



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

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To: To File (BLA STN 125430/0)

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Applicant: Cangene Corporation

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

Subject: (Final) Review : Process Validation

Recommendation

The process validation section is acceptable. All in-process and final specifications have been met.

Executive Summary

Cangene Corporation submitted a BLA on June 29, 2012 for Varicella Zoster Immune Globulin (Human), VariZIG. VariZIG is a lyophilized powder in a Type 1 glass vial (6 ml) with a ----b(4)----- rubber stopper (20 mm), aluminum seal and a plastic flip-off cap and comes in a kit with Sterile Diluent. Each vial contains 125 IU VariZIG. The final formulation contains 0.04 M sodium chloride, 0.1M glycine and 0.01% (w/w) polysorbate 80. The Sterile Diluent contains 0.8% sodium chloride and 10 mM sodium phosphate. The reconstituted VariZIG is intended for post-exposure prophylaxis of varicella in high risk individuals by the intramuscular route (IM). VariZIG is manufactured by a process similar to that used for Cangene's other licensed hyperimmune products: WinRho SDF, HepaGamB and CNJ-016 (VIGIV). Cangene submitted process validation data for one (1) VZIG conformance Drug Substance Lot --b(4)--- at the --b(4)-- scale, which was --b(4)----- final drug product lots (-----b(4)-----). The conformance batch and final lots were compared to b(4) clinical drug substance lots and b(4) consecutive hyperimmune drug substance lots. The process validation was conducted within the approved process parameters, the acceptance criteria were met and there were no deviations. All in-process and final specifications have been met and the process validation section is acceptable.

CMC Review Assignments

Malgorzata Norton

Maria Luisa Virata

Process Validation

Product specifications, analytical methods and method validation studies (except for potency testing), serological and NAT testing of plasma, TSE safety

Douglas Frazier

Stability studies, lot release protocol, potency testing

Christine Harman and Pei Zhang

Viral clearance validation

Phil Krause (consult)

Potency testing

Michael Vardon and Destry Sullivan
(DMPQ)

Lyophilization, fill and finish

Supplement Review Summary

1. Process Validation consists of manufacture of VariZIG (lyophilized powder) and Sterile Diluent
 - a. VariZIG is a lyophilized powder in a Type 1 glass vial (6 ml) with a ---b(4)----- rubber stopper (20 mm), aluminum seal and a plastic flip-off cap. Each vial contains 125 IU VariZIG.
 - b. Sterile Diluent is provided in -b(4)----- clear -b(4)----- glass vials with ---b(4)----- aluminum seals and plastic flip-off caps. Each vial contains 0.8% sodium chloride and 10 mM sodium phosphate. The nominal volume is 8.5 mL.
2. VariZIG is manufactured at Cangene Corporation, 155 Innovation Drive, Winnipeg, Manitoba R3T 5Y3, Canada.
 - a. Manufactured in area used for other hyperimmune products on a campaign basis – only one product manufactured at a time. A validated changeover procedure is used between campaigns.

VariZIG manufacturing process

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

Table 10 Summary of Bulk Batches Presented

Batch No.	Date of Manufacture	Scale (L)	Fill Lot No.	Use	Comments
b(4)	b(4)		0407501	Clinical trial, stability studies	VZ-001
			0405601	Clinical trials, stability studies	VZ-003 & VZ-006
			0040501	Clinical trials, stability studies	VZ-008 & VZ-009
			b(4)	Commercial lot (Canada), stability studies	
			10703686	Clinical trial	VZ-009
			10906580 ^a	Clinical trial, commercial lot (Canada), stability studies	VZ-009
			10906581	Clinical trial	VZ-009
			b(4)	Conformance lot, commercial lot (Canada), stability studies	
				Conformance lot, commercial lot (Canada)	

^a Although Lot 10906580 was used for clinical trials, it was also a commercial lot for Canada..

[b(4)]

[b (4)]

Table 2 Batch Analyses Summary (Excluding Impurities)

Test Parameter	Acceptance Criteria	Range of Results for Clinical Study Lots (n=5 unless noted) ^a	Range of Results for Conformance Lots (n=2)	Range of Results for Commercial Production Lots (n=2 unless noted) ^b
b(4)	b(4)	b(4)	b(4)	
	b(4) 125 IU/vial			
	b(4)			
Total Protein	<250mg/vial			
pH				
pH (1%)	b(4)			
Safety	Meets 21 CFR 610.11 requirements			
Bulk Material Sterility	Meets 21 CFR 610.12 requirements			
Final Container Sterility	Meets 21 CFR 610.12 requirements			
Polysorbate 80	b(4)			
Glycine				
Chloride				
Reconstitution Time	<10 minutes			

M.R. = Meets Requirements

^a Lot 10906580 was used for both a clinical study and commercial lot for Canada. The data for this lot is included in the range for commercial lots.

^b There are 4 lots included as commercial product lots; however, 2 of the lots are also designated as conformance runs.

Table 1 Release Specifications for Varicella Zoster Immune Globulin (Human)^a

Reference Number:	6.4000		
Approval Date:	2012/01/15		
Test Parameter	Method Type	Method No.	Acceptance Criteria
Contaminants			
Bacterial Endotoxins	b(4)		
Potency			
b(4)			
General Tests			
Glycine			
Polysorbate 80			
Sodium			
b(4)			

1. Final Specifications

Table 1 Release Specifications for VariZIG

Reference No.		7.4000		
Approval Date:		2012-01-15		
Test Parameter	Method Type	Method No.	Acceptance Criteria	
Identity				
b(4)	b(4)	b(4)	b(4)	
Purity				
b(4)				
Impurities – Product Related				
b(4)	b(4)		b(4)	
Immunoglobulin A				≤40 µg/mL
b(4)				b(4)
b(4)				
b(4)				
b(4)				
Impurities – Process Related				
b(4)	b(4)	b(4)		
Bioburden ^a				
Bacterial Endotoxins				
TnBP				
b(4)				

Reference No.	7.4000		
Approval Date:	2012-01-15		
Test Parameter	Method Type	Method No.	Acceptance Criteria
Triton X-100	b(4)	b(4)	b(4)
b(4)			
Potency			
b(4)			b(4) 25 IU/vial
			b(4)
Quantity			
Total Protein			<250 mg/vial
General Tests			
pH			b(4)
pH (1%)			b(4)
General Safety Test ^b			Meets 21 CFR 610.11 requirements
Bulk Material Sterility ^a			Meets 21 CFR 610.12 requirements
Final Container Sterility			Meets 21 CFR 610.12 requirements
Polysorbate 80			b(4)
Glycine			
Chloride			
Reconstitution time			
b(4)			

1. ---b(4)
 - a. -----b(4)-----
 - b. -----b(4)-----
 - c. -b(4)-----
 - i. ---b(4)-----

b(4)

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

b(4)

2. b(4)

- a. The Sterile Diluent for Reconstitution is manufactured at Cangene Corporation.
- a. ---b(4)----- used in reconstitution of VariZIG
- b. Provided in b(4) clear b(4) glass vials with –b(4)----- rubber stoppers -----b(4)-----
----- aluminum seals and plastic flip-off caps.
- c. Each vial contains 0.8% sodium chloride and 10 mM sodium phosphate, the nominal volume is 8.5 ml. It does not contain preservatives.

Table 3 Batch Formula

Batch Size (No. of Dosage Units)		b(4)	
Component		Quality Standard	Quantity per Batch
Sodium Chloride		b(4)	
Sodium Phosphate	b(4)		
Sodium Phosphate			
b(4)			
b(4)			

- d. –b(4)-----

- e. –b(4)-- -----

- f. ---b(4)-- -----