

Inspections, Compliance, Enforcement, and Criminal Investigations

Kirkwood, John M., MD

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Public Health Service
Food and Drug Administration
Center for Biologics Evaluation
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SEP 15 2009

Warning Letter

John M. Kirkwood, M.D.
University of Pittsburgh Cancer Institute
Hillman Cancer Research Pavilion Suite 1.32c
5115 Centre Avenue
Pittsburgh, Pennsylvania 15213-2584

Dear Dr. Kirkwood:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from March 18 through April 24, 2009. An FDA investigator met with you to review your conduct of the following clinical studies:

- Phase I Evaluation of **(b)(4)** (Study **(b)(4)** hereinafter "Study 1"), in which you were the clinical investigator; and,
- Randomized Phase II Evaluation of **(b)(4)** (Study **(b)(4)** hereinafter "Study 2"), in which you were the sponsor and clinical investigator.

FDA conducted this inspection under the agency's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational drugs. At the end of the inspection, a Form FDA 483, Inspectional Observations, was issued to and discussed with you and the staff from your institution. We reviewed the Form FDA 483, your letter dated May 1, 2009, responding to the Form FDA 483, and the inspection report. 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.

1. You failed to ensure that the investigation was conducted according to the signed investigator statement, the investigational plan, and the applicable regulations in order to protect the rights, safety, and welfare of subjects under your care. [21 CFR § 312.60].

A. You failed to follow the protocols for Studies 1 and 2. The required screening, treatment, and follow-up procedures are described in Study 1 protocol sections 5.1 to 5.4, and in Study 2 protocol sections 4.1, 4.2, and 4.3, and 6.0. You failed to perform the protocol-required procedures as illustrated in the following table.

Subject #	Missing protocol procedures
Study #	
(b)(6)	Screening: urinalysis, CPK, phosphorous and magnesium
	Course #1: Weeks # 2, #5, #6, and #7: physical examination (PE) and performance status (PS)
Study 1	Week #10: ANA, CSC, differential, platelet, chemistry, PT/PTT, DTH
	Course #3: Weeks #1 and #2 follow-up PE and PS
	Course #4: Weeks #1, #2, and #4 follow-up PE and PS
(b)(6)	Screening: LDH
Study 1	Course #1: Weeks #2 and #3 PE and PS
(b)(6)	Screening: CPK and urinalysis
Study 1	Course #1: Weeks #2, #3, and #4 PE and PS
(b)(6)	Study 1 Course #1: Weeks #2 and #3 follow-up PS
Study 1	
(b)(6)	Study 1 Screening: LDH, GGT, CPK, phosphorous and magnesium
Study 1	

Screening: urinalysis and CPK

Cycle #1:

Vaccine #1, #2, #3, and #4 glucose, CPK, phosphorous, magnesium, and calcium

(b)(6)

Study 2

Week #5 PE and all laboratory tests

Week #6 PE and glucose, CPK, phosphorous, magnesium, and calcium

Cycle #2:

Vaccine #1, #2, #3, and #4 glucose, CPK, phosphorous, magnesium, and calcium

Screening: CPK, phosphorous, magnesium, and urinalysis

Cycle #1:

Vaccine #1 CPK, LDH, phosphorous, and magnesium

Vaccine #2 PE, CPK, phosphorous, and magnesium

Vaccine #3 and #4 CPK, LDH, phosphorous, and magnesium

(b)(6)

Study 2

Cycle #2:

Vaccine #1, #2, #3, and #4 LDH, CPK, phosphorous, and magnesium

Weeks #5 and #6 follow-up CPK, LDH, phosphorous, and magnesium

Week #8 follow-up PE and laboratory tests

Cycle #3:

Vaccine #1 and #4 CPK, phosphorous, and magnesium

Vaccine #2 CPK

Vaccine #3 phosphorous and magnesium

In your letter of May 1, 2009, you state that the protocols have been amended because you determined that some tests were not medically required or appropriate for the screening or ongoing assessment of the eligibility of subjects. You also described that you have developed new protocol-specific forms to ensure that

the appropriate tests are performed. However, only a sponsor of a study may amend a study protocol requiring omission of tests and that the sponsor is responsible for submitting such amended protocols to the FDA and the Institutional Review Board (IRB) for review as required by 21 CFR 312.30 (b). You are not the sponsor of Study 1 and therefore are not authorized to amend a study protocol requiring omission of tests. Furthermore, while you are the sponsor of Study 2, you are required to submit the amended protocol to FDA and the IRB for review under 21 CFR 312.30(b). We further remind you that any such revisions made to the protocol regarding study procedures be reflected on the consent form and approved by the IRB.

B. You failed to follow-up and collect adverse event information as required by the Study 1 protocol. Section 3.2 of the protocol, "Risk management procedures," requires you to monitor the subjects and review the study data and subject safety issues, and section 5.4 requires that "subjects will be observed one, two, and four weeks after [a course of] vaccination, and then monthly for 6 months for evidence of untoward responses as part of routine follow-up of subjects for underlying disease." The protocol further requires you to contact and follow-up with subjects until their deaths and according to a specific study schedule. You failed to follow-up with at least five subjects as required while they were still considered to be active participants in the study.

- Subject # **(b)(6)** was initiated therapy on 10/10/06 and died on **(b)(6)**. Only during the inspection did your study staff report that the subject was removed from the study in November 2006 due to progressive disease.
- Subject # **(b)(6)** was enrolled in the study on 1/29/07 and received course #1 and #2 of the study vaccines between 1/30/07 and 3/9/07. During the inspection, in a memo dated 4/15/09, you report that the subject was removed from the study on 3/28/07 due to progressive disease. The case history for this subject does not document that you followed up with this subject as required by the protocol.
- Subject # **(b)(6)** received the study vaccine starting on 7/17/07. A note dated 4/20/09 indicated that the subject cancelled all visits. A document dated 4/15/09 that you sent to the FDA investigator acknowledged that there was no documentation of the cancelled study visits and that the subject died on **(b)(6)**.
- Subject # **(b)(6)** was initiated therapy on 9/24/07. Your document dated 4/15/09 states that the subject was removed from the study on 11/13/07 and that the subject died on **(b)(6)**. The case history for this subject does not document that you followed up with this subject as required by the protocol.
- Subject # **(b)(6)** was initiated therapy on 2/12/08. Your document dated 4/15/09 indicates that the subject was removed from the study on 3/14/08 and the subject died on **(b)(6)**. The case history for this subject does not document that you followed up with this subject as required by the protocol.

We recommend that the sample Treatment Visit Follow-up Form attached to your letter also document all contacts made to subjects in order to clearly identify if or when subjects have withdrawn or are removed from a study.

C. You failed to report serious adverse events (SAEs) experienced by three subjects enrolled in Study 1 in a timely manner to the Data Safety Monitoring Committee (DSMC) as required by the protocol. Protocol section 6.2 requires the investigator and study staff to meet weekly to review the study data and subject safety issues, and to submit a cumulative summary of all adverse events occurring during the study to the IRS according to the established IRS guidelines on an annual basis. You failed to report the following SAEs until this inspection:

- i. On 11/6/06, subject # **(b)(6)** experienced infected melanoma lesions which resulted in amputation on 11/27/06. These SAEs were not reported to the DSMC until 4/14/09, more than 2 years later.
- ii. Subject # **(b)(6)** experienced the SAEs of pleural effusion, left sided chest pain, and subsequent surgery in March 2008. These SAEs were not reported to the DSMC until 4/1/09.

iii. Subject # **(b)(6)** experienced the SAE of a lower leg cellulitis infection which resulted in hospitalization on 12/19/08. This SAE was not reported to the DSMC until 4/1/09.

In your May 1 letter you acknowledged the lapses in your reporting of the SAEs to the DSMC as required by the protocol and describe corrective action plans to be implemented, including regular meetings between the investigators, nursing staff, clinical research coordinators, and associates. We recommend that all meetings include the study staff with knowledge of the day-to-day study activities and that you document your meetings, describing any discussion relating to the safety of study subjects.

D. You failed to perform the protocol-required blood cultures in Study 2 after the vaccine and the DTH antigen were found to be contaminated. Protocol section 3.7.3 describes the actions to be taken when positive sterility tests are encountered after a vaccine has been administered. For subject # **(b)(6)**, you did not perform blood cultures after tests for both cycle #1, vaccine #1 on 9/9/08 and the DTH on 10/28/08 were found to be contaminated with *Propionibacterium acnes*.

E. Section 5.4 of the Study 1 protocol requires that baseline evaluations be conducted within 1 week prior to the start of protocol therapy, and that in the event a subject's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to the initiation of the next course of therapy. You did not follow this protocol requirement for the subjects listed below.

i. Subject **(b)(6)** was administered the study drug on 10/10/06, but baseline evaluations were conducted on 8/30/06, nearly 6 weeks prior to the start of the therapy.

ii. Subject **(b)(6)** was administered the study drug on 7/17/07, but no baseline evaluation was found in the case file during the inspection except an undated and unidentified eligibility checklist.

2. You failed to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation. [21 CFR § 312.62(b)].

A. Section 3.1 of the protocol for Study 1 requires that prospective subjects have an ECOG performance status of 0 or 1 to be included in the study. For the following subjects the ECOG status was either not documented or was discrepant between documents.

i. For subject # **(b)(6)** the progress note on 8/30/06 indicates an ECOG status of 3. However, an undated and unsigned eligibility checklist indicates an ECOG status of 1.

ii. For subject **(b)(6)** the progress note dated 9/13/07 does not include an ECOG status even though the subject received the vaccine #1 for course #1 on 9/25/07. However, an undated and unsigned eligibility checklist indicates an ECOG status of 1.

iii. For subject **(b)(6)**, the progress note dated 1/14/09 denotes an ECOG status of 3. The Treatment Visit Follow-up form dated 3/4/09 did not document the ECOG status, but during the inspection this form was changed to indicate an ECOG status of 1.

B. Study 1 protocol section 3.1 requires pretreatment laboratory tests, including AST, ALT, GGT, LDH, and Alkaline Phosphatase, to be less than or equal to 2.5 times the upper limit of normal. There is no documentation of screening LDH values for subjects **(b)(6)**

C. Study 2 protocol section 4.4 describes the re-treatment requirements for subjects who finished the first course of vaccination. According to the protocol, before re-treatment, subjects should be evaluated at 1, 2, and 4 weeks post-immunization, and subjects with stable disease may be retreated with additional cycles of the vaccine. Subject **(b)(6)** was administered the Cycle #2 vaccines #1 through #4 starting 12/6/05.

However, there is no documentation to indicate that the subject was evaluated for re-treatment.

D. You assigned duplicate study identification **(b)(6)** for two subjects in Study 2.

3. You failed to promptly report all changes in the research activity to the IRS. [21 CFR § 312.66].

In your May 1 letter you state that you amended the research protocols for Study 1 and Study 2 because you determined that some tests were not medically required or appropriate for the screening or ongoing assessment of the eligibility of subjects. However, you did not report these changes in the research activity to the IRS as required.

4. You failed to obtain a list of the names of the sub-investigators who will be assisting the investigator in the conduct of the investigation. [21 CFR § 312.53(c)(1)(viii)].

You failed to identify **(b)(4)** as sub-investigators for Study 2. **(b)(4)** performed **(b)(4)** vaccine injections for subject **(b)(6)** on 10/19/2005 and 12/28/2005, respectively.

5. You failed to monitor the progress of the clinical investigation conducted under your IND. [21 CFR §§ 312.56(a) and 312.50].

As a sponsor for Study 2, you failed to monitor the progress of the investigation as required by the general investigational plan and protocols contained in the IND, as described in item 1, above.

We note that you are currently participating in at least 37 clinical studies. You are responsible for supervising study staff and ensuring proper study conduct. We recommend that you develop and maintain logs or other records that prospectively identify each study staff member's roles and responsibilities, the beginning and end dates of each person's involvement, and their signatures and initials. We further recommend that the study personnel be provided appropriate training in study procedures and that the training be documented and updated as needed.

This letter is not intended to contain an all-inclusive list of violations that may exist with your conduct of clinical studies. It is your responsibility to ensure compliance with the Act and all applicable regulations.

Within fifteen (15) business days of receiving this letter, please provide written documentation of the actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies for which you prevent the recurrence of similar violations in current and future studies for which you are the clinical investigator. Failure to respond to this letter and to take appropriate corrective action could result in FDA taking regulatory action without further notice to you. FDA could initiate disqualification proceedings against you in accordance with 21 CFR 312.70.

Please send your written response to:

Ms. Bhanu Kannan
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
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Rockville, Maryland, 20852-1448
Telephone: (301) 827-6221

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

Sincerely,

/S/

Mary A. Malarkey, Director
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: Karyn Campbell
Acting District Director, HFR-CE100
Food and Drug Administration
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