DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
95021d

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

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By Certified Mail - Return Receipt Requested
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CBER - 05 - 001

Warning Letter

Jon M. Richards, M.D., Ph.D.
Lutheran General Cancer Care Center
1700 Luther Lane
Park Ridge, Illinois 60068

Dear Dr. Richards:

This letter describes the results of a Food and Drug Adminstration (FDA) inspection that concluded on June 4, 2004. FDA investigator Lisa Hayka met with you to review your conduct of a clinical study entitled *A Phase II Study of High-Dose Allovectin-7 in Patients with Advanced Metastatic Melanoma*. 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 you a Form FDA 483, Inspectional Observations, and discussed the observations with you at the end of the inspection. We reviewed the Form FDA 483, the inspection report, and your written response to the Inspectional Observations dated July 16, 2004.

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.

1. **You failed to protect the rights, safety, and welfare of the subjects under your care, and to conduct an investigation according to the signed investigator statement, investigational plan, and protocol. [21 CFR § 312.60].**

A. Protocol section 3.3.3 states the test article will be administered [redacted] for [redacted] weeks, and if no clinically significant disease progression occurs, the cycle may be repeated starting on Week [redacted] Subject [redacted] was continued on the study despite reports of disease progression. A radiologist reported the presence of a new mass over the right flank at week 7 (1/7/03). Despite this report, the cycle 1 "Week 8 Tumor Response" form shows "stable disease" marked for the subject, and at Week [redacted] the subject began a new cycle of the study drug. On 3/10/03, after the subject began the new cycle, the radiologist reported that the right flank mass increased in size. A note to the file dated 3/19/03 explains that the 1/7/03 report was not interpreted correctly and that the subject should have been removed from the study on 1/7/03 due to disease progression. Instead, the subject was discontinued from the study after completing cycle 2.

   In your letter, you explain that, "at the end of Cycle 1, observations made upon physical examination of the patient were equivocal with regard to disease progression, and were judged to be non-clinically significant." You explain that you exercised your "discretionary authority as the treating oncologist to allow the subject to proceed through Cycle 2." This response is unacceptable as you are required to follow the approved protocol provisions for test article administration.

B. On 8/13/03, you continued subject [redacted] to cycle 3 of the study. On this date, the "Stable Disease" box was checked on this subject's Week 17 Tumor Response form, even though on 8/6/03 a radiologist reported a large mass in the left adrenal gland measuring 4.4 cm to be suspicious for a metastatic lesion. The left adrenal gland area had previously shown a suspicious uptake according to a PET scan on 3/26/03. A note to the file on 10/22/03 describes your version of the radiological events for the subject.

Under the protocol, these subjects should not have continued to receive the study drug once radiology reports noted the presence of metastatic lesions. The protocol also states that "a complete disease status assessment (chest, abdomen and pelvic CT/MRI) is required at pre-study and at weeks [redacted] and [redacted]. . . " Please assure us that radiology reports will be reviewed prior to continuing future subjects in your clinical trial.

C. Protocol section 6.1 requires that the clinical investigator must grade the adverse events and determine if the event is related to the study material or the injection procedure. Protocol section 4.4 requires that data from the study be recorded on the case report form. However, adverse events in the medical charts were not recorded on the case report forms. For example, the following information from your progress notes was not entered into case report forms:

Subject #	Adverse Event/Date	Date you signed case report form complete/end of study
[redacted]	Rt. Side abdominal pain on 12-6-02	1-17-03/ 2-28-03
	Diffuse joint pain on 12/16-17/02	
[redacted]	Vomiting grade 1 reported on 12-31-02	3-30-03/1-14-03
	Constipation grade 1 reported on 1/7/03	
[redacted]	Injection site pain X 2 days on 7-15-03	10-28-03/ 10-23-03
	2 days of flu-like symptoms and injection site pain on 7-9-03	
	Infection right tooth extraction site 10-1 to 16-03	

We note that you added these adverse events to the case report forms during the FDA inspection on 5/20/04. In your letter, you explain that "these adverse events were likely not recorded on the case report forms due to oversight." You commit to "conduct an additional due diligence review of the progress notes for all patients on the. . . protocol to ensure that all adverse events have been appropriately recorded." Please advise us whether these adverse events were reported to the sponsor.

D. Protocol section 5.5.3 requires that vital signs be measured prior to and following the injection, and the sponsor, in the case report forms, advised you to take vital signs at specific times, including pre-study. For subject [redacted] the following were not recorded on the case report form for cycle 1:

i. all vital signs prior to week 1 injection and after week 3 injection.

ii. respiration rates prestudy and prior to week 2 injection.

In your letter, you explain that these vital signs were probably "assessed but inadvertently not recorded on the progress notes." You state that you "understand the importance of recording all data required by clinical trial protocols and wish to provide assurance that" you "do strive for such consistency."

2. **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 gave varying information to the IRB regarding the number of subjects withdrawn from the study, information that is required by your IRB on the Continuing Review Report form. Although you notified the IRB that the total number of withdrawals reported for the study in continuing review reports due to the IRB on 6/10/03 and 3/10/03 needed to be increased to five on both reports, subsequent reports due on 9/10/03 and 11/15/03 reported two as the total number of withdrawals in each report. Moreover, the "Patient Tracking Log" is not clear as to how many subjects withdrew at your site. Please clarify for us how many subjects have withdrawn and how many have discontinued the study to date.

B. By letter dated 5/2/2003, the sponsor informed you of a serious, unexpected adverse event relating to this investigational product, which had occurred in a study at another site. The sponsor directed you to report this event to your IRB and Institutional Biosafety Committee (IBC), but you did not report this event to your IRB until one year later, on 5/20/04, during the FDA inspection. The letter from the sponsor stated, "Per 21 CFR § 312.66, it is your responsibility to notify your IRB and IBC of this serious adverse event. In addition, per 21 CFR § 50.27(a)(5), it is your responsibility to inform patients of pertinent information that may affect their willingness to continue to participate in a study."

   Section 11.4 of the protocol states, [redacted] will notify the Investigator if significant new information develops during the course of the study that may relate to a patient's willingness to continue participation. Upon such notification by the Sponsor, it is the Investigator's responsibility to notify the local IRB and IBC, update the consent form, notify each affected patient accordingly, obtain a signed copy of the updated consent form from each affected patient, and deliver to the Sponsor a copy of the updated consent form."

   In your letter, you acknowledge that, prior to the FDA inspection, the IND Safety Report was reported only to the IBC and not the IRB, and that you will ensure that all future IND Safety Reports are sent to both groups, as required by the investigational plan. Please explain how you communicated this adverse event to your subjects as instructed by the sponsor.

We note that you did not sign the informed consent form for subject [redacted] even though a line was provided for that purpose. In addition, study nurses conducted the informed consent discussions with this subject on four occasions. However, according to the Site Signature and Delegation of Responsibilities Form, they were not designated as having that duty delegated to them at the time the consent forms were signed.

This letter is not intended to be an all-inclusive list of deficiencies. 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) 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 you are in compliance with 21 CFR Part 312. Please respond to items 1(B), 1(C), 2(A), and 2B. 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 the 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 initiation of clinical investigator disqualification proceedings, which may render you ineligible to receive investigational new drugs, and/or injunction.

Please send your written response to:

Debra Bower
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:
Scott MacIntire, Director
Food and Drug Administration
550 West Jackson Blvd., Suite 1500
Chicago, Illinois 60661

[redacted] Institutional Review Board
[redacted]