



CBER-00-017

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

WARNING LETTER

AUG 29 2000

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. James Gardner
Chief Executive Officer
Christus St. Patrick Hospital
524 South Ryan Street
Lake Charles, LA 70601

Dear Mr. Gardner:

During an inspection that concluded on April 24, 2000, Ms. Dana M. Daigle, an investigator with the Food and Drug Administration (FDA), inspected the Institutional Review Board (IRB) at Christus St. Patrick Hospital. The purpose of this inspection was to determine if the IRB's procedures for the protection of human research subjects comply with FDA regulations, published in Title 21, Code of Federal Regulations, Parts 50 and 56 [21 CFR 50 and 56].

Based on information obtained during the inspection, we have determined that the Christus St. Patrick Hospital IRB has violated applicable federal regulations contained in 21 CFR Part 50 and 56. A copy of the List of Inspectional Observations (Form FDA 483) provided to Dr. Walter Divers, the IRB chairman, at the conclusion of the inspection is enclosed.

The violations listed below are not intended to be an all-inclusive list of deficiencies in your IRB operation. The applicable provisions of the CFR are cited for each violation.

1. **Failure to prepare and follow adequate written procedures for conducting the review of research, including periodic review. [21 CFR 56.108(a),(b), and 56.115(a)(6)]**
 - a. The Christus St. Patrick Hospital IRB handbook does not constitute adequate written procedures. The regulations require that the IRB shall adopt and follow written procedures for conducting its review of research. The procedures must, for example, describe the IRB organization and membership, how many voting members make up the IRB, explicitly outline how applications are processed, who will receive pre-meeting materials to review, how the review is to be conducted, how decisions are made, what criteria are used to determine the basis of approval of research proposals, the frequency of continuing review, how continuing review is conducted, how controverted issues are decided, and how records must be maintained to fulfill federal requirements.

- b. There are no adequate written procedures for conducting periodic review. 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, 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 adequate written procedures the IRB will follow (a) for reporting its findings and actions to the institution; and (b) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since the previous IRB review.
- d. There are no adequate written procedures for ensuring prompt reporting to appropriate institutional officials and FDA of the following: (1) any unanticipated problems involving risks to human subjects or others; (2) any instance of serious or continuing non-compliance with FDA regulations or the requirements or determinations of the IRB; and (3) any suspension or termination of IRB approval.
- e. The IRB written procedures do not describe which medical device studies pose significant risk (SR) or non-significant risk (NSR), nor do they define the IRB's responsibility in regard to these areas.
- f. The IRB's written procedures should provide a definition of a "quorum" which complies with the requirements of 21 CFR 56.108(c).
- g. The IRB should have written procedures outlining how adverse events would be handled. The procedure describing adverse events reporting should also include a description of what actions will be taken by the IRB following review of the adverse event. In addition, there are no written procedures to describe how adverse reaction reports are reviewed, by an "expedited" process or by the full IRB.
- h. Written procedures do not describe the conflict of interest policy.
- i. The IRB written procedures for emergency use situations are not adequate.

The emergency use of experimental drugs portion of the IRB Handbook (Section H) needs to be rewritten. The term "compassionate use" is often used to refer to the use of investigational drugs outside of an ongoing clinical trial to a limited number of subjects who are desperately ill and for whom no standard alternative therapies are available. The term "compassionate use" does not, however, appear in FDA or DHHS regulations.

The FDA human subjects regulations allow for a test article to be used in emergency situations without prior IRB approval, provided that the emergency use is reported to the IRB within five working days (21 CFR 56.104(c)). Any subsequent use of the test article at the institution is subject to IRB review in accordance with 21 CFR 56.109. An emergency is defined as a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)].

The IRB should develop a written procedure for its notification prior to emergency use of a test article as a means for the IRB to initiate tracking to ensure that the investigator files a report within the five-day time frame required by 21 CFR 56.104(c). However, if implemented, the procedure should make clear that the notification does not constitute an expedited IRB approval of the emergency use. Further use of the test article requires full IRB review and approval.

The emergency use provisions for investigational products are described in 21 CFR 312.36, which contain the regulations delineating a sponsor's responsibility when their investigational product is to be used in an emergency situation.

2. Failure to conduct adequate initial review of research. [21 CFR 56.108(a)]

The _____ study was approved by the IRB at the March 14, 1997 meeting; however, IRB members did not receive a copy of the protocol, a protocol summary or the informed consent document prior to the IRB meeting. There also is no record in the meeting minutes or in the study file documenting who reviewed the protocol or if the protocol ever received a thorough review.

During the inspection, FDA was informed that the IRB members are provided with an agenda prior to meeting, but they do not receive any study materials for review, such as a summary of the research protocol or an informed consent document, prior to the IRB meetings.

When an IRB receives a study for review, it should have at least one copy of all pertinent documents, including the full protocol, a draft of the informed consent document, the investigator's brochure (if one exists) and any advertising intended to be seen or heard by potential subjects. If the IRB uses a primary reviewer system, the primary reviewer should perform an in-depth review of all pertinent documentation. The other members of the IRB should each receive, at a minimum, a copy of the consent document, any advertising, and a summary of the protocol. In addition, the complete documentation should be available to all members for their review. If a primary reviewer system is not used, all members should receive a copy of the complete documentation. These materials should be received by members sufficiently in advance of the meeting date to allow review of this material.

3. Failure to review proposed research at convened meetings at which a majority of the members of the IRB are present. [21 CFR 56.108(c)]

- a. The IRB reviewed and approved research at the meeting held June 24, 1999, when the requirement of a majority of voting members was not met, with eight (8) of — members in attendance. The June 24, 1999 IRB meeting minutes also indicate that a clinical investigator abstained from voting for two studies due to conflict of interest. Because of this situation, the studies were approved by a vote of 7 out of — members. An IRB member excluded from deliberations due to a conflict of interest cannot be counted toward the quorum because that individual cannot be involved in the voting process.
- b. IRB records include a revised consent form for the — study (protocol —), which contains a handwritten note regarding telephone approval of the changes in the consent form for the — study. The consent form was revised to include changes regarding the length of the study and the maximum amount of blood to be drawn during the course of the study.

As described below (Item 5b), the — study (protocol — amendment —) did not qualify for expedited review, and it should have been discussed and voted on at a convened meeting.

21 CFR 56.108(c) requires review of proposed research at convened meetings at which a majority of the members of the IRB are present. Convened meetings may take place by conference calls, as long as each IRB member can actively participate in any discussion of a protocol and has all pertinent material before the call. These meetings must follow the same requirements (minutes, etc.) as meetings with members physically present. A vote by mail or by telephone without a convened meeting does not allow for active discussion of issues and does not comply with regulations.

4. Failure to conduct adequate continuing review of research. [21 CFR 56.109(f)]

At a meeting held on March 14, 1997, the IRB approved — study, — to continue for a one-year period.

The continuation of the study was approved retroactively on December 3, 1999, for the period of March 1998 through March 1999.

In addition, the IRB retroactively approved the continuation of — study — on March 10, 2000, for the period of September 1999 through September 2000. Although progress reports were submitted by the clinical investigators, no determination was made by the IRB as to whether the study should be amended, terminated, or allowed to continue as originally approved.

We reviewed — quarterly progress reports and they did not address information required by the IRB during continuing review, e.g., a progress report form. The IRB approved the continuation of the study even though the clinical investigator submitted incomplete periodic reports.

Continuing IRB review must be substantive and meaningful. The purpose of continuing review is to review the progress of the entire study, not just changes in it. The file should be reviewed examining, at a minimum, any previous progress report including: the number of subjects accrued; a summary description of subject experiences (benefits, adverse reactions); number of withdrawals from the research; reasons for withdrawals; complaints about the research; research results obtained so far; a current risk-benefit assessment based on study results; and any new information since the IRB's last review. The IRB should obtain a copy of the current consent document and determine whether the information contained in it is still accurate and complete, including whether new information that may have been obtained during the course of the study needs to be added.

Continuing review of a study may not be conducted through an expedited review procedure, unless the study was eligible for and initially reviewed by an expedited review procedure or the study has changed such that the only activities remaining are eligible for expedited review.

The continuation of research after expiration of IRB approval is a violation of the regulations [21 CFR 56.103(a)]. If the IRB has not reviewed and approved a research study on or before the study's current expiration date, IRB approval will expire and all research activities, including enrollment must stop. Written notification of the IRB action should be provided to the investigator.

5. Failure to fulfill requirements for expedited review. [21 CFR 56.110]

Meeting minutes show that the IRB used expedited review inappropriately to approve research. The following are examples:

- a. Meeting minutes for 9/11/98 show that study _____ received expedited review inappropriately. The study involves the use of a _____ Study _____ should have undergone full committee review and approval; however, the study underwent expedited review because the IRB chairman (Dr. Conway Magee) reviewed and approved the protocol and consent form on behalf of the IRB. In addition, meeting minutes for 6/13/97 document that expedited approval was granted by the chairman on May 27, 1997, pending full Board approval.
- b. Meeting minutes for June 24, 1999 note that the IRB chairman granted expedited approval of _____ along with revisions to the protocol _____ Amendment _____ dated January 12, 1999, pending full board approval after consideration at the regular meeting of June 11, 1999.

Section 56.110 of the Federal regulations provides for expedited IRB review procedures for certain categories of research involving no more than minimal risk, and for minor changes in previously approved research during the period for which approval is authorized. The list that is referenced in section 56.110(a) was originally published in the Federal Register of January 27, 1981 (46 FR 8980), as a notice of a list of research activities that could be reviewed by the IRB through the expedited review procedures set forth in the FDA's regulations.

The revised list became effective November 9, 1998 and is available on the Internet at <http://www.fda.gov/ohrms/dockets/98fr/110998b.pdf>.

6. Failure to prepare and maintain adequate documentation of IRB activities. [21 CFR 56.115(a)(2)]

- a. The meeting minutes of June 12, 1998 document that a revised protocol for the _____ study was submitted to the IRB for review; however, the minutes do not document who reviewed the protocol revision or if it was reviewed.
- b. The _____ study was approved “with conditions” or “pending revisions” at the 9/11/98 IRB meeting; however, there is no documentation in the IRB meeting minutes or the study file that the protocol received a thorough review prior to the approval. The IRB minutes do not document who was the primary reviewer.
- c. The 9/10/98 IRB meeting minutes state that the clinical investigator submitted an updated Investigator’s brochure for the _____ study, which was to be included in the study file. However, the study file does not contain an Investigator’s brochure.

7. Failure to maintain an adequate list of IRB members. [21 CFR 56.115(a)(5)]

The IRB records do not contain all the required information listed in 21 CFR 56.115(a)(5). A list of current IRB members must identify members by name, earned degrees, representative capacity, indications of experience (such as board certifications and licenses) sufficient to describe each member’s chief anticipated contributions to IRB deliberations, and any employment or other relationship between each member and the institution (e.g., full-time employee, stockholder, paid or unpaid consultant, or a member of governing panel or board).

Please inform this office, in writing, within fifteen (15) working days from the date of receipt of this letter, of the actions you have taken or plan to take to bring the procedures of your IRB into compliance with the applicable regulations. Please include a copy of any revised documents, such as written procedures, with your response. Any plan of action should include projected completion dates for each action to be accomplished. Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions may include, but are not limited to, the termination of all ongoing studies approved by your IRB and the initiation of regulatory proceedings for disqualification of your IRB.

You may find it helpful to refer to the FDA Information Sheets on FDA’s Web site (<http://www.fda.gov/oc/oha/IRB/toc.html>). Appendix H of the FDA Information Sheets provides guidance to ensure that all required elements are included in your written procedures.

Should you have any questions or comments about the contents of this letter or any aspects of the operation and responsibilities of an Institutional Review Board, you may contact: Mr. Jose Javier Tavarez, Biochemist/Consumer Safety Officer, Bioresearch Monitoring Branch, Division of Inspections and Surveillance, at (301) 827-6221.

Please send your written response to:

Jose J. Tavarez, M.S.
FDA/Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Bioresearch Monitoring Branch (HFM-664)
1401 Rockville Pike
Rockville, Maryland 20852-1448

Sincerely,

A handwritten signature in cursive script, appearing to read "Steven A. Masiello".

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Enclosure:

Form FDA-483, List of Inspectional Observations, dated April 24, 2000

cc:

Walter A. Divers, M.D.
Chairman, Institutional Review Board
Christus St. Patrick Hospital
524 South Ryan Street
Lake Charles, Louisiana 70601

Michael Carome, M.D., Chief
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