

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research

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DATE September 27, 2012

FROM Erin McDowell, Bioresearch Monitoring Branch, HFM-664  
Division of Inspections and Surveillance  
Office of Compliance and Biologics Quality

THROUGH Patricia Holobaugh, Bioresearch Monitoring Branch Chief,  
HFM-664

TO Pei Zhang, HFM-345, Chair  
Nannette Cagungan, HFM-380, RPM  
Charles Maplethorpe, HFM-392, Clinical Reviewer

SUBJECT Bioresearch Monitoring Midcycle Review  
SPONSOR: Cangene Corporation  
PRODUCT: Varicella Zoster Immune Globulin (Human) [VariZIG™]  
BLA: STN 125430/0

**MidCycle Summary:**

Bioresearch Monitoring inspection assignments were issued for the following:

Study Number	Study Site	Location	Inspection Status
VZ-009	Children's Hospital of Michigan	Detroit, Michigan	Inspection in Progress
VZ-009	Oregon Health & Science University	Portland, Oregon	Inspection in Progress
VZ-009	Wesley Medical Center	Wichita, Kansas	Inspection completed; three-item 483 issued. Pending BIMO receipt, review of EIR package
VZ-006	Hospital for Sick Children	Toronto, Ontario Canada	Inspection scheduled to start late October 2012

**Sponsor Issues Identified to date:**

Several phone calls have occurred during the Wichita and Portland inspections which have revealed potentially widespread and significant sponsor-related issues. Neither site was prepositioned by the sponsor to administer the test article. The next inspection may reveal whether these problems were more widespread, or similar. The issues identified are as follows:

1. Study was conducted without an official clinical investigator.  
The clinical investigator at the Wichita study site did not sign the FDA Form 1572 (the investigator's commitment to follow the regulations) until a few weeks after subjects were vaccinated. This clinical investigator did not have previous clinical trial experience.
2. A fourteenth subject was administered the test vaccination by an obstetrician who was not listed as a sub-investigator for the study. The IgG Release Form was not prepared at the time of administration and to date does not appear that the clinical investigator submitted this subject's information to Cangene Corporation or FFF Enterprises. 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. It appears at the Wichita site that the investigational product was used as if it were a marketed product.
3. The sponsor did not conduct study-initiation and protocol-required monitoring visits at both the Wichita and Portland sites prior to study start or during the study as required by the protocol version 3 section 3.1.
  - a. There is no documentation showing that FFF Enterprises, the sponsor's contracted representative for distributing the test article to the test sites, had contacted the clinical investigators within 7 days after receipt of the test article, for follow-up and discussion of data collection.
  - b. In addition, there is no documentation of the sponsor (or designate) contacting the investigator by phone at least 3 times in order to collect data. Only a site monitor close-out visit was conducted at each site.
  - c. Per the investigator at the Portland site, the inspection documents reviewed thus far showed no evidence concerning study staff training, use of a subject screening log, or documentation of delegated study personnel activities or responsibilities.
  - d. Information from the sponsor on how to assign subject numbers was not included in the package received by the Wichita site causing a discrepancy between the site and the sponsor. The sponsor prepared a document to correlate the original subject number assigned to the actual subject number used by the site.
4. Case report forms were not completed or reviewed in a timely fashion.
  - a. Study documents from the Wichita site showed that the case report forms (CRFs) were apparently completed after the study ended. The information recorded on the CRFs was completed by sub-investigators through review of subject medical records beginning July 7, 2006 until November 30, 2006, when the information was submitted to the sponsor.
  - b. CRFs for subjects at the Portland site were not reviewed by the clinical investigator in a timely fashion. Some CRFs were not reviewed for 30-292 days after visit.

5. Informed consent issues.

- a. Per the investigator at the Portland site, there was no language on informed consent for undetermined risks for pregnant subject. In addition, informed consent forms do not have any wording for possible risks to unborn fetus.
- b. Preliminary findings at the Portland site show that 2/13 subjects did not sign an informed consent form and the time of informed consent not documented for 7/13 subjects.

We will tell the BLA Committee more about the inspections as soon as it becomes available. In addition, we are preparing a list of possible questions to ask the sponsor about how the studies were managed. Should you have any questions or comments about the contents of this memo or any aspect of Bioresearch Monitoring, please contact me at 301-827-2590.

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Erin McDowell  
Consumer Safety Officer