



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

FEDERAL EXPRESS

WARNING LETTER

Mary Sue Coleman, Ph.D.
President
University of Iowa
Jessup Hall
Iowa City, Iowa 52242

Dear Dr. Coleman:

During the period of February 2 - June 23, 1998, Mr. John A. Iwen, an investigator from the Food and Drug Administration's (FDA) St. Louis Branch Office visited the University of Iowa Institutional Review Board (IRB) Committee A. The purpose of the inspectional visit was to determine whether your procedures complied with Title 21, Code of Federal Regulations (21 CFR), Part 50 - Protection of Human Subjects and Part 56 - Institutional Review Boards. These regulations apply to clinical studies of products regulated by the FDA.

At the conclusion of the inspection, Mr. Iwen issued a Form FDA-483 to Dr. Kent S. Pearson, Committee A Chairperson, which describes the deviations from the requirements specified in 21 CFR Parts 50 and 56 and identified during the inspection. Ms. Deborah L. Barnard, Dr. David L. Wynes, and Dr. Mary Moore were present during this discussion.

FDA has reviewed the records and reports submitted by the St. Louis Branch Office relating to the IRB's responsibilities for the protection of research subjects contained in Mr. Iwen's inspection report. These documents show that the IRB has failed to comply with applicable federal regulations as contained in 21 CFR Parts 50 and 56 and the Federal Food, Drug, and Cosmetic Act.

We apologize for the delay in providing you with an official notice of the results of the inspection. Even at this late date, the significance of the following violations are of particular importance because many of them have been observed during past inspections where corrections were promised by your institution but not implemented. The following violations were found:

1. Failure to have written procedures for conducting initial or continued review of research and for ensuring prompt reporting to the IRB and the FDA as required by 21 CFR 56.108 and 21 CFR 56.115(a)(6).

The University of Iowa Institutional Review Board Standard Operating Procedures (SOP) document dated January 1998 does not contain procedures that specifically describe how IRB Committees A, C, and D conduct their initial and continuing review of research. The SOP does not describe the criteria for IRB review and approval of clinical studies at the institution, including, but not limited to ancillary committees, subcommittees, or a primary reviewer; and for clinical studies involving review by institutions in addition to University of Iowa. These procedures do not describe which projects require continuing review more often than annually, which projects need verification from other sources, and which projects require expedited review. The SOP does not describe how risk is determined, including how significant and non-significant risk determinations of medical device clinical investigations are made.

The University of Iowa IRB SOP does not specifically describe how the IRB ensures prompt reporting by the clinical investigators or others who are involved in research. The procedures do not describe how the IRB assures that clinical investigators are made aware of their reporting responsibilities. The procedures do not describe how instances of noncompliance with the IRB requirements and federal regulations are reported to the FDA. The SOP does not describe how suspensions or terminations of IRB approval are reported to the FDA.

The SOP does not adequately describe how the Human Subject Office prepares and maintains records of all IRB activities. The procedures do not describe how records and reports associated with IDEs are handled, processed, and retained.

The regulations require IRBs to adopt and follow written procedures for conducting their review of research. Using a multiple project assurance (MPA) document [approved by the Department of Health and Human Service (HHS) dated October 1997] as the IRB's written procedure would not necessarily satisfy the FDA requirement for written procedures. The MPA document is a commitment to follow the HHS regulations. It may not contain specific procedures required by the FDA regulation. Also, FDA Information Sheets is guidance and is not a substitute for written procedures – nor is referencing, restating, or rewording the federal regulations a substitute for written procedures.

- 2. Failure to prepare and maintain minutes of IRB meetings in sufficient detail to show the actual attendance at the meetings, show voting by IRB members, actions taken by the IRB, and a written summary of the discussion of controverted issues and the resolution of these issues per 21 CFR 56.115(a)(2).**

The IRB Committee A meeting minutes do not consistently document the details

of recommended changes to proposals and informed consent forms. The meeting minutes do not document attendance at the meetings, during the discussion and resolutions, and during the voting of studies.

For example, other than the number of members who voted, the December 12, 1996, minutes did not adequately record the IRB actions for studies [REDACTED] in the December 1, 1997, minutes for studies # [REDACTED]. On March 20, 1997, IRB minutes did not fully account for the voting of all members present at the meeting for studies [REDACTED]. On April 24, 1997, IRB minutes for studies [REDACTED] not fully account for the votes of all members present at the meeting, and they did not record the resolution of actions voted upon. The July 17, 1997, IRB minutes were not sufficiently detailed to describe the resolution of controverted issues, including actions voted upon and the conditions of approval for studies [REDACTED]. On February 19, 1998, the minutes did not adequately record the actions of the IRB regarding individual (unnamed) study protocols reviewed by the Subcommittee for Annual Review.

3. Failure to fulfill the requirements for expedited review per 21 CFR 56.110.

The IRB Committee A improperly used expedited review to approve changes in [REDACTED] in May 1997 and November 1997. There were no records available on the method adopted by the IRB to notify IRB members about expedited reviews. In addition, there were several drug studies for which expedited review was used to approve protocol and informed consent document changes which were under IND. Drugs and devices for which a research application (IND or IDE) is required may not be reviewed under expedited review procedures.

4. Failure to provide adequate review of research activities per 21 CFR 56.109 (b)(c).

The IRB Committee A failed to require adequate documentation of subject informed consent for some studies in that approved informed consent documents did not contain all required elements.

For example, the informed consent document reviewed and approved by the IRB in studies [REDACTED] did not identify the written information summary that the subject was orally presented.

The information summary used in study [REDACTED] did not fully disclose alternative treatments available that may be advantageous to the study subjects. The IRB approved the summary without this required element during its initial review of the study on March 20, 1997, and in its annual review of the study on February 9, 1998.

The information summary used in study [REDACTED] did not state that FDA might inspect the records of the study subjects. FDA may inspect and copy all study records per 21 CFR 312.68 and 21 CFR 812.145.

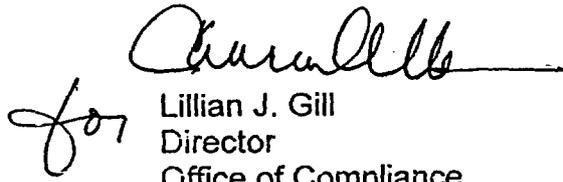
The above-cited violations may not be an all-inclusive list of the deficiencies in your IRB operations. It is your responsibility to assure that the IRB complies with federal regulations. FDA observed similar activities and practices by the IRB Committee in 1992 and 1995. Each time, the IRB promised to comply with FDA requirements. Despite the assurances provided in the IRB's various responses, violations similar to those noted above persisted.

Following the 1992 visit, Drs. David Skorton, Vice President for Research of the University of Iowa, and Susan Johnson, the Committee A Chairperson promised compliance of FDA requirements in their letter dated July 30, 1993, to the FDA. During the 1995 visit, Dr. Charles Riggs, the Committee A Chairperson promised to comply with FDA requirements and to correct the observations listed in the May 24, 1995, FDA-483. For your review and reference, we have enclosed a copy of the July 30, 1993, letter, and copies of the following FDA-483s: November 25, 1992; May 24, 1995; and June 23, 1998.

You must contact this office within fifteen (15) working days from the receipt of this letter by telephone after you have had an opportunity to evaluate the noncompliances described in this letter. Following that initial contact, you must inform this office, in writing, by July 30, 1999, of the specific actions you plan to take to bring the activities of the IRB into compliance with FDA requirements. Please include a copy of any revised documents, such as written procedures, with your response. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to take prompt action to correct these deficiencies may result in further regulatory action, including disqualification. Your corrective actions will be reviewed and verified during a future inspection.

Your initial telephone contact with this office should be made with Mr. David R. Kalins, Branch Chief at (301) 594-4723, extension #139. Any further questions should also be directed to Mr. Kalins. Your written response should be directed to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ-311), 2094 Gaither Road, Rockville, Maryland 20850, Attention: David R. Kalins. A copy of this Warning Letter has been sent to the Food and Drug Administration, St. Louis Branch Office, 12 Sunnen Drive, Suite 122, St. Louis, Missouri 63143. We request that you send a copy of your response to that office.

Sincerely yours,


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

Enclosures

cc: David Skorton, M.D.
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