



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

Recommendation

Approval

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. The viral validation studies provided in this submission were conducted during 1999-2005 for the viral clearance validation in support of licensure for the product WinRho (D). These same studies are included with this submission to support the viral safety for Varizig® with the rationale that since the manufacturing process for Varizig® ---b(4)----- for Cangene's other hyperimmune products including WinRho (D), the viral clearance capacity -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.

After review of the viral clearance validation, an Information Request was sent to Cangene 4 OCT 2012 regarding the lack of robustness studies at the Anion-exchange chromatography step. The sponsor response received 18 OCT 2012 indicated that robustness studies for the Anion-exchange chromatography step were not performed; however, the sponsor stated that the spiking studies were conducted under worst-case conditions. An approval is recommended based on: 1) the values reported in the viral clearance table in the PI are -b(4)----- to those values which have been previously reported and approved for the Hepatitis B Immune Globulin product (approval 07 APR 2007), and 2) the sponsor is not claiming any new viral clearance values or providing any additional numbers to increase the clearance.

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

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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)-----, provided 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

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1. 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	20–25	3.4	Removal by viral affinity to resin
		HAV	HAV	No	RNA	25–30	2.3	
20 N Filter	PV.HYP.04.002 Normal conditions	PPV	B19V	No	DNA	18–24	b(4)	Removal by size exclusion
	PV.HYP.04.006 Robustness	PPV	B19V	No	DNA	18–24		
	PV.HYP.04.008 Normal conditions	BVDV	HCV	Yes	RNA	50–70	≥3.5	
		PRV	herpes	Yes	DNA	120–200	≥5.6	
		EMC	HAV	No	RNA	b(4)	4.8	
		HIV	HIV	Yes	retro RNA	80–100	≥4.7	
Solvent/Detergent	L.100.00.004 Robustness	PRV	herpes	Yes	DNA	120–200	b(4)	Inactivation
	S58893 Robustness	BVDV	HCV	Yes	RNA	50–70		
	S56021 Normal conditions	BVDV	HCV	Yes	RNA	50–70		
		HIV	HIV	Yes	retro RNA	80–100		
		PRV	herpes	Yes	DNA	120–200		
	PV.HYP.03.001 Kinetics study	PRV	herpes	Yes	DNA	120–200		
		BVDV	HCV	Yes	RNA	50–70		

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	

Note: In the course of reviewing Package Insert, the reduction values for HAV and EMC were revised to be reported separately. In the same way, the values for MMV and PPV were reported separately. Total reduction values (log10) were revised accordingly.

Enveloped	Enveloped			Non-Enveloped			
Genome	RNA		DNA	RNA		DNA	
Virus	HIV-1	BVDV	PRV	HAV	EMC	MMV	PPV
Family	retro	flavi	herpes	picorna		parvo	
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.
20N Filtration (size exclusion)	≥ 4.7	≥ 3.5	≥ 5.6*	n.e.	4.8	n.e.	4.1
Solvent/Detergent (inactivation)	≥ 4.7	≥ 7.3	≥ 5.5	Not evaluated			
Total Reduction (log10)	≥ 9.4	≥ 10.8	≥ 11.1	2.3	4.8	3.4	4.1

*The PRV was retained by the 0.1 µm pre-filter during the virus validation. Since manufacturing employs a 0.1 µm pre-filter before the 20N filter, the claim of ≥ 5.6 reduction is considered applicable.

Abbreviations:

HIV-1: human immunodeficiency virus-1; relevant virus for human immunodeficiency virus-1 and model for HIV-2

BVDV: bovine viral diarrhea virus; model virus for hepatitis C virus (HCV) and West Nile virus (WNV)

PRV: pseudorabies virus; model for large enveloped DNA viruses, including herpes

HAV: human hepatitis A virus; relevant virus for HAV and model for small non-enveloped viruses in general

EMC: encephalomyocarditis virus; model for HAV and for small non-enveloped viruses in general

MMV: murine minute virus; model for human parvovirus B19 and for small non-enveloped viruses in general

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).

viruses including HIV-1, PRV and BVDV and EMC, a small non-enveloped virus.

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

- Viruses BVDV (model for HCV) , PRV (model for herpes), EMC (model for HAV) and HIV were selected to present viruses that are potential contaminants in the product and that provide a wide range of physico-chemical properties to challenge the manufacturing process.
- Log reduction values for PRV, BVDV, and EMC were reported as ≥ 5.6 , ≥ 3.5 , and 4.8 in the final clearance table (Table B notes in Section 3(i) of memo).
- For PRV the log reduction value of ≥ 5.6 was claimed for the 20N filtration step. However, PRV, the largest virus validated (120-200nm) showed complete retention over the 0.1 μ m pre-filter used for the spiking study thus no virus remained available for the filtration over the 20N filter. This pre-filter is used in the manufacturing process as an in-line filter prior to the 20N filter, thus the log reduction of ≥ 5.6 was claimed for the 20N filtration step.
- HIV log reduction factor was calculated from a validation run where the virus spike volume was optimized to ---b(4)- as compared to the other viruses in which a b(4) spike volume was used. The HIV virus spike volume had to be optimized as a result of two invalidated HIV runs employing spike volumes of ---b(4)----- These runs were invalidated because the sponsor claims that these runs were not representative of the manufacturing scale or of the qualified scale-down model (citing study L.100.05.002 not including in this submission). These invalidated runs demonstrated ---b(4)-----
------. The sponsor notes that there were significant differences in the flow rate and throughput for the HIV runs compared to the 1) flow rate of the other 4 viruses and 2) the follow rate of the baseline, virus-free sample load (See figure 3 in Section 3.2.A.2 Adventitious Agents Safety Evaluation). The sponsor notes that

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Reviewer's Comments: The sponsor's claim that the invalidated HIV runs with ---b(4)----- volume do not represent the manufacturing scale or qualified scale-down model seems reasonable. In the invalidated HIV runs the ---b(4)----- that occurred was a result of filter -b(4)- related to the presence of -b(4)-in the HIV spiking media which would not be present in the material during production. In addition, the explanation for the -b(4)----- at these spike volumes seems reasonable in that the HIV spike was the only one of the viral spikes containing b(4). The sponsor also notes that the spike volume potentially correlates with the viral clearance given that at a b(4) spike volume -b(4)- was achieved while at spike volumes of ---b(4)- ----- was achieved. Thus, calculating the HIV -b(4)----- with a spike volume of -----b(4)- does seem to be most optimal in representing the manufacturing process and demonstrating clearance of HIV with the manufacturing process.

- iii. ---b(4)-----
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Reviewer Comments: There are differences between the reduction values claimed in the PI and the study reports for BVDV and PRV at S/D step. It may not be a concern as the difference is within the margin of error –b(4)-- for viral infectivity assays. The lower reduction values of the two were chosen in the PI..

3. Information Request and Sponsor Response

This information request was sent to the sponsor 4 OCT 2012 to which the sponsor's response was received as under amendment STN 125430/0.6 (eCTD seq 0006) on 18 OCT 2012. Item 8 of the information request that was sent 4 OCT 2012 and which relates to the viral clearance of this review and the corresponding response from the sponsor are shown below.

Item 8 in information request sent 4 OCT 2012 under Amendment 0.6

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)---- --

[*b(4)*]

4. 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