



Via Federal Express

NOV 24 1999

WARNING LETTER

Larry R. Kaiser, M.D.
Hospital of the University of Pennsylvania
3400 Spruce Street, 6 Silverstein
Philadelphia, PA 19104-4283

Dear Dr. Kaiser:

During the period of August 10 through August 24, 1999, you were visited by Anthony A. Charity, an investigator from the Food and Drug Administration's (FDA) Philadelphia District office. The purpose of Mr. Charity's visit was to determine whether your activities and procedures as a clinical investigator for the [REDACTED] study (also known as [REDACTED]) sponsored by [REDACTED] complied with applicable regulations. This product is a device as that term is defined under Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

This inspection was conducted under a program designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approvals (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of the scientific investigation.

Our review of the inspection report submitted by the Philadelphia District Office revealed significant violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions, and 21 CFR Part 50 - Protection of Human Subjects. These deviations were listed on the Form FDA 483, "Inspectional Observations," which was presented to and discussed with you at the conclusion of the inspection. The Form FDA 483 was annotated to reflect corrective actions undertaken by you for items 5 and 9.

We acknowledge receipt of your letter dated September 8, 1999, regarding your response to the Form FDA 483. Your letter will be made a part of our official files. We appreciate your efforts in informing the Food and Drug Administration of your position on the issues raised during your recent FDA inspection.

The deviations noted on the Form FDA 483 and our subsequent data review are summarized below:

Failure to conduct an investigation in accordance with the signed agreement with the sponsor and the investigational plan [21 CFR 812.100 and 21 CFR 812.110(b)].

You failed to adhere to the signed Institutional Agreement and Investigational Plan. For example, you did not conduct the study for the investigational device [REDACTED] Clinical Protocol [REDACTED], according to the Institutional Agreement signed by you and dated [REDACTED]. The Institutional Agreement states that, as an investigator, you agree to maintain accurate, complete, and current records relating to the clinical investigation including all pertinent data documented as required by the protocol on case report forms (CRFs) ([REDACTED]). The protocol [REDACTED] states that, "The Investigator will be responsible for ensuring that all CRF's are completed in an accurate and timely manner."

Following a large-scale evaluation of the CRFs that you submitted, it was determined that there are multiple discrepancies and irregularities on the CRFs. For example, of the forty one (41) treatment patient charts and associated CRFs reviewed, 40.9% of the [REDACTED] assessments were changed from either "yes" to "no" (36%), or "no" to "yes" (4.9%). Nineteen (19) control patient charts were reviewed and showed a modification of 31.5% of the CRFs; 21% from "yes" to "no," and 10.5% from "no" to "yes." There is no documentation stating the reason for the modifications to the CRFs, and there are no dates and signatures or initials next to the CRF modifications. In some cases, the modifications to the CRFs changed the primary and secondary endpoints for the study.

In addition, several study subjects did not have source data available to confirm laboratory and clinical data entered on CRFs. Source data was also unavailable to clarify specimen identification discrepancies found between pathology reports and CRFs for study subjects [REDACTED].

Failure to maintain accurate, complete, and current records relating to your participation in an investigational study [21 CFR 812.140(a)(3)].

You failed to maintain accurate, complete, and current records relating to your participation in an investigational study including case report forms and supporting data. For example, in some instances, there is no source documentation to support clinical and laboratory data entered on case report forms.

Failure to maintain accurate, complete, and current records relating to device accountability [21 CFR 812.140(a)(1)(ii) and (iii)].

You failed to maintain accurate and complete documentation regarding the disposition of the study device. For example, the Clinical Inventory Reconciliation record for [REDACTED] does not provide the names of all persons who disposed of each device. The record merely states, "Temperature expiry. Discarded." In some cases, there is no explanation for the temperature failure, and no documentation of actions taken to prevent future temperature failures.

Failure to provide a study subject with an adequate informed consent, and failure to document informed consent by use of a written consent form approved by an institutional review board (IRB) [21 CFR Parts 50.25(a)(3), (4), and (6), and 50.27(a)].

- You failed to provide a study subject with adequate informed consent before allowing the subject to participate in an investigational study. For example, review of the informed consent form used for study subject [REDACTED] reveals that the signed informed consent form is not representative of the study under investigation, [REDACTED] and was not approved by the IRB. There is no documentation explaining why proper informed consent was not obtained from the subject.
- You failed to provide a study subject with an informed consent form containing the required basic elements of informed consent before allowing the subject to participate in an investigational study. For example, study subject [REDACTED] signed an informed consent form that did not contain adequate information regarding, (a) a description of benefits which may reasonably be expected from the research, (b) disclosure of appropriate alternative procedures or courses of treatment, and (c) an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs.

Specifically, respective to a description of benefits, the informed consent did not contain the following underlined language, "The use of this [REDACTED] may (or may not) result in a more rapid recovery after surgery and [REDACTED]. Also, [REDACTED]."

With respect to disclosure of appropriate alternative procedures or courses of treatment, the following underlined alternative language was not included in the informed consent form, "[REDACTED]."

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With respect to an explanation of available compensation, the informed consent form states that [REDACTED] required for the study not routinely performed as part of medical care and treatment will be paid for by the study sponsor. Whereas, the informed consent should state that [REDACTED] required for the study that are not routinely performed as part of medical care and treatment will be paid for by the study sponsor.

The deviations listed above are not intended to be an all-inclusive list of deficiencies at your site. As a Clinical Investigator, it is your responsibility to ensure that investigations that you participate in are conducted in accordance with applicable FDA regulations. To assist you, we have enclosed a copy of the *FDA Information Sheets*, guidance for clinical investigators.

Please advise this office, in writing, **within fifteen (15) working days of receipt of this letter** of the specific steps you have taken to correct these violations and other violations known to you, and to prevent the recurrence of similar violations in current or future studies. Failure to respond can result in further regulatory action, including disqualification, without additional notice.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Kathleen E. Swisher, R.N., J.D., Consumer Safety Officer.

A copy of this letter has been sent to our Philadelphia District Office, U.S. Custom House, RM 900, 2nd Chestnut Streets, Philadelphia, Pennsylvania 19106. We request that a copy of your response be sent to that office as well.

Sincerely yours,



for Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health

Enclosure