



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

To: STN 125430/0 File

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Applicant: Cangene Corporation

Product: Varicella Zoster Immune Globulin (Human)
Proposed Trade name: VariZIG®

Subject: **Mid-cycle Review: STN125430/0--** Viral Clearance Validation Section of BLA submission for
Varicella Zoster Immune Globulin (Human) Product by Cangene

Recommendation

The following information request should be sent to sponsor:

1. Please provide the robustness studies conducted for the Anion-exchange chromatography step to determine viral clearance capacity during extremes of the process parameters including –b(4)-----

Executive Summary

This is a review of the Viral Clearance Validation studies provided in support of BLA STN125430/0 submitted by Cangene for licensure of the product Varicella Zoster Immune Globulin (VariZIG®). Cangene submitted viral validation studies to support the viral clearance capacity of three steps in the manufacturing process which include Anion-exchange, 20N nanofiltration, and Solvent/Detergent treatment steps. Cangene provided the viral validation studies conducted from 1999-2005 covering the viral clearance validation for the product WinRho(D) to support the viral safety for VariZIG with the rationale that the manufacturing process for VariZIG –b(4)----- for Cangene's other hyperimmune products including WinRho(D); thus the viral clearance capacity of the manufacturing process –b(4)----- . The sponsor provided an abbreviated version of the virus validation studies conducted for WinRho(D) and included a summary of the results and tables reporting the final viral clearance capacity of each step. The package insert was provided with a final table demonstrating the viral clearance capacity of the manufacturing process and is identical to the viral clearance table used in the package inserts for the other Cangene hyperimmune products.

BLA Viral Clearance Validation Review Summary

This memo covers the review of the virus clearance validation section of the BLA STN125430/0 submitted by Cangene Corporation for the licensure of the product Varicella Zoster Immune Globulin

(Human). The sponsor provided the following documentation and information to support the viral clearance capacity of the manufacturing process for the Varicella Zoster Immune Globulin product.

1. Manufacturing process steps contributing to viral clearance

b(4)

- i. -b(4)-

- ii. ---b(4)---
- iii. ---b(4)---

2. Description of viral clearance study design and –b(4)----- process used for virus clearance validation studies

The virus clearance studies were performed at external laboratories including ---b(4)--- -----
----- . It was noted that all
pivotal studies were performed as independent studies in accordance with the principles of Good
Laboratory Practices. The contract facilities performed the ---b(4)-- -----
----- , if required, using
instructions prepared by Cangene Corporation. The -b(4)- process was executed by Cangene
Corporation and the studies were performed with appropriate -b(4)- ----- from production
batches to ensure batches were representative of the manufacturing scale. Data for the -b(4)- ----
studies was provided and is included in sections 3.3.3 and 3.3.4 and tables 6-10 in section 3.2.A.2
Adventitious Agents Safety Evaluation. Overall, the sponsor claims that the -b(4)- ----- process
used in viral validation studies is consistent with or worst-case to VariZIG manufacturing scale

3. Summary of Viral Clearance Studies

Summaries of individual viral clearance studies are described below.

- i. **Tables of Pivotal Studies for Calculation of the Total Viral Clearance Capacity of the Manufacturing Process**

- Table A (referred to Table 4 in Section 3.2.A.2 Adventitious Agents Safety Evaluation) provides an overall summary of the results obtained from all the pivotal virus validation studies for the three manufacturing steps including Anion-exchange chromatography, 20N filtration and S/D treatment which are claimed for viral clearance. Table B (referred to as Table 16 in Section 3.2.A.2 Adventitious Agents

Safety Evaluation) provides the final values of total virus clearance capacity of the manufacturing process and is the table that is found in the package insert for VariZIG. The values shown in Table B are derived from the values reported in Table A.

Table A: Pivotal Studies for Calculation of the Total Viral Clearance Capacity of the Manufacturing Process (also referred to as Table 4 in section 3.2.A.2 Adventitious Agents Safety Evaluation)

Manufacturing Step	Study No.	Virus Used	Model for	Enveloped ^a	Genome ^a	Size ^a (nm)	Average Log Reduction	Possible Mechanism of Clearance
Anion-Exchange Chromatography	L.100.00.001 Normal conditions	MMV	B19V	No	DNA	b(4)		
		HAV	HAV	No	RNA			
20 N Filter	PV.HYP.04.002 Normal conditions	PPV	B19V	No	DNA			
	PV.HYP.04.006 Robustness	PPV	B19V	No	DNA			
	PV.HYP.04.008 Normal conditions	BVDV	HCV	Yes	RNA			
		PRV	herpes	Yes	DNA			
		EMC	HAV	No	RNA			
		HIV	HIV	Yes	retro RNA			
Solvent/Detergent	L.100.00.004 Robustness	PRV	herpes	Yes	DNA			
	S58893 Robustness	BVDV	HCV	Yes	RNA			
	S56021 Normal conditions	BVDV	HCV	Yes	RNA			
		HIV	HIV	Yes	retro RNA			
	PV.HYP.03.001 Kinetics study	PRV	herpes	Yes	DNA			
		BVDV	HCV	Yes	RNA			

Table B: Virus Clearance Capacity of the Manufacturing Process (also referred to as Table 16 in section 3.2.A.2 Adventitious Agents Safety Evaluation)

Envelope	Enveloped Virus			Non-Enveloped Virus			
Genome	RNA		DNA	RNA		DNA	
Virus	HIV-1	BVDV	PRV	HAV	EMC	MMV	PPV
Family	Retrovirus	Flavivirus	Herpes virus	Picornavirus		Parvovirus	
Size (nm)	80–100	50–70	120–200	25–30	30	20–25	18–24
Anion Exchange Chromatography (partitioning)	Not evaluated			2.3	n.e.	3.4	n.e.
20 N Filtration (size exclusion)	≥4.7	≥3.5	≥5.6 ^a	n.e.	4.8	n.e.	4.1
Solvent/Detergent (inactivation)	≥4.7	≥7.3	≥5.5	Not evaluated			
Total Reduction (log ₁₀)	≥9.4	≥10.8	≥11.1	7.1		7.5	

i. Anion-Exchange Chromatography

Pivotal Study L.100.00.001: Validation of the Clearance of Small, Non Lipid Enveloped Viruses by Anion Exchange Chromatography Process

- Study L.100.00.001 was performed at –b(4)--- in 2000 to examine the clearance of Hepatitis A virus (HAV), a potential contaminant in plasma and Murine Minute virus, a model virus for B19 and small non-enveloped viruses in general.
- –b(4)- validation runs were performed with each virus, MMV and HAV using –b(4)--- production parameters. Results of the validation study conducted under normal operating parameters provided log reduction values of 3.4 log for MMV and 2.3 log for HAV, both of which are reported in the viral clearance table in the package insert for VariZIG (also refer to Tables A and B).

- ---b(4)-----

Reviewer's Comments: Robustness studies to evaluate the clearance capacity of the Anion-exchange chromatography step with variations in the chromatography operating parameters was not provided by the sponsor. An IR should be sent to the sponsor asking to provide the robustness studies performed for the Anion-exchange chromatography step to determine the viral clearance capacity during extremes of the process parameters including -----b(4)----- that could potentially occur during the manufacturing process..

ii. **20N filtration:**

Pivotal studies PV.HYP.04.002 and PV.HYP.04.006

- Studies **PV.HYP.04.002**: Evaluation of -b(4)----- Clearance by Planova b(4) and 20N Nanofiltration , **PV.HYP.04.006**: Validation of the Robustness for the Planova 20N Nanofiltration Step for Clearance of PPV and **PV.HYP.04.008**: Validation of the Viral Clearance Capability of the 20N Nanofilter for EMC, HIV, PRV and BVDV (See Table 4) were submitted to support the validation of viral clearance for this manufacturing step. These studies were conducted with -b(4)-- -----

- Studies **PV.HYP.04.002** and **PV.HYP.04.006** were performed at --b(4)----- in 2004. Both of these studies evaluated clearance of PPV virus.
- Study **PV.HYP.04.002** consisted of a -b(4)----- conducted under -b(4)-- conditions while study **PV.HYP.04.006** was conducted to validate the robustness of this step comparing -b(4)-- -----
----- . The virus PPV (with size 18 to 24 nm) was selected for robustness studies because it represents a challenge to the size exclusion capability of the nanofilter given that this virus is of smaller size than other viruses that are potential contaminants of human plasma including Hepatitis A virus (25 to 30 nm), Hepatitis B virus (42nm) and HIV-1/HIV-2 viruses (80-120nm).
- The -b(4)-- PPV run conducted under -b(4)- conditions yielded the greatest -b(4)----- while the -b(4)-- performed using -----b(4)----- conditions for robustness yielded log -b(4)-----in the range of -b(4)----- logs. The -b(4)-- value -b(4)----- was obtained from -b(4)--- of the robustness study conducted under conditions of ---b(4)---- -----

- The average log reduction of the two studies under -b(4)-- conditions is 4.1 which is the value reported for PPV at the 20N filtration step in the final Viral Clearance table of the package insert (Table B in Section 3(i).

Pivotal Study PV.HYP.04.008

1 page determined to be not releasable: b(4)

4. Summary of Reviewer Comments

The following IR should be sent to sponsor to clarify IR issues noted in the Reviewer Comments of this memo:

- 1) Please provide the robustness studies conducted for the Anion-exchange chromatography step to determine viral clearance capacity during extremes of the process parameters

--b(4)-----

5. References

- a. Ireland T, Lutz H., Siwak M, Bolton G. Viral filtration of plasma-derived human IgG: a case study using Viresolve NFP. 2004: 38-44
- b. Bailey M. Normal flow virus filtration—detection and assessment of endpoint in bioprocessing. PDA Viral Safety Conference. 2005 May