DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Warning Letter

By Certified Mail - Return Receipt Requested

CBER - 00 - 030

Thomas W. Montag, M.D.
Cancer Treatment Centers of America
355 Crawford Parkway, Suite 300
Portsmouth, Virginia 23704

AUG 15 2000

Dear Dr. Montag:

During the period of May 25 to June 23, 2000, Mr. David Glasgow and Ms. Christine Whitby, investigators from the Food and Drug Administration (FDA) FDA Baltimore District Office, visited your office and reviewed the records of your clinical study of an investigational ——— biological product. At the close of the inspection, a Form FDA 483, Inspectional Observations, was given to you and discussed. The inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational new drugs.

Based on information obtained during the inspection, we conclude 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) Parts 312 and 50. These regulations are available at http://www.access.gpo.gov/nara/cfr/index.html. The applicable provisions of the CFR are cited for each violation listed below.

At the time of the inspection, Subject —— was the only person enrolled in the study. All violations listed below were identified in the files relating to Subject ——

1. **Failure to fulfill the general responsibilities of investigators. [21 CFR § 312.60 and Part 50].**

   You failed to identify a sub-investigator on the Form FDA 1572, and permitted an unauthorized person to participate in the study. You permitted Dr. ——— to complete the study form entitled ———————————————— On the Form FDA 1572, Statement of Investigator, you did not identify that Dr. ——— would participate in this study as a sub-investigator. The sponsor has the responsibility of reviewing the qualifications of all sub-investigators assisting the conduct of a clinical trial.

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

A. You failed to perform all of the required testing to determine whether Subject —— was eligible to participate in the study. Serum chemistry testing was not performed following Cycle 1 before the subject was randomized into the clinical trial.

B. You did not calculate the dosage of ——— using the method specified in the protocol. Instead of the —— method specified in the protocol, you used the ——— formula, which resulted in an underdose in the medication for Cycles 1 through 4.

C. You used an arbitrary creatinine value to calculate the dose of —— for Cycles 1 through 3. Rather than perform the test after each cycle to determine the actual creatinine level, you based the chemotherapy dose calculations on an unsubstantiated creatinine value of 1.0. –

D. You performed a creatinine test ten days before the beginning of cycle 4, but did not use the result ——— in the calculation of the ——— dose. Instead, you used the arbitrary value of 1.0 mg/dL.

E. You miscalculated the dose of ——— in Cycle 5. The protocol-specified method was used to calculate the dose, but arithmetic errors resulted in an underdose in the medication ——mg instead of the correct ——— mg).

F. The Cycle —— dose was miscalculated. The subject was administered —— mg rather than the correct dose of —— mg.

G. You did not perform protocol-required tests, or performed the tests ouside of the specified time frames:

i. Cycle 1. Day 1 and Day 8 serum chemistries were not performed.

ii. Cycle 2. Day 1 and Day 8 serum chemistries and Day 8 hematology test were not performed. Day 1 CBC, differential, and platelet count tests were performed seven days before chemotherapy instead of — days as required by the protocol.

iii. Cycle 3. Day 1 and Day 8 serum chemistries were not performed. ——— sample was obtained and analyzed approximately three weeks late.

iv. Cycle 5. Karnofsky score not determined.

3. **Failure to assure initial and continuing review and approval of a clinical study by an Institutional Review Board (IRB). [21 CFR §§ 56.103(a), 312.66].**

   A. You began the screening process for Subject —— before the IRB approved the protocol. The screening test is not part of routine patient care, and should not have been performed before the IRB approved the study.

   B. Subject —— signed two informed consent documents before the IRB approved the research: the screening informed consent form signed on October 27, 1999, and informed consent to participate in the study signed on October 29, 1999. The IRB did not review the protocol or approve the informed consent documents until November 29, 1999. This represents a failure to adequately protect the rights of subjects.

4. **Failure to maintain adequate case histories of individuals treated with investigational drugs. [21 CFR § 312.62(b)].**

   A, The case report form does not document the start and stop dates for medications taken as Previous or Concomitant Therapy.

   B. The case report form did not accurately and completely report an adverse events: the case report form does not identify the start and stop date for the adverse event "chest pain."

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

Please notify this office, in writing, within fifteen (15) business days of receipt of this letter, of the actions you have taken to correct these violations and to prevent the recurrence of similar violations in other current and in future studies. Any plans of action must include projected completion dates for each action to be accomplished. If corrective actions cannot be completed within fifteen business days, state the reason for the delay and the time within which the corrections will be completed.

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

Please send your written response to:

Patricia Holobaugh (HFM-664)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448
Telephone (301) 827-6221

We request that you send a copy of your response to the Northern Virginia Resident Post, Food and Drug Administration, 101 W. Broad Street, Suite 400, Falls Church, VA 22046-4200.

Sincerely,

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

cc: Institutional Review Board
Maryview Medical Center
3636 High Street
Portsmouth, Virginia 23707