



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

g3653d

OCT 23 2002

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

By Certified Mail – Return Receipt Requested
And by Facsimile Transmission

CBER-03-002

Warning Letter

Juan L. Tellez, M.D.
Illinois Center for Clinical Trials
737 N. La Salle St., 3rd Floor
Chicago, Illinois 60610

Dear Dr. Tellez:

During an inspection ending on November 16, 2001, Ms. Alicia Mozzachio, an investigator with the Food and Drug Administration (FDA), reviewed your conduct of the clinical study entitled [REDACTED] is the sponsor of the clinical study. The inspection was conducted under FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational products. At the close of the inspection, a Form FDA 483, List of Inspectional Observations, was issued to and discussed with you.

We have determined that you 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>). The applicable provisions of the CFR are cited for each violation listed below.

1. **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)].**
 - A. Several laboratory reports supporting one of the study's endpoints show that the sample "collected" and "received" dates were altered without explanations. It is not clear when and by whom these changes were made. These changes cast doubt on whether the pre-infusion and post-infusion blood samples were actually collected at the time points required by the protocol. Please explain these discrepancies and provide complete documentation of the actual dates that these samples were collected and received.

The following table describes the alterations made on the lab reports:

Subject	Laboratory Accession No.	Original lab report		Altered lab report	
		Collected date	Received date	Collected date	Received date
		07-07-00	07-07-00	06-27-00	06-27-00
		07-07-00	07-07-00	06-27-00	06-27-00
		07-07-00	07-07-00	06-27-00	06-27-00
		07-03-00	07-04-00	06-30-00	06-30-00
		07-07-00	07-07-00	06-27-00	Not altered

The protocol requires that corrections of data on the case report form "can only be made by crossing out the incorrect data with a single line and inserting the correct values next to those crossed out. Each correction must be initialed and dated by the individual authorized to make data changes."

- B. You did not always document whether laboratory reports and other test results required during the screening and pre-infusion phase were reviewed prior to subject treatment. There is no documentation that study personnel reviewed several laboratory reports for safety analysis, as described in the table below. During the inspection, you acknowledged that several lab reports were not reviewed in a timely manner.

Subject	Visit Date	Lab Tests	Clinical Investigator Review
	6/16/00	Serum Chemistries	Signed but not dated
	6/16/00	_____ : Lewis Type, DAT, HIV	Not signed or dated
	6/27/00	_____ haptoglobin, HGB, DAT	Not reviewed until 10/31/00
	6/16/00	Serum Chemistries	Signed but not dated
	6/16/00	_____ : Lewis Type, DAT, HIV	Not signed or dated
	6/27/00	_____ : haptoglobin, HGB, DAT	Not reviewed until 10/31/00
	6/16/00	Serum Chemistries	Not reviewed until 10/31/00
	6/16/00	_____ : Lewis Type, DAT, HIV	Not signed or dated
	6/27/00	haptoglobin, HGB, DAT	Not reviewed until 10/31/00
	6/16/00	Serum Chemistries	Signed but not dated
	6/16/00	_____ : Lewis Type, DAT, HIV	Not signed or dated
	6/27/00	_____ : haptoglobin, HGB, DAT	Not signed or dated

The safety of the individual subject, and potentially all subjects in the study, is put in jeopardy when safety data such as lab tests are not reviewed and signed off until weeks/months after the tests are performed.

C. You did not record the following adverse events in the case report form as required.

i. Subject # _____ experienced shortness of breath during the infusions of the study product on 6/29/00.

ii. Subject # _____ had a free hemoglobin plasma (hemolysis) value of 6.9 mg/dL (range 0.0-4.0) at the 24-hour post-infusion time point. You determined this to be clinically significant. The protocol requires that " _____

2. **You failed to carry out the general responsibilities of an investigator by not conducting the investigation according to the investigational plan and by not protecting the rights, safety, and welfare of subjects. [21 CFR § 312.60]. You also failed to assure IRB review of the clinical study by not promptly reporting to the Institutional Review Board (IRB) changes in the research activity and by making changes in the research without IRB approval [21 CFR § 312.66].**

The investigational plan approved by the IRB required you to sign, within _____, each subject's signed informed consent form to document your review of each subject's screening and pre-infusion tests and your agreement that your study staff had appropriately enrolled that subject. You failed to provide this required signed certification within _____; in fact, you did not sign the forms until 12/5/00, more than five months after the subjects signed the informed consent documents on 06/15/00. This is a violation of 21 CFR 321.60, which states that "an investigator is responsible for ensuring that an investigation is conducted according to the . . . investigational plan" and "for protecting the rights, safety, and welfare of subjects under the investigator's care."

21 CFR 312.66 requires an investigator to "assure that he or she will promptly report to the IRB all changes in the research activity . . . and that he or she will not make any changes in the research without IRB approval." You made changes in the research by certifying your review of subjects' tests and by your agreement with your staff's decision to enroll these subjects five months after such tests and decisions, not within _____, as provided in the investigational plan and the IRB-approved consent form. By failing to report this change to the IRB and by making this change without IRB approval, you have also violated 21 CFR 312.66.

Page 4 – Juan L. Tellez, M.D.

The Form FDA 1572 Statement of Investigator did not include two clinical laboratories, _____ and _____, used from June 2000 until February 2001. The inspection revealed that the Form 1572 was revised only after completion of the study. We remind you that the Form 1572 requires listing the name and address of any clinical laboratory facilities to be used in the study.

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.

Please 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. If corrective action cannot be completed within 15 business days, state the reason for the delay and the time within which corrections will be completed.

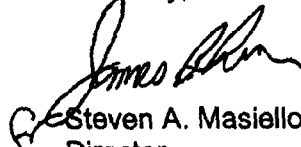
Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs, and/or injunction.

Please send your written response to:

Jose Javier Tavarez, M.S.
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) 827-6351

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

Sincerely,



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