DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
Rockville MD 20857

Via Federal Express

AUG 14 2000

WARNING LETTER

Michael Hansen, M.D., Chair
Institutional Review Board
St. Francis Medical Center
400 45th Street
Pittsburgh, Pennsylvania 15201

Dear Dr. Hansen:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB) and to request your prompt response. The inspection took place during the period of March 29 through April 11, 2000, and was conducted by Ms. Gladys B. Casper, an investigator from FDA's Philadelphia District Office. The purpose of the inspection was to determine whether your procedures complied with Title 21, Code of Federal Regulations (21 CFR), Part 50-Protection of Human Subjects, Part 56-Institutional Review Boards, and Part 812 – Investigational Device Exemptions. These regulations apply to clinical studies of products regulated by the FDA.

Our review of the inspection report submitted by the district office revealed serious violations from pertinent regulations. You received a form FDA-483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed with you. The deviations noted include the following:

Failure to conduct continuing review of research no less than annually [21 CFR 56.109 (f)].
Twelve of the fifteen files reviewed did not give evidence of adequate continuing review. Several files showed late continuing review with reapproval made retrospective to the anniversary date of the initial approval.

Failure to have a quorum present when proposed research was reviewed [21 CFR 56.108(c)].
Review of IRB meeting minutes along with membership rosters for the times reviewed showed that a majority of members were not present for several meetings where research was reviewed and decisions made.

Failure to maintain adequate standard operating procedures (SOPs) governing the functions and operations of the IRB [21 CFR 56.108(b)].
There are no written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and FDA of unanticipated problems involving risks to human subjects or others; instances of serious or continuing non-compliance; or any suspension or termination of IRB approval.

Failure to follow IRB written procedures [21 CFR 56.108(a)].
Applications do not routinely include the required cover sheets and study files do not routinely contain the required progress reports.

The deviations listed above are not intended to be an all-inclusive list of the deficiencies noted. The IRB is responsible for adhering to each requirement of the law and relevant regulations.

In addition, further review of your SOPs, titled "Summary of Guidelines to the Use of Human Subjects in Biomedical Research," revealed serious deficiencies. The omissions and inaccuracies found reflect a general lack of understanding of IRB responsibilities for review and approval of investigational studies as required by 21 CFR Part 56. The discrepancies noted include the following:

- The introduction cites 45 CFR 46 as the regulations to be met. For FDA-regulated studies 21 CFR 56 is the appropriate regulation.

- Under **C. The Process for Introducing Research Within St. Francis Medical Center**, submission of the study protocol is included. However, under **D. The Procedure For Applying For IRB Approval**, only a summary of the proposed research is listed. You need to add the study protocol to the list of required application submissions.

- In section **D. 2. Application**, only studies with investigational drugs are referenced. The only mention of medical devices is under **G. Types of Review, 4. Review of Novelle/Avant Garde Medical Procedures/Devices**. Your IRB has several investigational medical device studies under continuing review which do not fit this special category. Moreover, when reviewing medical devices, an IRB needs to have written procedures regarding significant risk/non-significant risk device study determinations as specified in 21 CFR Part 812, Investigational Device Exemptions, specifically in 21 CFR 812.66 (copy enclosed).

- Exempt reviews found under **G. Types of Review** do not apply to FDA-regulated studies, only to those done under 45 CFR 46. 21 CFR 56 does not allow an IRB to waive its review of a study; only FDA has that authority under 21 CFR 56.105. Please clarify this section or delete it, if only FDA-regulated studies are involved.

- Your SOPs should refer specifically to 21 CFR 56.110 where expedited review under **G. Types of Review** is discussed. To assist you with this type of review, a copy of the most recent Federal Register notice regarding categories of research that may be reviewed through an expedited review procedure is enclosed.

- 21 CFR 56.108(a)(1) requires that an IRB follow written procedures for conducting initial and continuing review and for reporting its findings and actions to the investigator and the institution. Your SOPs do not contain such procedures. The only procedures described are for review of the novelle/avant garde category. The section on **Full Board Review** merely lists the studies that must be so reviewed.

- Under **Appeal Process for Novelle/Avant Garde Procedures/Devices** it states that, if the IRB ultimately fails to approve the study, the Directors of Research have the prerogative of reconvening the ad hoc committee to conduct a second review during the appeal by the principal investigator. 21 CFR 56.112 states that institution officials may disapprove studies that an IRB approves but may not approve research if it has not been approved by the IRB. It should be made clear in these statements that the IRB has the final decision regarding disapproval for all studies.

- 21 CFR 56.108(a)(2) requires written procedures for determining which projects require review more often than annually. Your SOPs do not contain such procedures. Moreover, under **Reporting Requirements,** progress reports are referred to as a "yearly report" rather than a progress report that can be required no less frequently than annually. Also, as with initial reviews, progress reports cannot be exempted from IRB review under 21 CFR 56.

- 21 CFR 56.108(a)(3) requires written procedures for ensuring prompt reporting of changes in research activity to the IRB. In this same section, (4) requires that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval, except to protect subjects from undue harm. In your SOPs, the only mention of the need to have changes reviewed is under **Report of Adverse Events**. Study protocol and/or informed consent changes are not always related to adverse events. A separate section related to these issues is needed.

- In **Appendix C, Example Informed Consent**, on page 22, investigators are advised to include a statement that the subject can call the investigator to obtain information about treatment for illness or injury. An informed consent should contain information regarding contacts who can supply three different types of information: what to do if injury or illness occurs during the study; general questions concerning the study; and information about subject rights in general. These need not be three separate individuals, though the latter should be someone not connected with the specific study. See also the section on informed consents in the FDA Information Sheets (copy enclosed).

- **Appendix E, Serious Adverse Event Reporting Form**, is specific to pharmaceutical studies. Information relevant to investigational device studies needs to be added.

In addition, in October of 1996 a new section was added to 21 CFR Part 50 regarding exception from informed consent requirements for emergency research. A copy of this section (21 CFR 50.24) is enclosed for your use. This section is also discussed in the FDA Information Sheets.

The inspection report contains a copy of an April 6, 2000, letter you sent to Ms. Casper (copy enclosed). The letter mentions that you assumed the position of first acting and then full chair of the IRB upon the death of [redacted] about two years ago. You indicate that the IRB was working on revised guidelines at the time of his death. You also mention that changes are in progress regarding timing of submission of the study protocol relative to informed consent as well as to the review and reapproval processes. Moreover, the hospital administration has pledged that adequate time will be allotted to the IRB secretary to carry out necessary bookkeeping and database functions. These actions should assist in addressing the deviations noted.

Review of files during the inspection revealed that continuing review of on-going studies has been initiated as of the start of this calendar year. No progress reports were found for the last two years in the IRB files reviewed and it does not appear that continuing review occurred during your tenure before this year. Moreover, the present SOPs are seriously deficient, as noted above. Please inform us within 15 working days of receipt of this letter of the further progress you have made in bringing this IRB into compliance with regulations and in becoming current regarding all on-going studies. Please include an updated copy of your SOPs or an estimate of when they will be available for our review.

Please send the information requested 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. Failure to respond can lead to further regulatory actions, including, as described in 21 CFR 56.120 and 56.121, withholding approval of new studies, directing that no new subjects be added to on-going studies, terminating on-going studies, notifying relevant State and Federal regulatory agencies, and disqualification of the IRB.

A copy of this letter has been sent to FDA's Philadelphia District Office, 900 U.S. Customhouse, 2nd and Chestnut Street, Philadelphia, Pennsylvania 19106. We request that a copy of your response also be sent to that office.

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

Sincerely yours,

Charmaine Connor, RPh

for Steven M. Niedelman
Acting Director
Office of Compliance
Center for Devices and Radiological Health

Enclosures

cc:
Michael Carome, M.D.
National Institutes of Health
Office for Protection from Research Risks
Compliance Oversight Branch, MSC 7507
6100 Executive Boulevard, Suite 3B01
Rockville, Maryland 29892-7501