



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

CBER-01-020

April 3, 2001

WARNING LETTER

By Certified Mail—Return Receipt Requested

Arnold D. Rubin, M.D., Chairman,
Department of Oncology and Hematology
St. Joseph's Hospital and Medical Center
703 Main Street
Paterson, New Jersey 07503

Dear Dr. Rubin:

During the inspection that ended on November 1, 2000, investigators with the Food and Drug Administration (FDA) reviewed your conduct of clinical studies at St. Joseph's Hospital and Medical Center. The studies involved the administration of investigational new drugs provided by the sponsor, the _____
The inspection was conducted under the FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational drugs.

At the close of the inspection, a Form FDA 483 (enclosed) was issued. We reviewed the letter dated January 24, 2001, submitted in your behalf by Nancy Stanek, Administrative Director, Medicine and Oncology Services, St. Joseph's Hospital and Medical Center (enclosed). We 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), Parts 50 and 312 (available at <http://www.access.gpo.gov/nara/cfr/index.html>).

The applicable provisions of the CFR are cited for each violation. A listing of the violations follows. The term "protocol" refers to the investigational plan for a clinical study sponsored by the _____

1. Failure to document that informed consent was obtained prior to participation in the study. [21 CFR § 312.62(b)].

You failed to document that informed consent for the protocols was obtained prior to initiation of protocol procedures in your institution, St. Joseph's Hospital and Medical Center.

a. For multiple subjects, protocol procedures were performed in your institution prior to obtaining a signature on the protocol informed consent documents. At a later date, these subjects signed a consent form witnessed by staff in the sponsor's facility. Three examples are listed below:



During the inspection you explained that _____, was not part of the protocols. However, _____ included in the documentation for the _____ protocols in the following places:



b. Subjects, including 1754 and 1824, signed non-protocol consent forms such as the one entitled "Informed Consent to Operate or Other Special Procedure." This form does not explain to patients that they will be subjects participating in a research protocol and that, as a result, the cost of some procedures may not be covered by insurance. The form lacks required elements of informed consent to participate in research with investigational products, including the following: a statement that the study involves research; an explanation of the purposes of the research; a description of the risks to the subject from participation in the protocol; an explanation of whom to contact with questions related to the research and the research subject's rights; a statement that participation is voluntary; and a statement about any additional costs that may result from participation in the protocol.

c. For multiple subjects, the protocol consent form signature page was not completely filled out. Protocol consent forms used during the period from 1995 to 2000 had two different lines for subject signatures. The sponsor's staff witnessed one signature, while the second signature was to be witnessed by staff in your institution. While subjects in (1.)(a.) above had signatures witnessed by the sponsor's staff after initiation of protocol procedures in your institution, these subjects did not sign the part of the consent form page to be witnessed by your staff in your institution prior to those procedures.

d. Although subject 1674 _____ on 12/10/96 and 9/24/97, there was only one signed consent form, dated 12/2/96. _____ was performed before the 9/24/97 dose, requiring a consent form that described the additional protocol procedures : _____

2. Failure to maintain adequate case histories. [21 CFR 312.62(b)].

a. You failed to document clinical data required to establish eligibility for the protocols prior to administration of potentially toxic doses of investigational products. _____

_____ performed in the sponsor's facility. Each subject agrees to this eligibility criterion, which is stated in all of the patient informed consent documents. _____

i. Sixteen dosing records (for 13 subjects) from your institution were reviewed during the inspection. For 12 of 16 records (ten of 13 subjects) there were no results for the _____. This included dosing records for the following ten subjects: 1437, 1460, 1490, 1508, 1528 (received three doses on 8/8/94, 12/5/94, and 8/26/96), 1555, 1639, 1674, 1766, and 1824.

ii. When the inspection revealed that _____ results were missing from subject records, one of your subinvestigators, Dr. Herskovic, was able to provide _____ reports that he retrieved from the sponsor. However, there is no documentation that the data in these retrieved reports was reviewed by anyone at your institution prior to the administration of the investigational products. For example, three of the _____ reports are dated after the administration of _____ to subjects in your institution.

<u>Subject</u>	<u>Date of Administration</u>	<u>Date of Report</u>
1490	5/17/94	11/9/94
1639	2/6/96	2/22/96
1824	6/9/99	7/27/00

Furthermore, _____ reports for subjects 1437, 1460, 1555, and 1639 were addressed to physicians at other facilities. There is no documentation that these _____ results were also sent to your institution before the investigational products were administered.

b. You did not ensure that the Case Report Forms (CRFs) were completed for each subject. The only CRF observed to be utilized on a consistent basis was the page entitled _____

c. You failed to document and report adverse events occurring in your institution. Review of source documents in your institution revealed numerous adverse events that were not graded, classified as "expected" or "unexpected," entered onto CRFs, or reported to the sponsor, as required by the protocols. Representative examples are listed below:

<u>Subject</u>	<u>Adverse Events</u>	<u>Date</u>
	Anemia	5/17/94
	Constipation	5/20/94
	Redness, central catheter site	5/25/94
	Central catheter site red, draining	5/26/94
	Headache	5/26/94
	Nausea/Vomiting	5/26/94
	Nausea/Vomiting	4/2/95
	Photophobia	4/2/95
	Severe headache	4/2/95
	Epidural patch	4/2/95
	Diarrhea	4/15/95
	Diarrhea	4/16/95
	Diarrhea	4/18/95

<u>Subject</u>	<u>Adverse Events</u>	<u>Date</u>
1639	Nausea	2/8/96
	Diarrhea	2/9/96
	Nausea/Vomiting	2/9/96
	Ascites	2/9/96
	Nausea	2/10/96
	Diarrhea	2/10/96
1674	Diarrhea	9/26/97
1754	Vomiting	1/1/98
	Nausea	1/2/98
	Nausea	5/3/99
	Circumoral tingling	5/4/99
	Nausea	5/27/99
	PT > 70 (units not given)	4/27/00
	PTT = 65 (units not given)	4/27/00
	Itching	4/27/00
	Shortness of breath	4/27/00

3. Failure to maintain adequate records of the disposition of the drug. [21CFR § 312.62(a)].

You failed to maintain documentation to show that every dose of investigational product was prepared, assayed, and appropriately administered.

The sponsor's label was missing for 16 of 117 _____ doses administered in your institution. These labels identify the investigational products, and include the following information: name of subject; lot number; activity in milliCuries; isotope; and date prepared.:

The prescription, assay, and administration records at your institution were reviewed for the 16 doses with labels missing. For all 16, the CRF page entitled "Injected Material for Therapy Study" lacked consistent and complete documentation. Examples of missing CRF entries include: "Method of administration," "Volume infused," "Start time," and "Finish time." For 13 of 16 records, there was no entry on the line for "Medical Coverage" giving the name of the physician who was responsible for administration of the investigational product.

4. Failure to retain records of assurance of Institutional Review Board (IRB) review and continuing review of clinical studies. [21CFR § 312.62(c) and 312.66].

- a. You do not have documentation to verify that the Institutional Review Board (IRB) reviewed, approved, and renewed the approval of the majority of your protocols. During the inspection, you explained that you sent protocols and amendments to the IRB, but that you did not keep a list of what was submitted. Copies of two IRB letters of approval, dated 3/21/96 and 6/27/96, were available for review. Other than these two letters, you do not have any other correspondence from your IRB.
- b. You do not have documentation to show that the IRB approved the informed consent documents, both original as well as revised versions, used for the protocols.
- c. You do not have documentation that you requested and received IRB approval for advertisements of protocols.

5. Failure to retain records. [21CFR § 312.62(c)].

You failed to maintain copies of all of the 30 protocols identified from source documents as having been conducted in your institution. Protocols were maintained in three different places within your institution. When your staff were unable to locate all of the protocols, they tried to retrieve those that were missing from the sponsor. However, even with assistance from the sponsor, 8 of 30 protocols were not available for review. You must keep copies of all protocols for which you have oversight in order to ensure that you follow the proper investigational plan for each subject.

6. Failure to ensure that an investigation is conducted according to the signed investigator statement. (Form FDA 1572). [21 CFR 312.53(c) and 312.60]

You failed to ensure that every Form FDA 1572 included the names of all subinvestigators. During the inspection, you explained that you were not licensed to administer the _____ for these protocols, but that the subinvestigators, Dr. Herskovic and Dr. Pereira, were licensed to do so. The inspection revealed several examples where the subinvestigators administered _____ investigational products without being listed on the corresponding Form FDA 1572. You must include the names of subinvestigators on the Form FDA 1572 when they are responsible for the administration of _____ investigational products in your clinical studies.

This letter is not intended to be an all-inclusive list of deficiencies in your clinical studies of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations.

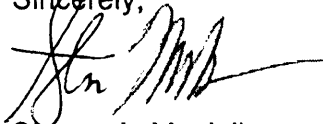
Please notify this office in writing, within fifteen (15) business days after receipt of this letter, of the specific actions you have taken to correct the violations, and to prevent a recurrence of similar violations. If corrective action cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include initiation of clinical investigator disqualification proceedings which may render a clinical investigator ineligible to receive investigational new drugs. Your written response should be sent to the following address:

Office of Compliance and Biologics Quality, HFM-664
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, Maryland 20852-1448
Telephone (301) 827-6221

We request that you send a copy of your response to the New Jersey District Office, Waterview Corporate Center, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054.

Sincerely,



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

Enclosures:

Form FDA 483, Inspectional Observations, dated November 1, 2000.
Letter to the FDA, dated January 24, 2001, signed by Nancy Stanek, St. Joseph's
Hospital and Medical Center

cc:

Douglas Ellsworth, Director
FDA/New Jersey District Office
Waterview Corporate Center
10 Waterview Boulevard, 3rd Floor
Parsippany, New Jersey 07054