



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

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CBER – 04– 011

Warning Letter

Anton J. Bilchik, M.D., Ph.D.
John Wayne Cancer Institute
2200 Santa Monica Boulevard
Santa Monica, California 90404

Dear Dr. Bilchik:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from May 4 through June 1, 2004. FDA investigator Ronald Koller met with you to review your conduct of a clinical study entitled [REDACTED]

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

At the end of the inspection, a Form FDA 483, Inspectional Observations, was issued and discussed with you. We received and reviewed your written response to the Form FDA 483, dated June 25, 2004, addressed to FDA Investigator Koller at the FDA Los Angeles District Office.

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 50 and 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.

1. You failed to protect the rights, safety, and welfare of the 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. Protocol section 4.B.1. requires that enrolled subjects have confirmed metastatic colon cancer (Stage IV) to be eligible to participate in the study. Subject [REDACTED] had confirmed metastatic melanoma, and did not have confirmed metastatic colon cancer. You enrolled subject [REDACTED] in the study although this subject failed to meet inclusion criteria. In your response to the Form FDA 483, you agreed that the subject should not have been admitted to the clinical trial.

B. Section 11.A. of the June 24, 1998 protocol states, "Therapy will be discontinued after one year or sooner if patient develops recurrence or progression of disease." You failed to discontinue the following subjects from the study at the time disease progression was documented:

1. A computerized axial tomography (CAT) scan on 7/8/98 shows progression of disease for subject [REDACTED]. This subject was continued on the study for three additional months.
2. A pathology report for Subject [REDACTED] on 4/23/99 shows a diagnosis of metastatic adenocarcinoma. The subject was not removed from the study until 10/22/99.

In your response, you acknowledged, "These observations are also correct."

C. Protocol section 10.A. states "In a given patient, recurrent severe (grade 3) or a single instance of life threatening (grade 4) toxicity will be considered cause to stop treatment." You continued to administer treatment to the following subjects although they developed recurrent grade 3 and/or at least one episode of grade 4 toxicity:

1. Laboratory reports for Subject [REDACTED] show grade 3 or 4 toxicity for lymphocytes on the following dates: 2/19/99, 3/19/99, 5/14/99, 6/11/99, 7/9/99, 8/6/99, and 9/3/99. The subject continued on the study until 9/11/99.
2. Laboratory reports for Subject [REDACTED] show grade 3 toxicity for bilirubin on the following dates: 4/24/01, 8/21/01, and 12/11/01. Nevertheless, the subject continued on the study until 3/26/03 when the subject was removed from the study due to study closure.

3. Laboratory reports for Subject [REDACTED] show grade 3 or 4 toxicity for lymphocytes on the following dates: 4/16/02, 5/14/02, 6/11/02, 7/9/02, 10/1/02, 1/7/03, and 2/4/03. The subject continued on the study until 3/26/03 when the subject was removed from the study due to study closure.

In your response, you acknowledged, "These observations are also correct."

- D. You failed to conduct test procedures at intervals required by Sections 6 and 8 of the protocol. In your response, you stated, "These observations are also correct, and document that the study protocol was not always followed . . . these observations highlight the importance of strict protocol adherence." Examples of your failures to conduct required tests include:

Subject	Test Procedure(s) Not Conducted
[REDACTED]	Pre-study Human Leukocyte Antigen test (HLA); 14 day Purified Protein Derivative (PPD) skin test; 7 month chest X-ray; month 3 complete blood count (CBC); month three computerized tomography (CT) scan
[REDACTED]	Pre-study HLA
[REDACTED]	Pre-study HLA; month 3 CBC; month 3 blood chemistry; months 6 and 12 CT scans
[REDACTED]	Pre-study HLA, LDH, and chest X-ray; day 56 laboratory tests; CT scans for months 6, 9, and 12, year 2 month 6, and year 4 month 6
[REDACTED]	Pre-study for HLA and Hepatitis A and B; day 14 and day 42 PPD skin tests; and month 6 tumor-associated 90-kD glycoprotein antigen (TA90)
[REDACTED]	Day 14 PPD skin test; Cancer VAX (C-VAX) skin test for month 6; TA 90 for months 6 and 9; CBC for months 6, 8, and 9; and differential portion of 7/30/02 CBC
[REDACTED]	Month 12 C-VAX skin test

- E. Subjects [REDACTED] did not sign the informed consent addendum approved by the Institutional Review Board (IRB) on April 5, 2000. This addendum provided new information to subjects regarding the occurrence of melanoma associated retinopathy, a serious adverse event that occurred in melanoma subjects utilizing the CancerVax vaccine. The addendum also provided subjects with information regarding a potential conflict of interest. In your response, you again acknowledged, "This observation is also correct."

2. You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21 CFR § 312.60].

Section 50.20 provides that, unless a narrowly described exception applies, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. Nevertheless, you involved human beings as subjects in this research before you obtained their legally effective informed consent, when study-required skin tests were performed on subjects before they signed the informed consent document. The following table shows the dates that skin tests were performed and the date the informed consent document was signed:

Subject	Consent Form Signed	Date of Skin Test
██████████	12/16/97	12/11/97
██████████	03/24/98	03/17/98
██████████	05/29/98	05/14/98
██████████	07/02/98	06/23/98
██████████	01/22/99	12/30/98
██████████	07/28/99	07/27/99

In your response letter, you agreed with this observation.

3. You failed to assure that the Institutional Review Board (IRB) would be responsible for the continuing review and approval of the study by failing to provide the IRB with information the IRB specifically required to be submitted. [21 CFR § 312.66].

You deprived the IRB of its oversight role by failing to report, for time periods ranging from four years to five and a half years, the following serious adverse events to the IRB as required by Standard Procedure 00-701/1.00-201.

- A. Subject ██████████ was hospitalized for colon resection surgery on ██████████. You did not report this hospitalization to the IRB until 8/28/03.
- B. Subject ██████████ was hospitalized for a colostomy on ██████████. You did not report this hospitalization to the IRB until 2/11/03.
- C. Subject ██████████ was hospitalized for an abdominal wound infection on ██████████. You did not report this hospitalization to the IRB until 3/20/03.

In your response letter, you agreed with these observations.

4. **You failed to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each subject, including case report forms (CRFs) and supporting data. [21 CFR § 312.62(b)].**

- A. Case histories did not include source documents for skin test results for the following subjects: [REDACTED]. These source documents were missing at the time of the inspection.

Item 4.A. was not included on the Form FDA 483.

- B. You did not document serious adverse events on the Adverse Event CRF, which the sponsor required to be used as part of subjects' case histories, until years after the events occurred.

1. Subject [REDACTED] was hospitalized for colon resection surgery on [REDACTED]. This event was entered on the Adverse Event CRF on 8/15/03.
2. Subject [REDACTED] was hospitalized for a colostomy on [REDACTED]. This hospitalization was entered on the Adverse Event CRF on 3/25/03.
3. Subject [REDACTED] was hospitalized for an abdominal wound infection on [REDACTED]. This event was entered on the Adverse Event CRF on 8/15/03.

At the time of the inspection, you agreed that the adverse events described above should have been promptly reported to the sponsor because they required hospitalization. You stated to Investigator Koller that there was no procedure in place for describing and reporting adverse events at the time these hospitalizations occurred. In your response letter, you explain that new Standard Operating Procedures (SOPs) require that all hospitalizations be reported to the sponsor.

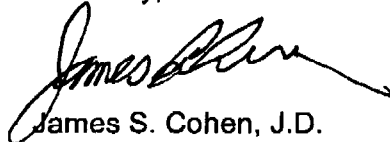
This letter is not intended to contain an all-inclusive list of deficiencies in your clinical studies of investigational new drugs. It is your responsibility as the clinical investigator to ensure adherence to each requirement of the law and applicable regulations and to protect the rights, safety, and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

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 effectively put into practice the corrective actions you have described in your response letter and/or the commission of further violations, may result in the initiation of enforcement actions 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.

We do not request a response to this letter. If you have any questions or comments about the contents of this letter or any aspects of clinical testing or investigational drugs, you may contact:

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Sincerely,



James S. Cohen, J.D.
Acting Director
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cc: Alonza E. Cruse, Director
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