



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

To: STN 125590/0

From: Pei Zhang, LPD/DHRR/OBRR

Through: Michael Kennedy, LPD/DH/OBRR
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Applicant: ADMA Biologics Inc.

Product: Immune Globulin Intravenous (Human), 10% Liquid
Proposed Trade name: ASCENIV

Subject: Original BLA: Viral Validation/CMC Review

Recommendation:

A Complete Response Letter will be sent to the sponsor.

Executive Summary

This original Biologics License Application (BLA) submission from ADMA Biologics Inc. for Immune Globulin Intravenous (Human) (IGIV), 10% Liquid, ASCENIV (RI-002) for the treatment of primary immune deficiency disease was received by FDA CBER on July 31, 2015. The product contains 10% human protein of which at least 96% is immunoglobulin G.

ADMA utilizes Biotest Pharmaceuticals, Inc. (Biotest) and (b) (4) as contract manufacturers for drug substance and drug product. The CMC sections regarding the viral safety of this product were reviewed. Scaled down viral validation studies were performed for the manufacturing steps including precipitation and removal of Fraction III including depth filtration (b) (4) with TnBP/Triton X-100 (b) (4) filtration (b) (4) low pH treatment. Viral safety studies described in the submission are (b) (4) as that of Biotest's product, Bivigam. The data related to the viral validation studies were found to be acceptable.

Viral Validation/CMC Review

ADMA Biologics Inc submitted this BLA on July 31, 2015 for its Immune Globulin Intravenous (Human) (IGIV), 10% Liquid for the indication of treatment of patients with primary immune deficiency disease. ASCENIV is a human plasma-derived IgG solution of protein concentration of 100 mg/mL with 100-140 mM sodium chloride, 200-290 mM glycine, 0.15 – 0.25% polysorbate 80 at pH 4.0–4.6. The product is filled into 50 mL glass vials. The proposed shelf life of ASCENIV is 24 months, stored at 2-8 °C.

This review is focused on the viral safety of the product. The product is manufactured by utilizing Biotest Pharmaceuticals, Inc. (Biotest) as contract manufacturer for drug substance and drug product. Source Plasma obtained from FDA-approved plasmapheresis centers in the US. All units used in the plasma pool have been screened by both antibody and NAT testing. Individual plasma units are tested negative for HBsAg, Anti-HCV and anti-HIV1/2. Plasma minipools have been tested negative for HIV RNA, HCV RNA, HBV DNA, and HAV RNA. Parvovirus B19 DNA in the manufacturing pool is (b) (4) .

Viral clearance studies were performed by Biotest. The four major viral clearance steps are precipitation /removal of Fraction III including depth filtration, S/D treatment, (b) (4) filtration and low pH treatment. The process intermediates used to evaluate each respective viral clearance step were produced at manufacturing scale in the Biotest manufacturing facility. These intermediates were then used in the scaled down viral validation studies to determine the clearance value for each step. The viruses used in the validation studies are summarized in Table 1.

Table 1. Summary Characteristics of the Viruses Used in the Validation Studies

Virus	Family	Envelope	Genome	Size (nm)*	Model for
Human Immune-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 (SV 40)	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

The results of viral validation studies are summarized in Table 2 representing reduction factors obtained for the steps of the Biotest IGIV manufacturing process.

Table 2. Virus Removal and Inactivation by the Steps of the Biotest IGIV Production Process

Virus Type Family	Virus Reduction (log10)								
	Enveloped Viruses					Non-enveloped Viruses			
	Retro	Flavi			Herpes	Parvo		Picorna	Polyoma
Step / Test Virus	HIV	BVDV	SinV	WNV	PRV	PPV	BPV	MEV	SV40
Precipitation and Removal of Fraction III	-	1.87	-	-	-	2.83*	-	< 1.0	2.00
Precipitation and Removal of Fraction III and Depth Filtration	-	-	-	-	-	4.00	-	5.29	-
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
Low pH (as part of S/D treatment and/or virus filtration)	(b) (4)								
Total Clearance	> 9.62	> 11.79	> 12.02	> 4.96	> 8.65	4.00	6.18	5.29	> 7.02

* not used for calculation of total clearance as no kinetic studies of inactivation were performed
 - not done

Viral Validation Studies

Validated steps of the Biotest IGIV process using ASCENIV intermediates for viral clearance are:

(b) (4)

[Redacted text block]

- 1) (b) (4)
- [Redacted text block]

[Redacted text block]

7 pages determined to be not releasable: (b)(4)