



MAR 20 1998

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Via Federal Express

WARNING LETTER

Lois H. Dickerman, Ph.D.
Center for Human Genetics
Walker Center, 6th Floor
10524 Euclid Avenue
Cleveland, Ohio 44106

Dear Dr. Dickerman:

During the period of January 4-23, 1998, the Center for Human Genetics was visited by Mr. Stephen J. Kilker, an investigator from the Food and Drug Administration's (FDA) Cincinnati District Office. The purpose of that visit was to determine whether activities regarding your participation in the investigational study of [REDACTED] test kit for the detection of [REDACTED] [REDACTED] complied with applicable FDA regulations. This product is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notifications [510(k)] 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 scientific investigations.

Title 21, Code of Federal Regulations, (21CFR), Part 812 - Investigational Device Exemptions and Part 50 - Protection of Human Subjects were used as guidance to audit your in-vitro diagnostic study. Serious deficiencies were noted during the inspection. These were listed on form FDA-483, "Inspectional Observations," which was presented to and discussed with you at the conclusion of the inspection. Among the deficiencies noted were:

- There was no validation of the computerized methods used to report the test data to the sponsor, nor complete verification of the data transferred and merged. This lack of validation/verification raises questions about the integrity of the data transmitted to the sponsor. Three investigational findings support this: [REDACTED], the sponsor's statistician who was responsible for merging the data and demographic files, detected mismatches between the numbering of the two file sets, as well as missing files; the inspectional data audit detected a data mismatch between the site and sponsor files as well as two incorrect outcome dates in the demographic files; and the number of samples measured, as totaled during the inspection, differed from the number in the investigator's cover letter accompanying submission to the sponsor, and both differed from the number quoted in the PMA submission.

It is the responsibility of the clinical investigator to maintain accurate, complete and current records related to the study. While an amendment to the protocol, specific to this site, allowed for use of electronic data storage in lieu of the standard sponsor case report forms (CRFs), the investigator remains responsible for verification of the data submitted.

- There are no records of receipt, use or disposition of the device. Records must be maintained as to the type and quantity of the device, the dates of its receipt, and the batch number or code mark, as well as the number of units of the device not used. Records of the disposition of unused devices shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by you or another person, and the reasons for and method of disposal.
- The Institutional Review Board (IRB) was not informed about the March 14, 1996, clinical protocol amendment. While it was your understanding that the IRB waived supervision of the study and was not interested in amendments, the study reviewed by the IRB was for use of discarded tissue samples from Mac Donald/University Hospital patients only. These patients had signed an informed consent form which included such future use of discarded samples. The study, however, included samples from patients at Mt. Sinai Hospital, Fairview General Hospital, and several Akron hospitals, via the Genetics Counselor at Akron General.
- Neither annual reports nor a final report were submitted to the IRB. Ms. ██████████, a monitor for the sponsor, informed you that the sponsor required submission of a final report to the IRB.
- The protocol was not adhered to with regard to the standard curves for runs 51, 87, 96, 97 and 03. It is the responsibility of the investigator to ensure that the investigation is conducted according to the signed agreement and the investigational plan.

The deviations listed above are not intended to be an all-inclusive list of deficiencies. It is your responsibility as a clinical investigator to ensure that your investigation is conducted in accordance with the signed agreement, the investigational plan, and applicable FDA regulations.

Please advise this office, in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to prevent recurrence in future studies of violations similar to those listed above. Please send 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: Jean Toth-Allen, Ph.D.

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A copy of this letter has been forwarded to our Cincinnati District Office, 1141 Central Parkway, Cincinnati, Ohio 45202-1097. We request that a copy of your response be sent to that office.

If you have any questions or concerns, feel free to contact Jean Toth-Allen at (301) 594-4723, ext. 141.

Sincerely yours,



for

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