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

CBER - 02 - 008

WARNING LETTER

Robert M. Hardaway III, M.D.  
Texas Tech University Health Sciences Center  
Department of Surgery  
4800 Alberta Avenue  
El Paso, Texas 79905

Dear Dr. Hardaway:

Between May 29 and June 5, 2001, Ms. Vivian Garcia, an investigator from the Food and Drug Administration (FDA) Dallas District Office, met with you to review your conduct of a clinical study using Urokinase for treatment of acute respiratory distress syndrome. You were the sponsor of the research and the clinical investigator responsible for the study. The inspection was conducted under FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational products.

We determined that you have violated regulations governing the proper conduct of clinical studies involving investigational new drugs as published under Title 21, Code of Federal Regulations (CFR), Part 312 [21 CFR 312] (available at <http://www.access.gpo.gov/nara/cfr/index.html>).

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

- 1. You failed to fulfill the general responsibilities of investigators. [21 CFR § 312.60].**

An investigator is responsible for ensuring that an investigation is conducted according to the investigational plan (protocol), and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. You failed to adequately protect the safety and welfare of subjects and to ensure that an investigation is conducted according to the protocol. See item 2 below. In addition, you assessed the condition of subject #84-69-68 at Thomason Hospital and gave orders for administration of the study drug even though you did not have medical staff privileges with that institution at that time.

**2. You failed to ensure that an investigation is conducted according to the investigational plan (protocol). [21 CFR § 312.60].**

- a. The protocol is designed to study urokinase, yet you administered streptokinase to subject #84-69-68. You obtained the consent from the subject to participate in the urokinase study, but substituted streptokinase when the investigational product was unavailable.
- b. The protocol requires eligible subjects to be under — years of age; however, you enrolled two subjects who exceeded this age limit, at — and — years of age.
- c. The protocol requires that subjects were to be randomized to receive study drug or a ————. However, all subjects were administered the study drug.

All modifications to the study protocol must be reviewed and approved prior to implementing any changes, except where necessary to eliminate apparent immediate hazards to human subjects. Protocol modifications that impact on subject safety or the scope of the investigation must be approved by the IRB before initiation. Clinical investigators are not permitted to change the protocol without the permission of the sponsor (who must submit the protocol revision to FDA) and the institutional review board (IRB) as required by 21 CFR § 312.66.

**3. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21 CFR § 312.60].**

- a. The informed consent form for study “Treatment of Acute Respiratory Distress Syndrome with Urokinase” and ———— lacks several required elements of informed consent as required by 21 CFR § 50.25.
- b. The consent form statement, “I understand that in the event of physical injury resulting from the research procedures described to me, that Texas Tech University Health Sciences Center, or Thomason General Hospital and their affiliates are not to offer financial compensation nor to absorb the cost of medical treatment,” appears to waive the subject’s legal rights and is, therefore, exculpatory. All consent forms must strive to avoid making statements that appear to waive a subject’s legal rights or appear to release the investigator, the sponsor or the institution from liability for negligence.

- 4. You failed to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation. [21 CFR § 312.62(b)].**

The inspection revealed serious deficiencies in study documentation, including the lack of case report forms and source documents. You did not adequately maintain source documents for the subjects participating in the study. You were unable to locate a copy of the consent forms signed by two subjects. The available records are inadequate to evaluate whether the study was performed according to the protocol.

- 5. You failed to retain records pertinent to the investigation. [21 CFR §§ 312.57(c) and 312.62(c)].**

- a. You failed to retain a copy of all study-related documents when the study was completed. You requested discontinuation of IND — on April 20, 2001.
- b. You did not maintain records to document the sub-investigators whom you supervised on the study. Sponsors are required to obtain a signed Form FDA 1572 (Statement of Investigator) in which a clinical investigator acknowledges that he/she understands and intends to conduct your clinical trial according to the federal regulations, and which identifies the personnel authorized to participate in the research.

We recommend that you undergo training in the responsibilities of sponsor and clinical investigators under 21 CFR before you initiate any new clinical study. Good Clinical Practice (GCP) is essential to maintain the quality of data collection regarding the conduct of clinical trials.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations.

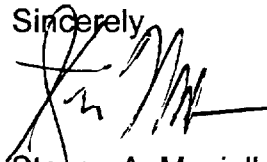
Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs.

You should notify this office in writing, within fifteen (15) business days of receipt of this letter, of the specific actions you have taken to correct the noted violations, including an explanation of each step you plan to take to prevent a recurrence of similar violations. Please send your written response to:

Jose Javier Tavarez, M.S. (HFM-664)  
Division of Inspections and Surveillance  
Food and Drug Administration  
1401 Rockville Pike  
Rockville, Maryland 20852-1448  
Telephone: (301) 827-6351

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

Sincerely,

A handwritten signature in black ink, appearing to read 'Steven A. Masiello', written over the word 'Sincerely'.

Steven A. Masiello  
Director  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research

cc: Thomas A. Allison, Director  
Food and Drug Administration  
3310 Live Oak Street  
Dallas, Texas 75204

Dr. Paul R. Casner, Chair  
Institutional Review Board  
Office of Regional Dean  
Texas Tech University Health Sciences Center at El Paso  
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