



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

34015d

Warning Letter

Food and Drug Administration  
Center for Devices and  
Radiological Health  
2098 Gaither Road  
Rockville, MD 20850

Via Federal Express

**MAY 14 2003**

Mr. Jeffrey A. Leimgruber  
Chief Administrative Officer  
Fairview Hospital  
Cleveland Clinic Health System  
18101 Lorain Avenue  
Cleveland, Ohio 44111

Dear Mr. Leimgruber:

The purpose of this letter is to inform you of objectionable practices and activities found during a Food and Drug Administration (FDA) inspection of the Fairview Hospital Institutional Review Board (IRB) and to request corrective actions. The inspection took place during the period of August 21-27, 2002. Ms. Karen M. Kondas, an investigator from FDA's Cincinnati District Office, conducted the site inspection.

The purpose of the inspection was to determine whether your activities and procedures as an IRB comply with applicable federal regulations. The regulations apply to your oversight of clinical studies of all products regulated by the FDA.

Our review of the information contained in the establishment inspection report prepared by the district office reveals violations of FDA regulations contained in Title 21, Code of Federal Regulations (21 CFR), Part 50 – Protection of Human Subjects and Part 56 – Institutional Review Boards. Ms. Kondas listed her observations on the form FDA-483, "Inspectional Observations," and discussed her findings with Dr. Sudhakar Chandurkar, the IRB Chairman, at the conclusion of the inspection. Meses. Susan Favorite and Margaret Barnes and Mr. Raymond Marvar also attended this meeting.

We acknowledge receipt of your August 30, 2002, letter regarding the FDA-483 observations, which will be part of our official files. Your response inadequately addresses the 483 items.

This letter informs you of the violations found during the recent inspection. The significance of these violations is of particular importance because several items were observed and brought to the attention of the IRB during a previous inspection FDA conducted from April 22 until June 6, 1997. Your institution promised to correct these violations, but changes were not implemented. For your review and reference, we have enclosed a copy of the FDA-483 from the 1997 inspection and a copy of your institution's June 18, 1997, response to those observations.

The violations listed below are not intended to be an all-inclusive list of objectionable practices that may exist at your institution. Fairview Hospital, the parent institution, is responsible for ensuring that its IRB adheres to each applicable requirement of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq.) and all pertinent federal regulations (21 CFR 56.120(c)).

**1. Failure to have written procedures for conducting initial and continuing review of research [21 CFR 56.115(a)(6)]**

The regulations require IRBs to adopt and follow written procedures for conducting their review of research. Your institution's procedural manual entitled "Fairview Hospital Institutional Review Board Policy and Procedures," amended September 18, 2001, does not meet all regulatory requirements.

For example, the manual does not adequately describe the criteria for review of research and information associated with a device study (21 CFR 56.111). The manual also does not include procedures for how the IRB determines whether an investigation involves a significant risk device (21 CFR 812.66). Furthermore, the manual does not have any procedures or directives for the review of a device available under a Humanitarian Device Exemption (21 CFR 814.124).

In addition, the manual does not address all required functions and operations of the IRB set forth in 21 CFR 56.108, including:

- the prompt reporting to FDA of any serious or continuing noncompliance with the regulations and IRB requirements;
- the prompt reporting to the IRB of changes in research activity by clinical investigators and others affiliated with the research;
- the required approval by the IRB of changes in approved research before the changes are initiated.

**2. Failure to follow written procedures [21 CFR 56.108]**

The IRB has written procedures requiring that informed consent documents contain all information required by 21 CFR 50.25. The IRB failed to follow these written procedures. For example, the consent document approved by the IRB for the clinical study entitled [REDACTED]

[REDACTED] did not disclose the expected duration of the research, did not include specific information regarding the schedule of required follow-up visits and the necessary testing, and did not describe details of procedures encountered by subjects during the investigation, such as the echocardiogram required during the one-month follow-up visit, the post-treatment use of Aspirin along with either Plavix or Ticlid, a 12-month follow-up assessment, and the possibility of an emergency coronary artery bypass graft (CABG) procedure in the event of an abrupt or threatened closure. Additionally, in the study entitled [REDACTED]

[REDACTED] the IRB did not require its requested addition of pregnancy warnings to the informed consent document to be completed and approved before the clinical investigator initiated the study enrollment.

The IRB's written procedures state that expedited review is to be used on "some or all of the research appearing on the list published periodically by the Federal Register and found by the reviewer to involve no more than minimal risk research" and for minor changes in previously approved research for which approval is authorized. FDA published a notice in the Federal Register setting forth the list of research activities which IRBs may review through expedited procedures [46 Fed. Reg. 8980 (January 27, 1981)]. Pursuant to that notice, expedited review may be used for research involving no more than minimal risk and for which an Investigational New Drug application (IND) or Investigational Device Exemption (IDE) is not required. Your IRB failed to follow its written procedures when it expedited the approval of two study amendments requiring changes in the risks and eligibility requirements of the [REDACTED] investigational study mentioned above, which was being conducted under [REDACTED].

The IRB's written procedures require it to document the votes that occur during the review of research, including the members who voted for and against a study and those who abstained. However, the IRB's meeting minutes do not indicate the voting members and the number voting for and against and abstaining for each study. In addition, there is no documentation in the minutes that guests and certain members (ex officio) did not vote. For example, during the October 10, 2001, meeting, a quorum was reached by the inclusion of a guest when only five of eleven members attended the meeting. There was no documentation in the minutes that the guest did not vote.

The IRB's written procedures state that anyone with an actual or potential conflicting interest in the review of specific research will leave the IRB meeting before deliberations of that research. The IRB minutes do not document the departure of members with conflicting interests before the deliberation of their studies and before the deliberation and voting on their studies for continuing review. The meeting minutes also do not record the departure during deliberation and voting of members who serve as part of the research team.

### **3. Failure to prepare and maintain adequate documentation of IRB activities [21 CFR 56.115(a)(1)-(a)(5)]**

FDA's regulations at 21 CFR 56.115(a) require that IRBs prepare and maintain adequate documentation of their activities. Your institution's documentation of its activities is inadequate in several respects. First, the IRB failed to maintain adequate records of its review of research. Second, the IRB's practice of filing protocols, periodic reports, and other correspondence is inadequate. The record-keeping system does not allow the IRB to locate readily for review all documentation associated with specific research.

Further examples of the institution's recordkeeping deficiencies are illustrated in your response to the FDA-483. In your response to FDA-483 item 1B, you state that the IRB reviewed amendments and revised informed consent for a *randomized*, prospective, multicenter trial entitled [REDACTED] during the June 14, 2000, meeting and approved these documents during the July 19, 2000, meeting. This statement is incorrect. The minutes of that meeting indicate that the IRB reviewed and approved amendments and a revised informed consent of a *nonrandomized* multicenter trial entitled [REDACTED]. Please refer to your records of the [REDACTED] including the June 15, 2000, and July 20, 2000, approval letters to the principal investigator.

Additionally, in your response to FDA-483, item IC, you state that a death was not reported to the IRB until February 2001. This statement is incorrect. The clinical investigator reported the death of the subject in the [REDACTED] earlier. Please refer to the November 20, 2000, letter from the principal investigator to Dr. Sudhakar Chandurkar. The death was not reviewed at the next scheduled monthly IRB meeting; instead, it was reviewed on March 7, 2001.

The IRB also failed to record its review of the information regarding the death of a patient who received the test article [REDACTED] in the clinical study [REDACTED].

#### **4. Failure to have the proper IRB membership [21 CFR 56.107]**

The regulations set forth requirements regarding the IRB membership, including that the IRB members possess the professional competence necessary to review the specific research activities and to ascertain the acceptability of proposed research in terms of institutional commitments and regulations and applicable law (21 CFR 56.107(a)). Your IRB's failure to have the required membership is evident by the fact that the IRB study files contain numerous approval letters to principal investigators of *device* studies in which the IRB requested, as part of its conditions for approval, the investigator's compliance with the Investigational New Drug (IND) regulations at 21 CFR Part 312 rather than the applicable Investigational Device Exemption (IDE) regulations in 21 CFR Part 812.

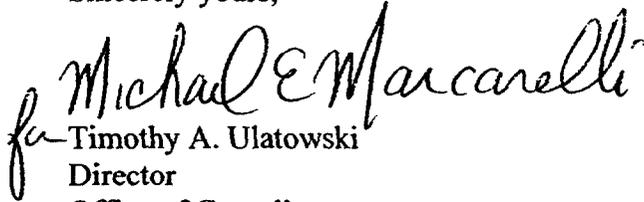
Please acknowledge receipt of this letter within 15 working days, and provide in writing the specific steps Fairview Hospital will take to correct all of the violations discussed in this letter and to prevent the recurrence of similar violations in current and future studies. Your corrective action plan should include the projected dates for each action to be accomplished and should document those corrective actions that have already been completed.

We strongly recommend the use of The FDA Information Sheets, Guidance for Institutional Review Boards and Investigators (<http://www.fda.gov/oc/gcp/default.htm>) as a resource when writing standard operating procedures (see appendix H, A Self-evaluation Checklist for IRBs). We also recommend that you convene a working group to revise the IRB's standard operating procedures. You may want to consult an expert to assist you or contact another IRB for advice. When writing your formal written procedures, you must ensure compliance with all pertinent federal regulations.

Any revised institutional policy and procedures submitted in response to this letter must include the date of the revision, signatures of approval officials, and the date of implementation. Failure to achieve prompt correction may result in enforcement action without further notice.

Please direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 2098 Gaither Road, Rockville, Maryland 20850, Attention: Kevin M. Hopson, Consumer Safety Officer. If you have questions, you may contact Mr. Hopson at (301) 594-4720, extension 128. We have sent a copy of this letter to our Cincinnati District Office at 6751 Steger Drive, Cincinnati, Ohio 45237, and request that you copy the district on your response.

Sincerely yours,

  
for Timothy A. Ulatowski  
Director  
Office of Compliance  
Center for Devices and Radiological Health

Enclosures (2)

cc: Louis P. Caravella, M.D., Chief Executive Officer, Fairview Hospital  
Sudhakar Chandurkar, M.D., Chairman, Fairview Hospital