DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

SEP 10 2004

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CBER - 04 - 018

Warning Letter

Dawn M. Sokol, M.D.
Ochsner Foundation Hospital
1514 Jefferson Highway
New Orleans, Louisiana 70121

Dear Dr. Sokol:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from May 3, 2004 to May 10, 2004. FDA investigators Traci Armand and Claire Minden met with you to review your conduct of a clinical study entitled [redacted] FDA conducted this inspection under the agency's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational drugs.

The investigators issued and discussed with you the Form FDA 483, Inspectional Observations, at the end of the inspection. You responded in a letter to FDA dated June 18, 2004. We reviewed the inspection reports, the Form FDA 483, and your response. Our comments on your response are provided below.

We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Part 312, (available at http://www.access.gpo.gov/nara/cfr/index.html. The applicable provisions of the CFR are cited for each violation listed below. Some of the violations were not cited on the Form FDA 483, but were evident from the documents that the FDA investigator collected during the inspection.

1. **You failed to protect the rights, safety, and welfare of subjects under your care, and you failed to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan. [21 CFR § 312.60].**

   A. You enrolled subject [redacted] who did not meet the study eligibility criteria. The study protocol requires subjects with serious chronic disease to be excluded from the study. This subject's medical records document that

the subject was hospitalized on [redacted] for Deep Venous Thrombosis (DVT). The subject was still taking Coumadin when you enrolled the subject and administered the test article on 6/26/01. You did not inform the sponsor of the protocol violation. During a visit on 8/30/01, the sponsor noted this event as a protocol violation and instructed you to notify the Institutional Review Board (IRB).

In your response you failed to acknowledge this violation and instead explain that the subinvestigator who enrolled the subject did not view the above condition as a serious chronic disease.

B. You failed to store the [redacted] as required by the protocol. The protocol states "all [redacted] will be stored in a secure, temperature-monitored area at [redacted] The [redacted] must not be [redacted]" The storage temperatures at the Ochsner Lapalco clinic were below the required temperature for at least 70 days between April 2001 and July 2001. You administered the [redacted] to at least 14 subjects during this time period. Furthermore, the [redacted] was stored [redacted] on 5/23/01.

In your response you acknowledge the [redacted] storage temperature violations that occurred at the Lapalco clinic. You describe that no visual anomalies were reported by the study personnel who administered the [redacted] We remind you that product quality cannot be judged based on a visual check. In your response you also describe a corrective action plan to perform continuous temperature monitoring, which if successfully implemented, appears adequate.

C. You failed to maintain the required temperatures when you transported the [redacted] to the other clinics under your supervision. The protocol requires that [redacted] shipment temperatures be maintained at [redacted] and be monitored. The temperatures were below the required range for at least 15 doses transported to satellite sites on 4/18/01. You also failed to document the temperature of 37 doses transported on 4/26/01 and 6/18/01.

D. [redacted] storage temperature logs were not maintained for the Rothchild-Ochner Pediatric Clinic in Destrehan participating in your study. You failed to maintain the [redacted] storage temperature log to document that the [redacted] were stored at the protocol-required temperature.

In your response you acknowledge that you could not locate the temperature log for this clinic. You state that the monitoring reports show that the monitor checked these records during site visits. We remind you that you are responsible for maintaining all records pertinent to the study.

E. Under your supervision, an unauthorized person conducted protocol-required procedures. The protocol required unblinded personnel to randomize and [redacted] study subjects. [redacted] is not identified on the [redacted] Personnel Team List" as a staff member participating in the conduct of the study. "[redacted] subjects [redacted] and [redacted], and randomized subjects [redacted] and [redacted]

In your response, you acknowledge the observation. We disagree with your explanation that, as part of the blinded team, you did not have access to the randomization and medication dispensing log, implying that you did not know what staff were conducting study procedures. As the clinical investigator, you are responsible for selecting and training the personnel conducting study-related activities and ensuring that the investigational plan is followed. You are also responsible for the control of study drugs under investigation.

F. You failed to submit a final study report to the IRB. The sponsor notified you on 7/24/02 after the close-out monitoring visit that you are responsible for submitting the report to the IRB. You have not submitted a final report to the IRB as of this inspection date.

2. You failed to maintain adequate and accurate case histories. [21 CFR § 312.62(b)].

A. The regulatory binder containing the original screening log and other documents was inadvertently destroyed. Your staff attempted to recreate the log from other records at the site, but the replacement is incomplete. There is no information about 76 enrolled subjects. We remind you that you are responsible for the security and storage of the study documents. You are responsible for retaining records according to the requirements in 21 CFR 312.62(c).

In your response you explain that your staff had maintained these documents, but that they were destroyed in error.

B. Changes were made to records without documenting who made the changes, and when the changes were made. For example, some subjects' data have been crossed out without identifying the personnel making the corrections. The sponsor provided instructions for this process in a study manual but such instructions were not always followed.

C. The enrollment log was used to track the progress of the study. The log did not document the required study Day 8 telephone contact to assess the safety of the study [redacted] for subjects [redacted] through [redacted] (with the

exception of subject [redacted] and the six month telephone contact for subjects #[redacted]

D. The initials and study numbers for subjects [redacted] and [redacted] are transposed in the investigational product accountability records and [redacted] log.

3. **You failed to assure that the Institutional Review Board (IRB) would be responsible for the initial and continuing review and approval of the proposed clinical study and failed to report promptly all changes in the research activity. [21 CFR § 312.66].**

A. You failed to report the enrollment of an ineligible subject to the IRB. As described in item 1A above, the sponsor required you to notify the IRB regarding the 6/26/01 enrollment of subject [redacted] You did not report to the IRB until 10/4/01.

In your response you state that the IRB was notified after the sponsor determined that the subject was ineligible for the study.

B. You failed to promptly notify the IRB that the Lapalco clinic did not store the study drugs at the required temperature as described in item 1B above. Your report to the IRB dated 10/24/01 identifies only two instances of storage temperature violations.

Your response does not explain why you did not report to the IRB the full extent of the temperature violations.

This letter is not intended to contain an all-inclusive list of deficiencies in your clinical studies of investigational drugs. 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 new drugs.

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
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, Maryland, 20852-1448
Telephone: (301) 827-6221

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

Sincerely,

James S. Cohen, J.D.
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

H. Tyler Thornburg, District Director
Food and Drug Administration
6600 Plaza Drive, Suite 400
New Orleans, Louisiana 70127

Joseph Breault, M.D., Chair
Ochsner Institutional Review Board
Ochsner Clinic Foundation
1514 Jefferson Highway
New Orleans, Louisiana 70121