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CBER-99-21

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

WARNING LETTER

JUL 22 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ronald W. Cotliar, M.D.

Dear Dr. Cotliar:

During an inspection ending on March 10, 1999, Mr. Armando Chavez, an investigator with the Los Angeles District Office of the Food and Drug Administration (FDA), met with you and Dr. Sid Rosenblatt to review your conduct of a clinical study using _____ in human subjects with moderate to severe _____. The clinical study is sponsored by '_____'. The inspection was conducted under FDA's Bioresearch Monitoring Program that includes inspections designed to monitor the conduct of clinical research involving investigational drugs.

Based on information obtained during the inspection, we have determined that you have 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 [21 CFR 312] (copy enclosed). Our investigation revealed that you did not fulfill your obligations as a clinical investigator in the use of unlicensed investigational new drugs for the reasons listed below. The applicable provisions of the CFR are cited for each violation.

1. **Failure to ensure that the investigation is conducted according to the investigational plan (protocol). [21 CFR 312.60]**
 - a. The physical examination reports for subjects #001(visits 13 and 14) and #004 (visit 11) were signed and dated by you, even though you were not present during these assessments. You made a note on the reports that these examinations "were not done" by you.

A note to the file dated December 15, 1998, from Dr. Rosenblatt documents that he asked you to review a list of subjects enrolled in the _____ study who had visits scheduled at times when you were generally not available at the center/clinic. In your affidavit, you admitted that you did not conduct the physical examination for subjects #001 and #004 at the visits listed above.

- b. Inspection of records at the Irvine Clinical Research Center (ICRC) revealed that during a routine monitoring visit at the ICRC on 11/04/98, it was determined by the ██████ monitors that the body temperature values and respiration rates for all subjects' visits prior to 11/04/98 were not done, even though the values were improperly filled in for each subject. In fact, because these data were false, Mr. ██████ (████████████████████ Project Manager) instructed the monitors to delete respiration rate and temperature values from the source documents and the case report forms. Exactly one hundred ninety-one (191) temperature values and one hundred ninety-one (191) respiration values were deleted. "ND," for Not Done, was noted in the source documentation and the case report forms.

Moreover, the Study Coordinator, Ms. ██████, admitted in a separate affidavit that she did not take temperatures and respiration rates for all subjects, even though she filled in the values in the case report forms for each subject at each visit. She admitted entering false data on the case report forms.

According to the protocol, measurement of vital signs was supposed to be performed at visits 1 through 13, and visits 15, 16, and 17 for each subject. Vital signs (i.e., temperature and respiration rate) are a clinical safety assessment required in the protocol. This is an essential component of the study to assess the safety of the investigational product.

- c. According to the protocol, blood samples for pharmacokinetic (PK) analysis were supposed to be drawn several times during the study (e.g., visits 1, 3, 7, 12, 15, and 17). The inspection disclosed that Ms. ██████ did not draw any of these samples.

It is your responsibility as principal investigator to ensure that all tests and evaluations are conducted at the time points indicated in the protocol. It is your responsibility to ensure that blood samples were taken for PK assay of ██████ levels, hematology tests, blood chemistries, HIV antibody tests, pregnancy tests, and other tests described in the protocol.

In your affidavit, you stated that you assumed that the drawing of blood samples was a lab function and as such "Dr. Sid Rosenblatt would handle it." Under the protocol, Dr. Rosenblatt, who was the "unblinded" sub-investigator, was to review the blood test results for safety issues only. Specifically, the protocol states that one investigator was to be unblinded only to review the subjects' hematology results in order to assess continuation of dosing.

- d. Review of records at your site revealed that you did not conduct the global assessment of efficacy for subjects #001 (visits 13 and 14) and #004 (visit 11), even though the data was entered in the case report forms. You made a note on the case report forms that indicates that you did not perform the subjects' evaluation on these visits. In her affidavit, Ms. ██████ admitted that on certain occasions you delegated authority to her to perform the global assessments of efficacy.

In regard to the [redacted] area and severity index [redacted] assessment and [redacted] assessment, Ms. [redacted] also stated in her affidavit that on certain occasions she would fill in the information from other assessments.

These practices are unacceptable. The data generated from these efficacy assessments may be inaccurate. Also, the Study Coordinator is not a physician. The Study Coordinator was not authorized (as per protocol) to perform these clinical efficacy assessments.

The protocol requires that all efficacy assessments be performed **by the same investigator for each subject**. The primary endpoint of the study is to determine the severity of subjects' disease as measured by global assessment at 2 weeks after the last dose of study drug. Other endpoints include [redacted] assessment and [redacted] assessment. These are essential components of the study to assess the efficacy of the investigational product.

- e. In many instances, the delayed-type hypersensitivity test was not read within the required timeframe.

The protocol requires that reading of [redacted] test results must be performed [redacted] after application. Furthermore, the Study Coordinator often instructed the subjects to read their own results at home and record them on the test forms. The test was supposed to be read by site personnel within [redacted] hours.

- f. Subjects #001 and #006 did not receive a follow-up telephone call between visits 15 and 16.

The protocol requires telephone monitoring (weekly) to assess the subject's health condition during the 12-week post-dosing period.

2. Failure 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. The inspection revealed that not all adverse events reported in the source documents were recorded in the case report forms.
- b. One of the assessments to be completed by the subject was for [redacted]. The subject's evaluation form has a line which was to be used as a scale, with "[redacted]" at one end, and "[redacted]" at the other end. The subject was asked to draw a vertical line through the horizontal line to indicate the amount of [redacted] he or she was experiencing at the time of the visit. The Study Coordinator, Ms. [redacted], transferred this information from the source document to the case report form by estimating the distance from the vertical mark to the end of the scale. The two scales were not even the same length. It appears she used the wrong scale for the [redacted] assessment.

A note to the file dated December 5, 1998, from Dr. Rosenblatt documents that he recalls discussing the [redacted] assessments with you and Ms. [redacted]. Dr. Rosenblatt learned that Ms. [redacted] was not using the sponsor's scale but one she created herself. The note indicates that you believed that Ms. [redacted] scale was "fine" and that these evaluations had very little merit.

Deviations in this study appear to be the result of a serious lack of supervision of personnel involved in conducting this study. Staff who were delegated the authority to perform certain functions were not adequately trained and monitored. You should recognize that although authority may be delegated, it is the principal investigator who is ultimately responsible. Proper oversight or supervision of medical personnel is necessary to ensure the investigation is conducted according to the protocol. In addition, there is no documentation that you actively reviewed the case report forms for accuracy. Clinical investigators are responsible for assuring that the data contained in the case report forms and submitted to the sponsor are complete and correct.

You failed to provide adequate supervision to study personnel who contributed false information to study records or reports. We remind you that you are responsible and may be held accountable for the conduct of your Study Coordinator regarding the performance of clinical trials. Adequate training and supervision of your study personnel are essential to maintaining the quality of data collection regarding the conduct of clinical trials.

You deviated from an authorized study plan, investigator statement, or other conditions imposed on the study by the sponsor, IRB, or FDA. Your signature on Form FDA 1572, Statement of Investigator, indicates your agreement to comply with all requirements regarding the obligations of clinical investigators conducting human clinical trials and all other pertinent requirements in 21 CFR Part 312. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, 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.

Our investigation revealed that you and Ms. [redacted] attended the investigator meeting for the [redacted] study that was held in [redacted]. This meeting thoroughly reviewed all aspects of the study, including the protocol, good clinical practices (GCPs), and the specific responsibilities of each participant. In addition, you and Ms. [redacted] attended the on-site training at ICRC. This training was conducted by [redacted] (a contract research organization contracted by [redacted]) to reinforce the procedures and training conducted during the investigator meeting for this study. Dr. Rosenblatt has indicated that personnel from [redacted] and [redacted] were available to answer questions from either you or Dr. Rosenblatt.

According to Dr. Rosenblatt, The ICRC relied entirely upon the background, professional training, and ethical standards of you and Ms. [redacted] in the conduct of the blinded portion of the [redacted] study.

In your affidavit, you stated that the problems encountered in this study were primarily due to _____

_____. As the "unblinded" sub-investigator, Dr. Rosenblatt was prohibited from supervising the conduct of either you or Ms. _____. This study was double-blind; therefore, Dr. Rosenblatt was not allowed to perform subject evaluations, review source documents, or review case report forms. Ms. _____ was to work directly with you under your close supervision.

A note to the file dated December 5, 1998, from Dr. Rosenblatt documents that he recalls counseling you regarding an incident where you left the center prior to a subject being seen on this study. The incident was reported to Dr. Rosenblatt by Ms. _____. According to Dr. Rosenblatt, he stressed to you the importance of your presence for the evaluations because they must be performed within a specified time frame or "window" to be statistically evaluable. The note reports that you apologized and affirmed that it would not happen again.

A note to the file dated December 9, 1998, from Dr. Rosenblatt documents that he called you on November 30, 1998, regarding subject #007, who was scheduled to be seen that day. _____ RN, telephoned you several times that day to arrange for the visit. The subject did not appear for his scheduled appointment on November 25, 1998, and was rescheduled to accommodate the protocol. The subject was seen by Ms. _____. She contacted you, but you refused to come in for the visit. According to the note, Dr. Rosenblatt discussed the importance of your function as the principal investigator on this study and that you should have come in for the evaluation.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of investigational _____. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations. We request that you inform us, in writing, within fifteen (15) business days after receipt of this letter of the steps you have taken or will take to correct these violations and to prevent the recurrence of similar violations in current and future studies. If corrective action cannot be completed within 15 business days, state the reason for the delay and the time within which the corrections will be completed.

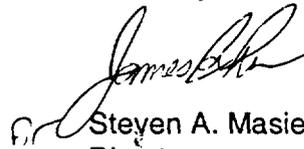
Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include initiation of clinical investigator disqualification proceedings which may render a clinical investigator ineligible to receive investigational new drugs, a clinical hold, or termination of an investigational new drug application (IND).

Please send your written response to:

Jose Javier Tavarez, M.S.
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Bioresearch Monitoring Team (HFM-650)
1401 Rockville Pike
Rockville, Maryland 20852-1448
Tel. (301) 827-6221

We request that you send a copy of your response to the Food and Drug Administration's Los Angeles District Office, Director, Compliance Branch, 19900 Mac Arthur Blvd., Suite 300, Irvine, California 92612. If you require additional time to respond, or have any questions concerning this matter, please contact Mr. Tavarez at the telephone number above.

Sincerely,



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

Enclosures

21 CFR Part 312
Form FDA 483

cc:

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Sid Rosenblatt, M.D., F.A.C.P.
President
The Irvine Clinical Research Center
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Irvine, California 92618