



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

To: BLA STN 125430\0 File

From: Maria L. Virata-Theimer, Ph.D., LPD/DH/OBRR, HFM-345

Through: Dorothy E. Scott, M.D., Chief, LPD/DH/OBRR, HFM-345

CC: Nannette Cagungun, RPM, DBA/OBRR, HFM-380

Applicant: Cangene Corporation, Winnipeg, Manitoba, Canada

Product: Varicella Zoster Immune Globulin (Human)
Proposed Trade name: Varizig®

Subject: Midcycle CMC Review: Original BLA - Product Specifications, Analytical Methods and Method Validations, Nucleic Acid Testing of Viruses in Plasma Pools, Transmissible Spongiform Encephalopathy Safety

Recommendation

An information request will be sent to the firm (see Letter-Ready Comments).

Background Summary

FDA CBER received on 29-JUN-12 this original Biologics License Application (BLA) submission from Cangene Corporation for Varicella Zoster Immune Globulin (Human), with the proposed trade name, "Varizig®". Cangene is claiming an Orphan Drug Designation for Varizig (as per the letter dated 7-NOV-06). Varizig is indicated for the post-exposure prophylaxis of varicella in high-risk individuals.

Pei Zhang, M.D. of LPD/DH/OBRR, HFM-345 and I are the co-chairs of this BLA submission. My CMC review covers the following assigned topics: Product Specifications, Analytical Methods and Method Validations (except for potency testing, which will be reviewed by Philip R. Krause, M.D. of OVR, HFM-457), Nucleic Acid Testing (NAT) and serological testing of viruses in the plasma pools, and Transmissible Spongiform Encephalopathy (TSE) Safety.

Supplement Review Summary

Varizig is a sterile freeze-dried immunoglobulin fraction containing high titers of antibodies to *Varicella zoster* virus (anti-VZV), purified from donor Source Plasma pools collected at FDA-licensed plasma collection centers in the United States and Health Canada/FDA-licensed collection establishments in Canada from donors who have been immunized or have naturally high titers of anti-VZV antibodies. Varizig comes as a lyophilized powder vial contained in a kit with Sterile Diluent for administration as an injection. Varizig is contained 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 is filled with a target potency of b(4)125 IU/vial to ensure b(4) 100 IU Varizig over the shelf life of the product. The final product formulation has 0.1 M glycine, 0.04 M sodium chloride and 0.01% (w/w) polysorbate 80. The Midcycle Review STN 125430/0 ML Virata-Theimer

accompanying Sterile Diluent contains 0.8% (mg/mL) sodium chloride and 10 mM sodium phosphate in a 6 mL vial as well. Reconstituted Varizig contains no preservatives and is intended for single use by the intramuscular route.

The Varizig manufacturing process includes a solvent/detergent treatment step, a viral filtration step and the removal of lipid and non-lipid enveloped viruses by size exclusion. The proposed shelf life of Varizig is 36 months, stored at 2-8 °C.

Manufacture, filling, in-process and most of the lot release testing of Varizig are performed at the Cangene facility in Winnipeg, Manitoba, Canada.

I. Product Specifications

I compared the proposed product specifications of Varizig with those of a licensed Cangene immune globulin product, HepaGam B, which is a 3-7% protein solution containing antibodies to hepatitis B surface antigen (information based on the 2011-12 Annual Report, STN 125035/178 and 125237/144). In-process and lot release testing are performed primarily at the Cangene facility in Winnipeg, except where noted.

Table 1: Specifications for Varizig Drug Substance vs HepaGam B Drug Substance

[b(4)]

Table 2: Specifications for Varizig (Lyophilized) Drug Product vs HepaGam B (Liquid) Drug Product

| Standard Test Method (STM) | Varizig | |
|----------------------------|-------------|-------------|
| ----- | --b(4)----- | --b(4)----- |
| ----- | --b(4)----- | |
| ----- | --b(4)----- | |
| ----- | --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) 125 IU/vial ^a | --b(4)----- |
| ----- | --b(4)----- | |
| ----- | b(4) 250 mg/vial | |
| ----- | --b(4)----- | |
| ----- | --b(4)----- | |
| 4)----- | Meets 21 CFR 610.11 requirements | |
| ----- | Meets 21 CFR 610.12 requirements | |
| ----- | Meets 21 CFR 610.12 requirements | |
| ----- | --b(4)----- | |
| ----- | --b(4)----- | |
| ----- | --b(4)----- | |
| ----- | < 10 minutes | |
| ----- | --b(4)----- | Free |
| ----- | --b(4)----- | |
| ----- | --b(4)----- | --b(4)----- |
| ----- | --b(4)----- | --b(4)----- |

^a A fill volume coverage 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)----- and Bulk Material Sterility are performed on Varizig DS but the results are reported with the final product.

Reviewer's Comments:

1. Most of Varizig specifications are very similar to that of HepaGam B, which are within the acceptable ranges of most immune globulin products. There are a few notable differences between Varizig and Cangene's other immune globulin products, HepaGam B, WinRho SDF and CNJ-016, which are associated with their active ingredients and different formulations.

- a. ---b(4)-----
- b. --b(4)-----
- c. ---b(4)-----
- d. --b(4)-----
- e. --b(4)-----

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

2. Varizig does not have specifications for appearance, --b(4)----- . HepaGam B has specifications for the 3 abovementioned tests.

a. Appearance: While an appearance specification was not listed in the Varizig product specifications table, I did find an acceptance criterion for appearance in Section 3.2.P.8.3 Stability Data, which says “white, lyophilized cake, essentially free of foreign particles upon reconstitution”, and tested by Test Method no. --b(4)--, the same visual inspection method used for HepaGam B. Actually, most of the current lyophilized immune globulin products, which were licensed many years ago, do not have appearance specifications. I saw only three products that had set appearance specifications. Cangene’s lyophilized WinRho SDF has “white to off-white lyophilized cake essentially free of foreign particulates in a --b(4)- glass container with a --b(4)- closure and white flip-off seal” (by visual inspection). Baxter Gammagard S/D only states “Satisfactory” (by visual inspection), while CSL Behring AG Carimune has “white or slightly yellow solid friable mass”. The -----b(4)----- describes the freeze-dried preparation as --b(4)-- ----- We will request Cangene to set an appearance specification.

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

Since Varizig will be administered intramuscularly and in small doses, the risk for hemolysis is expected to be very low, therefore we will not ask Cangene to set an --b(4)----- specification for Varizig.

To verify the risk of hemolysis, I requested Scott Winiecki, M.D. of OBE/DE/TBSB to check the Adverse Events database (AERS) for any hemolysis case reports associated with use of Immune Globulin (Human) or hyperimmune IG products that are administered intramuscularly. His database search did not find any hemolysis reports for the Grifols IG and hyperimmune IG products. I also asked him to search for hemolysis case reports associated with any of Cangene’s hyperimmune IG products. He did not find any with CNJ-016, HepaGam B, and WinRho SDF. However for the WinRho S/D product, there were 5 reports. This is not surprising for Rho(D) IG products, which have very high titers of --b(4)-- anyway. As of 1-SEP-12, there were approximately 340 cases for all Rho(D) IG products. Dr. Winiecki cautioned that “few or zero cases only means that we don’t have any reports. This should not be interpreted as hemolysis doesn’t happen, only that it hasn’t been reported (or is reported infrequently).” (email dated 26-SEP-12) David Menschik, M.D. also of OBE/DE/TBSB repeated the search focusing on the hyperimmune IG products. He did not find any hemolysis cases (email dated 27-SEP-12).

c. ---b(4)-----

3. If we request Cangene to set a specification for appearance, this will only apply to the b(4) Varizig lyophilized product lots since they are currently seeking BLA approval based on b(4) conformance lots (both filled from Midcycle Review STN 125430/0 ML Virata-Theimer

-b(4)-----). FDA initially agreed at the Type B pre-BLA meeting on 15-DEC-11 to accept b(4)conformance lot to support licensure of Varizig. At the same meeting, Cangene also informed FDA that they -----
--b(4)----- the end of 2012. -b(4)-----
-----as per their existing licensed liquid hyperimmune products. FDA concurred with Cangene's proposal to use the Prior Approval Supplement (PAS) approach for the --b(4)-----
----- . Cangene also said that they do not intend to conduct any clinical trials -b(4)----- Varizig, since the bioavailability of the -b(4)----- formulation has been previously demonstrated for other Cangene products. (see IND 7201, CRMTS #8280 Meeting Response Memo dated 12-DEC-11, and Official Meeting Summary Memo dated 13-JAN-12).

4. The --b(4)-- ----- for intramuscular administration states that it complies with the -b(4)-----, except for the minimum number of donors, the minimum total protein content and where authorized, the test for antibody to hepatitis B surface antigen. In addition, it says that the stated potency should be ----- -b(4)----- . Varizig's potency minimum is b(4) 125 IU/mL. Cangene utilizes a commercial -b(4)- test kit from -b(4)----, which uses a WHO International Standard (First International Standard for varicella zoster immunoglobulin, NIBSC code W0144, made in 1987, contains 50 IU varicella zoster antibody) (see Section 3.2.S.5).
5. In Section 3.2.P.5.4, Batch Analysis, Cangene provided the drug substance and drug product test results of the lots that were used in the clinical trials (6 lots), the conformance studies (b(4) lots) along with results of b(4) commercial lots that are available for sale in Canada. All lots appeared to be acceptable; their test results met all the set specifications.

II. Analytical Methods and Method Validations

A. Cangene provided the validation studies and summaries for the following non-pharmacopoeial methods for testing drug substance (see Section 3.2.S.4.3):

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

B. In addition, they provided validation studies and summaries for the following in-process testing:

1. HAV, HBV, HCV, HIV and Parvovirus B19 - tested and validated by -b(4)-----
--b(4)-----
--b(4)-----
4. ----- -b(4)-----

C. The sponsor also provided the validation studies and summaries for the following non-pharmacopoeial methods for testing the final product (see Section 3.2.P.5.3):

- b(4)-----

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

D. ---b(4)-----

Reviewer’s Comments: All the method validation results included in the original BLA appear to be acceptable i.e., all passed set specifications for each test attribute. Cangene’s test methods for testing –b(4)-----activity are comparable to the testing procedures of FDA CBER (Dr. Mikhail Ovanesov’s laboratory at OBRR/DH). For review comments on Cangene’s potency –b(4)- methods and the associated validation studies, please refer to Dr. Krause’s review memo.

With regards to the viral NAT methods, only the b(4) validation study summaries were provided. Cangene did not provide the –b(4)--- validation study summaries in this submission.

III. Nucleic Acid Testing (NAT) of Viruses in Plasma Pools

All Source Plasma used for manufacturing Varizig is screened for viral markers in compliance with the Canadian Food and Drug Regulations (C.04.412, C.04.413) and the U.S. 21 CFR 610.40 at FDA-licensed laboratories using FDA-licensed test kits. Cangene lists –b(4)-----) is listed as the test site for viral marker testing of plasma units, while the –b(4)- ----- as the test site for viral marker testing of plasma manufacturing pools (see also Section 3.2.S.2.1 Manufacturers, Table 1). According to Cangene, the following viral markers listed in Table 3 below are tested:

Table 3: Plasma Screening

| Test | Donation Units ^a | In-Process Specification |
|-----------------------|-----------------------------|--------------------------|
| HIV-1/2 Antibody | b(4) | |
| HCV Antibody | b(4) | |
| HBsAg | b(4) | |
| HIV-1 –b(4)- | b(4) | |
| HIV-1 RNA | b(4) | b(4) |
| HCV –b(4)- | b(4) | b(4) |
| HBV –b(4)- | b(4) | b(4) |
| HAV RNA ^d | b(4) | b(4) |
| Parvovirus B19 –b(4)- | b(4) | b(4) |
| Syphilis | b(4) | |

Note: Donation testing (which includes minipool testing) is performed by the plasma suppliers. Manufacturing pool testing is performed by Cangene as an in-process test (see Section 3.2.S.2.2 for details on testing done at the manufacturing pool level)

^aTest sites that perform release testing on the donation units are listed in Section 3.2.S.2.1

^bThe HIV-1 antigen test is no longer available at most contract testing laboratories. As an alternative for this assay, an HIV-1 nucleic acid test is now performed on minipooled samples. At this time, the plasma units in inventory may have been tested by either method.

^cCommonly performed using a validated strategy where minipools (test pools) of samples representative of individual donations are tested. A negative test result on the minipools indicates that all donations in the minipool are negative. If the minipool test is positive, resolution testing is performed to detect infective unit(s) for exclusion from the manufacturing plasma pool.

^dFDA-licensed test kit not available at this time

^eCommonly performed using a validated strategy where minipools (test pools) of samples representative of individual donations are tested.

Reviewer’s Comments:

b(4) and -b(4)----- viral NAT methods, especially for B19 and HAV, have been reviewed extensively in previous submissions (e.g., see my Final Memos for Biotest Bivigam BLA, STN 125389/0, dated 12-APR-12, Cangene CNJ-016 CBE, STN 125109/78, dated 27-MAY-08, Cangene WinRho SDF CBE, STN 103649/5340, dated 27-MAY-08). However, we will still send Cangene IR questions to verify details about their minipool and

manufacturing pool testing, as these can vary among different clients. This original BLA submission did not contain any supporting documents with details on the NAT testing of the plasma pools for the blood-borne viruses, e.g., HIV, HAV, HBV, HCV, and B19.

Draft Package Insert Wording on Viral NAT Testing

“The source plasma used in the manufacture of this product was tested by FDA licensed nucleic acid testing (NAT) for HIV-1, hepatitis B virus (HBV) and hepatitis C virus (HCV) and found to be negative. Plasma also has been tested by in-process NAT for hepatitis A virus (HAV) and parvovirus B19 (B19) via minipool testing; the limit for B19 in the manufacturing pool is set not to exceed 10⁴ IU of B19 DNA per mL.”

Reviewer’s Comments:

The proposed wording in Section 11, Description, of the draft package insert pertaining to viral marker testing appears to be acceptable. Of the three FDA-licensed NAT tests mentioned, the b(4) HBV NAT was recently approved on 1-SEP-11. Most of the in-process viral marker tests are not required by the FDA, but many sponsors do the tests to comply with the EU requirement. The only in-process test that FDA recommends is for B19. The wording for the B19 limit in the manufacturing pool is based on the FDA Guidance on B19 NAT (July 2009).

IV. Transmissible Spongiform Encephalopathy Safety

Cangene evaluated their hyperimmune product manufacturing process for the potential risk of transmission of TSE and prion disorders. They concluded that the risk is considered extremely minimal due to the following:

1. Adequate donor selection/exclusion criteria, employing FDA and Canadian approved procedures
2. Implementation of a Supplier Qualification Management Program with evaluation of all raw material sfor risk of prion transmission
3. Validated cleaning methods for the facility and equipment, employing solutions of –b(4)----- followed by extensive –b(4)-----, which may minimize the possibility of prion carryover (Section 3.2.A.1 Facilities and Equipment, part 6 Cleaning Procedures and Validation)
4. Review of available literature assessing the effectiveness of manufacturing steps for reduction of prions (--b(4)-----). (Refer to Figure 1 in Section 2.3.A.2 Adventitious Agents Safety Evaluation for a flow diagram of the manufacturing process indicating the potential prion reduction steps).
5. Completion of a process specific spiking study assessing the virus filtration step employed in the manufacturing process for viral clearance. In Study 854616, the viral filtration step yielded a log reduction of –b(4)--, using the ---b(4)-----

Study 854616 Section (3.2.A.2 Adventitious Agents Safety Evaluation) assessed the ability of the –b(4)--- to remove prions, the causative agent for new variant Creutzfeld Jakob disease (nvCJD). The smaller –b(4)---- 20N filter provides increased safety against small viruses, particularly small non-enveloped viruses. The 20N filter was demonstrated by Study PV-0026 as comparable to the –b(4)---- (Section 3.2.S.2.6 Manufacturing Process Development) with respect to components of manufacture and product identity, purity and potency. Since the 20N is comparable to the b(4) and there has been no change in the critical process parameters, the data generated from the –b(4)----- study is applicable to the 20N process step.

--b(4)-----

Reviewer’s Comments:

In Section 3.2.A.1 Facilities and Equipment, part 6 Cleaning Procedures and Validation, Cangene only gave a general description of its Clean-In-Place (CIP) System and did not provide details on the concentrations of their cleaning solutions or detergents as well as the washing conditions (temperature, duration, conductivity, etc). The Midcycle Review STN 125430/0 ML Virata-Theimer

equipment and facilities reviewer, Michael J. Vardon of OCBQ/DMPQ, HFM-676, said that he will request Cangene to provide more details on their cleaning methods.

Draft Package Insert Wording on TSE Risk

“Because VariZIG is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The plasma donors are screened for the presence of certain infectious agents and the manufacturing process for VariZIG includes measures to inactivate and remove certain viruses [see DESCRIPTION (11)]. Despite these measures, products derived from human plasma can still potentially transmit diseases. No cases of transmission of viral diseases, vCJD or CJD have been associated with the use of VariZIG.”

Reviewer’s Comments:

The proposed wording in Section 5.2, Transmissible Infectious Agents, of the draft package insert pertaining to TSE agents appears to be acceptable. The proposed wording on TSE risk complies to some degree with the recommended wording for the warning section of “plasma-derived products other than albumin” stated in the May 2010 FDA Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Product as the following:

“Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.”

LETTER-READY COMMENTS

The following questions will be sent as an Information Request to the sponsor:

1. Please confirm that –b(4)----- will be performing the viral NAT testing of the plasma minipools, and that the –b(4)----- will be performing the viral NAT testing of the plasma manufacturing pools.
2. Please provide the pool sizes, NAT sensitivities, and cut-off levels for minipool testing and original single plasma donation for each of the viruses tested.
3. Please provide the pool sizes, NAT sensitivities, and cut-off levels for manufacturing pool testing for each of the viruses tested.
4. Please provide a detailed summary about how the quarantine and proper disposal of NAT-positive donations for HIV/HBV/HCV/HAV/parvovirus B19 are done.
5. You did not list a drug product specification for appearance in Section 3.2.P.5.1. Please set a specification for appearance in order to ensure the product quality of Varizig. In addition, please provide your method SOP for visual inspection of a lyophilized product.

APPENDIX

Supporting Documents in the Original BLA Submission that were reviewed:

1. 2.3.S.4 Control of Drug Substance
2. 2.3.S.5 Reference Standards or Materials
3. 3.2.S.1.3 General Properties
4. 3.2.S.2.1 Manufacturer(s)

5. 3.2.S.2.2 Description of Manufacturing Process and Process Controls
6. 3.2.S.2.3 Control of Materials
7. 3.2.S.3.2 Impurities
8. 3.2.S.4.1 Specification
9. 3.2.S.4.2 Analytical Procedures
10. 3.2.S.4.3 Validation of Analytical Procedures
11. 3.2.S.4.5 Justification of Specification
12. 3.2.P.1 Description and Composition of the Drug Product
13. 3.2.P.5 Control of Drug Product
14. 3.2.P.5.1 Specification
15. 3.2.P.5.2 Analytical Procedures
16. 3.2.P.5.3 Validation of Analytical Procedures
17. 3.2.P.5.4 Batch Analysis
18. 3.2.P.5.6 Justification of Specifications
19. 3.2.A.1 Facilities and Equipment
20. 2.3.A.2 Adventitious Agents Safety Evaluation
21. 3.2.A.2 Adventitious Agents Safety Evaluation
22. Varizig draft package insert