



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: (Midcycle) Review : Process Validation

Recommendation

The process validation section is acceptable. All in-process and final specifications have been met. One concern is the elevated –b(4)-- impurity found in VariZIG. However, VariZIG is administered at a relatively small dose –b(4)---- and by the IM route; therefore, the safety concern is minimal.

Background 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). A similar product was licensed in 1980 and manufactured by Massachusetts Public Health Biologic Laboratories (Varicella Zoster Immune Globulin (Human), VZIG); however, the product was discontinued in 2007. VariZIG was licensed in Canada on January 18, 2001. It is manufactured by a process similar to that used for Cangene's other licensed hyperimmune products: WinRho SDF, HepaGamB and CNJ-016 (VIGIV).

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 6mL–b(4)----- clear –b(4)----- glass vials with -----b(4)----- rubber stoppers ---b(4)----- aluminium 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 manufacturet 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

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b(4)

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5 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)	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	
			b(4)	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)		
Total Protein	<250mg/vial			
pH	b(4)			
pH (1%)				
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)		b(4)
Potency			
Potency 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)	
Purity				
b(4)				
Impurities – Product Related				
b(4)	b(4)	b(4)	b(4)	
Immunoglobulin A				≤40 µg/mL
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)			
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%)			
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			<10 minutes
b(4)			

b(4)