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September 16, 2005

Ms. Bhanu Kannan  
Division of Inspections and Surveillance (HFM-664)  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research  
1401 Rockville Pike, Suite 200N  
Rockville, Maryland, 20852-1448

Dear Ms. Kannan:

This letter responds to your warning letter CBER-05-026 dated August 23, 2005 and received by my office on August 31, 2005. I request that you post this response letter on the FDA's Warning Letter website for availability to the public under the Freedom of Information Act. Please redact the names of personnel. I will address each numbered point in the following paragraphs. For convenience, your comments are duplicated in italics, with the responses appearing below:

1. *You failed to protect the rights, safety, and welfare of the subjects under your care, and you failed to ensure that the investigation was conducted according to the signed Investigator's agreement, the Investigational plan, and applicable FDA regulations. [21 CFR § 812.100].*
  - A. *The protocol required that subjects must be between the ages of 18 and 64 to be eligible to participate in the study. You enrolled at least thirteen subjects who were above the age of 64.*

Response: We mistakenly enrolled 13 subjects (out of 907 total) who were above the age of 64. I will improve existing policies and procedures at our site by October 1, 2005 regarding subject screening and enrollment in order to prevent this type of oversight in the future.

- B. *The protocol required shipping of subject serum and plasma samples to the Central Reference Laboratory within 36 hours following sample collection. You did not document the sample collection time and shipment date and time for any subjects to verify that this protocol requirement was met.*

Response: The observation that the protocol required samples to be sent to the reference lab within 36 hours of collection is not correct. The protocol states in section 7.2 "...samples and on-site test results within 36 hours of collection." On site test results are required for the reference lab to proceed. The package insert allows for refrigeration of

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samples for up to three days prior to testing. Therefore, recording the collection time was not a requirement of the protocol. Standard practice at Synergy is to package and forward all samples for reference testing immediately after they are processed.

*C. The protocol required that samples be shipped on business days, Monday through Thursday only. It further required that enrollment not be performed on Friday. At least 340 subjects were enrolled and had samples collected on Friday and Saturday.*

Response: The collection and shipping of samples on Fridays, Saturdays, and Sundays was approved and arranged with the reference lab by the study sponsor. The initial protocol specification of business days (Monday-Thursday) was established for the purpose of avoiding shipments over a weekend. Since our site(s) had the capability to perform work on Fridays and weekends and is within the routine courier coverage area for the reference laboratory, the sponsor arranged for the reference laboratory to pick up and process specimens on both Saturdays and Sundays as well as weekdays. In future studies I will not agree to changes until the protocol has been formally amended by the study sponsor.

*D. The instructions included with the [redacted] test kit protocol required the samples to be refrigerated at 2-8° C immediately following collection if they could not be tested immediately. You and your study personnel visited the five satellite clinics where you recruited the subjects and performed the finger stick testing. However, the venous whole blood, serum, and plasma samples were transported at ambient temperatures to the Synergy Hematology-Oncology Associates location, up to [redacted] miles away, for testing. Failure to store samples as required by the protocol may have impacted the integrity of the samples and the performance of the devices.*

Response: Standard laboratory practice refers to "immediately" as meaning as soon as is reasonably possible, which is the same day or same shift. Refrigerated specimens are required to sit at room temperature for a minimum of [redacted] prior to use. The transportation of specimens to the testing site was completed within this time frame, and was intended to allow specimens to be ready to test upon arrival. However, I will institute a policy at our site by October 1, 2005 to use an ice chest to transport specimens that require immediate refrigeration.

**2. You failed to maintain accurate, complete, and current records relating to the receipt, use and disposition of devices. [21 CFR § 812.140(a)(2)].**

The inventory logs document the receipt of 220 [redacted] kits and 176 [redacted] kits for control testing and testing the samples from study subjects. The protocol stated that each [redacted] and [redacted] kit contained 20 and 25 devices, respectively. Thus, your inventory log accounted for the receipt of 4,400 devices of each type. The monitor reported the return of 358 and 348 [redacted] and [redacted] devices, respectively, to the sponsor at the conclusion of the study. Accurate, complete, and current records were not available for the total number of devices used and disposed of at your study site. Please provide documentation to account for the number of [redacted] and [redacted] devices used for control testing and subject testing, and the number of devices returned and destroyed, including all dates.

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Response: I have attached to this letter logs of device inventory received and test kits used for subjects and controls by date. A total of 358 [redacted] and 348 [redacted] devices were returned to the manufacturer on 2/10/05. I will upgrade policies and procedures at our site by October 1, 2005 to provide additional certainty that there are accurate and complete records relating to the receipt, use and disposition of investigational devices to include real time inventory verification.

**3. You failed to maintain accurate, complete, and current records of each subject's case history and exposure to the device.**  
**[21 CFR § 812.140(a)(3)].**

*You failed to maintain accurate and complete names of subjects who participated in the study and were exposed to the investigational devices. The enrollment log collected during the inspection did not record each subject's first and last name. For at least sixteen enrollment numbers in the enrollment log, subjects' names were not complete. The sponsor later determined that the following eight enrollment numbers represented duplicate enrollments: [redacted] and [redacted] and [redacted] and [redacted] and [redacted] and [redacted] and [redacted] and [redacted].*

Response: The enrollment log was corrected to include full names of the subjects prior to your inspection. The sixteen partial names were residual evidence of the oversight. Concerning the duplicate enrollment, the exclusion criteria in Section 9.0 of the protocol states:

"Individuals responding that they meet any of the following exclusionary criteria cannot be enrolled in the study:

1. Have a life threatening illness (with the exception of HIV, AIDS or viral infections).
2. Have a suppressed immune systems (i.e. transplant patients, individuals diagnosed with non-HIV immunosuppressive illness, etc.).
3. Have participated or are participating in a clinical trial for an HIV vaccine.
4. Have participated in this clinical trial more than one time."

There was no deviation from the protocol, because when interviewed, the individuals who were enrolled twice did not reveal that they had previously participated in the study. The study monitors employed methods to identify repeat enrollments and excluded them from the data analysis.

*We also have the following additional concern: You enrolled at least 200 subjects in the study on Sundays. Please provide the following information: (1) the normal operating hours for each location where subjects were enrolled on Sundays; (2) identify the study personnel who conducted the Sunday study activities; (3) describe precisely which study tests were performed on Sunday; (4) describe precisely how samples were stored and transported to another location for testing, if applicable.*

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Response:

(1) The methadone clinics operated from 5 a.m. to 11 a.m. on both Saturdays and Sundays. We opened the medical office on Sunday mornings specifically for the study.

(2) Work on Sundays was conducted by the following individuals with training dates: [REDACTED] 5/13/04; [REDACTED] 5/13/04; [REDACTED] 5/13/04; 7/10/04; [REDACTED] 7/10/04; [REDACTED] 7/10/04; [REDACTED] 8/18/04; and by myself, 5/13/04.

(3) Study tests performed on Sunday were identical to testing during the week and on Saturdays. The tests done on Sundays included [REDACTED] on finger stick samples, on serum, plasma and whole blood, controls, and serum and plasma separation and packaging.

(4) After processing at the lab, packaged serum and plasma samples were picked up the same day (Sunday) or occasionally the next morning (Monday) by the reference laboratory. When picked up on Monday they were stored overnight in the refrigerator.

Please let me know if I can provide any additional information regarding these issues.

Sincerely,

*Michael Gottlieb*

Michael S. Gottlieb, M.D.

cc: Alonza Cruse, District Director  
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[REDACTED]