped viruses

Reviewer's comments: -----  
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**FDA Information Request (April 07, 2011):** Please select the lower values for your claims of virus reduction in your overall LRF table. In addition, please take the value of bench controls into consideration when the final reduction values are calculated.

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