



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

OCT 7 1997

Certified-Return Receipt Requested

WARNING LETTER

Frederick L. Datz, M. D.
Professor of Radiology
Department of Nuclear Medicine
University of Utah School of Medicine
50 North Medical Drive
Salt Lake City, Utah 84132

Dear Dr. Datz:

During an inspection ending on June 17, 1997, Mr. Ted M. Steinke, an investigator with the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study entitled, "Evaluation of the Safety and Efficacy of [redacted]"

[redacted] The inspection is part of FDA's Bioresearch Monitoring Program which includes inspections designed to monitor the conduct of research involving investigational drugs.

Based on our review of the inspection report and information submitted with the report, we identified deviations from applicable federal regulations as published in Title 21, Code of Federal Regulations, Part 312 [21 CFR 312]. The deviations include, but are not limited to the following:

1. **Failure to ensure that the investigation is conducted according to the investigational plan (protocol). [21 CFR 312.60]**

There are several protocol deficiencies regarding collection and analysis of various specimens, eligibility criteria of subjects, and changes of initial results. For example:

- a. The protocol required that a bone biopsy/aspiration be obtained to evaluate the suspected sites of [redacted] involvement via histological techniques and microbiological cultures. The following examples lacked required testing:

- i. A bone biopsy and cultures were not performed on the amputated toes of subject #86517.
 - ii. A bone biopsy/aspiration was not analyzed for subject #86523 because the specimen was lost.
 - iii. Bone biopsy results were deemed indeterminate for subject #86543 because a microscopic examination was conducted without a microbiological culture of the amputated toe as requested by the Nuclear Medicine Department.
- b. The eligibility criteria included requirements that subjects have a life expectancy of at least six months, the ability to return for follow-up visits, and be able to give written informed consent in accordance with institutional policies. The following are examples of deviations from these requirements:
- i. The Discharge Summary for subject #86506 describes the subject's history with a hospitalization in February 1993. The subject was sent home and bedridden. The family understood the subject would die soon. The Medical History and hospital records show the subject entered the study on 4/23/93 with end stage congestive heart failure, chronic obstructive pulmonary disease, and other serious medical problems. The subject suffered a CVA on 5/3/93 and expired on 5/14/93, 21 days after entering the study.
 - ii. Records show subject #86523 was an unemployed, homeless, drug abuser, with a history of alcoholism. The subject was unlikely to return for follow-up visits but was enrolled in the study.
 - iii. Records show subject #86536 with dementia, personality changes, and hypomania was entered into the study even though the sponsor indicated in a pre-study letter to you that no mentally impaired subjects were to be enrolled.
- c. [redacted] subjects (80%) missed one or more follow-up [redacted] tests. Follow-up [redacted] test results were not available for at least [redacted] subjects (50%) at both the 4-6 week interval and the 3-4 month interval. In addition, [redacted] results were not available for an additional [redacted] subjects at the 3-4 month interval. Records usually do not show why these tests were not performed.
- d. Blood chemistry and hematology tests were sometimes not done at baseline, 24 hours, or 7-10 days post injection of the test article. For at least [redacted] subjects (37%) the tests were not done or results were missing. The records usually do not show why the tests were not performed.

- i. [redacted] case report forms (CRFs) reviewed include examples of missing hematology labs as follows:

<u>Subject #</u>	<u>Test</u>	<u>Subject #</u>	<u>Test</u>
86544	Baseline	86521	24 hour and
86515	24 hour labs	86546	7-10 day labs
86530	7-10 day labs		
86539			

- ii. Examples of missing or partial blood chemistries include the following:

<u>Subject #</u>	<u>Test</u>
86543	No blood chemistries at 24 hours. BUN, blood sugar, and creatinine were the only chemistries obtained at baseline and 7-10 days.
86545	BUN, blood sugar, and creatinine were the only chemistries obtained at baseline and 24 hours.

- e. The protocol required that Erythrocyte Sedimentation Rates (ESRs) be performed at baseline, 24 hours, and 7-10 days. One or more ESRs are missing for at least [redacted] of the [redacted] subjects (65%). The following are missing ESRs out of [redacted] CRFs reviewed:

<u>Subject #</u>	<u>Test</u>	<u>Subject #</u>	<u>Test</u>
86519	Baseline	86521	Baseline, 24 hour
86527		86544	and 7-10 days
86501	24 hour	86536	Baseline & 7-10 days
86515		86546	24 hours & 7-10 days
86504	7-10 days		
86510			
86530			
86539			

- f. Urinalysis was required to be performed at baseline, 24 hours, and 7-10 days. The following are missing out of [redacted] CRFs reviewed:

<u>Subject #</u>	<u>Test</u>	<u>Subject #</u>	<u>Test</u>
86501	Baseline	86518	7-10 days
86504	24 hour	86530*	
86515*		86539*	
86512	24 hour &	86536	Baseline, 24 hour, &
86521*	7-10 days		7-10 days
86544			
86546*			

*Indicates subjects and time periods when other or all lab tests for the time period were missed.

- g. The protocol requires that the clinical investigator be made aware of changes to the CRF following the original review and sign-off of the CRF. The clinical investigator is to document the awareness by initialing and dating the changes. The sponsor changed the interpretation of subject #86509's outcome via a data collection form more than two years after the subject was studied. The subject was administered the test article on 5/11/93. The results on the CRF were originally listed as FP (False Positive). The data correction form changed the interpretation of results by dividing the site into a soft tissue site and a bony tissue site, and gave the latter an interpretation of TN (True Negative). The Data Correction form was signed off by the study coordinator on 9/27/95, with no input, approval and signature from the clinical investigator.
2. **Failure to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21 CFR Part 312.60]**

The consent form lacks the following:

- a. A statement regarding the expected duration of the subject's participation.
 - b. A description of the timing of follow-up laboratory tests required by the protocol.
3. **Failure to prepare and maintain adequate case histories designed to record all data observations pertinent to the investigation. [21 CFR 3123.62(b)].**

There are several discrepancies between the data entries on CRFs and source documents. Explanations are not provided regarding missing lab values for two subjects and missing [redacted] and lab values for one subject that moved out of state. For example:

- a. The CRF for subject #86544 shows the biopsy/aspirate was collected on 7/19/95, but the microbiology and [redacted] reports for the subject show the collection date as 7/27/95.
- b. Page 5 of the CRF for subject #86543 indicates that a biopsy/aspiration was already obtained or was to be obtained from the left hallus/distal phalanx. No report was found in the subject's record. The toe was amputated.
- c. The narratives and dates of [redacted] and test article [redacted] in the [redacted] reports do not correspond to time frames of injection reported for the test article on [redacted] Preparation and Quality Control sheets of the CRFs for subjects #86513 and 86546.
- d. Subject #86544 had no 24 hour labs done. The 24 hour labs listed in the CRF are really 7-10 day values, according to the FDA investigator. Values presented as the 7-10 day values in the CRF are 15 days post test article administration.
- e. There are no explanations why 24 hour lab values are missing for subject #86515 and 7-10 day lab values are missing for subject #86545.
- f. Subject #86521 moved out of the state. There is no indication in the CRF that attempts were made to obtain labs and [redacted].

4. Failure to provide the IRB with accurate information. [21 CFR 312.66]

Records show that you submitted an Annual Request for Approval of a Continuing Project to the IRB on 8/30/93 but did not report three subject deaths and two adverse events that occurred in April and May 1993 until 4/18/94. The following events occurred:

- a. Subjects #86501 and #86504 experienced CVAs on 4/11/93 and 4/22/93, respectively.
- b. Subjects #86508, 86506, and 86504 died on 5/3/93, 5/14/93, and 5/24/93, respectively.

CBER recommends that all subject deaths be reported to the IRB and sponsor concurrently. The CVAs should have been reported to the IRB on the 8/30/93 report whether related to the test article or not.

Please explain why the results from the test article [redacted], the [redacted], and the bone scan for subject #86544 are reported on the same report. Please explain why the results from the test article [redacted] and the [redacted] for subject #86546 are reported on the same report.

It appears there is a lack of communication between you, the hospital staff, and laboratory staff regarding the requirements and necessity for obtaining laboratory data as required by the protocol for subjects in clinical trials. Please explain how you intend to improve data collection in future studies you may conduct.

Deviations in the conduct of this study appear to be the result of your lack of understanding of the procedures and requirements that govern the use of investigational new drugs. By signing the Statement of Investigator (Form 1572), you agreed to follow FDA regulations while conducting human clinical trials. The commitment includes ensuring that you will conduct the study in accordance with the protocol, that the requirements relating to obtaining informed consent and IRB review are met, and that adequate and accurate records of the study are maintained. Inspection results indicate that you did not follow the protocol, that you did not provide the IRB with accurate information, that elements of informed consent were lacking, and that you did not maintain complete and accurate records.

 Continued non-compliance with the regulations governing the use of investigational drugs could affect not only the acceptability of the trial data but also the safety of the human subjects of research.

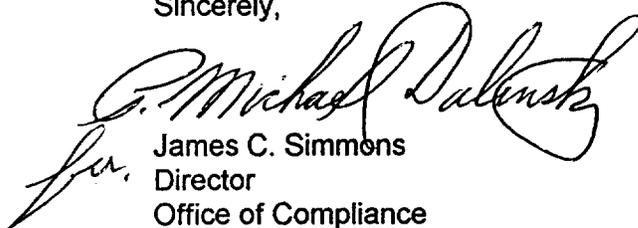
Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step you plan to take to prevent a recurrence of similar violations. If corrective action cannot be completed within 15 working 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 include clinical investigator disqualification which determines a clinical investigator ineligible to receive investigational drugs.

Should you have any questions or comments about the contents of this letter or any aspects of clinical testing of investigational drugs, you may contact Debra Bower, Consumer Safety Officer, Bioresearch Monitoring, Division of Inspections and Surveillance, at (301)827-6221.

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Your response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852-1448, Attention: James C. Simmons, HFM-600.

Sincerely,


James C. Simmons
Director
Office of Compliance
Center for Biologics and Evaluation
and Research

Enclosures

FDA Form 483, Inspectional Observations

21 CFR Part 312

FDA Information Sheets for Institutional Review Boards and Clinical Investigators
(includes 21 CFR Part 50)

cc:

Jay Jacobson, M.D.

Chairman, Review of Research with Human Subjects Committee - Health Sciences

University of Utah School of Medicine

50 North Medical Drive

Salt Lake City, Utah 84132