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

To:	STN: 125389.0
From:	Lilin Zhong, M.S., LPD, DH, OBRR, HFM-345
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Through:	Dorothy Scott, M.D., LPD Chief, DH, HFM-345
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:	Final-cycle Review (Viral Validation)

Recommendation
Approval with following Post Marketing Commitment:

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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

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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)	Picorna	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)

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2.6. Results of Virus Validation Studies and Proposed Viral Reduction

An IR was sent to sponsor on April 07, 2011 regarding viral validation study locations:
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
Virus	HIV, WNV, BPV	BVDV, PRV, SinV, PPV, MEV, SV40

Reviewer's comments: Sponsor's response is acceptable.

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Reviewer's comments: For calculation of the total clearance, values printed in bold have been used---. --(b)(4)--. An IR will be sent to the sponsor to address this issue on April 07, 2011--:

Table 5. Proposed Viral Reduction

Virus type Family	Virus Removal/Inactivation (log$_{10}$)								
	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$_{10}$ 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

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.

Sponsor's Response (May 09, 2011):--(b)(4)--.

Reviewer's Comments (April 10, 2012): Biotest claimed Log Reduction Factors based on ---------------
-----(b)(4)--------- assays. --------(b)(4)-------- prediction was used to calculate the virus (b)(4) when the
virus was not detectable by the (b)(4) assay. In the telecon with Biotest held on 10-APR-2012, FDA
required Biotest to provide data supporting that the number of infected (b)(4) corresponds to those
predicted with the ----------(b)(4)-------- of probability. Under this condition, the virus (b)(4) could be
deduced based on --------(b)(4)-------. The sponsor agreed to submit these data and agreed to the
following PMC:

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FDA Information Request (April 07, 2011): 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.

Sponsor's Response (May 09, 2011): Sponsor agreed and will claim the reduction of $> 4.96 \log_{10}$ for
WNV by the SD step.

Table 6. Final Log10 virus reduction values in Package Insert

Virus type Family	Virus Removal/Inactivation ($\log_{10}$)								
	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		1.87							2.00
Precipitation and Removal of Fraction III and Depth Filtration	--	--	--	--	--	5.29	--	4.00	--
TNBP/Triton X-100 Treatment	> 4.43	> 5.04	> 7.11	> 4.96	> 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	> 4.96	> 8.65	5.29	6.18	4.00	> 7.02

Reviewer's comments: Sponsor's response is acceptable.

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