Inspections, Compliance, Enforcement, and Criminal Investigations

[redacted]RB 2/1/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

FEB 1, 2013

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

[redacted]

Dear Mr. [redacted]

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB) that was conducted between July 2, 2012, and July 23, 2012, by Ms. Barbara D. Wright, representing FDA. The purpose of this inspection was to determine whether the IRB procedures for the protection of human subjects complied with Title 21 of the Code of Federal Regulations (CFR), parts 50 and 56. These regulations apply to clinical investigations of products regulated by FDA.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to help ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Wright presented and discussed Form FDA 483, Inspectional Observations, with Ms. Angela M. Magee, IRB Chairperson. We acknowledge receipt of the IRB's August 10, 2012, written response to the Form FDA 483. From our review of the FDA's establishment inspection report, the documents submitted with that report, and the IRB's written response, we conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. We wish to emphasize the following:

1. The IRB failed to prepare, maintain, and follow required written procedures governing the functions and operations of the IRB [21 CFR 56.108(a), 21 CFR 56.108(b), and 21 CFR 56.115(a)(6)].

In order to fulfill the requirements of the IRB regulations, each IRB must prepare, maintain, and follow written procedures describing IRB functions and operations specified in the regulations. The IRB failed to adhere to this requirement. Specifically:

a. The IRB's "Policy and Procedures Guidebook" does not include all the required written procedures. The IRB does not have procedures 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 previous IRB review; and
- Ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB.

b. The IRB does not follow all required written procedures listed in the "Policy and Procedures Guidebook." For example:

- Under the heading, "Pre-Meeting Activities" the IRB's "Policy and Procedures Guidebook" indicates that "[o]ne week prior to the scheduled meeting, the Chairperson will develop and distribute the IRB materials. These materials will include, but are not limited to, a written agenda, copies of the initial and continuing review application and **all attachments** of any projects being presented for review and approval, a copy of the last meeting's minutes and any other material pertinent to the upcoming meeting" (emphasis added).

  Our inspection revealed that the packets distributed prior to the April, May, and June 2012 IRB meetings did not include all attachments of any projects being presented for review and approval. For example, the research application submitted by the clinical investigator for **(b)(4)**, "**(b)(4)**," indicates that the submission included the following items: "IRB application, informed consent document, protocol, and recruitment materials." Packets provided to IRB members did not include the protocol. Nevertheless, this study was approved by the IRB on April 10, 2012.

- Under the heading "Expedited Review," the IRB's "Policy and Procedures Guidebook" indicates that after the Chairperson or his or her designee grants expedited review approval, "[t]he Chairperson will notify the investigator in writing that the project has received approval and then circulate the protocol to the entire IRB Committee at the next monthly meeting."

  Our inspection revealed that this procedure has not been followed, in that all committee members have not been advised of research proposals that have been approved using the expedited review procedure. During the inspection, our investigator was provided with a binder containing documents that discussed research activities that had been approved by the expedited review procedure. When the FDA investigator asked how all members are informed of research activities that are approved by expedited review, she was informed that the IRB had stopped complying with this written procedure.

We acknowledge the IRB's written response, which includes the following corrective actions: (1) Revising the IRB's process to ensure that IRB members have access to all supporting documents prior to the start of each meeting; (2) revising the Singing River Health System (SRHS) IRB Policy Manual to include the missing procedures listed above; and (3) revising the SRHS IRB Policy Manual to require that all expedited reviews be documented in the agenda and reviewed by the IRB during the next convened meeting, and that the IRB's review of the expedited approvals be documented in the minutes. In addition, the written response indicates that "[a]ll cancer related studies are approved through the **(b)(4)**'s (**(b)(4)**) central IRB prior to activation at the SRHS IRB, including review of risk and/or benefit to study populations."

The IRB's response is inadequate because it does not include a copy of the revised written procedures. Moreover, it was the IRB's responsibility to prepare, maintain, and follow required written procedures governing the functions and operations of the IRB. We also wish to emphasize that, although an IRB may rely on the review of another qualified IRB under certain circumstances (see 21 CFR 56.114), review by **(b)(4)**'s IRB does not exempt the SRHS IRB from following its written procedures with respect to review of research.

Please submit a copy of your written procedures, or any draft procedures in development, and a timeline for the implementation of any new procedures. In addition, please provide a description of any training provided to IRB staff on the new procedures and a list of attendees, or a projected timeline of planned training.

2. The IRB failed to fulfill membership requirements [21 CFR 56.107].

The IRB did not possess the professional competence necessary to adequately review the specific research activities. For example:

The IRB's member list and meeting minutes indicate that the SRHS IRB met, reviewed, and voted on oncology research without a physician member present on the following dates:

February 9, 2010	January 11, 2011	January 10, 2012
March 9, 2010	February 8, 2011	February 14, 2012
May 11, 2010	March 4, 2011	March 13, 2012
June 8, 2010	May 5, 2011	April 10, 2012
August 10, 2010	June 14, 2011	May 7, 2012
September 14, 2010	July 12, 2011	
October 12, 2010	August 9, 2011	
November 9, 2010	September 13, 2011	
December 14, 2010	October 11, 2011	
	November 2, 2011	
	December 13, 2011	

We wish to emphasize that without having a physician member present at these meetings, the IRB lacked the experience and expertise to review the oncology research activities.

During the inspection, the IRB Chairperson indicated that a new physician member, Dr. **(b)(6)**, had been recruited and would begin participating as a voting member at the August 2012 IRB meeting. We note that Dr. **(b)(6)** has been added to the IRB membership list. We find this corrective action to be adequate.

We note that the IRB's written response asserts that the IRB possessed expertise adequate to review all presented and approved studies because scientific review was conducted by individuals or organizations other than the IRB, such as the medical staff of the Regional Cancer Center (RCC) and **(b)(4)**'s IRB. We recognize that it is possible to rely on the review of another qualified IRB under certain circumstances (see 21 CFR 56.114). However, review by the medical staff of the RCC does not constitute review by another qualified IRB. Additionally, the IRB's "Policy and Procedures Guidebook" does not discuss cooperative review of research, or contain procedures that would allow the SRHS IRB to rely on the **(b)(4)** IRB for certain aspects of the review. Therefore, any reliance of the SRHS IRB on the scientific review conducted by the RCC medical staff or the **(b)(4)** IRB does not satisfy the requirements of 21 CFR 56.107.

3. The IRB failed to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas [21 CFR 56.108(c)].

Except when an expedited review procedure is used, the IRB may only review proposed research at convened meetings at which a majority of the IRB members (i.e., a quorum) is present, including at least one member whose primary concerns are in nonscientific areas.

Our inspection revealed that the IRB reviewed research at meetings at which a majority of the IRB members was not present. For example:

a. Minutes of the August 9, 2011, IRB meeting indicate that the IRB had twelve members. Therefore, in order to review research, at least seven members needed to be present (including a nonscientist). The minutes indicate that six members were present when FDA-regulated research was reviewed.

b. Minutes of the October 11, 2011, IRB meeting indicate that the IRB had thirteen members. Therefore, in order to review research, at least seven members needed to be present (including a

nonscientist). The minutes indicate that six members were present when FDA-regulated research was reviewed.

We acknowledge the IRB's written response, which indicates that meeting minutes will reflect the presence of a majority of IRB members. The response is inadequate because it does not include a description of any training provided to IRB staff, or a projected timeline of planned training, on compliance with the requirement that proposed research only be reviewed at convened meetings at which a majority of member are present. Moreover, it was the IRB's responsibility to review proposed research only at convened meetings at which a majority of the IRB members was present.

4. The IRB failed to prepare and maintain adequate documentation of IRB activities [21 CFR 56.115(a)].

An IRB is required to prepare and maintain adequate documentation of IRB activities including, but not limited to, copies of progress reports submitted by investigators, minutes of IRB meetings in sufficient detai to show the vote on IRB actions, and copies of all correspondence between the IRB and the investigators. The IRB failed to adhere to this requirement. Specifically,

a. During the inspection, the FDA inspector noted that documents such as revised protocols and safety reports were missing from the IRB's files.

We acknowledge the IRB's written response that subsequent to the FDA inspection, the electronic storage files for the oncology studies were re-organized to complement the hard copy regulatory binders that are maintained in the RCC office. A separate folder containing copies of all regulatory documents was created i the IRB's electronic file for each study, and this system will be maintained for all future IRB submissions. We find this corrective action to be adequate.

b. On three occasions (December 14, 2009; June 7, 2011; and April 2, 2012), the IRB met by teleconference and approved FDA-regulated research; however, no minutes were kept of these teleconference meetings.

We acknowledge the IRB's written response indicating that the IRB Policy Manual has been revised to address how to correctly document the scheduled teleconferences for full reviews to ensure the presence of a quorum. The IRB's response is inadequate because it does not address the IRB's failure to prepare and maintain minutes of these teleconference meetings, and it does not include a copy of the revised written procedures. Moreover, it was the IRB's responsibility to prepare and maintain minutes of IRB meetings in sufficient detail to show the vote on IRB actions. Please submit a copy of your written procedures, or any draft procedures in development, and a timeline for the implementation of any new procedures. In addition, please provide a description of any training provided to IRB staff on the new procedures and a list of attendees, or a projected timeline of planned training.

This letter is not intended to be an all-inclusive list of deficiencies for the protocols reviewed and approved by the IRB. It is your responsibility to ensure that Singing River Health System IRB's practices and procedures comply fully with all applicable statutes and regulations.

Within fifteen (15) business days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Your written response should include any documentation necessary to show that full and adequate correction will be achieved. Please include the projected completion dates for each action to be accomplished. Failure to explain the violations noted above adequately and promptly may result in regulatory action without further notice.

We recommend that you visit the following FDA Web page for information on human subject protections that may assist you in your efforts to bring the IRB into compliance with FDA regulations:

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm[1].

We appreciate the cooperation shown to FDA Investigator Wright during the inspection. If you have any questions, please contact Catherine Parker at 301-796-5553; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to: