



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

D1198B

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

FEB 18 1997

Certified-Return Receipt Requested

WARNING LETTER

Mr. Roger Collins, Administrator
Valley Hospital Medical Center
620 Shadow Lane
Las Vegas, Nevada 89106

Dear Mr. Collins

During an inspection ending on December 20, 1996, Mr. Luis Chavarria, an investigator with the Food and Drug Administration (FDA), inspected the Valley Hospital Institutional Review Committee (IRC). The purpose of the inspection is to determine if the Institutional Review Board's (IRB) 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 you 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 establish adequate written procedures for conducting the review of research, including periodic review. [21 CFR 56.108(a) and (b), 56.115(a)(6)]**
 - a. There are no detailed instructions as to how the IRB is to operate. Addendum No. 1 of the Valley Hospital Medical Center Bylaws is an outline of the purpose, composition, and duties of the IRB but does not fulfill the requirement of the regulations. The regulations require that the IRB shall adopt and follow written procedures for conducting its review of research. The procedures should include a description of the IRB organization and membership, explicitly outline how the review is to be conducted, how decisions are made, what criteria are used to determine the basis of approval of research proposals and the frequency of continuing review, how continuing review is conducted, how controverted issues are decided, and describe how records must be maintained to fulfill federal requirements. Written procedures should describe how the IRB will determine when an investigation involves a significant risk device. Written procedures should include information for appointing members and alternates and voting authority.

- b. The procedures for conducting periodic review are not adequate. Written procedures should describe in detail the following aspects of IRB operations: the content of progress reports, how and when renewal notices are sent to clinical investigators, procedures for determining which projects require review more often than annual review, how administrative staff process interim reports, the voting method the IRB will use for continuing reviews, and IRB follow-up activities in the event of a lack of response or an incomplete response. The procedures should specify how the IRB will document its actions for ensuring that progress reports are submitted and reviewed at the specified time intervals.
 - c. There are no written procedures for emergency use requests, reviews, and approvals.
 - d. There are no written procedures for expedited review.
 - e. There are no written procedures to describe how adverse reaction reports are reviewed, by an "expedited" process or by the full IRB.
 - f. There are no written procedures to describe how the IRB is to conduct business and voting when there is an apparent conflict of interest.
 - g. There are no written procedures for ensuring prompt reporting to the appropriate institution officials and FDA of the following:
 - i. Any unanticipated problems involving risks to human subjects or others
 - ii. Any instance of serious or continuing noncompliance with FDA regulations or the requirements or determinations of the IRB.
 - iii. Any suspension or termination of IRB approval
2. **Failure to meet the criteria for IRB membership. [21 CFR 56.107(c)]**
- The current membership does not include a member whose primary concerns are in nonscientific areas
3. **Failure to retain copies of all research proposals and supporting documents [21 CFR 56.115(a)(1)]**
- a. The IRB does not identify the submitted and approved versions of informed consent documents for all reviewed studies. The FDA investigator could not differentiate the approved informed consent documents from unapproved drafts. Consent documents on file did not have a signature or stamp identifying the form as the approved copy

- b. The IRB was unable to provide a copy of the informed consent form for the GUSTO study and study #M-7550-0017.
- 4. **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 fail to document which members voted for approvals/disapprovals or which members posed questions.
 - b. Meeting minutes do not document the names of all principal investigators/coinvestigators, the associated protocols, and the requested approval period.
 - c. Meeting minutes should be in sufficient detail to document abstention from voting where conflict of interest exists.
- 5. **Failure to maintain records of continuing review activities. [21 CFR 56.115(a)(3)]**

The IRB does not have a systematic method in place for tracking open/closed studies, for informing and reminding clinical investigators of their reporting responsibilities (i.e., anniversary review dates, progress reports due, final reports due, reporting of serious unanticipated adverse events within a defined time period, etc.).

- 6. **Failure to prepare correspondence and maintain copies of all correspondence between the IRB and the investigators [21 CFR 56.115(a)(4)]**

The IRB failed to prepare and maintain documentation of correspondence between the IRB and clinical investigators regarding initial and continuing review. For example:

- a. There is no record of written approval to the clinical investigator, _____, for the _____ study. The only documentation of the approval is a copy of an unsigned letter from the Chairman of the IRB to the sponsor
- b. There is no record of written IRB approval for study #M-7550-0017.
- c. The IRB lacked all documentation of continuing review and approval (1992 to 1995) for _____
- d. There is no record of written approval or any correspondence with Dr. Edward Quinn, the clinical investigator for the GUSTO study
- e. The IRB approved _____ protocol during a meeting in November 1990, but did not notify him in writing until July 29, 1991

- f. There is no written record from the IRB to _____ notifying her that the study was forwarded to the Pharmacy and Therapeutics Committee.

7. **Failure to prepare an adequate listing of IRB members. [21 CFR 56.115(a)(5)]**

- a. The IRB membership listing provided to the FDA investigator fails to meet the requirements of a membership roster. The regulations require that IRB records be inclusive of a list of IRB members identified by name, earned degrees, representative capacity, indications of experience such as a board certification, licenses, etc., sufficient to describe each member's chief anticipated contributions to the IRB deliberations, and any employment or other relationship between each member and the institution.
- b. The membership roster fails to identify alternate members and their voting authority. Review of meeting minutes shows twelve additional members attending and voting, or excused and absent. There is no indication in the minutes of IRB meetings that these individuals function as anything other than voting members of the IRB on the following dates: 7/24/91, 4/24/91, 5/4/94, 6/13/96, and 9/10/90.

FDA believes the records that an IRB or an institution must maintain provide significant evidence of whether the procedures utilized by the IRB are adequately protecting the human subjects of the investigations that the IRB is reviewing. Compliance is intended to ensure that the IRB fulfills its primary responsibility of protecting the rights and welfare of human subjects involved in clinical investigations.

The FDA investigator found the IRB's files were incomplete and in disarray. The IRB does not maintain a separate file for each study. The IRB does not have documentation for at least the GUSTO study and the studies of _____ that shows the number of subjects enrolled and/or any adverse events. The IRB could not provide a list or number of the open and closed studies at the initiation of the inspection. A handwritten list was compiled during the inspection and provided to the FDA investigator at the conclusion of the inspection. The IRB does not maintain an inventory regarding the principal/co-investigators or subinvestigators of studies. For example, the Medical Staff Supervisor could not inform the FDA investigator which studies involved the Chairman of the IRB.

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The Valley Hospital Medical Center participates in the Cooperative Protocol Research Program and has a Cooperative Project Assurance (CPA) document with DHHS/OPRR. The CPA approved by the DHHS is a commitment to follow the DHHS regulations, 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).

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, and apparent lack of understanding of the applicability of the FDA regulations, we have no assurance that your procedures are adequately protecting 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 the Valley Hospital Medical Center Institutional Review Committee 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. Your response should include a discussion addressing appropriate staffing needs and any other reorganization plans that you will implement.

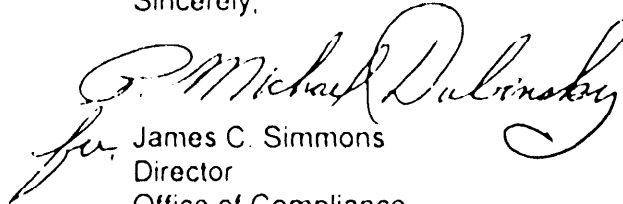
If your institution does not have the resources to bring your IRB into compliance with federal regulations, it is acceptable for you to use another IRB. Please notify us if you intend to disband the Valley Hospital Medical Center Institutional Review Committee.

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

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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 21 CFR Parts 50 and 56)

cc:

Edwin Kingsley, Chairman
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