



## DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Center for Biologics Evaluation and  
Research Office of Compliance and Biologics Quality  
Division of Manufacturing and Product Quality

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**To:** Administrative File, BLA, and STN 125430\0  
Cangene Corporation – License No. 1201

**From:** Michael Vardon, CSO, CBER/OCBQ/DMPQ/MRBI, HFM-676

**Through:** Destry Sullivan, Acting Branch Chief, MRB II, HFM-676

**Subject:** BLA Review Memo - Varicella Zoster Immune Globulin (Human)

**Due Date:** December 29, 2012

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### Recommended Action

Based on the information provided, I recommend approval of this BLA for Cangene Corporation to manufacture Varicella Zoster Immune Globulin (Human).

### Summary

This review memorandum covers the CMC sections of the Biologics License Application (BLA) submission, pertaining to DMPQ review responsibility, from Cangene Corporation (Cangene). Cangene submitted this BLA on June 28, 2012 with manufacturing information for Varicella Zoster Immune Globulin (Human), trade name Varizig<sup>®</sup>, a sterile freeze-dried gamma globulin (IgG) fraction of human plasma containing antibodies to the varicella zoster virus. Each 6 mL vial contains a target potency of –b(4)– of Varicella Zoster Immune Globulin (Human). Cangene manufactures this product in their multi-hyperimmune product facility using very similar processes as the following three U.S. licensed products; Rho (D) Immune Globulin Intravenous (Human), Hepatitis B Immune Globulin Intravenous (Human), and Vaccinia Immune Globulin Intravenous (Human). The manufacturing process from human plasma to the formulation stage for liquid and lyophilized products is -----b(4)--- for these products which all are manufactured using –b(4)----- facility equipment at the 155 Innovation Drive, Winnipeg, Manitoba, Canada facility.

This BLA has been granted priority review, and therefore is on a six month review clock. Currently, there is no U.S. licensed Varicella Zoster Immune Globulin (Human) available in the United States. Previously, Massachusetts Public Health Biologic Laboratories manufactured a Varicella Zoster Immune Globulin, however production was discontinued.

The pre-license inspection of Varicella Zoster Immune Globulin (Human) was waived based on the criteria in CBER SOPP 8410.

**Post Marketing Commitments (PMCs)**

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**Facility**

Cangene Corporation utilizes the Winnipeg facility for the manufacture of Varicella Zoster Immune Globulin (Human). However, other facilities listed below are used for the viral marker testing, general safety testing, and back-up on the sterility testing. The name, address, and responsibility of each manufacture are provided below:

<b>Manufacturer</b>	<b>Responsibility</b>	<b>Registration Number</b>
<u>Cangene Corporation</u> 155 Innovation Drive Winnipeg, Manitoba R3T 5Y3 Canada	Manufacturing, In-process/release testing, and stability.	FDA Establishment Identifier: FEI 3003153579
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Cangene manufactures Varicella Zoster Immune Globulin (Human) in ---b(4)----- at the 155 Innovation Drive, Winnipeg, Manitoba, Canada facility. -b(4)--- is a multi-hyperimmune product facility using very similar processes and shared equipment for all three U.S. licensed

products; Rho (D) Immune Globulin Intravenous (Human), Hepatitis B Immune Globulin Intravenous (Human), and Vaccinia Immune Globulin Intravenous (Human). This is a multi-product facility, which is limited to the manufacture of hyperimmune products. Activities for manufacturing in this area include everything from –b(4)----- to production of bulk drug substance to filling and lyophilization of final product and capping. Packaging occurs in a -----b(4)----- --

Varicella Zoster Immune Globulin (Human) is lyophilized while all of Cangene's other U.S. licensed hyperimmune products are currently in liquid form. WinRho was previously approved for lyophilized dosage form in the United States however, Cangene currently only distributes in the U.S. a liquid formulation of WinRho but retains a lyophilized formulation for non-U.S. markets

The following table illustrates the Manufacturing process rooms and Varicella Zoster Immune Globulin (Human) manufacturing activities that take place.

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### **Inspection Waiver**

The pre-license inspection (PLI) was waived for Varicella Zoster Immune Globulin (Human) manufactured in Cangene's multi-product facility located at 155 Innovation Drive, Winnipeg, Canada, based on meeting the five criteria in CBER's SOPP 8410 "Determining When Pre-License/Pre-Approval Inspections (PLI/PAI) Are Necessary." The five criteria include that the manufacturer holds an active U.S. license (#1201), and that the facility has been inspected over the last two years by FDA. FDA inspected this Cangene facility on June 12-21, 2012, October 10-19, 2011 and on April 12-22, 2010. The 2012 and 2010 inspections included areas that

manufacture hyperimmune products. All of these inspections were determined to be Voluntary Action Indicated per FACTS Cangene FEI 3003153579 meeting the criteria for no significant GMP deficiencies. The remaining criteria regarding similar manufacturing process and performing manufacturing steps in the same area using shared equipment were also met.

### **Manufacturing Operations**

Only human hyperimmune products and Sterile Diluent are purified and formulated in the Manufacturing --b(4)----- . All human hyperimmune products and Sterile Diluent are manufactured or filled on a campaign basis, that is, only one product is present in the manufacturing area at a time. Manufacturing rooms follow line clearance and approval procedures for product changeover. Logbooks are used to record line openings (approvals) and line closings (clearances) for all products entering each room. Raw material dispensing is conducted in a --b(4)----- room from the -----b(4)-----  
----- to minimize contamination risk.

### **Manufacturing Process**

The Varicella Zoster Immune Globulin (Human) manufacturing process includes:

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### **Control of Critical Steps and Intermediates**

The specifications for the critical steps in the Varicella Zoster Immune Globulin (Human) process are:

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The in-process tests and acceptance criteria have been established to confirm that the manufacturing operation resulted in product of expected quality. Additional manufacturing controls are specified in the master batch records and performed throughout the process.

### Process Validation

#### *Manufacturing Process Development Background:*

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Varicella Zoster Immune Globulin (Human) drug substance has been manufactured at the –b(4)----- manufacturing scale. The proposed commercial production scale is at –b(4)-- based on the conformance lot size.

**Bacterial Endotoxin and Bioburden tests**

Total bioburden and bacterial endotoxin is controlled using the following acceptance limits. The table below shows the conformance batch, -b(4)----, manufactured in 2012, compared to the ranges obtained for the -b(4)- clinical batches manufactured in 2005, 2007 and 2009 of Varicella Zoster Immune Globulin (Human). The table below shows the in-process manufacturing steps where bioburden and endotoxin testing is performed.

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### **Equipment Computer Systems**

A Process Automation System is used to control various processing steps including filtration, chromatography, and --b(4)----- . Stand alone Programmable Logic Controllers (PLC) are used to control the --b(4)----- of Sterile Diluent, and the lyophilizer. The computer systems are validated. FDA Team Bio inspected Cangene's facility and computer systems in 2012, 2011 and 2010. All of these inspections were determined to be Voluntary Action Indicated per FACTS Cangene FEI 3003153579.

### **Building Management Computer System**

Cangene states that their computerized systems are validated and compliant with 21 CFR Part 211 to continuously monitor and alarm facility cleanroom conditions (differential pressure, temperature and relative humidity).

**Environmental (Particulate) Monitoring**

Routine air monitoring for both viable and non-viable particles is performed on a weekly basis. The weekly schedule rotates so that each room is sampled on a different day in a rotating weekly schedule. Viable air particle monitoring includes ---b(4)-----  
----- Environmental Monitoring Investigation Reports are generated when an action level is exceeded on a single occasion. The following Action and Alert Limits were provided.

[ b(4) ]

**Personnel, Equipment, Waste and Material Flows**

Flow drawings were provided which I reviewed and found to be adequate.

**Product Contact Equipment**

Equipment is shared between hyperimmune products manufactured at Cangene. The equipment cleaning has been validated for each different hyperimmune product formulation composition. Product contact equipment used for Varicella Zoster Immune Globulin (Human) manufacturing is dedicated to human hyperimmune production at Cangene. The following major process equipment is shared among Cangene's hyperimmune products: --b(4)-- -----  
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----- for Cangene's hyperimmune products. Additional information regarding manual and automated clean-in-place (CIP) was requested and found acceptable. See information request on October 4<sup>th</sup>, 2012 and Cangene's response below.

**Other Products Manufactured in the Facility**

Varicella Zoster Immune Globulin (Human) is manufactured in --b(4)----- manufacturing areas dedicated to the production of human hyperimmune products and the Sterile Diluent. Human hyperimmune products are defined by Cangene as Products manufactured from human Source Plasma. Cangene's U.S. licensed hyperimmune products include the following three products:

1. Anti-D Immune Globulin (Human)
2. Hepatitis B Immune Globulin (Human)
3. Vaccinia Immune Globulin (Human)

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### **Changeover Controls**

--b(4)----- is used for all manufacturing operations of Varicella Immune Globulin (Human) and other hyperimmune products including --b(4)-----, chromatography, filtration, --b(4)-----, solvent detergent viral inactivation, and formulation of the bulk product. Product is manufactured in dedicated campaigns, so that only one product is present in the manufacturing/filling areas at any time. Manufacturing --b(4)----- is limited to the manufacture of hyperimmune products and sterile diluent, preventing any contamination by non-hyperimmune products, and Cangene has implemented validated cleaning procedures to prevent contamination from prior campaigns. All manufacturing rooms follow line clearance and approval procedures for product changeover. Logs are maintained to record line openings (approvals) and line closings (clearances) for all products entering each room. ---b(4)----- are taken from equipment utilized prior to the start of a new campaign to verify no product carry over.

### **Contamination Precautions**

Cangene's description of its segregation and contamination control processes, which are based on facility design, personnel access and gowning, manufacturing operations, environmental monitoring and equipment testing appears to provide appropriate control precautions to prevent contamination. The following control descriptions were reviewed:

- Facility Design and HVAC systems
- Nature of Construction and Finishes
- Building Management System
- Facility Access
- Magnetic Door Interlocks used to Maintain Room Differential Pressure
- Personnel and Clothing
- Campaign Manufacturing and Filling
- Raw Material Dispensing, Quarantine and Release
- Use of Manufacturing Room Logs
- Environmental Monitoring
- Equipment Sanitization, Segregation, and Change-Over Procedures

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### **Cleaning Validation**

The following cleaning and sanitizing agents used on the equipment are suitable for use based on Material Safety Data Sheet indications:

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A bracketing cleaning strategy was used for equipment similar in product contact, cleaning process, and design. Equipment was validated with b(4) consecutive trials. Cleaning validation generally consisted of:

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Manual cleaning and sanitizing is used on all small-scale process equipment, --b(4)-----

-----that come in contact with

product, --b(4)-----

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The manual cleaning and sanitization acceptance criteria are referenced below based on Cangene's response to IR number 1. Manual cleaning and sanitization consists of the following steps

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### Container Closure

#### Description of Container Closure System

Component	Description	Supplier	Identity
Vial	6 mL tubing vial	--b(4)----- -----	Type I g -b(4)--
Stopper	20 mm – b(4)----- rubber – b(4)----- stopper	--b(4)-----	--b(4)----- -----
Seal	20 mm seal with flip-of cap	--b(4)-----	Alumin -----

### Container Closure System (Final Product)

Varicella Zoster Immune Globulin (Human) and the Sterile Diluent are --b(4)-----  
6 mL Type 1 ---b(4)-----glass vials manufactured by --b(4)-----  
----- The product vials are sealed with a 20 mm –  
b(4)- stopper supplied by --b(4)-- and a 20 mm aluminum seal with a plastic flip top cap supplied  
by ---b(4)-----

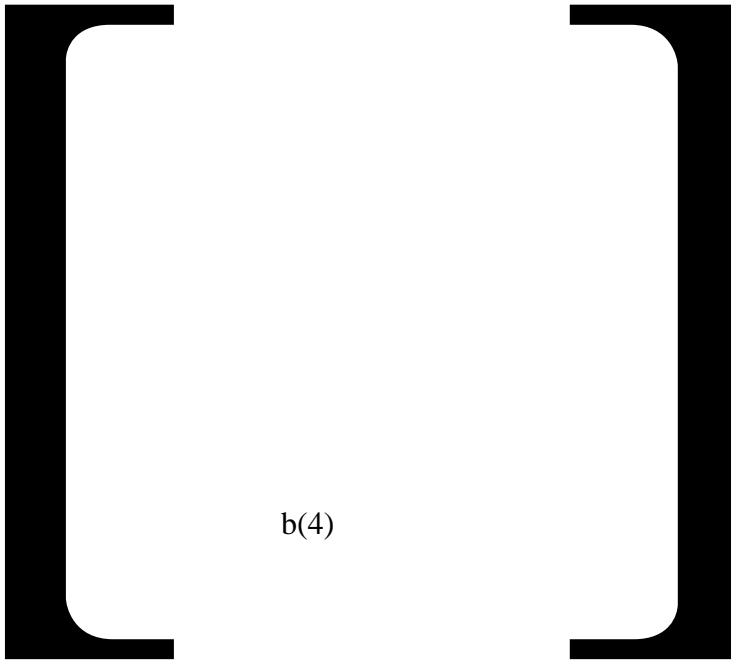
Cangene container closure integrity test (CCIT) Protocol PV\_0175 was not successful because it  
did not utilize --b(4)----- controls, and the test did not challenge the vials under ---b(4)-----  
----- Notable aspects of the protocol included:

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**Lyophilization**

The lyophilizer is dedicated to the human hyperimmune products. It was qualified using an IQ and OQ protocols to validate the lyophilization cycle. The lyophilizer has both --b(4)----- functionality. The validated lyophilization cycle consists of the following steps:

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### **Capping**

The 6 mL vials are ink-jet coded with the lot number by a capping machine. --b(4)-- -----  
----- detects raised stoppers. Vials with raised stoppers are rejected. Samples are removed following capping for QC finished drug product testing.

### **Inspection/Labeling/Packaging**

All product vials are inspected, manually, by trained operators, to ensure that they are free of container defects and foreign material.

### **Storage**

Once the labeling and packing process has been completed, the drug product is stored in a

temperature controlled and monitored warehouse at 2-8 °C, awaiting final distribution.

**Packaging and Shipping**

Cangene routinely ships the lyophilized Varicella Zoster Immune Globulin (Human) drug product from their facility in Winnipeg, Manitoba, Canada to domestic or international destinations. A qualification for ground shipments was documented in PQ\_2300 using a vendor supplied trailer for ground shipments. All criteria were met, confirming the shipping procedure is adequate to maintain the 2 to 8 °C temperature requirement.

Air shipments of Varicella Zoster Immune Globulin (Human) were also qualified (OQ\_2350) at 2 to 8 °C in the ---b(4)----- shipping container for a period of ---b(4)-----  
-----for both winter and summer conditions based on historical shipping profiles. The  
--b(4)----- shipping container is also qualified to maintain --b(4)--- for shipments of  
---b(4)----- for worst-case summer conditions based on historical shipping profiles. Load configurations at or between the minimum and maximum tested loads of --b(4)--- shippers, comparable to ---b(4)----- or equivalent.

**Information Requests (IR) and Responses:**

Additional information was requested from DMPQ on October 4<sup>th</sup>, 2012.

**1. IR** - Please clarify the following equipment cleaning procedures:

**1.A IR** - Define the Manual and Clean-in-Place cleaning solutions, concentrations, and washing conditions (temperature, duration, conductivity).

**Summarized Response:**

The following tables summarize parameters used for the Manual and Clean-in-Place procedures.

**Manual Cleaning Parameters**

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3.B IR - Provide a more detailed justification as to why you believe data from CCIT studies performed in support of a given vial may be extrapolated to another similar vial.

**Summarized Response:**

Cangene's procedure for Pre-Qualification and Qualification Activities to Determine Functional Suitability of Type 1 Glass Containers (SOP 11.012.0001) identifies that functional suitability of Type 1 glass containers need to be evaluated for:

- Changes in manufacturing location or supplier
- Revision to material specifications
- New container size.

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**Conclusion**

I found the information submitted in the BLA and the appropriate amendments adequate to support its approval, noting the PMCs described above.