



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

CBER - 04 - 007

Warning Letter

MAY 14 2004

Robert O. Dillman, M.D.
Hoag Cancer Center
Hoag Memorial Hospital Presbyterian
One Hoag Drive, Building 41
Newport Beach, California 92658-6100

Dear Dr. Dillman:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from December 9, 2003, to January 15, 2004. FDA investigator Gene Arcy reviewed your activities as a sponsor and clinical investigator testing investigational products in the following studies:

- Protocol CBRG 98-09: Intralesional Adoptive Cellular Therapy of Gliomas with Interleukin-2-Stimulated Lymphocytes. (hereinafter Study 1)
- [REDACTED]
- Phase II Study of a TGF- β 2 Antisense Gene Modified Allogeneic Tumor Cell Vaccine in patients with Stage-IV Non-Small Cell Lung Cancer. (hereinafter Study 3)

We note that you are the sponsor and the clinical investigator for Studies 1 and 2, while a third party is the sponsor of Study 3.

FDA conducted this inspection under the agency's Bioresearch Monitoring Program that includes inspections designed to review the conduct of clinical research involving investigational drugs.

The investigator issued to you a Form FDA 483, Inspectional Observations, and discussed with you his observations at the conclusion of the inspection. We reviewed the Form FDA 483, the inspection report, and associated Investigational New Drug Application (IND) documents. FDA has not received from you a response to the observations noted in the Form FDA 483.

We have determined that you 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 (available at <http://www.access.gpo.gov/nara/cfr/index.html>).

The applicable provisions of the CFR are cited for each violation listed below. Some of the violations were not cited on the Form FDA 483, but were evident from the documents that the FDA investigator collected during the inspection.

Sponsor responsibilities:

1. **You shipped the investigational drug to investigators not participating in the investigation. [21 CFR § 312.53(b)]**

With respect to Study 2, your study records indicate that you manufactured and shipped investigational [REDACTED] to two investigators who were not mentioned in your IND or subsequent amendments, in that:

- A. Between 11/23/98 and 1/18/02, you manufactured and shipped at least 12 [REDACTED] product lots to [REDACTED] for use by subject [REDACTED]
- B. Between 7/22/99 and 9/30/03 you manufactured and shipped at least 47 [REDACTED] product lots to [REDACTED] use by subject [REDACTED]

During the inspection you provided signed documents admitting that you manufactured the investigational [REDACTED] for both of these subjects because the former manufacturer of a similar product ceased operations in 1998.

In your response to this letter, please describe your role and the roles of Drs. [REDACTED] regarding the management of these subjects in this study.

2. **You failed to obtain signed investigator statements from the investigators participating in the investigation [21 CFR § 312.53(c)(1)] and failed to submit a protocol amendment to FDA when you added these investigators [21 CFR § 312.30(c)].**

As indicated in item 1, you failed to obtain signed investigator statements from Drs. [REDACTED]. According to your records, Drs. [REDACTED] supervised the administration of the investigational drug in Study 2. In addition, you included subjects [REDACTED] and [REDACTED] in a Study 2 report that you submitted to your IND on [REDACTED]. You did not amend the IND to notify FDA that you had added new investigators.

Clinical investigator responsibilities:

3. **You failed to protect the rights, safety, and welfare of subjects under your care, and you failed to ensure that the investigation was conducted according to the investigational plan and the signed Investigator statement. [21 CFR § 312.60].**
- A. The Study 1 protocol limited enrollment to 40 subjects with recurrent tumor and 40 subjects with primary tumor. However, you enrolled and treated at least 42 subjects with recurrent tumor in the study.
 - B. According to the study records, the recurrent arm of the study was closed to subject accrual on 7/30/02. However, on 9/5/02 you enrolled subject [REDACTED] whose brain tumor was diagnosed as "recurrent glioblastoma multiforme" according to the operation notes dated [REDACTED].
 - C. The Study 1 protocol requires the evaluation of subjects one month after infusion of the investigational autologous LAK cells. You failed to perform such evaluation for several subjects. The table "Day 0-30 Toxicity Data" indicates that subjects [REDACTED] were not examined one month after infusion.

We request that you provide a table documenting the follow-up evaluations for these subjects as part of your response to this letter.
 - D. Your investigator statement required the identification of all sub-investigators. You did not identify Dr. [REDACTED] or Dr. [REDACTED] as sub-investigators for Study 1 on a Form FDA-1572. Drs. [REDACTED] discussed the study and obtained the informed consent for subjects [REDACTED] and [REDACTED] respectively.
4. **You failed to maintain adequate and accurate case histories. [21 CFR § 312.62(b)].**
- A. Toxicities occurring within the first month following infusion of the investigational cells in Study 1 were not graded in a timely manner. For example, subject [REDACTED] was administered the investigational drug on [REDACTED] yet you did not assure that the "Toxicity Grading Form" was completed until 2/24/03. In addition, the form indicated that toxicities were to be recorded as grade 0 to 5. "NR" was entered as toxicity ratings for several criteria; the meaning of "NR" is unclear.

B. The Study 3 protocol required exclusion of subjects who tested positive for HIV. There was no source documentation to support the results of such testing for subject [REDACTED]

C. The Study 1 protocol required that investigational autologous LAK cells be

[REDACTED] According to the "LAK reinfusion datasheet," the investigational product for subject [REDACTED] was suspended in a volume of [REDACTED] ml for administration via a [REDACTED]. The operative report does not document the volume administered to the subject.

5. You failed to maintain adequate records of the disposition of the drug. [21 CFR § 312.62(a)].

You failed to maintain adequate vaccine accountability records indicating the receipt, use, disposition, and number of vials remaining for each of the cell lines used in the investigational product preparation for administration to subjects in Study 3. For example, you did not complete product accountability information for the [REDACTED] cell lines used in the preparation of the vaccine for at least six subjects [REDACTED] enrolled in the study indicating, among other things, when the product was used or destroyed.

6. You failed to assure that the Institutional Review Board (IRB) would be responsible for the initial and continuing review and approval of the proposed clinical studies and failed to report promptly all changes in the research activity and all unanticipated problems involving risk to human subjects. [21 CFR § 312.66].

A. You failed to submit a protocol amendment to the IRB requesting to increase the number of enrolled subjects in the recurrent arm of Study 1, as indicated in item 3A above.

B. The IRB requires all serious or unanticipated adverse reactions (serious adverse events [SAE], including death, hospitalization or serious illness), whether or not study related, to be reported no later than five days after the adverse reaction has been recognized. You did not report the following serious adverse events at all or within the required time frame:

Subject	LAK cell instillation date	SAE	Date of SAE	SAE reported to IRB
[REDACTED]	[REDACTED]	Pulmonary embolism	5/12/01	Not reported
		Lethargy, confusion	5/25/01	Not reported

██████████	██████████	Infected cranial flap, resection	3/19/01	Not reported
██████████	██████████	Brain abscess	3/4/02	10/9/02

C. With respect to Study 3, you failed to report SAEs to the IRB within five days as required by the IRB:

Subject	SAE	Date of SAE	SAE reported to IRB
██████████	Abdominal pain and abdominal mass	3/25/03, 4/11/03, 5/10/03	5/19/03

We note that Dr. ██████████ a neurosurgeon, extensively participated in Study 1 and is identified as a co-clinical investigator on the Forms FDA-1572 which you signed on 7/7/03 and 12/16/03. If Dr. ██████████ assumes and shares responsibility for the study obligations listed on the Form FDA-1572, then Dr. ██████████ must also sign the investigator statement, as required by 21 CFR 312.53(c)(1).

We note that the informed consent document for Study 1, approved by the IRB and signed by subjects ██████████ and ██████████ states that subjects will be seen in weekly visits for the first month after the infusion of the investigational drug, but the protocol does not require these weekly visits. We recommend that you amend your protocol accordingly.

This letter is not intended to contain an all-inclusive list of deficiencies in your clinical studies of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations and to protect the rights, safety, and welfare of subjects under your care.

You should notify this office, in writing, within fifteen (15) business days of receipt of this letter, of the steps you plan to implement to prevent the recurrence of similar violations in future studies and to assure that they are conducted in compliance with 21 CFR Part 312. In your response to the above-mentioned violations, please include supporting documentation.

This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspection. Please be advised that failure to implement effective corrective actions and/or the commission of further violations may result in the initiation of enforcement action(s) without further notice. These actions could include injunction and/or initiation of clinical investigator disqualification proceedings, which may render you ineligible to receive investigational new drugs.

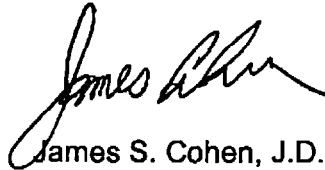
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Please send your written response to:

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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) 827-6221

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

Sincerely,



James S. Cohen, J.D.
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

Alonza E. Cruse, District Director
Food and Drug Administration
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Irvine, California 92612-2506

Arlene Gwon, M.D., Chair
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One Hoag Drive, P.O. Box 6100
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