DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

FEB 2 3 2001

Warning Letter

By Certified Mail - Return Receipt Requested

CBER - 01 - 016

Lloyd A. Shabazz, M.D.
Cancer Treatment Centers of America
355 Crawford Parkway
Portsmouth, Virginia 23704

Dear Dr. Shabazz:

Between May 25 and June 23, 2000, two Food and Drug Administration (FDA) investigators conducted an inspection of the following clinical studies in which you participated:

(1) [ ] Prostate Cancer" (hereafter referred to as Protocol 1). There were six subjects enrolled in the study at the time of the inspection.

(2) [ ] Non-Hodgkin's Lymphoma" (hereafter referred to as Protocol 2). There were five subjects enrolled in the study at the time of the inspection.

(3) [ ] Non-Small Cell Lung Cancer" (hereafter referred to as Protocol 3). There were four subjects enrolled in the study at the time of the inspection.

This inspection was conducted as part of the FDA's Bioresearch Monitoring Program which includes inspections designed to review the conduct of research involving investigational products.

Based on information obtained during the investigation, 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), Parts 312 and 50 (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 fulfill the general responsibilities of investigators. [21 CFR § 312.60 and Part 50]**

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, the investigational plan, 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. On June 2, 1999, (Protocols 1 and 3) and on December 14, 1999, (Protocol 2) you signed FDA Forms 1572, Statement of Investigator, in which you agreed to conduct the study in accordance with the protocol and applicable regulations.

Our investigation revealed that you did not fulfill your obligations as a clinical investigator in the use of investigational new drugs in that you failed to follow the investigational plan and to adequately protect the safety and welfare of subjects.

A You enrolled subjects who were not eligible according to the requirements stated in the protocol. See items 2A and 2B, below.

B You failed to follow protocol requirements. See item 2, below

2 **You failed to follow the investigational plan. [21 CFR § 312.60]**

FDA documented numerous protocol violations in its review of subject records for Protocols 1, 2, and 3. These violations include, but are not limited to, the following:

A You enrolled the following subjects who had one or more conditions that excluded them from participation in Protocol 2.

Subject	Randomization Date	Exclusion Criterion
1302	2/25/00	Pleural effusion
1303	3/8/00	Pleural effusion
1305	5/12/00	Elevated creatinine level

Although the sponsor proposed to amend the protocol on April 24, 2000, to permit subjects with pleural effusions under certain restrictions, you enrolled two of the subjects before the amendment was proposed, and all three subjects before the Institutional Review Board (IRB) approved the protocol revision on May 22, 2000.

B. You enrolled a subject who did not meet all of the inclusion criteria required in Protocol 3. Subject 1031 failed to meet the inclusion criterion of having non-small cell lung cancer proven by histology or cytology.

C. You did not perform all of the required assessments to determine whether subjects were eligible to participate in the studies. Without these tests, the following subjects were not eligible according to the criteria stated in the protocols:

Protocol	Subject	Required Screening Tests Not Done (ND) or Not Performed According to the Required Schedule (ARS)
1	1304	chest x-ray (ARS)
1	1342	electrocardiogram (ND), urinalysis (ARS), hematology (ARS), chemistry (ARS)
1	1349	electrocardiogram (ND) and urinalysis (ND)
1	1416	PT, PTT or INR * (ND)
1	1436	chest x-ray (ARS) and PT, PTT or INR (ND)
1	1447	chest x-ray (ARS)
2	1304	electrocardiogram (ARS), pregnancy test (ARS), physical exam (ARS)
2	1305	CBC (ARS)

* *PT = Prothrombin time; PTT = Partial Thromboplastin time; INR = International Normalized Ratio*

D. You administered the test article to Subject 1416 before the sponsor authorized the subject's entry into Protocol 1. The study records document that Subject 1416 was initially dosed with the study drug on February 21, 2000, but the sponsor did not confirm the randomization until the next day.

E. You did not administer chemotherapeutic drugs according to the study protocol. This is not a complete list, but is provided for illustration.

Protocol	Subject	Course or Date	Protocol Violation
3	1010	2	Day 1 -- [redacted] was not administered
3	1031	12/20/99 1/10/00 1/31/00 2/21/00 3/13/00	[redacted] administered before [redacted]
3	1031	1, 2, and 3	Days 1 and 8 -- incorrect dose of [redacted] [redacted] administered instead of the protocol-required dose of [redacted]
3	1059	1	Day 1 -- Subject was administered [redacted] dose of [redacted] instead of the correct dose of [redacted] based on a Body Surface Area

F You failed to collect pharmacokinetic samples according to the requirements in Protocol 1.

Subject	Pharmacokinetic Sample Not Obtained or Incorrectly Obtained
1304	Course 2 samples were collected [redacted] apart instead of [redacted] apart as required by the protocol
1349	Course 2 pharmacokinetic samples drawn incorrectly — first sample was drawn after the start of chemotherapy Course 4 — not done Course 6 — not done
1416	Course 2 — not done Course 4 — not done
1436	Course 2 — not done Course 4 — not done

G You failed to perform the following tests required by the protocols. This is not a complete list, but is provided for illustration.

Protocol	Subject	Tests not performed or incomplete
1	1304	Courses 1, 4, 5, 6 — chemistry Course 2 — prostate serum antigen Courses 2, 6, 8, — Day 1 physical examinations Course 5 -- [redacted] questionnaire Course 6 — [redacted] Pain Inventory, prostate serum antigen Course 7 — week 2 hematology
1	1342	Course 2 — Day 1 chemistry, prostate serum antigen, and [redacted] Pain Inventory Courses 3 and 4 -- Day 1 physical examinations Course 4 — weeks 2 and 3 hematology
1	1349	Courses 1, 3, and 4 -- Day 1 chemistry Course 2 -- Day 1 prostate serum antigen Courses 3 and 4 -- Day 1 physical examinations Courses 3 and 7 — week 2 hematology Course 5 -- [redacted] Pain Inventory
1	1416	Courses 2 and 3 — Day 1 physical examinations Course 3 — chemistry and week 1 hematology
1	1447	Course 2 — Day 1 chemistry
2	1303	Cycle 1 — Vital signs during infusion
3	1031	Course 1 — Day 8 hematology Course 2 — Days 1 and 8 hematology Course 3 — Day 8 hematology

H You failed to follow additional requirements in Protocol 2

During Cycle 1, Subject 1304 was discharged five minutes after the infusion although the protocol requires that subjects remain in the clinic for [redacted] after infusion of the test article.

Subject 1304 experienced an adverse event during the infusion of the test article. The rate of test article infusion was increased from [redacted] cc/hour to [redacted] cc/hour, rather than decreased by [redacted] as specified in the protocol.

You failed to maintain the proper storage temperature for the test article used in Protocol 2. The protocol requires refrigeration at ——— The temperature records for the month of February, 2000, the only month for which records were available, show that the temperature ranged between ——— There were no records for January, March, April, or May, 2000. The minimum/maximum thermometer intended to monitor the refrigerator temperature was not properly set and the instructions for use were not available.

J The test article for Protocol 2 was dispensed on one occasion by the data manager — who was not identified as a sub-investigator on the Form FDA 1572 or on the site personnel signature log.

3. **You failed to maintain adequate and accurate case histories of individuals treated with the test drug. [21 CFR § 312.62(b)].**

A Some adverse events were not reported in the case report form adverse event log:

Neuropathy in Subject 1010 on February 17, 2000 (Protocol 3).

ii Constipation, rash, and redness to extremities in Subject 1031 on March 20, 2000 (Protocol 3).

B. There is no flow chart record of chemotherapy for Subject 1059 for Course 1, Day 1 in Protocol 3. You signed orders for the chemotherapeutic agents to be administered, but there are no source documents to verify that the drugs were administered.

C Source documents for chemotherapy for Subject 1059 in Protocol 3 for Course 1, Day 8 contained many corrections using white correction fluid. The protocol requires that any modification of previously entered data be made by striking through the original entry with a single line, initialing and dating the change, and entering the correct data.

D The — form Quality of Life Questionnaire dated August 25, 1999, contained in the Protocol 3 binder for Subject 1010 did not include any subject identifying information.

E. There are discrepancies between the case report forms and source records, resulting in the submission of inaccurate information to the study sponsors.

Protocol	Subject	Course	Source Document	Case Report Form
1	1304	2	Pharmacokinetic samples collected at 10:10 and 11:10	Pharmacokinetic samples collected at 9:15 and 11:10
1	1304	4	Pharmacokinetic samples collected at 9:27, 10:27, and 11:45	Pharmacokinetic samples collected at 9:27 and 11:15
1	1304	8	Plasma collected at 10:49 and 12:05	Plasma collected at 10:30
1	1342	2	Pharmacokinetic samples were collected on 12/7/99	Not reported
1	1342	3	Physical examination performed on 12/23/99	Physical examination performed on 12/28/99
1	1342	4	Physical examination performed on 1/17/00	Physical examination performed on 1/14/00
1	1342	4	Pharmacokinetic samples were collected on 1/18/00	Not reported
1	1342	4	Blood sample for plasma correlative lab studies collected on 1/18/00	Not reported
1	1342	5	Chemistry sample collected on 2/10/00	Chemistry sample collected on 2/8/00
1	1416	screen	History of [redacted] and [redacted] administration.	[redacted] not listed— it is an excluded concomitant therapy
1	1010	2/29/00	Started the concomitant medication [redacted] for dizziness	Not reported
2	1304	2 and 3	No record that vital signs were taken	Vital signs are recorded
3	1059	2	Day 1 pharmacokinetic samples collected at 11:25, 14:05, and 15:15	Day 1 pharmacokinetic samples collected at 11:25, 14:00, and 15:55
3	1059	2	Day 8 [redacted] infused between 11:35 and 12:05	Day 8 [redacted] infused between 13:00 and 14:00

4. **You failed to maintain adequate records of disposition of the investigational drugs. [21 CFR § 312.62(a) and (c)].**

A You failed to maintain accountability of the test article for Protocol 3. There are no records of the distribution of the following nine bottles of test article tablets: [redacted] The protocol requires that the Control Record be completed whenever test article is received or dispensed, with dates of bottle returns, number of tablets returned by the subject, the initials of the site personnel making the entry, and the initials of the monitor verifying the return or destruction of study drug at the study site.

B There are no records of receipt for test article received in January, 2000, for Protocol 2.

C The study coordinator for Protocol 1 initialed the column intended for the sponsor's monitor rather than the column intended for the pharmacy technician.

D The test article accountability Control Record for Protocol is incomplete and inadequate.

The records do not show the distribution of any test article to Subject 1416 although packages [redacted] were dispensed.

ii Subjects in Protocols 1 and 3 were required to return the test article bottles and any unused medication on a periodic basis. The case report forms for the following subjects did not record the number of test article tablets returned at the time new tablets were dispensed.

Protocol	Subject	Dates
1	1342	12/28/99
1	1416	3/4/00, 3/13/00, 6/6/00
1	1436	4/11/00, 5/24/00
3	1007	10/4/99, 1/17/00
3	1010	4/28/00
3	1059	10/14/99, 1/17/00

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

Please notify 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 future studies. If corrective action cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed.

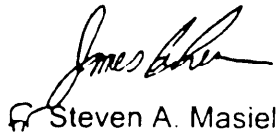
Failure to achieve correction may result in enforcement action without further notice. The actions could include initiation of disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs.

Please send your written response to:

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

We request that you send a copy of your response to the Food and Drug Administration's Baltimore District Office, 900 Madison Avenue, Baltimore, Maryland 21201.

Sincerely,



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

cc Institutional Review Board

[ ]

Robert Bowers, Director
Food and Drug Administration
900 Madison Avenue
Baltimore, Maryland 21201

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