DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

Via Federal Express

WARNING LETTER

SEP 26 2000

Kevin P. Britt
Co-Chairman, Institutional Review Board
Holy Cross Hospital
4725 North Federal Highway
Fort Lauderdale, Florida 33308

Dear Mr. Britt:

During the period June 9-15, 2000, Mr. Bill Tackett, an investigator with the Food and Drug Administration (FDA), Florida District Office, conducted an inspection of the Institutional Review Board (IRB) at Holy Cross Hospital. The purpose of the inspection was to determine whether the IRB's activities and procedures relating to clinical studies of FDA-regulated products complied with applicable FDA regulations, and to determine whether or not corrections had been made to address deficiencies identified in a February 1993 inspection.

Our review of the inspection report and exhibits submitted by the district office revealed that there were violations from the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 56 - Institutional Review Boards, and Part 812, Subpart D - IRB Review and Approval. The violations were listed on the Form FDA 483, "Inspectional Observations," which was presented to and discussed with you and others at the conclusion of the inspection. The description of violations that follows is not intended to be an all-inclusive list of IRB deficiencies.

1. Failure to ensure adequate review of research [21 CFR 56.108]

Based on our review of IRB meeting minutes, the following primary reviewers for various protocols were neither identified as IRB members nor were in attendance at meetings where those protocols were discussed: [redacted], protocol [redacted] (May 21, 1997); [redacted], protocols [redacted], and [redacted] (January 14, 1998); [redacted], protocol [redacted] (May 31, 2000). According to your IRB Guidelines, the protocol was to be forwarded to an IRB physician member for review of the study's appropriateness and to assure soundness of the science.

For protocol [redacted], numerous adverse reaction reports (safety updates) covering the period March 1999 through May 2000 had been submitted to the IRB by the investigator on behalf of the sponsor. The informed consent was not updated to include these new findings. In the meeting minutes available for our review, we found no documentation that the adverse events related to this study were brought up for discussion.

Protocol [redacted] was presented and approved pending revision of the informed consent at the May 21, 1997, meeting. However, the IRB's records for this study did not include an approved protocol or informed consent. The IRB suspended approval of the study September 18, 1997, but there was no documentation that the investigator, appropriate institutional officials, and the FDA were notified as required (21 CFR 56.113).

At the IRB meeting on May 21, 1997, even though it was noted that [redacted] was excused from the room during voting on his protocol ([redacted]), his vote was included in the vote tally. His vote was also included in acceptance of the progress reports for studies in which he was an investigator. As you are aware, a member may not participate in initial or continuing review of any project in which the member has a conflicting interest. Furthermore, without Dr. [redacted]'s vote, there would not have been a quorum present to conduct IRB business.

2. Failure to perform continuing review at the required frequency and ensure investigator compliance with reporting requirements [21 CFR 56.109(f) and 56.108(a) and (b)]

Examples of late or missing continuing reviews of research were observed. Protocol [redacted] was approved February 25, 1997, but it was not reviewed in 1998. The protocol's termination (closure) report was scheduled for the IRB's February 16, 1999, meeting. Protocol [redacted], approved June 2, 1993, failed to have an annual review in 1994 and 1998, and the review in 1996 was eight months late. Protocol [redacted], a four-month study, was approved June 15, 1999, but has received no further review since its approval.

Several progress reports were identified as pending or overdue in meeting minutes and in the active studies listing. It is unclear what specific IRB actions were taken. The requirement for investigators to provide a written progress report 30 days prior to renewal was included in your Guidelines for the Clinical Investigator. Continued approval for the research would be withdrawn if the investigator did not submit the report or materially failed to comply with other IRB requirements. There was no documentation that studies were actually suspended or terminated because of delinquent progress reports or investigator non-compliance with FDA and/or IRB requirements.

The fact that it may be difficult to obtain physicians' compliance with deadlines for re-evaluation does not relieve you of your responsibility to ensure investigator compliance. When a clinical investigator fails to submit the required progress report by the due date established by the IRB, the IRB must have and be prepared to exercise procedures to withdraw its approval of the research. Whenever the IRB withdraws its approval of research, it must notify the FDA.

3. Failure to have and follow adequate written procedures as required by 21 CFR 56.108(a) and (b), 56.115(a)(6), 812.60, and 812.66

The IRB must have and follow written procedures that describe the IRB's functions and operations. The current Institutional Review Board (IRB) Guidelines (revised 4/3/00) do not meet the FDA requirements for written procedures (i.e., how the process is accomplished) in several areas. The procedures that should be added or revised include, but are not limited to, those discussed in this section.

The Guidelines lack procedures to ensure that members receive all required study documentation within a time frame that would allow for an appropriate review prior to convened meetings. According to the Guidelines, materials are to be distributed at least five days prior to an IRB meeting. However, a review of the June 15, 1999, IRB meeting minutes note that members had voiced concerns over not receiving any study materials prior to the convened meeting and action on new and existing studies was tabled. Furthermore, a primary reviewer (IRB physician member) is to review research applications. The primary reviewer system is acceptable to FDA if each member receives, at a minimum, a copy of informed consent documents and a summary of the protocol. However, as discussed previously, physicians who were not identified as IRB members conducted some reviews.

Procedures have not been developed for suspending or terminating a study. This includes the subsequent reporting of suspensions or terminations to the investigator, the institution, and FDA. You do not describe how the process is accomplished or how you ensure that investigators comply with FDA and IRB requirements.

Your procedures for reporting and review of adverse events are unclear. Also, there are no specific time frames for reporting. According to your Guidelines for the Clinical Investigator, investigators must report immediately all significant or unexpected complications or other research-related injuries to the IRB Committee via the Director, Risk Management. It was also stated that all adverse events would be reviewed by the Department of Pharmacy Services, with forwarding to Risk Management, if additional scrutiny was recommended. It was noted in meeting minutes that specific adverse events were acknowledged but it is unclear if those events were actually discussed at the meetings.

Your Guidelines note that patient accrual may commence only after the IRB approves both the informed consent and protocol, but you do not describe how you ensure that all requested changes to the protocol/ informed consent are made by the investigator prior to subject enrollment.

Under "Expedited Review," you do not describe how the members are advised of research studies that have been approved by expedited review. We noted that expedited reviews have been discussed during IRB meetings, but the actual process is not included in your procedures.

There are no procedures for determining, during initial review, if a device study is a significant risk or for documenting this risk determination. Note that it is the IRB's responsibility to determine study risks, the frequency of review, and verify, if necessary, the regulatory status of a device.

Your Guidelines pertain primarily to drug studies even though device studies are conducted at your institution. For example, under "Emergency Exemption from Prospective IRB Approval," only the use of investigational drug and biological products is covered. In Guidelines for the Clinical Investigator, reference is made to drug studies specifically (#2, #11, and #12).

4. Failure to prepare and maintain adequate documentation of IRB activities in accordance with 21 CFR 56.115(a)(2) and (a)(5)

The minutes of convened meetings are inadequate. For protocols that were approved pending revisions/modifications, there is no notation in subsequent minutes that the changes were made and the date the protocol was approved and the study allowed to begin. Risk determinations (significant/nonsignificant) for device studies were not documented in the minutes. In the June 19, 1999, minutes, those abstaining from voting on protocol [redacted] were not identified. At that same meeting [redacted] signed the attendance log but is not listed as present.

It is unclear which membership list is current. Specifically, the list in your Guidelines (rev 4/00) shows 15 members; the Cooperative Project Assurance list dated 4/19/2000 identifies 16 members. Your Guidelines indicate that a majority of 9 votes is necessary for approval; however, depending on which IRB membership listing is current, a majority could be either 8 or 9.

In addition to the above, we noted that the composition of your IRB appears to be adequate at this time. However, you should specify which member(s) meet the "non-scientist" requirement to ensure that the quorum requirements of 21 CFR 56.108(c) are met. Your Guidelines ([redacted]) state that at least one non-scientific/non-affiliated member must be present. We recognize that one member can meet both requirements, but this is not necessary. The regulations do require that the non-scientific member be present to constitute a quorum.

We also noted that some of the violations revealed during the February 1993 inspection, and for which an FDA Warning Letter had been issued by the Center for Devices and Radiological Health, still had not been corrected. This included numerous deficiencies in the IRB's written procedures and in the initial and continuing review process.

Within fifteen (15) working days of receipt of this letter, please provide this office with written documentation of any specific steps you have taken or will be taking to bring your Institutional Review Board into compliance with FDA regulations. The corrective actions should include revisions to the IRB's written procedures and the timeframes within which these procedures will be developed and implemented. Failure to respond may result in further regulatory action such as that described in 21 CFR 56.120 and 56.121.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I, 2098 Gaither Road, Rockville, Maryland 20850, Attention: Barbara A. Crowl. A copy of this letter has been sent to FDA's Florida District Office, 555 Winderley Place, Maitland, Florida 32751. We request that a copy of your response also be sent to that office.

Please direct all questions concerning this matter to Ms. Crowl at (301) 594-4720.

Sincerely yours,

Chauncey Connor, RPh

for Larry D. Spears
Acting Director
Office of Compliance
Center for Devices and
Radiological Health

cc: Richard L. Brown (purged copy)
Chief Operating Officer
Holy Cross Hospital
4725 North Federal Highway
Fort Lauderdale, Florida 33308

Michael Carome, M.D.
Compliance Oversight Branch, MSC 7507
Office of Human Research Protections
National Institutes of Health
6100 Executive Boulevard, Suite 3B01
Rockville, Maryland 29892-7507