



**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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**CC:** Pratibha Rana, RPM, HFM-370

**Applicant:** Biotest Pharmaceuticals Corporation (BPC)

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

**Subject:** Mid-cycle Review (Viral Validation)

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**Recommendation**

The following Information Request needs to be sent to the sponsor:

1. 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.
2. In your viral validation study for the S/D treatment, the WNV reduction value of ---(b)(4)--- is claimed in the overall LRF table instead of the value of  $4.96 \log_{10}$ . If higher value was obtained under the influence of downstream ----(b)(4)----, please provide related validation data to demonstrate the combined effects of these two steps on the WNV reduction or validate these two steps separately.
3. 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.
4. Please provide SOP SV-T: EV-043-01/ concerning the virus stock preparations and conditions.
5. Please provide SOP SV-T: EV-137-00/ concerning -----(b)(4)-----.

**Background Summary**

This 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 BLA 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) is the starting material for the production of BIVIGAM, which 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.

Three manufacturing steps are designed specifically for the removal and/or inactivation of the virus:

- 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**

The materials used in the virus validation are the ---(b)(4)--- collected from a -----(b)(4)----- manufacturing process at Biotest Pharmaceuticals Corporation, Boca Raton, Florida. The materials were -----(b)(4)-----.

### **2. Viral Validation Study Design**

#### **2.1. Manufacturing steps validated for virus removal/inactivation**

**Figure 1. Manufacturing steps that are designed specifically for viral reduction**

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**2.2. Viruses used in the viral validation studies**

Both non-enveloped and enveloped viruses were selected for the viral validation studies (Table 2).

**Table 2. Characteristics of selected viruses for viral validation**

Virus	Family	Envelope	Genome	Size (nm)*	Model for
Human Immuno-deficiency Virus (HIV)	Retro	Yes	RNA	80 - 100	Relevant Virus
Pseudorabies Virus (PRV)	Herpes	Yes	DNA	120 - 200	Herpes viruses, HBV
Bovine Viral Diarrhea Virus (BVDV)	Flavi	Yes	RNA	50 - 70	HCV
Sindbis Virus (SinV)	Flavi	Yes	RNA	60 - 70	HCV
West Nile Virus (WNV)	Flavi	Yes	RNA	40 - 60	Relevant Virus
Murine Encephalomyelitis Virus (MEV)	Picornia	No	RNA	25 - 30	HAV
Porcine Parvo Virus (PPV)	Parvo	No	DNA	18 - 24	Parvo B19
Bovine Parvo Virus (BPV)	Parvo	No	DNA	18 - 24	Parvo B19
Simian Virus 40 (SV40)	Polyoma	No	DNA	40 - 50	non-lipid-coated, highly resistant DNA viruses

\*as listed in Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses;CPMP/BWP/268/95 rev.2 (2)

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

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

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**Reviewer's comments:** -----  
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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	Picornia	Parvo		Polyoma
Step/Virus	HIV	BVDV	SinV	WNV	PRV	MEV	BPV	PPV	SV40
<b>Precipitation and Removal of Fraction III and Depth Filtration</b>	--	1.87*	--	--	--	5.29	--	4.00	2.00*
<b>TNBP/Triton X-100 Treatment</b>	> 4.43	> 5.04	> 7.11	(b)(4)	> 4.01	--	--	--	--
<b>35 nm Virus Filtration</b>	> 5.19	> 4.88	--	--	> 4.64	<1.0	6.18	< 1.0	> 5.02
<b>Total Clearance</b>	> 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:** For WNV the -----(b)(4)----- was selected, despite this result might have been influenced by -----(b)(4)----- . However, -----(b)(4)----- and consequently part of the production process of Biotest-IGIV. An IR will be sent to the sponsor to request additional validation data to support the claims of the combined effects of these two steps on the WNV reduction, and to request additional data if the sponsor wishes to validate these steps separately.

**2.7. -----(b)(4)-----**

2.7.1. -----(b)(4)-----:

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