

Summary Basis for Regulatory Action

Date: December 20, 2012

From: Pei Zhang, Chair of the Review Committee

Maria Luisa Virata-Theimer, Co-chair of the Review Committee

BLA/ STN#: STN 125430/0

Sponsor Name: Cangene Corporation, Winnipeg, Manitoba, Canada

Date of Submission: June 29, 2012

PDUFA Goal Date: December 28, 2012

Proprietary Name/ Established Name: VARIZIG®/ Varicella Zoster Immune Globulin (Human)

Indication: Post-exposure prophylaxis of varicella in high risk individuals

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: For Jay S. Epstein, M.D. _____

☐ I concur with the summary review.

☐ I concur with the summary review and include a separate review to add further analysis.

☐ I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted Specific documentation used in developing the SBRA
Reviewer Name – Document(s) Date
Clinical Review: Charles Maplethorpe
Clinical Pharmacology Review: Iftekhar Mahmood
Statistical Review: Boris Zaslavsky
CMC Review: Douglas Frazier, Christine Harman, Philip Krause, Malgorzata Norton, Maria Luisa Virata-Theimer, Pei Zhang
Pharmacology/ Toxicology Review: Evi Struble
Biomonitoring Review: Erin McDowell, Anthony Hawkins
Facilities Review (DMPQ): Michael Vardon, Syin Chiang, Destry Sullivan
Labeling Review (APLB): Alpita Popat
Pharmacovigilance/Epidemiology Review (OBE): David Menschik
Lot Release Testing Review: Karen Campbell, Catherine Poole
RPM: Nannette Cagungun

1. Introduction

VARIZIG[®] is a sterile lyophilized immunoglobulin G (IgG) powder for solution, which contains antibodies to Varicella zoster virus (VZV) for intramuscular administration and is indicated for post-exposure prophylaxis to reduce the severity of varicella infection in high risk individuals. VZV is the causative agent for varicella (chickenpox) in children and adults, and zoster infection (shingles) in adults and rarely in children.

VARIZIG[®] is manufactured and filled at the Cangene facility in Winnipeg, Manitoba, Canada (US License No. 1201). All facilities for the manufacture of VARIZIG[®] have been inspected and licensed.

VARIZIG[®] is manufactured from human Source Plasma collected at FDA-licensed plasma centers from healthy donors who have high titers of anti-VZV antibodies. The VARIZIG[®] manufacturing process includes an anion exchange chromatography step and two viral reduction steps (a solvent/detergent treatment step and a 20N viral filtration step). Except for the starting plasma material and the lyophilization step, the manufacturing process for VARIZIG[®] is similar to that of Cangene's currently licensed hyperimmune globulin products, Rho(D) Immune Globulin Intravenous (Human), WinRho[®] SDF, Vaccinia Immune Globulin Intravenous (Human), CNJ-016[®], and Hepatitis B Immune Globulin Intravenous (Human), HepaGam B[®].

The final product formulation of VARIZIG[®] has 0.1 M glycine, 0.04 M sodium chloride and 0.01% (w/w) polysorbate 80. Each vial is filled to a target potency of (b)(4) 125 IU/vial to ensure (b)(4) 100 IU of anti-VZV activity over the shelf life of the product. Lyophilized VARIZIG[®] is stable up to 36 months, stored at 2-8 °C.

VARIZIG[®] is supplied as a kit in a carton box containing approximately 125 IU of freeze-dried anti-VZV in a 6 mL Type 1 glass vial fitted with a -----(b)(4)----- rubber stopper (20 mm), an aluminum seal and a plastic flip-off cap. A single use vial of 8.5 mL non-pyrogenic Sterile Diluent, containing 0.8% (mg/mL) sodium chloride and 10 mM sodium phosphate, is also supplied for reconstitution of the product prior to intramuscular administration. The reconstituted VARIZIG[®] has a pH of 7 and does not contain preservatives.

2. Background

The primary defense against VZV infection is cell-mediated immunity. However, the medical literature supports the practice of prophylactic administration of high-titered anti-VZV antibody products to VZV-exposed high risk patients who are not VZV-immune from lack of previous VZV exposure or from decreased VZV cell-mediated immunity.

The following table shows outcomes of immunocompromised children who contracted varicella at the St. Jude Children's Hospital and who received no anti-VZV treatments during the years 1962-1981:

Table 1: Outcome of Untreated Varicella in Immunocompromised Children Undergoing Cancer Treatment at St. Jude Children's Hospital (1962 to 1981)

Malignancy and Status		N	Mortality			Varicella-Zoster Virus Pneumonitis			Mortality for Varicella-Zoster Virus Pneumonitis		
			No.	%		No.	%		No.	%	
Acute leukemia											
	Remission	81	8	10	10	28	35	32†	8	29	31
	Relapse	10	1	10	*	1	10		1	100	
Others‡											
	Remission	30		0	0*	6	20	19†	0		
	Relapse	6		0		1	16		0		
Total		127	9	7		36	28		9	25	

*p = .06

†p > .1

‡Solid tumors, non-Hodgkin's lymphoma, chronic myelocytic leukemia, bone marrow transplantation, Hodgkin's disease, and histiocytosis X

Adapted from: *Feldman S., Lott L, Pediatrics* 80(4):465-472 (1987) Table 2

The observed 28% rate (36/127) of varicella pneumonitis in untreated immunocompromised children was reported to have decreased to 11% (5/45) in immunocompromised children who received various varicella immune globulin products after 1981 but before the availability of acyclovir (*ibid.*). Varicella-zoster immune globulin (VZIG™), licensed in 1981, was produced by the Massachusetts Public Health Biologic Laboratories (MPHBL) until 2006. The preponderance of evidence indicates that VZIG™ is effective in reducing the severity of VZV infections. The use of varicella immune globulin to ameliorate the effects of VZV infection in high-risk subjects is now considered to be standard of care at many centers.

Thus any new VZV immune globulin product could demonstrate efficacy if shown to be comparable to VZIG™. The approach taken by Cangene was to compare VARIZIG® to VZIG™ in head-to-head pharmacokinetic (PK) and clinical studies.

This original Biologics License Application (BLA) from Cangene Corporation (Winnipeg, Manitoba, Canada) was received by CBER on June 29, 2012, requesting U.S. licensure of a Varicella Zoster Immune Globulin (Human) product, trade name VARIZIG®. The sponsor received an Orphan Drug designation for this product and was granted a 6-month Priority Review schedule. The clinical studies were conducted under BB-IND 7201 for the passive immunization of exposed, susceptible individuals at risk of complications from varicella.

3. Chemistry, Manufacturing and Controls (CMC)

a) Product Quality

Source Plasma: The Source Plasma used for the manufacture of VARIZIG® is collected at FDA-licensed plasma collection centers in the United States and Health Canada from

healthy screened plasma donors, who have high titers of antibodies to VZV. Each plasma donation is tested for antibodies to human immunodeficiency virus (HIV) types 1/2 and hepatitis C virus (HCV), including hepatitis B virus surface antigen (HBsAg). Plasma pools are also tested by Nucleic Acid Tests (NAT) for HIV-1, hepatitis B virus (HBV), HCV, hepatitis A virus (HAV) and parvovirus B19 (B19V) at FDA-licensed testing laboratories. Plasma units found to be non-reactive (negative) in these tests (except for B19V NAT) are used for further manufacturing; for B19V, the manufacturing pool limit is set not to exceed 10^4 IU of B19V DNA per mL.

Only Source Plasma screened for high titers of anti-VZV is used for manufacturing VARIZIG[®] at the Winnipeg, Manitoba, Canada facility (U.S. License 1201). Plasma supplied to Cangene is frozen, stored, and transported under appropriately validated processes.

All facilities for the manufacture of VARIZIG[®] have been inspected and licensed. All other raw materials used in the manufacture of VARIZIG[®] are obtained from appropriately qualified vendors, quarantined on receipt, tested by validated methods, and released to manufacturing by QA personnel.

Manufacturing Process of VARIZIG[®]:

1. Process validation consisted of manufacture of VARIZIG[®] (lyophilized powder) and Sterile Diluent.
 - a. VARIZIG[®] is a lyophilized powder in a 6 mL Type 1 glass vial with a -----(b)(4)----- rubber stopper (20 mm), aluminum seal and a plastic flip-off cap. Each vial contains 125 IU of VZV antibody.
 - b. Sterile Diluent is provided in nominal 6 mL clear Type 1 glass vials with -----(b)(4)----- rubber stoppers (----- (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. VARIZIG[®] is manufactured in an area used for other hyperimmune globulin products on a campaign basis, with only one product manufactured at any time. A validated changeover procedure is used between campaigns.

3. Manufacturing Process Steps

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

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

The manufacturing date is the date of the sterile filtration and is used to set the expiration date.

Specifications: Specifications and validation of analytical methods have been evaluated by review personnel. Potency is measured using a validated ----- (b)(4) ----- method (----- (b)(4) -----) and the WHO International Standard for varicella zoster immunoglobulin (National Institute for Biological Standards and Control lot W1044, which contains 50 IU anti-VZV). The remainder of the final specifications and acceptance limits established for VARIZIG[®] by Cangene are within the ranges seen for other immune globulin products and were determined to be acceptable (Table 1). The specifications were established based on the results of a conformance lot, historical product data, and testing plans for Cangene's other licensed hyperimmune globulin products. The lot release testing program for VARIZIG[®] includes appropriate measures of product quality attributes, product impurities, and parameters known to affect product safety. All routine methods used as control or release testing of starting materials, process intermediates, drug product, and stability samples, were validated.

Table 2: Specifications for VARIZIG[®] (Lyophilized) Drug Product

Test	Standard Test Method (STM)	Specification
Identity	-(b)(4)-	----- (b)(4) ----- -----
--- (b)(4) --- -----	-(b)(4)-	-(b)(4)-
----- (b)(4) -----	-(b)(4)-	-(b)(4)-
----- (b)(4) -----	-(b)(4)-	-(b)(4)-
IgA	-(b)(4)-	≤ 40 µg/mL
-(b)(4)-	-(b)(4)-	----- (b)(4) ----- ----- ----- -----
-(b)(4)-	-(b)(4)-	----- (b)(4) -----

		(b)(4)----- ----- -----
------(b)(4)----- -----	-(b)(4)-	------(b)(4)-----
------(b)(4)-----	-(b)(4)-	-----(b)(4)----
Bacterial Endotoxins	-(b)(4)-	------(b)(4)-----
TnBP ------(b)(4)-----	-(b)(4)-	------(b)(4)-----
Triton X-100 ------(b)(4)-----	-(b)(4)-	------(b)(4)-----
------(b)(4)-----	-(b)(4)-	-(b)(4)-
Potency	-(b)(4)- -(b)(4)-	-(b)(4)- 125 IU/vial ^a Report results ^b
Total Protein	-(b)(4)-	< 250 mg/vial
pH	-(b)(4)-	-(b)(4)-
pH (1%)	-(b)(4)-	-(b)(4)-
General Safety Test	-(b)(4)-	Meets 21 CFR 610.11 requirements
Bulk Material Sterility	-(b)(4)-	Meets 21 CFR 610.12 requirements
Final Container Sterility	-(b)(4)-	Meets 21 CFR 610.12 requirements
Polysorbate 80	-(b)(4)-	------(b)(4)-----
Glycine	-(b)(4)-	------(b)(4)-----
Chloride	-(b)(4)-	------(b)(4)-----
Reconstitution Time	-(b)(4)-	< 10 minutes
Appearance (lyophilized product)	-(b)(4)-	White to off-white lyophilized cake
Appearance (reconstituted product)	-(b)(4)-	Clear to slightly opalescent colorless liquid, essentially free of foreign particles

^a A fill volume overage of -(b)(4)- 125 IU/vial is included to ensure label claim potency of -(b)(4)- 100 IU/mL throughout the shelf life). Note that the adult dose of VARIZIG[®] is 125 IU (one vial) per 10 kg body weight, where one vial is reconstituted with 1.25 mL Sterile Diluent. The maximum dose is 625 IU (equal to contents from 5 vials). Half a dose (62.5 IU, equal to half a vial) is being recommended for body weights ≤ 2 kg based on clinical data.

^b The ------(b)(4)----- results are reported as FIO (for information only), pending collection of sufficient data to set a specification at a later date.

Stability of Final Drug Product: The stability study data provided in the BLA were deemed sufficient to support the proposed shelf life of 36 months at 2 -8 °C for the

VARIZIG[®] final drug product. The shelf life of VARIZIG[®] was established based on real-time stability studies using the current container-closure system and based on samples taken from lots made via the commercial-scale production process. Testing included: potency, reconstitution time, pH, -----(b)(4)-----, appearance, total protein, sterility, and bacterial endotoxins.

Control of Adventitious Agents: The manufacturing process contains two steps implemented specifically for virus reduction. The solvent/detergent step (using -(b)(4)-TnBP and (b)(4) Triton X-100) is effective in the inactivation of enveloped viruses, such as HBV, HCV and HIV-1. Virus filtration, using a Planova 20N virus filter, is effective for the removal of viruses based on their size, including some non-enveloped viruses. These two viral reduction steps are designed to increase product safety by reducing the risk of transmission of enveloped and non-enveloped viruses. In addition to these two specific steps, the process step of anion-exchange chromatography was identified as contributing to the overall viral clearance capacity for small non-enveloped viruses.

Table 3: Virus Reduction Values (Log₁₀) Obtained through Validation Studies

Enveloped	Enveloped			Non-Enveloped			
Genome	RNA		DNA	RNA		DNA	
Virus	HIV-1	BVDV	PRV	HAV	EMC	MMV	PPV
Family	retrovirus	flavivirus	herpesvirus	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	Not evaluated	3.4	Not evaluated
20N Filtration (size exclusion)	≥ 4.7	≥ 3.5	≥ 5.6*	Not evaluated	4.8	Not evaluated	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

Conclusion: The CMC reviewers find that sufficient data and information have been provided on the chemistry, manufacturing, and controls to support licensure of VARIZIG[®].

b) CBER Lot Release

Mode of Lot Release: VARIZIG[®] has been designated as an Orphan Drug. CBER is expecting to release one lot about every 2 years. Protocol review will be the mode of lot release because of the long history with Cangene's licensed WinRho[®] SDF (STN 103649). The manufacturing process for VARIZIG[®] ---(b)(4)--- as for WinRho[®] SDF except that the starting plasma is collected from selected donors with increased titers of VZV antibodies. There are no product quality or safety concerns that would dictate CBER confirmatory testing. The BLA submission review showed that all of the release tests are appropriately performed and validated.

The following forms the rationale for the testing plan:

Safety and Purity:

1. The safety and purity of the final product are evaluated based on the information in the lot release protocols submitted to CBER. Tests for safety and purity performed by Cangene and reviewed by CBER include: Sterility, General Safety, Endotoxins (by -----(b)(4)----- assay), -----(b)(4)-----, Immunoglobulin A, Anti-A and Anti-B Antibodies. Confirmatory testing by CBER is not recommended at this time.
2. VARIZIG[®] is produced only from Source Plasma collected at FDA-licensed plasma collection centers. All plasma donations are screened for viral markers, including anti-HIV-1/2 antibodies, HBsAg, anti-HCV antibodies. Plasma is also tested by NAT for HIV, HBV, HCV, HAV and B19V. The B19V DNA limit for the manufacturing plasma pools is set at less than or equal to 10⁴ IU/mL.
3. The manufacturing process for VARIZIG[®] contains no unusual or unique manufacturing steps, and is ---(b)(4)--- to that of Cangene's licensed WinRho SDF product.
4. The manufacturing process for VARIZIG[®] contains two viral reduction steps to ensure product safety from both enveloped and non-enveloped viruses.

Potency and Identity:

The potency and identity of the final product are evaluated from the information in the lot release protocols submitted to CBER. Tests for potency and identity performed by Cangene and reviewed by CBER include: Identity, Total Protein, -----(b)(4)-----, -----, and Potency (-(b)(4)-). Confirmatory testing by CBER is not recommended at this time.

c) Facilities Review/Inspection

The pre-license inspection of the Winnipeg, Manitoba facility in Canada was waived for Cangene BLA STN 125430, VARIZIG[®]. Cangene (FEI Number 3003153579, U.S. License Number 1201, CFN# 9611419) is already licensed for the manufacture of other

hyperimmune globulin products, such as WinRho[®] SDF (BLA STN 103649, approved in 1996), CNJ-016[®] (BLA STN 125109, approved in 2005), and HepaGam B[®] (BLA STN 125035, approved in 2006; STN 125237, approved in 2007).

The process for manufacturing VARIZIG[®] is similar to that for the abovementioned products. The address for the facility is: Cangene Corporation, 155 Innovation Drive, Winnipeg, Manitoba R3T 5Y3, Canada.

d) Environmental Assessment

On November 28, 2012, DMPQ recommended that Cangene be granted a categorical exclusion under 21 CFR 25.31 (c).

4. Nonclinical Pharmacology/Toxicology

There were no pharmacology and toxicology studies performed with VARIZIG[®]. Given the preclinical and clinical experiences with immune globulin products produced from the same manufacturing process, this is considered acceptable. A risk analysis of the excipients and impurities was performed that raised no toxicological concerns for VARIZIG[®]. As such, there are no preclinical pharmacology and toxicology issues that would prevent the product from being licensed.

5. Clinical Pharmacology

The objective of the Pharmacokinetic (PK) study was to establish the comparative bioavailability of two different varicella zoster human immune globulin products, VARIZIG[®] (test product, Cangene Corporation, Canada) and VZIG[™] (reference product, Massachusetts Public Health Biological Laboratories, USA), following intramuscular administration to healthy volunteers.

This study was originally designed as a double blind, randomized, parallel arm trial comparing VARIZIG[®] and VZIG[™] in 60 healthy adult subjects. Regulatory approval for investigational product importation from the Drug Controller General, India (DCGI) was not received until just prior to expiry of the final lot of VZIG[™]. Therefore, only 35 subjects were enrolled and randomized to receive treatment before VZIG[™] was no longer available for the trial. VARIZIG[®] was administered to 18 subjects, while VZIG[™] was given to 17 subjects.

The PK study was a Phase 1 single-center, double-blind, randomized study with two parallel arms. Intramuscular injections of either VARIZIG[®] or VZIG[™] were administered to male healthy volunteers between the ages 19 and 39. The subjects received the test product, VARIZIG[®], at a dose of 12.5 IU/kg of body weight by intramuscular (IM) injection. An equal volume of VZIG[™] was given to avoid unblinding. Based on potency using a validated --(b)(4)--, the VZIG[™] dose was 2.29 fold higher than the VARIZIG[®] dose. The statistical analysis plan for the PK data stated prospectively that a potency correction would be needed when analyzing the results.

There was no pre-determined maximum dose. The subjects were followed for 84 days after drug administration for pharmacokinetic analyses.

One of the inclusion criteria in the study was a negative anti-VZV screening test. However, subjects with positive baseline anti-VZV antibodies were inadvertently enrolled into the study. An initial screening test performed by a local laboratory indicated that 15 subjects were negative while 20 subjects tested positive. A confirmatory screening anti-VZV tests by the central laboratory indicated that every subject was anti-VZV negative. Cangene decided to use the central lab anti-VZV test results for subject inclusion. Further anti-VZV sample testing (post-study) performed with Cangene's validated pharmacokinetic anti-VZV --(b)(4)-- revealed that 17/35 subjects were positive at screening and baseline. At baseline 18 subjects had low/undetectable anti-VZV (<5 mIU/mL), 6 subjects had moderate levels (10 to < 200 mIU/mL) and 11 subjects had high anti-VZV titers (≥ 200 mIU/mL). In the analysis of the PK data baseline corrections were performed and the 11 subjects with ≥ 200 mIU/mL excluded.

Blood samples (15 mL) for pharmacokinetic study were collected after VARIZIG[®] or VZIG[™] administration for anti-VZV analysis at the following time-points: 12 hours, day 1, 2, 3, 4, 5, 7, 9, 11, 14, 21, 28, 42, 56 and 84. The 90% confidence interval (CI) for the assessment of comparability was applied on log transformed C_{max} and $AUC_{(0-28 \text{ or } 0-84)}$. Drug concentrations were measured by the --(b)(4)-- method at Cangene Corporation.

The results of the study are summarized in Tables 1-3. From Tables 1 and 2 it appears that the inter-subject variability for both formulations is substantially high. This high variability in both test and reference formulations may have resulted in the failure of 90% CI (the two products are not bioequivalent).

Table 4: Pharmacokinetic Parameters and 90% Confidence Interval (CI) for VARIZIG[®] and VZIG[™] (Baseline Uncorrected)

Parameters	VZIG [™] (reference)	VARIZIG [®] (test)	% difference	90% CI
C_{max} (mIU/mL)	297 \pm 186 (63)	221 \pm 266 (120)	26	26.4-77.7
$AUC_{(0-28)}$	10605 \pm 9366 (88)	9182 \pm 13090 (142)	13	18.9-89.1
$AUC_{(0-84)}$	19952 \pm 19012 (95)	14460 \pm 21420 (148)	28	17.1-84.3

AUC unit is (mIU*day/mL); n = 17 for both formulations

Numbers in parenthesis are percent coefficient of variation (%CV)

Due to high variability in the baseline, both AUC and C_{max} values were corrected for baseline and the potency of the products was also adjusted. In Table 2, the results of the study are summarized. Even after baseline and potency correction the products were not bioequivalent.

Table 5: Pharmacokinetic Parameters and 90% Confidence Interval (CI) for VARIZIG[®] and VZIG[™] (Baseline and Potency Corrected)

Parameters	VZIG [™]	VARIZIG [®] (test)	%	90% CI
------------	-------------------	-----------------------------	---	--------

	(reference)		difference	
C_{\max} (mIU/mL)	147 ± 40 (27)	164 ± 135 (82)	12	77.9-122.1
$AUC_{(0-28)}$	2335 ± 896 (38)	3044 ± 2900 (95)	30	82.2-154.3

N = 17 for VZIGTM and n = 14 for $AUC_{(0-28)}$ calculation; three subjects from VARIZIG[®] treatment group were excluded due to negative anti-VZV concentrations after baseline correction.

Numbers in parenthesis are percent coefficient of variation (%CV)

Following the baseline correction, a post-hoc analysis was performed excluding 11 subjects (VZIGTM treatment group: n=5; VARIZIG[®] treatment group: n=6) with high baseline anti-VZV concentrations (≥ 200 mIU/mL). The results of this analysis are summarized in Table 3.

Table 6: Pharmacokinetic Parameters and 90% Confidence Interval (CI) for VARIZIG[®] and VZIGTM (Baseline and Potency Corrected)

Parameters	VZIG TM (reference)	VARIZIG [®] (test)	% difference	90% CI
C_{\max} (mIU/mL)	138 ± 22 (16)	136 ± 66 (49)	1	76.4-112.8
$AUC_{(0-28)}$	2347 ± 535 (23)	2472 ± 970 (39)	5	84.1-124.6

AUC unit is (mIU*day/mL); n = 12 for both formulations

Numbers in parenthesis are percent coefficient of variation (%CV)

Conclusions: Based on the bioequivalence (BE) criteria (CI = 80% to 125%), the two formulations are not bioequivalent (with or without baseline and potency corrected) since both C_{\max} and AUC fail to meet the 90% confidence interval (CI) of 80% to 125%. However, when 11 subjects with high baseline anti-VZV levels (≥ 200 mIU/mL) were excluded, $AUC_{(0-28)}$ met the bioequivalence criteria of 80 to 125%, but C_{\max} failed to meet this limit. However, the two products can be termed as ‘pharmacokinetically comparable’ after excluding subjects with high baseline anti-VZV levels (≥ 200 mIU/mL).

6. Clinical/ Statistical

Efficacy

VZ-006 -- Varicella-exposed, serologically confirmed varicella-naïve pregnant women.

Sixty (60) women enrolled, and 3 were excluded from the efficacy analysis due to inappropriate enrollment (subjects -----(b)(6)----- were immune at baseline; -(b)(6)- had active varicella infection at enrollment).

There were two enrollment strata based on the time from exposure to treatment, as follows:

1. Stratum 1: 1-4 days from exposure
2. Stratum 2: 5-14 days from exposure

The proposed primary endpoint for study VZ-006 was changed by the sponsor over time, as follows:

1. 1997 (IND 7201): Constitutional Illness Score (CIS) at day 7 after treatment initiation
2. 2005 meeting: CIS at time of clinical varicella (rash)
3. BLA STN 125430 (and in places in IND 7201): rate of varicella infection determined clinically (rash, symptoms; but not by serological confirmation)

Table 7: Sponsor's Per Protocol Efficacy Analysis: Subjects with Clinical Varicella

Study Arm	No. Enrolled	No. with Varicella Infection (%)
VZIG™ i.m.	19	8 (42%)
VARIZIG® i.m.	17	5 (29%)
VARIZIG® i.v.	21	6 (29%)

These outcome differences between study arms are not statistically significant ($p = 0.643$). However, this does not establish VARIZIG® and VZIG™ arms as clinically equivalent, as there was no agreed upon statistical plan employing an *a priori* non-inferiority margin. Furthermore, any comparison of varicella infection rate between VZIG™ and VARIZIG® must take into account the lack of convincing data from the literature to demonstrate that VZIG™ reduced the incidence of chickenpox when given following VZV exposure.

The sponsor compares these outcomes to a theoretical historical control rate of 70%, and states that the 95% confidence interval for the 29% attack rate for VARIZIG® i.m. excludes the theoretical historical control rate of 70%.

The sponsor proposes this historical control rate based on an observed varicella attack rate of 87% in a household (sibling) contact study [Ross A.H. *et al.*, *NEJM* 267(8):369-376 (1962)]. The sponsor reduced the reported 87% attack rate in the Ross study to a proposed theoretical historical control attack rate of 70% for study VZ-006, recognizing that some varicella exposures in VZ-006 are likely to be less intense than those in the Ross study. There was no prospective agreement with FDA on the theoretical historical control attack rate of 70% for study VZ-006.

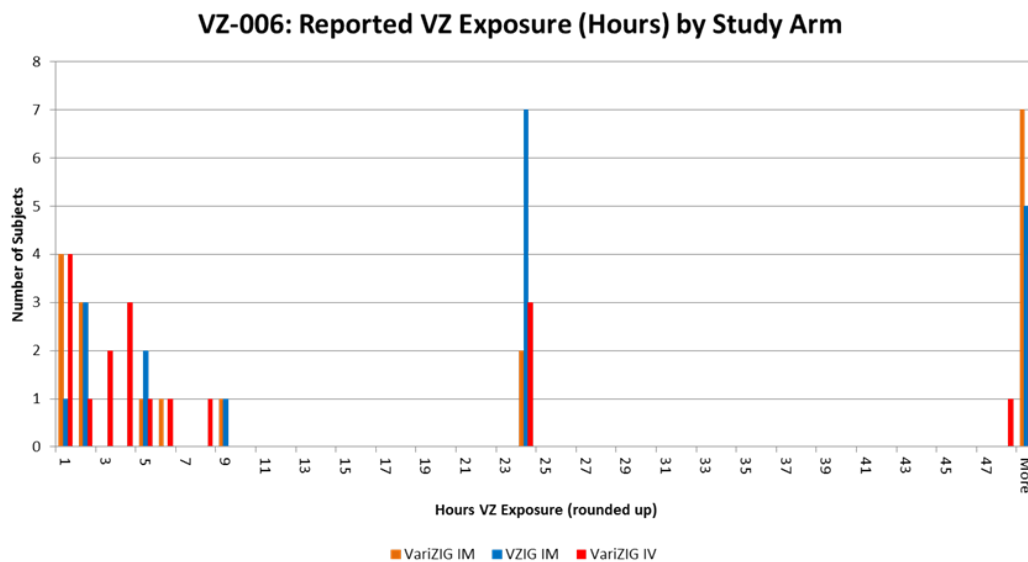
FDA Analysis of the Incidence of Clinical Varicella in VZ-006

Protocol VZ-006 did not precisely define 'clinical varicella'; however, it is apparent from the sponsor's analyses that 'clinical varicella' is to be interpreted as the observation of typical varicella pock lesions after exposure to persons experiencing chickenpox or zoster. By this definition, the sponsor includes subjects as having 'clinical varicella' even if the Constitutional Illness Score is zero at every time point.

Although a follow-up anti-VZ antibody measurement was made at day 42, the results of this test did not influence the determination of ‘clinical varicella’; therefore, subjects with subclinical varicella were not considered in the sponsor’s analysis.

FDA reviewed the reported varicella exposure times and derived the following frequency histogram after rounding times up to the nearest hour:

Figure 1: Reported VZ Exposure



It is apparent that the distribution of varicella exposure times for VZ-006 differs markedly from the expected distribution for a household contact study, such as the Ross study, where all exposure times are expected to be at least 24 hours.

Therefore, outcomes were analyzed by the extent of varicella exposure being less than or more than 24 hours. The following chart shows the results:

Table 8: Number of Subjects with Clinical Varicella by Strata and Exposure Time

	VARIZIG [®] IM		VZIG [™] IM		VARIZIG [®] IV	
Stratum	< 24 hours	>24 hours	< 24 hours	>24 hours	< 24 hours	>24 hours
1-4 days	1/8	3*/3*	0/3	5/8	0/7 [†]	3/5
Subject IDs of infected	-(b)(6)-	----(b)(6)---- -----		----(b)(6)---- -----		---(b)(6)--- -----
5-14 days	0/2	1/5	0/4	3/4	0/7	3/3
Subject IDs of infected		-(b)(6)-		----(b)(6)---- -----		---(b)(6)--- -----

* -(b)(6)- is excluded from the analysis because she had clinical varicella at baseline

[†]-(b)(6)-, in the non-infected VARIZIG[®] IV stratum 1 group, does not have a submitted VZ exposure time; therefore, for this analysis -(b)(6)- is included in the denominator of the less than 24 hours exposure group.

The low attack rate for subjects in the < 24 hours exposure group (1 case of clinical varicella in 30 subjects) implies that most of the subjects in this group did not have exposures intense enough to justify inclusion with the > 24 hours exposure group (18 cases of clinical varicella in 29 subjects).

Therefore, if the analysis considers only subjects with varicella exposure times more than 24 hours, and if the data for the two VARIZIG[®] arms are combined, the following numbers, rates, and 95% confidence intervals are obtained:

Table 9: Number of Infected Subjects and Attack Rates

	No. Infected/No. Subjects	Attack Rate	95% Confidence Interval
VARIZIG [®]	10/16	63%	(35.4%--84.8%)
VZIG [™]	8/12	67%	(35% -- 90%)

With the above analysis, the 95% confidence interval no longer excludes the sponsor's postulated theoretical untreated historical control attack rate of 70%.

In summary, data are not sufficient to conclude that VARIZIG[®] reduces the incidence of clinical varicella infection in pregnant women when given after exposure to VZV.

Sponsor's Analysis of the Constitutional Illness Score (CIS) in VZ-006

The original protocol VZ-006 stated that the primary endpoint was the CIS at day 7 after treatment. The CIS methodology was based on a study of the use of acyclovir to treat varicella patients [Wallace, et al. *Ann Int Med* 117:358-363 (1992)]. FDA requested justification for the day 7 endpoint in the context of the VZ-006 study design; however, this endpoint was not accepted by FDA as being adequately justified (see Appendix 1, Chronology of Regulatory Events).

The VZ-006 study results showed that the day 7 CIS was zero for every subject, except subject -(b)(6)- who was excluded from the analysis because the subject had varicella at study entry.

The sponsor then evaluated the CIS at the time of clinical varicella (time of rash onset). CIS for subjects contracting varicella gave the following results:

Table 10: Sponsor’s Post Hoc Analysis of CIS Scores at the Time of Clinical Varicella

Characteristic	Value	Treatment			Total (n=57)
		IM VZIG™ (n=19)	IM VARIZIG® (n=17)	IV VARIZIG® (n=21)	
CIS Score	CIS 0 ¹	13 ²	13 ³	16 ⁴	42
	CIS 1	0	0	2	2
	CIS 2	0	0	0	0
	CIS 3	1	0	1	2
	CIS 4	3	0	0	3
	CIS 5	0	1	0	1
	CIS 6	2	3	0	5
	CIS 7	0	0	2	2
Mean Weighted CIS Score		1.42	1.35	0.90	
Contracted Varicella ⁵	No	11 (58%)	12 (71%)	15 (71%)	38 (67%)
	Yes	8 (42%)	5 (29%)	6 (29%)	19 (33%) ⁶

1. Patients who did not develop clinical varicella were assigned a score of 0.

2. Patients -----(b)(6)----- developed varicella and had a CIS score of 0.

3. Patient -(b)(6)- developed varicella and had a CIS of 0.

4. Patient -(b)(6)- developed varicella and had a CIS of 0.

5. Omnibus comparison between groups for overall incidence of varicella, p=0.040. No significant differences noted for any pairwise group comparison.

6. Between group comparison for positive varicella, p=0.643.

Source: Original BLA 125430/0; Clinical Study Report for study VZ-006, Vol 5.3.5.1, p.23

The sponsor states the “comparison did not show significant differences between the test articles VARIZIG® and licensed VZIG™) or between strata (length of exposure to VZV: 1-4 days or 5-14 days).” [Original BLA 125430/0; Clinical Study Report for study VZ-006, Vol 5.3.5.1, p.49]

FDA agrees with the sponsor's conclusion that significant differences are not seen between study arms or strata. However, the fact that there was no agreed upon statistical plan for analysis of non-inferiority of VARIZIG[®] in comparison to VZIG[™] in terms of CIS using an a priori established non-inferiority margin precludes any definitive conclusion of clinical equivalence between the two products in reducing CIS. However, the generally similar pattern of CIS results and mean weighted scores among the VZIG[™] and VARIZIG[®] groups is supportive of the notion that the two products likely share similar efficacy in reducing CIS in varicella infection. This further supports the notion that VARIZIG[®] is comparable to VZIG[™] with regard to efficacy with regard to reducing VZV infection severity.

Study VZ-006 Safety.

There were no deaths. There were 4 serious adverse events (worsening asthma – VARIZIG[®] i.m. study arm; spontaneous abortion – 2 subjects – 1 in VZIG[™] arm, 1 in VARIZIG[®] i.m. arm; and 1 therapeutic abortion unrelated to treatment).

VZ-009 – Expanded Access for High Risk Subjects.

The objective of the expanded access protocol VZ-009 was to make the investigational product available nationwide to at-risk patients exposed to varicella. Collection of safety and efficacy data was undertaken to the extent possible. .

Study VZ-009 evaluated the incidence of varicella infection as the primary endpoint. Outcomes were compared to historical control rates.

Study VZ-009 was an open-label Expanded Access Protocol to provide VARIZIG[®] to high risk subjects following exposure to VZV in the USA. The study was conducted by the U.S. distributor of the product, FFF Enterprises, Inc.

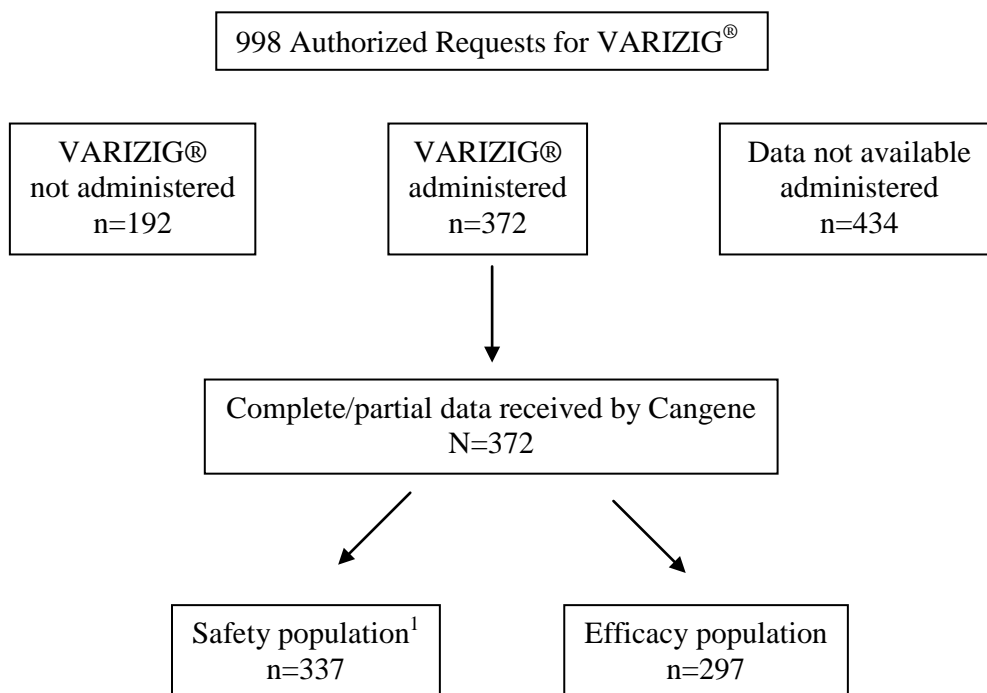
There were four visits prescribed in the protocol, as follows:

- Baseline visit (visit 1)
 - collection of eligibility data,
 - medical history,
 - varicella exposure history,
 - informed consent,
 - hematology and blood chemistry parameters (if available),
 - VARIZIG[®] administration and
 - adverse event monitoring.
- Two observational visits
 - Visit 2 conducted between Day 1-4 and
 - Visit 3, between Day 7-20, collect data on safety and efficacy.

- Visit 4 between Day 28-42, include the overall clinical review of varicella infection and completion of adverse event and safety data.
- Follow-up with for 4 weeks (or to resolution of varicella infection) and completion of the CRF was encouraged.

Out of 998 authorized requests for VARIZIG[®] under study VZ-009, partial or complete efficacy data were received by the sponsor for 297 subjects (30%).

Figure 2: Sponsor's Depiction of Data Available for Evaluation of Safety and Efficacy for Study VZ-009



n=numbers of subjects

¹ Safety data received by Cangene include information derived from CRFs and SAE forms

The following table gives these results of the sponsor's analysis of infection rate:

Table 11: Sponsor's Comparison of Incidence of Varicella in Subjects Treated with VARIZIG[®] and Historical Incidence of Varicella in Untreated Individuals

High Risk Population	Historical Incidence of Varicella in Untreated Individuals	n ¹	Incidence of Varicella in VARIZIG [®] -treated Subjects	95% Confidence Interval	P-value ²

Pregnant women	70%	70	5.7% (n=4)	(1.6% - 14.0%) ³	<.0001*
Immunocompromised patients	88%	153	5.2% (n=8)	(2.3% - 10.0%)	<.0001*
Infants including newborns, pre-term infants and infants <1 year	50%	78	12.8% (n=10)	(6.3% - 22.3%)	<.0001*

¹ n = number of VARIZIG[®] doses for post-exposure prophylaxis of varicella.

² One sample two-sided exact binomial test.

³ Gray shading has been added to this cell by the reviewer to emphasize this result that appears to be substantially different than the outcomes reported for the maternal exposure study VZ-006. The reasons for this difference are not known.

* Statistically significant ($\alpha=0.05$).

Source: Original BLA 125430/0; Clinical Study Report for study VZ-009, Vol 5.3.5.1, p.48 of 306

These results should be taken in the context of incomplete reporting, the lack of a prospectively agreed-upon statistical analysis plan, concomitant antiviral use in some cases, and variability in duration of exposure between the historical studies and VZ-009. Excluding pregnant women and infants, a total of 8 immunocompromised patients developed clinical varicella following exposure and treatment with VARIZIG[®]. None of these subjects were reported to have developed chickenpox pneumonia (0/8), or death (0/8). One infant developed probable encephalitis.

FDA comment on the evaluation of efficacy in study VZ-009

Study VZ-009 was incompletely monitored and reported. Therefore, comparing outcomes of VZ-009 to historical controls is not rigorous. Nevertheless, the zero reported incidence of chickenpox pneumonia of 8 immunocompromised patients and infants where the untreated incidence is expected to be on the order of 28% supports the notion that the efficacy of VZIG[™] in reducing the severity of chickenpox in patients exposed to VZV is likely shared by VARIZIG[®].

Study VZ-009 Safety.

There were 6 serious adverse events due to coagulopathy in the Expanded Access study VZ-009. Five reports involved bleeding, and the sixth report was of a thrombosis at the site of a deep venous catheter.

Adverse event reporting was not uniform across study sites for study VZ-009. Concerns about the monitoring and reporting of safety in VZ-009 were communicated to the sponsor on October 4, 2012, and the sponsor's response states that VZ-009 was intended to address a shortage of varicella immune globulin products for high-risk patients, and that the incompleteness of the study databases was known and expected. The sponsor stated that efforts to update the safety database for VZ-009 will continue.

Clinical Study Conclusions

1. The results of VZ-006 support a claim of safety in varicella non-immune pregnant women exposed to varicella virus. The results of VZ-006 do not support a claim for the prevention of varicella infection in varicella non-immune pregnant women exposed to varicella virus. The results of VZ-006 are consistent with mitigation of varicella infection severity. The CIS was similar for VZIGTM and VARIZIG[®] treatment groups. In women who developed clinical varicella, there were no reports of pneumonitis. Historically, the expected rate of pneumonitis in pregnant women was reported to be 17.5% (Paryani and Arvin, NEJM 1986; 314:1542-6). Comparisons of VZ-006 safety and efficacy outcomes for VARIZIG[®] to VZIGTM outcomes were under-powered to detect differences.
2. VZ-009, the expanded access study, was not originally designed to provide safety or efficacy data for product licensure. The lack of any cases of chickenpox pneumonia among 8 immunocompromised patients and infants in study VZ-009 is consistent with the notion that the efficacy of the VZIGTM in reducing the severity of chickenpox when given after exposure to varicella is shared by VARIZIG[®], notwithstanding important caveats such as incomplete reporting, concomitant use of antiviral medications, and variability in exposure type and duration.
3. Post-exposure prophylaxis of high-risk varicella-naïve patients with immune globulin products containing antibodies against VZV has become standard practice since the licensure of VZIGTM in 1981. A 1987 published review of all cases of varicella at St. Jude's Children's Hospital from March 1962 through 1986 [*Pediatrics* 80(4):465-475 (1987)] allowed a comparison of outcomes between the pre-VZIGTM era and the five-year period when VZIGTM was available. The authors state that in untreated immunocompromised children contracting varicella (N = 127), pneumonitis developed in 28% of cases; however, in a comparable group of children who received VZIGTM prophylaxis (N = 45), pneumonitis occurred in only 11% of cases. These data supported the licensure of VZIGTM. It is not possible to compare the rates of adverse events, such as pneumonitis, in study VZ-009 to rates reported in this paper because monitoring for adverse events in study VZ-009 was incomplete. In addition, the concomitant use of antivirals, such as acyclovir, would confound this comparison. However it is noted that the incidence of pneumonitis was 0/8 among immunocompromised children treated with VARIZIGTM who developed clinical varicella.

Recommendation.

Varicella can have serious, potentially fatal complications in immunocompromised patients and infants, including chickenpox pneumonia and encephalitis. FDA, in making its regulatory decision on this application, is taking into account the unmet medical need for a product to reduce the severity and incidence of complications of varicella and the difficulty of conducting clinical trials in this disease following the widespread availability and use of chickenpox vaccine.

VARIZIG[®] is recommended for licensure based on the totality of (a) the results of the pharmacokinetic study VZ-008 that showed pharmacokinetic outcomes reasonably comparable to those of the licensed product VZIG[™] can be achieved through appropriate dosing of VARIZIG[®]; (b) the similarity of CIS scores in pregnant women in VZIG[™] and VARIZIG[®] arms in study VZ-006 and lack of pneumonitis in pregnant, infected patients; and (c) the lack of reports of chickenpox pneumonia (and encephalitis) in expanded access study VZ-009, notwithstanding important caveats of the latter two studies. VZ-006 and VZ-009 can be considered supportive for licensure.

Safety Conclusions:

It is also the Statistical Reviewer's conclusion from the VZ-006 and VZ-009 clinical studies submitted that no serious safety issues were found.

Bioresearch Monitoring (BIMO) and Summary of Clinical Site Inspections

Four Bioresearch Monitoring (BIMO) inspections of clinical investigators were conducted in support of BLA STN 125430/0. The inspections revealed potential under reporting of AEs and incomplete subject data was submitted to the BLA. Seven BIMO-related information request (IR) questions were sent to the sponsor on October 4, 2012 concerning potential compliance issues. The sponsor's IR response dated October 25, 2012 confirmed various observed BIMO clinical investigator inspection deficiencies including study documentation, missing subject data, and lack of monitoring as described within the BIMO inspection reports.

The BIMO branch requested four clinical investigator inspections covering two clinical studies in support of the BLA. Information from the BLA was compared to source documents during the inspections. The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The BIMO inspection assignments included specific questions for the following clinical studies:

Protocol VZ-006

Randomized Trial of Varicella Zoster Immune Globulin (NP-001) to Prevent or Modify the Course of Varicella Zoster Infection in Pregnant Women

Protocol VZ-009

Safety and Efficacy of Varicella Zoster Immune Globulin (Human) (VARIZIG[®]) in Patients At-Risk of Varicella Infection

Table 12: Inspections of Clinical Investigators and Outcomes

Study Number	Study Site	Location	Form FDA 483 Issued	Inspection Final Classification
VZ-009	Children's Hospital of Michigan	Detroit, Michigan	Yes	VAI
VZ-009	Oregon Health & Science University	Portland, Oregon	Yes	VAI
VZ-009	Wesley Medical Center	Wichita, Kansas	Yes	VAI
VZ-006	Hospital for Sick Children	Toronto, Ontario Canada	Yes	VAI

Significant Inspectional Findings

The results from BIMO inspections included the following significant sponsor issues and study documentation deficiencies:

Study VZ-006: FDA noted that several source documents for the 46 enrolled subjects in study VZ-006 could not be found by the clinical investigator or the sponsor. Missing documents included subject visit records, informed consents, medical histories, concomitant medications, serology testing, physical exams, lesion counts, symptoms of varicella, measurement of vital signs, adverse events and severe adverse events. Each subject's CRF data could not be confirmed due to the lack of source data at the site. This study was not performed under IND and the clinical investigator stated he did not anticipate data from this study to be submitted to FDA.

Study VZ-009:

1. The VZ-009 study was conducted without an officially designated clinical investigator as stated in the sponsor's IR response dated October 25, 2012. Clinical investigators at several sites did not sign the Form FDA 1572, Statement of Investigator (the investigator's commitment to follow the regulations) until a few weeks after subjects received the investigational product.
 - a. A fourteenth subject at the Wichita site was administered the test vaccination by an obstetrician who was not listed as a sub-investigator for the study. The study staff neither submitted the above release form to the sponsor nor found the document until after the FDA investigator announced the inspection. In addition, one dose of the investigational drug was given to another area hospital without the clinical investigator's knowledge. This product was subsequently returned and destroyed.
 - b. Inspection documents reviewed for the Wichita and Portland sites showed no evidence of study staff training, use of a subject screening log, or documentation of delegated study personnel activities or responsibilities

2. Documentation showing clinical investigators had previous clinical trial experience was not required by the sponsor and there was no evidence showing investigator training.
3. Study VZ-009 clinical investigators did not complete or review case report forms in a timely fashion, as stated in the sponsor's IR response dated October 25, 2012. The Sponsor noted that the VZ-009 study is still ongoing and not all investigators provided requested data and regulatory documents and most information provided was incomplete.
4. For VZ-009, the sponsor did not conduct study-initiation and protocol-required monitoring visits at many sites prior to study start, or during the study, as required by the protocol. These omissions were confirmed in the sponsor's written IR response dated October 25, 2012.
 - a. There was no documentation showing that FFF Enterprises, the sponsor's contracted representative for distributing the test article to the Wichita, Portland, or Detroit sites, had contacted clinical investigators within 7 days after receipt of the test article, for follow-up and discussion of data collection.
 - b. There was no documentation showing the sponsor (or designate) contacted the clinical investigator by phone at least 3 times during the study to collect data, as required.
 - c. The sponsor (or designate) conducted the protocol-required site monitor close-out visit at only one study site (Wesley Medical Center).
5. Clinical investigators did not receive any onsite training prior to conducting the VZ-009 study. Site Training was not offered by the sponsor until August-September 2012, but the study was initiated in 2006.
6. Study VZ-009 clinical investigators at the Wichita and Portland sites did not complete or review case report forms in a timely fashion.
7. Study VZ-009 informed consent documentation issues at the Portland and Detroit sites include the following:
 - a. There was no language in the informed consent for describing undetermined risks for pregnant subjects or possible risks to unborn fetuses. Two of 13 subjects reviewed during the inspection did not sign an informed consent form. The time of informed consent was not documented for seven of 13 subjects reviewed at the Portland site.
 - b. The required native language Short Form Consent document for non-English speaking subjects was not utilized for one subject. There was no documentation showing oral assent for two subjects between the ages of 7 and 12 (Detroit site).

8. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this BLA.

10. Labeling

Proprietary Name: The sponsor's proprietary name, VARIZIG[®], was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and safety perspective. This name was found to be tentatively acceptable on December 6, 2012.

Physician Labeling: The final VARIZIG[®] Package Insert is PLR compliant.

Package Insert: The recommendation by an APLB reviewer that the proprietary name be rejected was not implemented on the basis of a final determination by the product office and clinical branch after further consideration and consultation with management (as specified in SOPP 8001.4). Cangene provided draft package insert with the original BLA submission on June 29, 2012. FDA comments on labeling were conveyed to the firm on November 29, 2012 and December 17 and 19, 2012, and Cangene resubmitted the labeling with incorporation of FDA comments on December 6, 18, and 20, 2012.

Carton and Immediate Container Labels: Cangene provided draft carton and container labeling with the original BLA submission on June 29, 2012. FDA comments on labeling, including that for carton and container were conveyed to the firm on November 29, 2012 and Cangene resubmitted the labeling with incorporation of FDA comments on December 6, 2012.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The recommended regulatory action is approval based on the comparable pharmacokinetic results to the licensed VZIG[™] product and the supportive data from the clinical trial in pregnant women and the expanded access study.

Epidemiologic data comparing the incidence of complications of varicella before and after the availability of varicella immune globulin (but before the advent of acyclovir therapy), are suggestive of efficacy for the licensed product VZIG[™]. Any such efficacy of VZIG[™] is expected to be shared by VARIZIG[®].

Although the clinical data suffered from deficiencies, a decision to approve VARIZIG[®], took into account the small number of cases available for enrollment and the unlikely prospect of more robust studies in the future.

b) Risk/ Benefit Assessment

VZV infections in pregnancy and in adults, especially immunocompromised individuals have serious outcomes, including encephalitis, pneumonitis, and mortality. VARIZIG[®] is anticipated to fulfill an unmet need to reduce the severity of infections in at risk individuals exposed to VZV.

Overall, the benefits of VARIZIG[®] in reducing the rate of infections and/or preventing severe infections in individuals exposed to VZV compared to the risks are acceptable, and favor use of VARIZIG[®].

c) Recommendation for Post-marketing Activities

POSTMARKETING COMMITMENTS

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[--(b)(4)-- **]**

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

FDA requested Cangene to label prominently all submissions, including supplements, relating to these postmarketing study commitments. For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, the status must be described in an annual report on postmarketing studies for this product. Label the annual report an “Annual Status Report of Postmarketing Study Commitments.”