



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

JUL 17 1997

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WARNING LETTER

Eugene B. Feigelson, M.D.
Interim President
State University of New York
Health Science Center at Brooklyn
450 Clarkson Avenue, Box 1
Brooklyn, New York 11203

Dear Dr. Feigelson:

During an inspection that concluded on March 11, 1997, Ms. Julia Johnson, an investigator with the Food and Drug Administration (FDA), inspected the State University of New York Health Science Center at Brooklyn Institutional Review Board (IRB). The purpose of the inspection is to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations, published in Title 21, Code of Federal Regulations, Parts 50 and 56 [21 CFR 50 and 56].

A copy of the list of Inspectional Observations (FDA-483) left with Dr. Leonard Glass at the end of the inspection is enclosed. The deviations noted in our inspection include, but are not limited to the following:

1. **Failure to prepare detailed written procedures for conducting the review of research, including periodic review. [21 CFR 56.108(a), (b), and 56.115(a)(6)]**

The FDA investigator found the State University of New York Health Science Center at Brooklyn Institutional Review Board lacks written procedures for the following:

- a. For the process of conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution.
- b. For determining which projects need verification from sources other than the investigator that no material changes have occurred since the previous IRB review.
- c. For ensuring prompt reporting to the IRB of changes in research activity.

- d. For ensuring prompt reporting to the IRB, and appropriate institutional officials, and the Food and Drug Administration of the following:
 - i. Any unanticipated problems involving risks to human subjects or others.
 - ii. Any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB.
 - iii. Any suspension or termination of IRB approval.
2. Failure to require that information given to subjects as part of informed consent is in accordance with 50.25. [21 CFR 56.109(b)]
- a. The informed consent form for study [] amended on 6/15/96 lacks the following:
 - i. A statement that clearly defines the expected duration of the subject's participation.
 - ii. A statement that significant new findings developed during the course of research that may relate to the subjects' willingness to continue participation will be provided to the subject.
 - b. The informed consent form for study [] lacks the following:
 - i. A statement that clearly defines the expected duration of the subject's participation.
 - ii. A statement that clearly identifies whom to contact for answers to questions about research subjects' rights. The consent form should provide complete phone numbers and contact persons for various categories of information that may become important to the subject at a later date. The contact for research subjects' rights ideally should be someone other than the clinical investigator and not associated with the clinical study to encourage openness and good research practices.
 - c. The consent forms for [] lack the following:
 - i. A statement that clearly defines the expected duration of the subject's participation.
 - ii. A statement regarding whether or not the subjects will be hospitalized to receive treatments.
 - iii. A statement that the subject will undergo CT, x-rays, or MRI scans.

- iv. A statement that defines how many treatments will be given, how often, and over what period of time.
- v. A statement to include parties in addition to the FDA with access to subject records.
- vi. A statement that clearly identifies whom to contact for answers to questions about research subjects' rights.

In addition to the deviations noted above, we would like to comment on the following statements found in consent forms:

The first page of consent forms for [] studies contain the statement, "...which I completely understand to be as follows:" Use of the wording "I understand. . ." may be inappropriate. The subjects may certify that they understand the statements in the consent form and are satisfied with the explanation provided by the consent process, but many may not comprehend the underlying scientific and medical significance of all the statements. For example, subjects may not completely understand the nature of the study, the operations, procedures and investigational drugs to be used, and/or the risks and benefits. Subjects are not in a position to judge whether the information provided is complete and should not be required to certify such understanding or completeness of disclosure.

The consent form for study [] contains the statement, "Your doctors feel that your treatment on this study will give you at least as good a chance of controlling your cancer as you might expect from other therapies." The purpose for conducting the study is to determine whether or not the study drug alone is comparable to nephrectomy followed by study drug.

**3. Failure to ensure that research is reviewed free from conflict of interest.
[21 CFR 56.107(e)]**

Meeting minutes for 10/23/96 do not indicate that [] abstained from voting on [] is a member of the IRB and clinical investigator for the protocol. Meeting minutes should be in sufficient detail to document abstention from voting where conflict of interest exists.

**4. Failure to ensure prompt reporting of changes in research activity to the IRB.
[21 CFR 56.108(a)(3)]**

[] were placed on clinical hold by CBER on 5/5/94. These INDs consist of the studies conducted by [] under the IRB's review. [], an IRB member, did not report his clinical hold to the IRB until 6/5/95.

5. Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present, and include members with primary concerns in scientific and nonscientific areas. [21 CFR 56.108(c)]

Meeting minutes reveal that a majority of members was not present at four convened meetings and the nonscientific member was not present for one meeting where research was reviewed and approved as follows:

- a. Nine of 24 members were present at the 8/2/95 meeting. No member representing the nonscientific community attended the meeting.
- b. Eleven of 24 members were present at the 11/15/95 and 11/20/96 meetings.
- c. Twelve of 26 members were present at the 12/20/95 meeting.

6. Failure to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. [21 CFR 56.109(e)]

Examples of studies which were not reviewed at least on an annual basis include the following:

- a. [] received initial approval on 5/15/91. [] submitted his first annual report late. The report was approved on 6/17/92. The study was reviewed in June 1993 and June 1994. These annual reviews were required to be completed prior to May 15th, the anniversary date of the initial approval.
- b. [] was inactivated by a letter dated 2/27/97. [] submitted only one annual report dated 1/11/91. There is no documentation that the annual report was approved by the IRB. There is no documentation of additional annual reports by [] for the study.
- c. There is no documentation that [] submitted an annual report for study [] until receipt of a letter from him dated 5/5/95. The letter informed the IRB of the clinical hold. Annual review was required to be completed prior to [].
- d. [] initially approved on 9/6/89 was reviewed by the IRB in October during 1990, 1991, 1992, and 1993. We note that since 1993, the study received annual review by the IRB during the month of September.

7. Failure to fulfill requirements for expedited review. [21 CFR 56.110]

Records or meeting minutes show that the IRB used expedited review inappropriately or "compassionate review," not recognized by the FDA, to approve research. The following are examples of protocols that involve more than minimal risk and should have received full IRB review:

- a. Meeting minutes for 9/18/96 show that studies [] received expedited review inappropriately. The studies involve the use of [].
- b. Meeting minutes for 9/18/96 show that study [] received "compassionate review." The protocol is for treatment of [].
- c. Meeting minutes for 6/21/95 show that study [] received expedited review for the use of [].
- d. A memorandum from the IRB Chairman dated 1/29/97 shows that study [] was granted expedited review inappropriately for use in one subject. The protocol is for treatment of [].

The term "compassionate use" is often used to refer to the provision for use of investigational drugs outside of an ongoing clinical trial to a limited number of subjects who are desperately ill and for whom no standard alternative therapies are available. The term "compassionate use" does not, however, appear in FDA or DHHS regulations. The FDA human subjects regulations allow for a test article to be used in emergency situations without prior IRB approval.

In emergency use situations, the IRB must either convene and give 'full board' approval of the emergency use or, if the conditions of 21 CFR 56.102 (d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval. Prior notification of the IRB without full IRB review and approval of the use of the test article is not to be interpreted as expedited approval for the emergency use. Instead, the notification is to allow the IRB to ensure that full reporting of the emergency use to the IRB occurs within five days of use. Further use of the test article requires full IRB review and approval. Protocols termed "compassionate" receive full board review prior to implementation unless circumstances warrant emergency use.

Page four of the "Application for Approval of Research Involving Human Subjects" defines expedited review and "compassionate use." Since FDA does not recognize the term "compassionate," we suggest that the IRB change the term on the form and eliminate the "compassionate use" block on page one of the application listed under "Type of Review."

The IRB should consider whether or not to define in the written procedures how to deal with single subject non-emergency requests. The IRB should define emergency use procedures in the written procedures.

8. Failure to notify the Food and Drug Administration of termination of IRB approval of research. [21 CFR 56.113]

CBER's Office of Therapeutics has no record that the IRB notified FDA of the termination of [] as required by federal regulations.

9. Failure to prepare minutes of IRB meetings in sufficient detail to show voting by IRB members and actions taken by the IRB. [21 CFR 56.115(a)(2)]

- a. Meeting minutes do not indicate the number of members voting for, against, and abstaining for protocols that receive less than unanimous approval.
- b. Meeting minutes for 6/21/95 indicate that discussion of [] were tabled until the next meeting due to [] absence. Meeting minutes for 8/2/95, the subsequent meeting, indicate no discussion or reference to the tabled protocols. Meeting minutes should show a written summary of the discussion and resolution of controverted issues.

The State University of New York Health Science Center at Brooklyn Institutional Review Board was last inspected by CBER in August 1993. We note that items #2, 5, 6, and 9 of this letter are items that were also noted in our letter to the IRB Chairman dated 1/13/94 regarding the 1993 inspection. The IRB failed to correct noted deficiencies from the 1993 inspection as promised.

The FDA investigator found the archived records of the IRB stored in boxes. Specific studies could not be easily identified because the former IRB secretary had no formal system of recordkeeping according to the current IRB Administrator. Please explain how these conditions will be improved.

Records from the FDA inspection of [] by CBER in April 1995 revealed that [] failed to conduct his studies according to the protocol. The IRB approved [] original protocol using [] of the test article. Four additional protocols with increased risk to subjects were approved by the IRB relying on information provided by []. One subject was administered the test article [] on 2/28/91 and 3/14/91 prior to IRB approval of [] on 5/15/91. Two of [] subjects were administered the test article [], a [] method not approved by the IRB. One subject received the first eight months of treatment []. These routes of administration were not listed in the consent form initially signed by the subject. Please explain how the IRB intends to prevent similar occurrences in future studies that [] may conduct.

The Institutional Review Board for SUNY at Brooklyn/University Hospital and Kings County Hospital has a Multiple Project Assurance (MPA) document with DHHS/OPRR. The MPA approved by the DHHS is a commitment to follow the DHHS regulation, but does not necessarily meet the requirement for written procedures in 21 CFR 56.108—IRB functions and operations. There are significant differences between the DHHS regulations (45 CFR 46) and the FDA regulations (21 CFR 50 and 56) which apply to research involving products regulated by FDA. These differences are outlined on pages 123-124 of the FDA IRB Information Sheets (copy enclosed).

We note that draft written standard operating procedures (SOPs) for the IRB are in preparation. Please inform us of the expected time frames for completion of the document and forward a copy to us for review. Your file will remain open until we receive a copy of your finalized version of the SOPs, and they are deemed adequate. We enclose the "FDA IRB Information Sheets" to assist you in implementing the changes necessary to bring the IRB into compliance with applicable standards. Pages 136-143 of the enclosure provide a guide to ensure that all required elements are included in your written procedures.

This letter is not intended to be an all-inclusive list of deficiencies with the IRB. The IRB is responsible to adhere to each requirement of the law and relevant regulations.

Based upon the demonstrated deficiencies in organizational guidelines, operational procedures, recordkeeping practices, the lack of improvement in a number of deficiencies noted during the 1993 inspection, and demonstrated difficulties in continuing review of an IRB member's studies, it appears that your procedures are inadequate to protect the rights and welfare of human subjects of research. As described in section 56.120 of the regulations, failure to make adequate corrections may result in regulatory action being initiated by the Food and Drug Administration. These actions include, but are not limited to, withholding approval of new studies, direction that no new subjects be added to ongoing studies, termination of ongoing studies, and notification of State and Federal regulatory agencies.

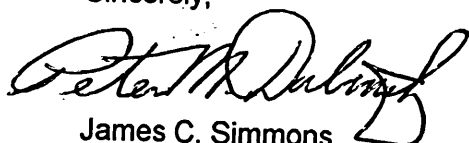
Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken or plan to take to bring the procedures of your Institutional Review Board into compliance with FDA requirements. If corrective action cannot be completed within 15 working days, state the time within which the corrections will be completed.

Should you have any questions or comments about the contents of this letter or any aspects of operation and responsibility of a review board, you may contact Debra Bower, Consumer Safety Officer, Bioresearch Monitoring, Division of Inspections and Surveillance, at (301)594-1077.

Page 8 - SUNY Brooklyn (Downstate), Health Science Center IRB

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

Sincerely,



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

Enclosures

FDA Form 483, List of Inspectional Observations
FDA Information Sheets (includes CFR Parts 50 and 56)
CBER letter to Leonard Glass, dated 1/13/94

cc:

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