



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

g318/d

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

April 17, 2002

By Certified Mail – Return Receipt Requested
and by Facsimile Transmission

CBER – 02 – 012

Warning Letter

Alice L. Yu, M.D., Ph.D.
University of California, San Diego Medical Center
200 W. Arbor Drive
San Diego, California 92103

Dear Dr. Yu:

During the period from November 6 through 16, 2001, Allen F. Hall and Robert S. Sweeton, investigators with the Food and Drug Administration (FDA), reviewed your activities as the sponsor of a multi-center clinical trial using experimental in pediatric subjects. You also are a clinical investigator at the University of California, San Diego Medical Center (UCSDMC) for the same study. The inspection was conducted as part of the FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of clinical research involving investigational drugs. At the close of the inspection, a Form FDA 483, Inspectional Observations, was issued to you.

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.

CLINICAL INVESTIGATOR RESPONSIBILITIES

1. You failed to ensure that the investigation is conducted according to the investigational plan. [21 CFR § 312.60].

- A. You failed to ensure that the investigation was conducted according to the study protocol when your staff administered the wrong investigational product to three pediatric subjects (— -2 doses, — 2 doses, and — -1 dose). You do not have an Investigational New Drug application (IND) in effect for this test article, and were not authorized to administer it, as required by 21 CFR § 312.40(d).

We acknowledge that, — the firm responsible for shipping your study drugs, sent the wrong investigational product to your institution. However, the vials, the box containing the vials, and the packing slip all were clearly labeled to reflect the actual (wrong) product that was shipped to you. UCSDMC pharmacy staff accepted the wrong investigational product, even though the product name did not match previous shipments of the correct study drug. In addition, pharmacy staff placed incorrect labels on five individual doses that were administered to the subjects listed above before the error was discovered by —.

During the inspection, you provided documentation of the corrective actions taken by the UCSDMC Investigational Drug Service to show commitment of your institution to prevent further misadministrations.

- B. You failed to follow the study protocol when you gave additional doses of the correct test article to two of the subjects in 1.A. above (— -1 dose and — -1 dose) after the above noted misadministrations. The protocol states that a subject "must not be on other anticancer therapy with the exception of, —." After receiving the wrong investigational — the subjects were no longer eligible to continue on the protocol.
- C. You failed to ensure that the refrigerator used to store the investigational product at UCSDMC maintained the proper temperature, as required by the protocol. The temperature log indicated that the refrigerator reached room temperature on 8/18/01. Furthermore, the refrigerator did not have a 24-hour temperature recording system to verify that the required temperature was maintained.

During the inspection, you said that you would request repair and improved monitoring of the refrigeration equipment.

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

You failed to maintain adequate records to verify the identity of the test articles administered to subjects. In your institution, different names were used for the investigational drug in the same lot. For example, product from lot number _____ was identified by the following names listed below.

<u>Name</u>	<u>Document</u>	<u>Date on Document</u>
_____	[TPI]etter extending shelf life of the lot	5/1/00
_____	UCSDMC drug accountability records	6/00 -- 8/01
_____	UCSDMC drug accountability record	8/23/01
_____	Drug Packing Lists sent to UCSDMC	10/18/00, 5/14/01
_____	Drug Packing Slip sent to UCSDMC	5/14/01
_____	Drug Packing List sent to UCSDMC	8/22/01

_____ and _____ are, of course, different investigational products. We acknowledge that _____ staff used different names when shipping the same investigational product. However, neither you, nor the staff in your institution, noted and corrected this problem. Furthermore, failure to specify the correct names of the test articles may have contributed to the misadministrations in 1. A. above.

Please verify the identity of the test article in lot _____ as well as the test articles in all other lots administered to your subjects. The following lots, listed in UCSDMC source documents, should be included:

3. **You failed to maintain adequate and accurate case histories.**
[21 CFR § 312.62(b)].

A. You failed to annotate the forms entitled "Study Drug Administration" to document the actual (incorrect) investigational product administered to the three subjects in item 1.A. above. These forms erroneously state that the three subjects received the correct test article. During the inspection, you said that you would correct the records. Please provide a copy of these revised records in your response to this letter.

B. The inspection revealed that there was incomplete documentation concerning your notification of parents about the misadministrations in 1.A. above. Although you provided notes where you described contacting the parents about the errors, you did not record the specific information that was discussed. For example, there is no documentation that you discussed with the parents your plan to monitor subject immune response on a more frequent basis than specified by the protocol.

4. You failed to provide a complete list of the subinvestigators who assisted you in the conduct of the investigation. [21 CFR § 312.53(c)(1)(viii)].

You failed to ensure that Dr. _____ was listed on a Form FDA 1572. During the inspection you said that Dr. _____ had been a "co-investigator" since the beginning of the study. The Form FDA 1572 you signed on 8/20/97 does not list any other UCSDMC subinvestigators. It is your responsibility as a clinical investigator to sign a Form FDA 1572 that includes all subinvestigators who will be assisting you.

SPONSOR RESPONSIBILITIES

5. You failed to monitor the progress of the clinical investigation. [21 CFR § 312.56(a)].

You failed to ensure that your clinical investigators at other sites sent flow sheets to you every two months, as required by protocol. Examples of missing data are given below:

A. In a letter to the FDA, dated 2/16/00, you promised to ensure the required monitoring after the FDA granted an exemption to enroll an ineligible subject at the University of Alabama at Birmingham. However, the inspection revealed that you did not have flow sheets (including vital signs and laboratory results) or any other study records for this subject at your institution.

During the inspection, you promised to obtain records for this subject. Please provide a copy of those documents.

B. You did not have any flow sheets for subject _____ treated at the Dana-Farber Cancer Institute from 9/00 to 3/01.

C. You did not have flow sheets for the entire first year of administration of the test article to subject [REDACTED] at the University of Maryland Medical Center. However, as the sponsor, you permitted the subject to continue receiving the test article during the second year on protocol, as documented by the only flow sheet available, dated from 6/11/01 – 8/6/01.

6. You failed to obtain a signed investigator statement, Form FDA 1572, from all investigators prior to permitting them to begin participation in the investigation. [21 CFR § 312.53(c)(1)].

The inspection revealed that you did not have signed Forms FDA 1572 for all clinical investigators participating in your study. You did not obtain signed Forms FDA 1572 for two clinical sites, [REDACTED] and the [REDACTED] after the previous clinical investigators left those institutions. As the sponsor of this research, you are required to maintain these signed forms so that investigational drugs are distributed only to authorized individuals and so that you can monitor the progress of the investigation. Furthermore, you must report new clinical investigators to the IND, as required by 21 CFR § 312.30(c).

In addition to your response to the above items, please provide a list of all clinical trials, including those not under an IND, in which you are participating. The list should give the title of the study, the protocol number, the source(s) of the investigational product(s), and the associated IND or BLA numbers, if applicable. We have not yet received this list, which was requested during the inspection.

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.

Please notify this office in writing, within fifteen (15) business days after receipt of this letter, of the specific actions 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 fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

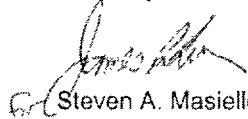
Failure to promptly correct these deviations may result in enforcement action without further notice. These actions could include initiation of investigator disqualification proceedings which may render a clinical investigator ineligible to receive investigational new drugs, termination of Investigational New Drug Applications, and/or injunction.

Please send your written response to:

Mary Andrich, M.D.
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 Food and Drug Administration's Los Angeles District Office listed below.

Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

Alonza E. Cruz, Director
Food and Drug Administration
19900 MacArthur Boulevard
Suite 300
Irvine, California 92612

Alan McCutchan, M.D.
Chairman, Institutional Review Board
University of California, San Diego Medical Center
9500 Gilman Drive
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