



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

WARNING LETTER

MAR 9 2001

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Tapas K. Das Gupta, M.D., Ph.D.
Professor and Head
Department of Surgical Oncology (M/C 820)
Clinical Sciences Building
The University of Illinois at Chicago
840 South Wood Street
Chicago, Illinois 60612

Dear Dr. Das Gupta:

Between May 9 and 19, 2000, Ms. Jeanne Morris, an investigator from the Food and Drug Administration (FDA) Chicago District Office, met with you to review your conduct of a clinical study using the investigational new drug _____
_____ Melanoma Cells in human subjects with metastatic malignant melanoma.
_____ 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. The inspection focused on the study protocol titled, _____
_____ Melanoma Cells _____
_____ In Patients With Metastatic Malignant Melanoma."

We have 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. None of the subjects enrolled in the study were eligible according to the requirements stated in the protocol; see item 2, below.

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

A. Each of the four subjects enrolled in the study failed to meet the protocol eligibility criteria. You administered the investigational product to the subjects even though they should have been excluded, as described in the following table:

Inclusion criterion	Subject #	Subject's screen result
Lactate dehydrogenase _____	003 004 005 007	_____ _____ _____ test not performed
Alkaline phosphatase _____	004 005 007	_____ _____ _____
Absolute lymphocyte count mm ³ _____	004 005	_____ _____
Hemoglobin _____	005	_____
Blood urea nitrogen _____	005	_____
Tumor expresses products of _____ _____	003 004 005 007	not performed not performed not performed not performed
Exclusion criterion		
Multiple hepatic metastases	007	CT scan revealed multiple hepatic metastases with at least three large lesions

The enrollment of ineligible subjects is a serious protocol deviation. Treatment of subjects outside the approved protocol may have exposed them to an unreasonable and significant risk of illness or injury.

- B. The protocol required that clinical/laboratory evaluations, including various immunoassays for cellular and antibody response, be conducted within the four weeks prior to _____ of the _____. The following evaluations were not performed during the screening process:

Laboratory evaluations	Subject #	Subject's screen result
Cellular immune response – _____ _____	003	not performed
	004	not performed
	005	not performed
	007	not performed
Antibody response to tumor	003	not performed
	004	not performed
	005	not performed
	007	not performed

- C. _____ evaluations were not conducted as required by the protocol.
- i. There is no documentation that immune assays (cellular immune response and antibody response) were conducted at _____ weeks 1, 2, 4, 8 and 12 for subjects #003, #004, #005, and #007. During the inspection, you and the sub-investigator acknowledged that these immune assays were not conducted.
 - ii. _____ tests were not conducted for subject #005 at week 1 _____ and for subject #007 at week 2.
 - iii. A chest-X ray was not performed at week 2 for subject #005.
 - iv. Hematology tests were not performed for subject #007 at week 1.

- D. [_____] the test article were not removed from the subjects upon withdrawal from the study as required by the protocol.

- i. Subject #003 had _____ on January 7, 1998. _____ according to the schedule described in the protocol, _____ when the subject was withdrawn from the study on February 27, 1998. However, _____

- ii. Subject #005 had _____ on April 14, 1998. _____ when the subject was withdrawn from the study on June 10, 1998.
- iii. Subject #007 had _____ on May 19, 1998. _____ when the subject was withdrawn from the study.

- E. _____ evaluations for immune assays (cellular immune response and antibody response) were not conducted, as required by the protocol, for subjects #003, #004, #005, and #007.
- F. You failed to report the deaths of subjects #003, #004, and #007 to the Institutional Review Board (IRB). The protocol required reporting of deaths to the IRB and sponsor. You reported the deaths of subjects #003, #004, and #007 to the sponsor on 8/17/98, after the study was closed in June, 1998. However, the protocol required that deaths be reported to the sponsor immediately by telephone and subsequently in writing within five (5) days.
- G. Your study files revealed two versions of protocol _____. You could not explain the differences between the two versions, and could not determine which version had been submitted to and approved by the IRB.

3. You failed to maintain adequate records of the disposition of the test article. [21 CFR § 312.62(a)].

- A. There is no drug inventory of the amount, lot number, and date of receipt from the manufacturer.
- B. There is no documentation of study drug dose administered to each subject. In addition, there are no records documenting the final _____ preparation, including _____ as described in the protocol.

4. You failed to submit safety reports to the sponsor. [21 CFR § 312.64(b)].

There is no documentation to indicate that you promptly reported to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the study drug. Subject #007 developed a skin rash that started in the abdomen [] and [] The rash was associated with a considerable amount of itching and discomfort. The Progress

Notes from June 5, 1998 state "...there is no other reason than the _____ to explain this occurrence."

5. 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)].

You did not adequately maintain source documents for the subjects participating in the study. The case histories did not contain progress notes, laboratory reports, and radiology reports to support entries in the case report forms. Examples include, but are not limited to, the following:

- A. There is no laboratory report to substantiate that the screening assessment hematology and chemistry tests were performed to determine whether subject #005 was eligible to participate in the study.
- B. There is no source document to substantiate that subject #007 had a chest-X ray evaluation performed on June 2, 1998.

6. You failed to retain records pertinent to the investigation. [21 CFR § 312.62(c)].

You failed to retain a copy of all study-related documents, including the case report forms, when the sponsor terminated the study and removed all the study records.

On December 3, 1996, you signed a Clinical Study Agreement with your institution and _____ in which you agreed to conduct the clinical study in accordance with the protocol, FDA regulations, and any conditions of approval imposed by the IRB or FDA. The agreement incorporated an attachment to list additional investigator responsibilities, including a commitment to adhere to the requirements set forth on Form FDA 1572 (Statement of Investigator) and all other pertinent requirements in 21 CFR Part 312. As evidenced by the deviations noted above, you failed to fulfill your obligations as clinical investigator in the use of investigational new drugs.

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.

Please send your written response to:

Jose Javier Tavarez, M.S.
Division of Inspections and Surveillance
Bioresearch Monitoring Branch (HFM-664)
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 FDA's Chicago District Office, Compliance Branch, 300 S. Riverside Plaza, 5th Floor, Suite 550 South, Chicago, Illinois 60606.

Sincerely,



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

cc:

Eric A. Gislason, Ph.D.
Interim Vice Chancellor for Research
The University of Illinois at Chicago
310 Administrative Office Building (M/C 672)
1737 West Polk Street
Chicago, Illinois 60612

Raymond V. Mlecko, Director
Chicago District Office
Food and Drug Administration
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5th Floor, Suite 550 South
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