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Center for Biologics Evaluation and
Research
1401 Rockville Pike
Rockville MD 20852-1448

By Certified Mail - Return Receipt Requested
And By Facsimile Transmission

CBER - 05 - 026

Warning Letter

Michael S. Gottlieb, M.D.
Synergy Hematology-Oncology Associates
5901 West Olympic Boulevard, Suite 407
Los Angeles, California 90036

Dear Dr. Gottlieb:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from April 28, 2005 to May 9, 2005. FDA investigator Ronald Koller met with you to review your conduct as a clinical investigator testing two investigational devices *HIV-1* [REDACTED] and [REDACTED] *HIV-1*. FDA conducted this inspection under the agency's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational devices.

At the end of the inspection the FDA investigator issued the Form FDA 483, Inspectional Observations, and discussed it with you.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational devices, as published in Title 21, Code of Federal Regulations (CFR), Part 812 (available at <http://www.access.gpo.gov/nara/cfr/index.html>).

The applicable regulation is cited for each violation listed below. Certain of these violations are not listed on the Form FDA 483, but are evident from related documents that the FDA investigator collected during the inspection referenced above.

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 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.

- 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.
- 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.
- 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.

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] [REDACTED] for control testing and testing the samples from study subjects. The protocol stated that each [REDACTED] and [REDACTED] 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.

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]
and [redacted] and [redacted]

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, and include the dates each person was trained to conduct 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.

This letter is not intended to contain an all-inclusive list of deficiencies in your clinical studies of investigational devices. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations and to protect the rights, safety, and welfare of subjects under your care.

You should notify this office, in writing, within fifteen (15) business days of receipt of this letter, of the steps you plan to implement to prevent the recurrence of similar violations in future studies. Your response should include any documentation necessary to show that correction has been achieved.

This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspection. Please be advised that failure to implement effective corrective actions and/or the commission of further violations may result in the initiation of enforcement action(s) without further notice. These actions could include injunction and initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational devices.

Please send your written response to:

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
Telephone: (301) 827-6221

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We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,



Mary A. Malarkey

Director

Office of Compliance and Biologics Quality

Center for Biologics Evaluation and Research

CC:

Alonza Cruse, District Director
Food and Drug Administration
19701, Fairchild, Suite 300
Irvine, California 92612-2506

