Monmouth Medical Center IRB 11/10/15

Department of Health and Human Services

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

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 16-HFD-45-11-01

Joseph Jaeger, Dr.P.H.
Chief Academic Officer
Monmouth Medical Center
300 Second Avenue
Long Branch, New Jersey 07740

Dear Dr. Jaeger:

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 April 1 and April 20, 2015,by Ms. Denise M. Visco, 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 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. Visco presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your May 1, 2015, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and the IRB's May 1, 2015, written response, we conclude that the IRB did not adhere to FDA regulations governing the protection of human subjects. We wish to emphasize the following:

1. The IRB failed to determine at the time of initial review that studies involving children are in compliance with 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations [21 CFR 56.109(h)].

Under 21 CFR 56.109(h), when some or all of the subjects in a clinical investigation are children, the IRB must determine that the clinical investigation is in compliance with 21 CFR part 50, subpart D (Additional Safeguards for Children in Clinical Investigations) at the time of the initial review of the research. Under 21 CFR 50.50, the IRB must review the clinical investigation and approve only those clinical investigations that satisfy the criteria described in 21 CFR 50.51 (clinical investigations not involving greater than minimal risk), 21 CFR 50.52 (clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects), or 21 CFR 50.53 (clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition).

Under 21 CFR part 50, subpart D (Additional Safeguards for Children in Clinical Investigations), the IRB must make certain findings with respect to clinical investigations involving children. In addition, under 21 CFR 56.115, the IRB is required to document its activities, including actions taken during IRB meetings.

However, there is no documentation, either in the meeting minutes or in any other materials reviewed during the inspection, of the IRB's requisite determination at the time of the initial review that the following clinical investigations involving pediatric subjects were in compliance with subpart D:

a) IRB Study **(b)(4)**, "**(b)(4)**

b) IRB Study **(b)(4)**, "**(b)(4)**

In the May 1, 2015, written response, you indicate that the IRB will implement the following corrective or preventive actions:

a) The IRB will place Protocol **(b)(4)**, which was closed to enrollment in February 2014, on an IRB agenda within the next fiscal quarter.

b) An IRB meeting supplement form will be drafted to identify the type of vulnerable subjects, if any, and the risk category.

c) The IRB will review and revise, as needed, its policy to include a reference to a standard operating procedure (SOP) for reviewing research involving children and other vulnerable subjects.

d) The IRB will review and revise, as needed, an IRB checklist used for evaluating pediatric studies.

We acknowledge that your written response contains documentation of the IRB's review of Protocol **(b)(4)** and subpart D determination on April 13, 2015. However, we are unable to undertake an informed evaluation of your written response because you did not provide documentation for the following items:

a) The IRB's subpart D determination for Protocol **(b)(4)**
b) A finalized copy of the IRB meeting supplemental form
c) A finalized copy of the IRB checklist used for evaluating pediatric studies
d) Any relevant SOPs that have been revised
e) A description of any training provided to the IRB staff and members on the new SOPs, and a list of staff and members trained, or a projected timeline of planned training

Please submit any corrective or preventive actions the IRB plans to take to ensure that the pediatric risk determinations are appropriately completed for all ongoing and future FDA-regulated pediatric studies in order to avoid the recurrence of the violations. Please include items a) through e) listed above.

Failure to determine that the additional safeguards for children in research are met may expose this vulnerable population to unnecessary risks, and may result in the child's parent(s) or guardian(s) not being fully informed about the proposed research.

2. 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 review proposed

research only at convened meetings at which a majority of the IRB members is present (that is, a quorum), including at least one member whose primary concerns are in nonscientific areas. The IRB failed to adhere to this requirement. Specifically:

The IRB reviewed FDA-regulated research at meetings where a majority of the IRB members was not present, and at meetings where the quorum was lost when an IRB member in attendance had a conflict of interest, as described below. Please note that an IRB member with a conflict of interest may not vote or be counted toward the quorum when the IRB is reviewing research in which the member has a conflict. If a quorum is lost during a convened meeting (for example, because those with conflicts are excused, because of early departures, or because of the absence of a nonscientist member), the IRB may not take further actions or votes unless the quorum can be restored [21 CFR 56.108(c)].

a) The IRB reviewed FDA-regulated research on June 11, 2012, and January 13, 2014, without a majority of members present. The IRB membership rosters in effect on these dates consisted of ten primary members on each roster, meaning that at least six voting members needed to be present (including a nonscientist) in order to review FDA-regulated research at these meetings. IRB meeting minutes indicate that just five voting members of the IRB attended each of these meetings.

b) The IRB reviewed and approved IRB Study **(b)(4)**, "**(b)(4)**," at the January 17, 2012, IRB meeting without a majority of members present. The meeting minutes indicate that the IRB had the required membership present for quorum (six of the ten IRB members including a nonscientist) except for when Study **(b)(4)** was reviewed and approved.

(b)(6), M.D., who was one of the six IRB members present, was the principal investigator for Study **(b)(4)**. As the principal investigator, Dr. **(b)(6)** had a conflict of interest and should not have counted toward the quorum for review and approval of this study. However, the meeting minutes indicate that Dr. **(b)(6)** was counted toward the quorum.

The IRB should not have reviewed or approved Study **(b)(4)** because the IRB did not have a quorum available for review of this study.

c) The IRB reviewed and approved the following studies at the February 13, 2012, IRB meeting without a majority of members present:

i. IRB Study **(b)(4)**, "**(b)(4)**"

ii. IRB Study **(b)(4)**, "**(b)(4)**"

The meeting minutes indicate that the IRB had the required membership present for quorum (six of the ten members, including a nonscientist), except for when the two studies above were reviewed and approved. **(b)(6)**, M.D., who was one of the six IRB members present, was the principal investigator for these studies. As the principal investigator, Dr. **(b)(6)** had a conflict of interest and should not have been counted toward the quorum for review and approval of these studies.

The meeting minutes indicate, however, that Dr. **(b)(6)** was counted toward the quorum. The IRB should not have reviewed or approved IRB Studies **(b)(4)** and **(b)(4)** because the IRB did not have a quorum present for review of these studies.

In your May 1, 2015, written response, you indicate that the IRB will implement the following corrective or preventive actions:

a) An IRB meeting supplement form will be developed for recording votes and identifying quorum deficiencies, if any, before and during an IRB meeting.

b) The IRB will review and revise, as needed, their policies and procedures to include a reference to an SOP regarding IRB meeting administration.

We acknowledge your written response; however, we are unable to undertake an informed evaluation of the written response because you did not provide documentation of the following items:

a) A finalized copy of the IRB meeting supplemental form
b) Any relevant written SOPs that have been revised
c) A description of any training provided to IRB staff and members on the new SOPs, and a list of staff and members trained, or a projected timeline of planned training

Please submit any corrective or preventive actions the IRB plans to take to ensure that a majority of the members of the IRB is present, including at least one member whose primary concerns are in nonscientific areas, when the IRB reviews proposed research. Please include items a) through c) listed above.

Under 21 CFR 56.107(a), the IRB is required to have members with varying backgrounds to promote complete and adequate review of research activities. Failure of the IRB to establish or maintain a quorum may result in an inadequate review of research activities, which can impact the protection of the rights and welfare of human research subjects.

3. The IRB failed to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings [21 CFR 56.115(a)(2)].

The IRB is required to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions, including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. The IRB failed to adhere to this requirement. Specifically:

The minutes of the IRB's February 11, 2013, meeting indicate that Dr. **(b)(6)**, who was either a principal investigator or a subinvestigator for three FDA-regulated studies (**(b)(4)**), attended the meeting and voted to approve these studies during the meeting. However, in letters dated April 6 and April 30, 2015, which were included in the IRB's response to the Form FDA 483, Dr. **(b)(6)** stated he had abstained from voting on these studies.

Please note that no IRB may have a member participate in the IRB's initial or continuing review of research in which the member has a conflict of interest, except to provide information requested by the IRB [21 CFR 56.107(e)]. Therefore, an IRB member with a conflict of interest may not participate in deliberation or voting on IRB actions taken for research in which the member has a conflict of interest.

Please submit any corrective or preventive actions the IRB plans to take to address the violation described above. With these corrective or preventive actions, please submit a copy of the IRB's written SOPs, or any draft SOPs in development, and a projected timeline for the implementation of any new SOPs. In addition, please provide a description of any training provided to IRB staff and members on the new SOPs, and a list of staff and members trained, or a projected timeline of planned training.

Failure to prepare and maintain adequate documentation of IRB activities, including IRB meeting minutes, raises concerns about the adequacy of the IRB's review process.

In addition, we note that in several of the IRB meetings described above, a member of the IRB abstained from voting on a review of research in which that member had a conflict of interest. We note that members are required to recuse themselves from voting altogether, and may not participate in deliberation, as opposed to simply abstaining from votes in which they have a conflict of interest [21 CFR 56.107(e)].

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 the

Monmouth Medical Center IRB's practices and procedures comply fully with all applicable statutes and regulations.

Within fifteen (15) working 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 address 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 bringing the IRB into compliance with FDA regulations: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm.

We appreciate the cooperation shown to the FDA Investigator during the inspection. If you have any questions, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397: FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity, M.D., M.P.H.
Branch Chief
Good Clinical Practice Compliance Oversight Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

{See appended electronic signature page}

David C. Burrow, Pharm.D., J.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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page is the manifestation of the electronic signature.

/s/

DAVID C BURROW
11/10/2015

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10903 New Hampshire Avenue
Silver Spring, MD 20993
1-888-INFO-FDA (1-888-463-6332)

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