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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

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

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CBER – 05-- 016

Warning Letter

MAY 26 2005

Niel T. Constantine, Ph.D.
University of Maryland School of Medicine
Institute of Human Virology, Room 407
725 West Lombard Street
Baltimore, Maryland 21201

Dear Dr. Constantine:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from January 25 through February 4, 2005. FDA investigators Stephanie Shapley and Janet White met with you to review your conduct of a clinical study entitled [REDACTED]

[REDACTED] The portion of the study in known-positive subjects was conducted at the Laboratory of Viral Diagnostics (LVD), University of Maryland School of Medicine Institute of Human Virology (IHV), and the Evelyn Jordan Center (EJC). The portion of the study in low-risk subjects was conducted at LVD and IHV. The portion of the study in high risk subjects was conducted at the [REDACTED]

[REDACTED] FDA conducted this inspection under the agency's Bioresearch Monitoring Program that includes inspections designed to review the conduct of research involving investigational devices.

We note that you were previously inspected in April/May 2001 and in July 2004. You were issued a Form FDA-483, Inspectional Observations, at the end of each inspection. FDA issued you a Warning Letter on November 17, 2004 citing the following deviations found during the July 2004 inspection: failure to obtain informed consent, failure to document the date that informed consent was obtained, failure to include the possibility that FDA may inspect the records in the consent forms, failure to follow the investigational plan, and failure to maintain disposition of devices. You responded to the Warning Letter on December 1, 2004, describing your proposed corrective actions. In a letter dated January 21, 2005, FDA responded that your proposed corrections appeared to be adequate if properly implemented.

The inspection that ended on February 4, 2005, was not a follow-up inspection, but was an inspection of a different study that you conducted approximately the same time as the study we inspected in July 2004. For that reason, we did not expect, during the February 2005 inspection, to see the corrective actions you promised after the July

2004 inspection. Although informed consent and device accountability violations, like those we observed during the July 2004 inspection were noted during the most recent inspection -- further confirming that your noncompliance in those areas was a pattern that you need to correct -- we did not repeat those violations in this letter. Instead, this letter describes several new deviations that we observed. At the end of the inspection, a Form FDA 483, Inspectional Observations, was issued and discussed with you. We received and reviewed your letter in response to the Form FDA 483, dated March 8, 2005, addressed to FDA Baltimore District Director, Mr. Lee Bowers.

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), Parts 50 and 812 (available at <http://www.access.gpo.gov/nara/cfr/index.html>). The applicable provisions of the CFR are cited for each violation listed 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 investigational plan, the signed agreement, and applicable FDA regulations, including Part 50. [21 CFR §§ 812.100 and 812.110 (b)].

- A. Protocol sections 8.0 and 9.0 require that enrolled subjects be between the ages of 18 and 55 years and able to sustain venipuncture. Subjects with life threatening illnesses (with the exception of HIV, AIDS, or viral infections), as well as those with suppressed immune systems, were to be excluded from the study. You enrolled 203 low-risk subjects, 206 known-positive subjects, and 203 high-risk subjects in the study, but you failed to document that any of these 612 subjects met the health status enrollment criterion. In addition, there is no documentation that the age criterion was evaluated for 113 of 203 high-risk subjects. Review of 98 high-risk subjects' medical records or consent forms showed that you enrolled five subjects not meeting the age requirements. Subjects [REDACTED] were enrolled although these subjects were under the protocol required age of eighteen. Subject [REDACTED] was enrolled although this subject exceeded the age requirement of 55. Review of fourteen known-positive subjects' records showed that you enrolled one subject, subject [REDACTED] although this subject exceeded both the protocol-required age of 55 and the monitor-approved required age of 60.

In your letter, you state the known-positive subjects were screened for life-threatening illnesses and immunosuppression, but you acknowledge the lack of documentation of these criteria. You do not address the known-positive subject exceeding the age requirement. In addition, you do not explain the lack of screening documentation for subjects in the high- and low-risk groups for meeting both the health status and age criteria. For future studies you plan to document inclusion and exclusion criteria

throughout the recruiting process. If you include these screening criteria on the Participant Results Form, your proposed corrective action appears to be adequate.

- B. There is no documentation that you were present for or reviewed records of the protocol-required test procedures involving the device at the IHV, [REDACTED] or EJC locations. As the clinical investigator, the protocol required you to be responsible for "monitoring all study results and assuring compliance to study protocol." As described in 2.A below, your signature on the subject screening documents suggests "review and subject acceptable for study," however these forms were photocopied prior to subject screening.

In your letter you state, "although it is correct that there was no documentation showing that records were reviewed by me, I would like to assure you that I was closely following the daily activities, and have been in constant touch with the director of the clinical trials." Without contemporaneous, written documentation, however, we have no way to review how consistently and thoroughly you monitored all study results and assured compliance with the study protocol, as the protocol required you to do. Please understand that for your promise to "document your oversight activities" to be meaningful, that documentation must be contemporaneous and sufficiently detailed for investigators to review what you did.

- C. You violated protocol section 10.0 which provides that "With the participant still available, test whole blood from the purple top tube." You failed to test 109 of 203 high-risk subjects' whole blood samples while the subject was available. The samples were tested between one and eight days after collection as shown in the table below.

Subject(s)	Collection Date	Date of Testing and Shipping	Days between Collection and Testing/ Shipping
[REDACTED]	12/30/03	1/7/04	8
[REDACTED]	12/19/03	12/24/03	5
[REDACTED]	12/19/03	12/23/03	4
[REDACTED]	1/9/04	1/13/04	4
[REDACTED]	12/19/03	12/22/03	3
[REDACTED]	12/23/03	12/26/03	3
[REDACTED]	1/2/04	1/5/04	3
[REDACTED]	12/17/03	12/19/03	2

[REDACTED]	12/20/03	12/22/03	2
[REDACTED]	12/29/03	12/31/03	2
[REDACTED]	12/31/03	1/2/04	2
[REDACTED]	12/17/03	12/18/03	1
[REDACTED]	12/29/03	12/30/03	1
[REDACTED]	12/30/03	12/31/03	1
[REDACTED]	1/5/04	1/6/04	1
[REDACTED]	1/7/04	1/8/04	1
[REDACTED]	1/8/04	1/9/04	1
[REDACTED]	1/14/04	1/15/04	1

In your letter you state that the Laboratory Manager at [REDACTED] explained that the “main reason for this was due to the late hour at which some patients presented themselves at the clinic.” This does not address why the samples were tested up to eight days after obtaining the sample. You have also stated that in the future the Laboratory Manager will “cease enrolling study participants unless all testing and sample shipping can be undertaken on the same day that samples are collected from the participant.” You also state you will be closely monitoring this site to make sure these requirements are met. Your proposed corrective action appears to be adequate.

- D. You violated protocol section 10.0 which provides that “Samples will be shipped to the Central Reference Laboratory daily.” Review of the specimen shipping forms shows that you failed to ship 109 of 203 high-risk subjects’ serum and plasma samples to the central laboratory on the day they were obtained. The delay in shipping ranged from one to eight days. Furthermore, you did not accurately complete the shipping notification form for 109 high-risk subjects’ specimens shipped to the central reference laboratory. The form requires “collection date,” but you entered “test date.” Since you recorded an inaccurate “collection date,” the central laboratory records also show the same wrong “collection date.” This also gives the appearance that specimens were “collected” and “shipped” on the same day as required by protocol. These specimens were shipped on the day of testing, but as shown in the table above, the collection dates and test dates differ from one to eight days.

In your letter you state that the Laboratory Manager at [REDACTED] explains the “main reason for this was due to the late hour at which some patients presented themselves at the clinic.” This does not address why the samples were shipped up to eight days after obtaining the sample. You do not explain why the shipping forms were not accurately completed with the requested information. You state that in the future the Laboratory Manager will “cease enrolling study participants unless all testing and sample shipping can be undertaken on the same day that samples are collected from the participant.” You also state you will closely monitor this site to make sure these requirements are met. Your proposed corrective action appears to be adequate.

- E. Review of nine of fifteen high-risk subjects’ records revealed no documentation of post-test counseling as required by protocol and the investigational plan.

In your letter you agree that the examples noted on Form FDA 483 are correct. You state in future studies you will ensure the staff’s completion and documentation of study-specific training to include regular review of daily study procedures. Please keep in mind that your responsibilities go beyond merely training personnel, and include ensuring that appropriate post-test counseling is provided.

- F. According to the [REDACTED] the [REDACTED] are to be stored at 15 to 30°C. You failed to document temperatures for the 1,000 test kits received at the [REDACTED] site showing proper storage of the investigational device as required by the protocol.

In your letter you state that the [REDACTED] laboratory has ordered “7 day/ 24 hour temperature monitoring devices.” Please provide us with more information about these room temperature monitoring devices.

2. **You failed to maintain accurate and complete records of each subject’s case history, including data on the condition of each subject upon entering, and during the course of, the investigation. [21 CFR § 812.140(a)(3)].**

- A. You used pre-filled checklists to prospectively evaluate the eligibility of all potential known-positive and low-risk subjects. A master checklist was pre-filled with checkmarks in the “yes” column for all inclusion and exclusion criteria, the name and signature of the person conducting the screen, and your signature, and then was photocopied for use in the study. The dates next to your signature and the screener’s signature were completed by an unknown person. Because the pre-printed form bears your signature and the name and signature of the person who purportedly

screened the subject, it is impossible to determine who actually performed the screening procedure. Many forms had the following section pre-filled: "Reviewed and subject acceptable for study: "YES." This practice creates the misleading impression that you personally approved the enrollment of each subject, and that [REDACTED] personally screened each subject.

- B. As described in item 1.A above, you failed to document that each of the 612 enrolled subjects met the health status enrollment criteria. You also failed to document date of birth for the low-risk subjects and at least 113 of the high-risk subjects.

This violation was not included on the FDA 483.

- C. Review of the times recorded on the study subject enrollment form and the [REDACTED] results form document that eleven samples collected on January 29, 2004, from known-positive subjects were tested in the lab before they were received by the lab. The study subject enrollment forms for subjects [REDACTED] and [REDACTED] document that the samples were received at LVD at 1545 on January 29, 2004. The [REDACTED] results form documents that the samples were tested between 1500 and 1510 on January 29, 2004.

This violation was not included on the FDA 483.

3. You failed to submit required reports to the Institutional Review Board (IRB). [21 CFR § 812.150(a)(4)].

You did not request IRB review or receive IRB approval for the following two protocol deviations.

- A. Change in finger-stick procedure: Although you received a letter dated November 21, 2003, from the sponsor's representative, [REDACTED] that permitted you to conduct the testing using three [REDACTED] devices per single fingerstick and to test whole blood in the lab, you never sought or received IRB approval to deviate from the protocol in that manner; and
- B. Change in sample shipping requirement: You also received an email dated February 5, 2004, from [REDACTED], stating it is "OK to ship samples on the next day following collection." You did not, however, seek or obtain approval from the IRB for that protocol deviation. We also note that the "approval" from [REDACTED] was granted after the majority of samples were collected.

4. You failed to prepare and submit a complete and accurate final report. [21 CFR § 812.150(a)(6)].

The information you submitted to the study sponsor in the final report dated November 10, 2004 is incomplete and inaccurate.

- A. Section (A) (III) notes the high-risk population is 202, but Section (C) notes that 210 samples were tested in the high-risk group. The number of subjects consented in the high risk group is 203 and the number of subjects tested is 202.
- B. Section (C) "Results" is incomplete and misleading since it does not include all protocol-required testing for concordant/discordant results and does not list correct number of subjects tested. Results reported by you and results recorded at the sites are shown in the table below. This discrepancy for total subjects tested may also change the overall sensitivity and overall specificity listed in Section (C)(1)(2).

Group	Final Report Section (C) Results	Results at Site NR=non-reactive; R=reactive; IND=indeterminate; TNP=test not performed
Low Risk	One sample (LVD [redacted] of 200 tested was [redacted]	200 subjects tested Sample LVD [redacted]
		Sample LVD [redacted]
	199 samples were [redacted]	198 subjects tested [redacted]
High Risk	Of 210 samples tested, 187 were [redacted] (NOTE: you do not address the remaining 12 samples)	202 subjects tested 189 subjects tested [redacted] 11 subjects tested [redacted]
		Sample [redacted]
		Sample [redacted]

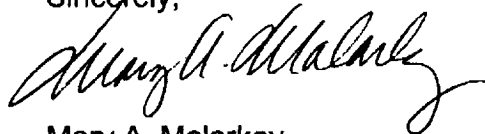
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Please send your written response to:

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Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland, 20852-1448
Telephone: (301) 827-6339

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: Roberta Wagner, Acting District Director
Baltimore District Office
Food and Drug Administration
6000 Metro Drive, Suite 101
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Robert Edelman, M.D., Chair
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