Inspections, Compliance, Enforcement, and Criminal Investigations

Salem Hospital IRB 11/29/12

Department of Health and Human Services

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

WARNING LETTER

VIA UPS Ref: 12-HFD-45-11-01

Joseph Schnabel, Pharm.D.
Director of Pharmaceutical Care Services
and IRB Chairman
Salem Hospital Campus
890 Oak Street SE, Building B-2-W
Salem, OR 97301

Dear Dr. Schnabel:

This letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your Institutional Review Board (IRB) between June 6, 2012, and June 25, 2012, by Dr. Anita Narula and Dr. Marijo Kambere, 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 rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Drs. Narula and Kambere presented and discussed with Ms. Helen A. Hampton, the Form FDA 483, Inspectional Observations. We acknowledge receipt of the IRB's written response dated July 11, 2012, 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 and maintain adequate documentation of IRB activities [21 CFR 56.115(a)(1) and (4)].

An IRB is required to prepare and maintain adequate documentation of IRB activities including, but not limited to, copies of all research proposals, copies of progress reports submitted by investigators and copies of all correspondence between the IRB and the investigators. The IRB failed to adhere to

this requirement.

Specifically, the IRB does not retain copies of the following:

a. Original protocols

b. Revised protocols

c. Informed consent documents

d. Protocol amendments

e. Progress report submissions, including all attachments

f. Correspondence between the investigators and the IRB

The maintenance of IRB documents is important in identifying what materials the IRB has reviewed during its deliberations, and is necessary to ensure that the IRB has met its responsibilities for review of research and protection of human subjects under 21 CFR 56.111.

2. The IRB failed to prepare and maintain adequate documentation of written procedures for the IRB, as required by 21 CFR 56.108(a) and (b) [21 CFR 56.115(a)(6)].

An IRB is required to prepare and maintain adequate documentation of written procedures for a variety of IRB functions and operations, in accordance with 21 CFR 56.108. The IRB failed to adhere to these requirements. Specifically, Salem Hospital IRB policies and procedures do not include written procedures to adequately address the following functions and operations:

a. Conducting initial and continuing review or research;

b. Ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects; and

c. Ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB, or any suspension or termination of IRB approval.

3. The IRB failed to prepare and maintain a list of IRB members identified by name; earned degrees; representative capacity; indications of experience sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution [21 CFR 56.115(a)(5)].

An IRB is required to maintain a list of IRB members in accordance with 21 CFR 56.115(a)(5). The IRB failed to adhere to this requirement. The IRB did not update its roster when membership changed between December 3, 2008, and March 21, 2011. Specifically:

a. The IRB meeting minutes dated January 21, 2009, indicate that **(b)(6)** is present as an IRB member. The IRB meeting minutes dated July 22, 2009, announce **(b)(6)**'s resignation from the IRB. However, the IRB roster dated December 3, 2008, through March 21, 2011, does not list **(b)(6)** as a member of the IRB.

b. The IRB meeting minutes dated October 21, 2009, indicate that **(b)(6)** was approved to become an IRB member. The IRB meeting minutes dated January 20, 2010, list **(b)(6)** as an IRB member and show her voting on IRB activities. However, the IRB roster dated December 3, 2008, through March 21, 2011, does not list **(b)(6)** as a member of the IRB.

The IRB membership rosters are not updated as changes in membership occur. Therefore, the FDA may not be able to determine that the IRB is duly constituted, as required by 21 CFR 56.107.

4. 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 are present, including at least one member whose primary concerns are in nonscientific areas. The IRB failed to adhere to these requirements. Specifically:

a. The IRB minutes dated March 18, 2009, indicate that six of eight IRB members were present. Two IRB members recused themselves during the initial review and vote for Study **(b)(4)**, titled "**(b)(4)**." Therefore, the study was approved with less than a majority of members being present.

b. The IRB minutes dated April 21, 2010, indicate that five of eight IRB members were present. One IRB member recused himself during the initial review and vote for Study **(b)(4)**, titled "**(b)(4)**." Therefore, the study was approved with less than a majority of members being present.

c. The IRB minutes dated October 20, 2010, indicate that five of eight IRB members were present. One IRB member recused himself during the review and vote for the protocol and informed consent document changes for Study **(b)(4)**, titled "**(b)(4)**." Therefore, the changes were approved with less than a majority of members being present.

The maintenance of IRB rosters is an important part of IRB activities in that it provides documentation of current membership. In addition, appropriate roster maintenance helps to ensure that a proper number of members is present at IRB meetings when approving research activities.

5. The IRB failed to follow FDA regulations regarding expedited review procedures [21 CFR 56.110(b)].

FDA regulations require that under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB; and that the IRB may use the expedited review procedure to review either or both of the following: (1) Some or all of the research appearing on the Federal Register list of categories of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk; or (2) minor changes in previously approved research during the period for which approval is authorized.

Furthermore, as stated in the Federal Register notice, an expedited review procedure may be used for continuing review as follows:

a. Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

b. Where no subjects have been enrolled and no additional risks have been identified; or

c. Where the remaining research activities are limited to data analysis.

The Salem Hospital IRB failed to comply with 21 CFR 56.110(b) when it used expedited continuing review for research that was not eligible for approval through an expedited review procedure. Specifically, the IRB meeting minutes dated January 21, 2009, indicate that the continuing review for Study **(b)(4)** was conducted by expedited review. However, a memorandum from the Clinical Investigator, dated December 23, 2008, requesting annual review for the **(b)(4)** study indicates that this study was open to enrollment and that 4 subjects were currently enrolled. Therefore, the continuing review of Study **(b)(4)** was not eligible for expedited review.

The IRB's written response to the Form FDA 483, dated July 11, 2012, acknowledges the validity of each of the violations listed above. The response states that the IRB will develop new written procedures to address each violation. However, the draft procedures were not submitted with this response and will not be available until February 28, 2013. In addition, the IRB's response is inadequate because it does not describe any process that the IRB will use to train and educate IRB members, staff, and clinical investigators with respect to its new written procedures. Without this information, FDA cannot conduct an informed evaluation of the proposed corrective and preventive action's potential ability to prevent the recurrence of these or similar violations in the future.

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 Salem Hospital 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. 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 webpage 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*

We appreciate the cooperation shown to FDA Investigators Narula and Kambere during the June 2012 inspection. If you have any questions, please contact Catherine Parker, R.N., at 301-796-5553 FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Catherine Parker, R.N.
Team Lead, Human Subject Protection Branch
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5247
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,
/S/
Thomas N. Moreno, M.S.
Acting Office Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Cc: Ellen A. Hampton
Director of Corporate Integrity,
Safety, and Risk Management
Salem Hospital
Salem, OR 97301

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/s/

THOMAS N MORENO
11/29/2012

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