



12/3/97

CBER-98-007

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

NOV 20 1997

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Douglas J. Ward, M.D.
Dupont Circle Physicians Group
1737 20th Street, N.W.
Washington, D.C. 20009

Dear Dr. Ward:

During an inspection ending on August 6, 1997, Ms. Marya Ricks and Ms. Christine Whitby, investigators with the Baltimore District Office of the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study using [redacted] [redacted] Data from the clinical investigation were submitted to FDA in support of a product license supplement by [redacted] The inspection was conducted under FDA's Bioresearch Monitoring Program that includes inspections designed to monitor the conduct of clinical research involving investigational drugs.

(b)(4)

We acknowledge receipt of your undated letter, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. We have completed a review of your response and it appears to adequately address the observations of the Form FDA 483, except for items #1, 2, 3, 8, and 15. The corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate.

Based upon review of the Form FDA 483, the inspection report, and evaluation of the material submitted with the report, we have identified significant deviations from applicable federal regulations as published in Title 21, Code of Federal Regulations, Part 312 [21 CFR 312]. These 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]

(b)(4)

- a. According to the protocol, [redacted]

[Redacted]

[Redacted]

(b)(4)

[Redacted]

(b)(4)

[Redacted]

[Redacted]

(b)(4)

[Redacted]

[Redacted]

2. Failure to maintain adequate records for the receipt and disposition of the investigational drug. [21 CFR 312.62(a)]

- a. Your written response to the FDA 483 indicates that you put in place procedures to correct deficiencies regarding drug accountability records. Please provide us with a copy of the written procedures for drug accountability.

- b. Your response letter states that dispensing records were maintained throughout the study; however, a letter dated April 23, 1996, from you to [redacted] revealed that Investigational Drug Dispensing Records were not maintained during the [redacted] study period.
- c. The inspection of records at your site revealed that a line was drawn through the Lot Number column of each "Dispensing/Accountability Record" form for each subject. There is no explanation why the line was drawn. Please explain why the lot numbers were not assigned on the Dispensing/Accountability Records.
- d. The Shipping Invoices and the Dispensing/Accountability Records indicate that the clinical site dispensed more test article than was received. For example, Shipping Invoices document a total of [redacted] study period were shipped to the clinical site between [redacted] from the sponsor; however, [redacted] vials were dispensed to subjects, and [redacted] used vials were returned by subjects.
- e. There are discrepancies between the Drug Administration forms and the Dispensing/Accountability records for [redacted] evaluable subjects. They are as follows:

(b)(4)

[redacted]

(b)(4)

[REDACTED] (b)(4)

[REDACTED] (b)(4)

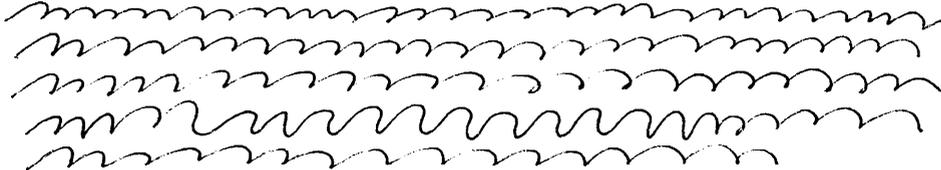
We remind you that as principal investigator of a clinical trial you are responsible for the control, storage, distribution, and return of the investigational drug supplied by the sponsor for the conduct of the study. An investigator is required to maintain complete and accurate records of the receipt and disposition of the investigational drug, including the quantities used and final disposition. These records serve as a check to detect unauthorized distribution, either to subjects or to other persons who might use the test article in humans or animals, to verify the case histories, to detect possible lot-to-lot variations of the test article, and, if recovery of the unused stocks of the test article is necessary to minimize health risks to subjects, to provide the most readily usable mechanism to identify which subjects have recently received the test article and the quantities they are likely to still have. An investigator also is required to return the unused supplies of the investigational drug to the sponsor when the investigation is completed.

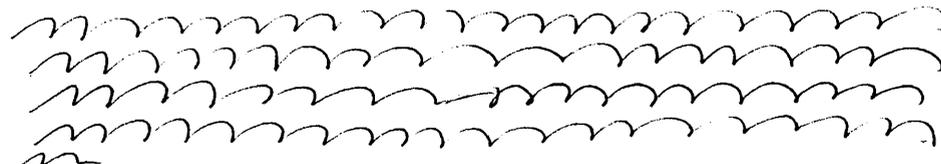
Even when a research pharmacist is involved in a study at a site, the clinical investigator is still responsible with ensuring that the test article was appropriately prepared, dispensed, and administered.

You informed the FDA investigators that when the Study Coordinator was not available, Mr. Mark Brillhart (office administrator) or Ms. Melanie Glynn (phlebotomist) distributed the study drug. When the FDA investigators questioned you further about Mr. Brillhart and Ms. Glynn, you informed them that you were not sure if either of these persons dispensed the test article. The protocol requires that the clinical investigator or responsible pharmacist record the receipt, dispensation by subject, and return of [REDACTED] on the Investigational Drug Accountability Records (IDAR). You should document on the IDAR who dispensed the study drug when you or the person with authority to dispense the drug are not available.

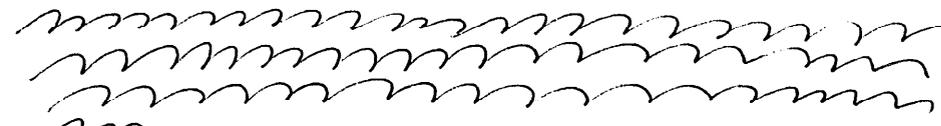
As principal investigator, you are required to assure that the drug is dispensed and administered only to subjects under your personal supervision or under the supervision of a sub-investigator responsible to you.

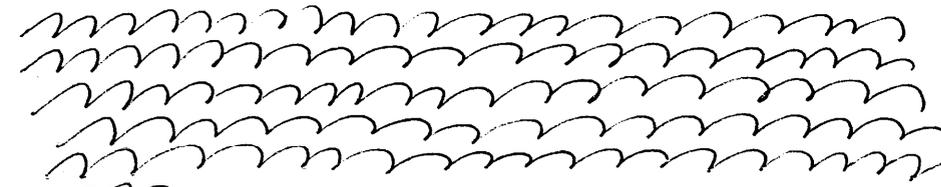
3. Failure to prepare and maintain adequate and accurate case histories designed to record all data observations pertinent to the investigation. [21 CFR 312.62(b)]

[] (b)(4)

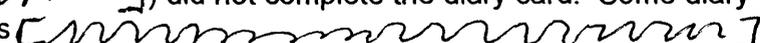
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During the clinical study, the subjects were permitted to self-administer the study drug at home. The study drug was dispensed to subjects during scheduled study visits in sufficient quantities to last until the subject's next scheduled visit. **What instructions/procedures for drug storage and handling were given to the subjects? How did you monitor these activities?**

The subject diary card is an essential component of the study to assess the safety of the investigational product and track all doses of the study drug (i.e., dose changes, missing doses). The study drug administration pages of the case report forms were completed using information from the subject diaries. The inspection revealed that several subjects () did not complete the diary card. Some diary cards were incomplete for subjects []

(b)(4)

How did the subjects keep track of all doses of the test article and adverse experiences, if a diary card was not completed? How did you collect the information? Was subject follow-up conducted to assure compliance with the protocol. If so, how was such follow-up documented? Did you make all reasonable attempts to obtain a completed diary card?

The inspection revealed that you submitted a letter to the IRB on June 5, 1995, to provide an update on the [mm] study but did not report the death of subject [mm] CBER recommends that all subject deaths be reported to the IRB and sponsor concurrently.

(b)(4)

Deviations in this study appear to be the result of your lack of understanding of the responsibilities of a clinical investigator, as well as procedures and requirements that govern the use of investigational new drugs. Your signature on Form FDA 1572, Statement of Investigator, indicates your agreement to comply with all requirements regarding the obligations of clinical investigators conducting human clinical trials and all other pertinent requirements in 21 CFR Part 312.

(b)(4)

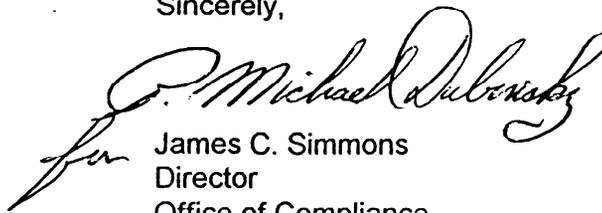
You are currently participating in the [mmmmmmmmmm] study. Continued non-compliance with the regulations governing the use of the investigational drugs could affect not only the acceptability of the trial data but also the safety of the human research subjects.

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. Failure to achieve prompt correction may result in enforcement action without further notice. Such action includes initiation of clinical investigator disqualification proceedings which may render 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 Jose Javier Tavarez, Consumer Safety Officer, Bioresearch Monitoring, Division of Inspections and Surveillance, at (301) 827-6221.

Your written response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 400S, Rockville, Maryland 20852-1448, Attention: James C. Simmons, HFM-600.

Sincerely,



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