



APR 9 1999

Certified-Return Receipt Requested

Warning Letter

C. Fordham von Reyn, M.D.
Dartmouth Hitchcock Medical Center
One Medical Center Drive
Lebanon, New Hampshire 03756

CBER - 99 - 017

Dear Dr. von Reyn:

During inspections conducted from November 30 to December 7, 1998, and January 27 to 28, 1999, Mr. Garry Stewart, an investigator from the Food and Drug Administration (FDA) New England District Office, met with you to review your current activities as a sponsor and clinical investigator. These inspections are part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research involving investigational drugs.

Based on information obtained during the inspections, we have determined that you have violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published under Title 21, Code of Federal Regulations (CFR), Parts 312, 50, and 56 (copies enclosed). Our investigation revealed that you did not fulfill your obligations as a sponsor and clinical investigator in the use of unlicensed biological investigational new drugs for the reasons listed below. The applicable provisions of the CFR are cited for each violation.

1. Failure to fulfill the general responsibilities of sponsors.

[21 CFR 312.50]

- A. You failed to maintain an effective IND with respect to the investigations in that you did not submit investigational plans (study protocols) to IND _____ before the clinical studies were initiated. Examples include, but are not limited to, the _____ or _____ for the _____ study, and the study of _____.
- B. You did not submit to IND _____ all case report forms for subjects administered the investigational _____ under the _____ study when CBER requested that you do so. You did not submit the case report forms for several ineligible subjects, identified in item 4(A)(iii)(e), below.

2. Failure to select investigators and monitors. [21 CFR 312.53]

- A. You failed to obtain information about the clinical investigation, including a signed investigator statement (Form FDA-1572) and curriculum vitae or other statement of qualifications, before permitting clinical investigators to begin participation in the clinical studies.
- B. You failed to limit shipment of the investigational test article to only those investigators identified prospectively in an IND. You did not submit IND amendments to identify _____ and _____ as clinical investigators participating in studies under IND _____

3. Failure to review ongoing investigations. [21 CFR 312.56]

You did not monitor the conduct of the _____ study at participating clinical sites. One of the sites (_____) did not comply with the protocol developed by the site. The site did not conduct the _____ evaluations in a blinded manner for at least _____ subjects, whose _____ were administered and evaluated by the same person. This is contrary to the procedure reported in the article in the *Journal of Infectious Diseases* 177:730-6, 1998 (hereafter referred to as 'JID article').

4. Failure to fulfill the general responsibilities of investigators. [21 CFR 312.60 and Part 50]

Federal regulations in 21 CFR 312.3 define an investigator as an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). An investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

- A. You failed to adequately protect the safety and welfare of subjects.
 - i. There was no prospective protocol used in several of your studies, including, but not limited to, the _____ study of at least _____ subjects with _____ and of _____ No investigational product may be administered without a study protocol.
 - ii. By not having a written protocol, you did not prospectively establish standard criteria which would result in the inclusion or exclusion of subjects.

- iii. During the inspection you told the FDA investigator, Mr. Stewart, that the eligibility criteria and study procedures that were in effect during the _____ study were identified in the *JID* article. Using the entry criteria described in the *JID* article, you administered the test article to at least _____ subjects who were not eligible for the study:
- a. Subject _____ did not undergo a _____ until more than _____ after the _____ was administered.
 - b. Subject _____ did not undergo a _____ until approximately _____ after the _____ was administered.
 - c. Subject _____ had a positive _____ result reported _____ after the _____ was administered.
 - d. Subject _____ was administered the test article approximately _____ before the _____ result was available.
 - e. You administered the test article to at least _____ subjects (_____) who were not eligible, as retrospectively defined in the *JID* article. These subjects were noted to be _____ and _____.
 - f. You administered the test article to at least _____ subjects (_____) without a documented test for human immunodeficiency virus (HIV). The *JID* article states that _____ patients must have an absence of known immunodeficiency.
 - g. Subject _____ was not tested for HIV. A negative ELISA for HIV was required for inclusion of _____ patients in the study, as identified in the *JID* article.
- iv. Using the _____ study procedure described in the *JID* article, you failed to follow the 'investigational plan' in that you did not administer or evaluate the _____ in a _____ manner for several subjects, including _____ and _____.

B. You failed to adequately protect the rights of subjects.

1. There is no documentation that you obtained the informed consent of subject _____ prior to entry into the _____ study.
2. You did not obtain the informed consent of _____ study subject _____ who signed a general hospital consent form. This form does not contain all of the required elements of informed consent for participation in a clinical study involving investigational products.
3. The consent form signed by _____ other _____ study subjects are broadly deficient; see item 7, below.
4. _____ subject _____ signed a consent form designed for AIDS patients, but the subject was not infected with HIV.
5. You administered the investigational _____ to subject _____ without obtaining the subject's informed consent. You wrote the following note in the case history: _____
_____ This practice is unacceptable for the following reasons: (1) The Institutional Review Board (IRB) did not conclude that this study is of minimal risk and exempt from the requirement for written informed consent; and, (2) the subject was not confronted by a life-threatening situation necessitating the emergent use of the test article. Since the subject was not expected to benefit from the _____, you should have deferred the study until the subject was able to discuss the study with you and decide whether to participate.

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

You administered an investigational _____ and an investigational _____ to a _____ subject who did not meet the protocol eligibility requirements. Subject _____ had a CD4 count of _____ on the date of screening, but the protocol required a CD4 count to be _____

6. **Failure to maintain adequate case histories of individuals treated with investigational drugs. [21 CFR 312.62(b)]**

The case report forms for _____ study subjects _____ and _____ do not contain the form used to document the placement of _____ and the subsequent evaluation of the _____

7. Failure to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21 CFR Part 312.60]

Several of the consent forms used in your clinical studies are deficient in that they do not contain all of the required elements of informed consent. Although the IRB approved some of these deficient consent forms, you are responsible, as a sponsor and clinical investigator, for ensuring that the consent forms meet federal requirements.

A. The consent form titled " _____ " was signed by _____ study subjects _____ and _____ and _____ The following required elements of informed consent are missing:

- * an explanation of the purposes of the research.
- * a description of all reasonably foreseeable risks or discomforts to the subject.
- * a description of any benefits to the subject or to others which may reasonably be expected from the research.
- * a description of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- * a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, and that FDA may inspect the records.
- * an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained.
- * An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of research-related injury to the subject.
- * a statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss or benefits to which the subject is otherwise entitled.

B. The consent form signed on _____ by _____ study subject _____ states, _____

Please account for this number of subjects, since the most recent report to the IRB (January 6, 1996) states that _____ subjects had participated at Dartmouth since study initiation.

C. The consent form signed by _____ study subjects _____ and _____ is missing the following required elements of informed consent:

- * a description of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- * a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, and that FDA may inspect the records.

D. The consent form signed by _____ lacks a required element of informed consent: a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained, and that FDA may inspect the records.

8. Failure to retain complete records, as required under 312.62(a), for the receipt and disposition of the test drug. [21 CFR 312.62(c)]

The dispensing records for the investigational _____ do not contain sufficient detail to document the _____ protocol and subject(s) who were administered the drug.

We have the following comments regarding the submission of new protocols to the IRB.

1. During our review of IRB documents relating to your clinical studies (_____ , _____), we note that multiple protocols are grouped under a single IRB approval. In our opinion, it is more appropriate to obtain separate IRB approvals, and therefore separate IRB files, for studies that involve different subject populations. This practice would facilitate assessments of risks and benefits to the various subject populations of the research.
2. It is inappropriate to completely change the subject population for an approved protocol without preparing a new protocol that would reassess entry criteria, study endpoints, protocol procedures, and safety/efficacy assessments. For example, the original subject population and protocol under the approval of _____ was for _____ patients. You later "changed" the protocol to

include only healthy subjects, but you did not submit a new protocol to reflect the issues identified above.

3. The periodic reports submitted to the IRB do not clearly identify the results of each study population's experiences with the test articles. This is another reason to treat each protocol as a completely separate entity rather than a collection of studies.
4. We recommend that the consent forms have an effective date to assure that only the most current approved form is used.

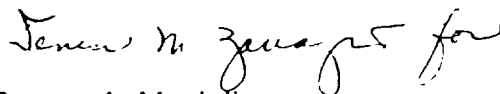
We request that you inform us, in writing, within fifteen (15) business days after receipt of this letter, of the steps you have taken or will take to correct these violations to prevent the recurrence of similar violations in current and future studies. If corrective action cannot be completed within 15 business days, state the reason for the delay and the time within which the corrections will be completed. Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include the initiation of disqualification proceedings, clinical hold, or IND termination.

Please send your written response to:

Patricia Holobaugh (HFM-650)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448
Telephone: (301) 827-6221

We request that you send a copy of your response to the Food and Drug Administration's New England District Office, One Montvale Avenue, Stoneham, Massachusetts 02180. If you require additional time to respond, or have any questions concerning this matter, please contact Ms. Holobaugh at the number above.

Sincerely,



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