



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

428
HFI-35

Food and Drug Administration
Rockville MD 20857

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Reference #: 97-HFD-340-0901

SEP 15 1997

Mark S. O'Halla
Executive Vice President and Chief Operating Officer
Clifton Springs Hospital and Clinic
2 Coulter Road
Clifton Springs, New York 14432

Dear Mr. O'Halla:

On June 30 and July 1 and 2, 1997, Steven J. Libal, an investigator with the Buffalo District Office of the Food and Drug Administration (FDA), inspected the institutional review board (IRB) at Clifton Springs Hospital and Clinic. The purpose of this inspection was to determine whether your procedures for the protection of human research subjects complied with Title 21 Code of Federal Regulations, Parts 50 and 56 (enclosure 1). These regulations apply to clinical studies of medical products regulated by the FDA.

At the conclusion of the investigation, Mr. Libal issued a form FDA 483 "*Inspection Observations*" (enclosure 2) to Daniel L. Biery, M.D., IRB Chairman, describing the deficiencies identified during this inspection. Two others were also present: Margaret Van Damme, LPN, present IRB Data Manager and Gail Morehouse, R.N., former IRB Data Manager.

Our review of the inspection report submitted by our field staff revealed significant violations from the requirements of 21 CFR parts 50 and 56.

1. Summary of Violations of Clifton Springs IRB's Operations and Functions [21 CFR 56.108 (a), (1), (2), (3), (4), (c), 21 CFR 56.111, 21 CFR 50.20, 21 CFR 50.25]

A. Deficient Procedures

1. No Written Procedures for Initial and Continuing Review

Your IRB's written procedures for initial and continuing review must describe how the IRB performs the initial and continuing review as stipulated in 21 CFR 56.108(a)(1). This should include the instructions you provide to IRB members for evaluating risks (21 CFR 56.111) and for evaluating the completeness and

adequacy of the consent documents (21 CFR 50.25 and 21 CFR 50.20). (Item 3 of the *Inspection Observation*.)

2. No Written Procedures for Determining Interval for Continuing Review

In the minutes, continuing review is referred to as annual review. Investigators need to be informed that the IRB will determine the interval of review based on the risks of the study [21 CFR 56.108(a)(2)]. Your written procedures should describe how the IRB determines which projects require review more often than once a year. (This is item 3 of the *Inspection Observation*.)

3. No Written Procedures to Direct Investigators on their Reporting Responsibilities

Your IRB must have written procedures for insuring that investigators promptly report any changes in research activity and unanticipated problems involving risks to subjects to the IRB [21 CFR 56.108 (a)(3), (a)(4), (b)(4)]. (This is item 3 of the *Inspection Observation*.)

B. Deficient IRB Requirements for Continuing Review Reports

It is insufficient to only require a summary of the number of patients enrolled. The investigator should be required to submit sufficient information so that the IRB can assess whether the risks to subjects have changed since the initial approval [21 CFR 56.109(f), 21CFR56.111(a)(1) and (2)]. (This is item 3 of the *Inspection Observation*.)

C. Failure to conduct IRB meetings with a quorum

Your IRB has convened meetings and FDA regulated studies have been approved at the meetings without a majority of members present. Examples are the April 24, 1997 and July 31, 1996 meetings. In order to approve studies that involve more than minimal risk, the IRB must have a quorum as stipulated in 21 CFR 56.108(c). (This is Item 4 of the *Inspection Observation*.)

2. Summary of Clifton Springs IRB's Membership Deficiencies [21CFR 56.107(c)(d)(e)]

A. Nonscientist

The IRB must have at least one member who is a nonscientist, as required by 21 CFR 56.107(c). Information about the expected contribution of members should be documented in a roster as stipulated in 21 CFR 56.115(a)(5). (This is Item 1 and 2 of the *Inspection Observation*.)

B. Non Affiliated Member

Your IRB has failed to include at least one member who has no affiliation with Clifton Springs Hospital as stipulated in 21 CFR 56.107(d). Information about the relationship of members to Clifton Springs should be documented in a roster as required by 21 CFR 56.115(a)(5). (This is Item 1 and 2 of the *Inspection Observation*.)

C. Conflict of Interest

When a clinical investigator is also a member of the IRB, s(he) may only provide information requested by the IRB and cannot participate in the initial or continuing review of the study [21 CFR 56.107(e)]. The minutes must demonstrate that the member with a conflict did not vote on his/her study. While your minutes do record the actual vote count, they do not indicate if members with a conflict of interest, such as your oncology investigators, abstain from voting as stipulated in 21 CFR 56.115(a)(2). (This is Item 5 of the *Inspection Observation*.)

The above observations should not be interpreted as all inclusive. You are responsible for assuring that all FDA regulations are not only adequately described, but also consistently implemented. A self evaluation of your written procedures can be done by using appendix H in the *Information Sheets for Institutional Review Boards and Clinical Investigators* (enclosure 3).

We have no assurance that your procedures are adequately protecting the rights and welfare of human subjects of research. For this reason we are imposing the following sanctions in accordance with 21 CFR 56.120:

(1) no new studies that are subject to Parts 50 and 56 of the FDA regulations should be approved by your IRB and

(2) no new subjects should be admitted to ongoing studies that are subject to Parts 50 and 56, until this office has assurance that adequate corrections have been made.

These restrictions do not apply to the emergency use of an investigational material when the conditions described in 21 CFR 56.102(d) exist and the procedures followed by your institution meet or exceed the requirements described in 21 CFR 56.104(c). Neither do they relieve the IRB from receiving and reacting to proposed amendments, reports of unexpected and serious reactions and routine progress reports from ongoing studies.

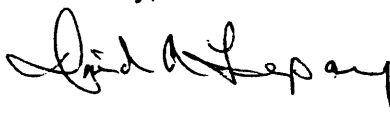
Please inform this office, in writing, within (15) calendar days from the date of receipt of this letter, of the actions you have taken or plan to take concerning the violations noted.

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Your failure to respond may result in further administrative actions. If you have any questions, please contact Sandra L. Titus, Ph.D. at 301-594-1026. Your response should be addressed to:

Anthony E. Rodgers, Acting Team Leader
Human Subject Protection Team, HFD-343
Division of Scientific Investigations
Center for Drug Evaluation and Research

Sincerely,

A handwritten signature in black ink, appearing to read "David A. Lepay".

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

Enclosures:

1. 21 CFR 50 and 56
2. FDA Form 483
3. Information Sheets for Institutional Review Boards and Clinical Investigators

cc:

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