

**U.S. Food and Drug Administration**  
Protecting and Promoting *Your* Health

# **Pikeville Medical Center Inc., Institutional Review Board 3/1/16**



Department of Health and Human Services

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

## **WARNING LETTER** MAR 1, 2016

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

Ref: 16-HFD-45-02-03

Walter E. May  
President and Chief Executive Officer  
Pikeville Medical Center, Inc., IRB  
911 Bypass Road  
Pikeville, Kentucky 41501

Dear Mr. May:

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 August 17 and August 21, 2015, by Mr. Richard W. Berning, 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, Mr. Berning presented and discussed with Holly

H. Gallion, M.D, IRB Chairperson, Form FDA 483, Inspectional Observations. We acknowledge receipt of your September 14, 2015, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your September 14, 2015, written response, we conclude that the IRB did not adhere to the applicable 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:

The Pikeville Medical Center, Inc., IRB (PMC IRB) failed to prepare, maintain, and follow the written procedures listed below that are required by FDA regulations.

- a. Written procedures for conducting the IRB's initial and continuing review of research and for reporting the IRB's findings and actions to the investigator and the institution [21 CFR 56.108(a)(1) and 21 CFR 56.115(a)(6)]
- b. Written 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 the previous IRB review [21 CFR 56.108(a)(2) and 21 CFR 56.115(a)(6)]
- c. Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any unanticipated problems involving risks to human subjects or others [21 CFR 56.108(b)(1) and 21 CFR 56.115(a)(6)]
- d. Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any instance of serious or continuing noncompliance with these regulations or with the requirements or determinations of the IRB [21 CFR 56.108(b)(2) and 21 CFR 56.115(a)(6)]
- e. Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any suspension or termination of IRB approval [21 CFR 56.108(b)(3) and 21 CFR 56.115(a)(6)]

We acknowledge that your September 14, 2015, written response to the Form FDA 483 states that PMC has decided to transition governance of the PMC IRB to a committee of PMC's Board of Directors. Your response also states that this committee will be responsible for reporting all recommendations made in reference to research, with final authority resting in the Board of Directors to make all decisions. We also acknowledge that your written response contains draft policies, and that your written response states that this new committee will prepare new

policies that should be approved and in place by November 2015. However, we note that the finalized policies and plan for training PMC's new IRB members on the new policies were not submitted with your response.

We are unable to perform an informed evaluation of your written response for the following reasons:

- a. We are unable to determine if the new committee will function as PMC's IRB for any period of time, or if it will serve only to govern the current PMC IRB. We note that your response indicates that the new committee will be responsible for reporting all recommendations made in reference to research, with final authority resting in the Board of Directors to make all decisions. With respect to the reporting of research recommendations, any difference in roles between the PMC IRB and the new committee is unclear. If the new committee will function as an IRB for any period of time, the committee must prepare and maintain adequate documentation of a list of IRB members identified by name; earned degrees; representative capacity; indications of experience, such as board certifications, licenses, etc., 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)].
- b. The response does not indicate how long the committee will govern the PMC IRB and be responsible for reporting all research recommendations made in reference to research.
- c. The response does not describe the process that will be used to train and educate IRB members, staff, and clinical investigators with respect to any new written procedures.

**Please submit the following:**

- a. If the new committee will be serving as an IRB for any period of time: A current list of committee members identified by names, earned degrees, representative capacities, 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
- b. A description of any difference in roles between the PMC IRB and the new committee with respect to reporting research recommendations
- c. An indication of how long the new committee will govern the PMC IRB and report all research recommendations
- d. A finalized copy of the required written procedures identified in Items 1.a through 1.e on page 2 of this letter
- e. A description of any training provided to IRB members and staff on the required written procedures

- f. A list of IRB members and staff who have been trained on the required written procedures, or a projected timeline of planned training

Failure of the IRB to prepare, maintain, and follow required written procedures raises concerns about the adequacy of the IRB's review processes for ensuring the protection of the rights and welfare of human research subjects.

**2. 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 must 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:

For nine IRB meetings (August 11, September 8, September 27, and December 1, 2011; January 24, March 27, August 28, and December 6, 2012; and January 14, 2015), the meeting minutes did not adequately document the vote on actions taken by the IRB, including the number of members voting for, against, and abstaining.

We acknowledge your written response that the minutes of meetings after June 2015 will be prepared in sufficient detail to show the vote of actions, including the number of members voting for, against, and abstaining. If properly carried out, your response appears adequate to prevent the recurrence of this violation in the future.

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.

**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 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. 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)]. Further, please note that when IRB members have a conflict of interest, those 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)].

a. The IRB reviewed FDA-regulated research on January 24, 2012, without a majority of members present. Minutes of the January 24, 2012, IRB meeting indicate that the IRB had ten members. Therefore, at least six voting members (including a nonscientist) needed to be present for the IRB to review FDA-regulated research. IRB meeting minutes indicate that only four voting members of the IRB attended the meeting.

b. The IRB reviewed FDA-regulated research on September 8, 2011, without a majority of members present. Minutes of the September 8, 2011, IRB meeting indicate that the IRB had nine members. Therefore, at least five voting members (including a nonscientist) needed to be present for the IRB to review FDA-regulated research. IRB meeting minutes indicate that only four voting members of the IRB attended the meeting.

We acknowledge that your written response states that the new committee of PMC's Board of Directors will review and adopt policies governing activities at convened meetings, as well as strictly outlining the majority requirements for action. We also acknowledge that your response indicates that these policies will outline attendance requirements, including the presence of at least one member from a nonscientific area. However, we are unable to perform an informed evaluation of the response for the following reasons:

a. As noted in Item 1 above, we are unable to determine if the new committee will function as PMC's IRB for any period of time, or if it will serve only to govern the current PMC IRB. We note that your response indicates that the new committee will review and adopt policies related to activities at convened meetings, majority requirements for action, and attendance requirements. We are unable to determine if the policies mentioned above are intended for the current PMC IRB or for the new committee (if it is to function as an IRB).

b. The response does not contain a copy of any finalized written procedures related to activities at convened meetings, majority requirements for action, or attendance requirements.

c. The response does not contain a description of any training provided to the IRB members and staff on such written procedures; a list of IRB members and staff who have been trained; or a projected timeline of planned training.

**Please submit the following:**

a. A finalized copy of the written procedures to be followed by the entity that will serve as PMC's IRB (that is, either the current PMC IRB or the new committee of PMC's Board of Directors) to ensure that a majority of the IRB members, including at least one member whose primary concerns are in nonscientific areas, is present when the IRB reviews proposed research

b. A description of any training provided to the IRB members and staff on the new

written procedures

- c. A list of IRB members and staff who have been trained on the new written procedures, or a projected timeline of planned training

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

**4. The IRB failed to conduct continuing review of research at intervals of not less than once per year [21 CFR 56.109(f)].**

In order to fulfill the requirements of the IRB regulations, the IRB is required to conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. The IRB failed to adhere to this requirement. Specifically:

- a. The PMC IRB reviewed and approved the following studies at the August 11, 2011, IRB meeting:

- i. **(b)(4), “(b)(4)”**
- ii. **(b)(4), “(b)(4)”**

Continuing review for Studies **(b)(4)** and **(b)(4)** was due by August 11, 2012. However, continuing review for both studies was not conducted until February 28, 2013.

- b. The PMC IRB reviewed and approved Protocol **(b)(4)**, “**(b)(4)**,” at the January 24, 2012, IRB meeting. Continuing review for this study was due by January 24, 2013. However, continuing review was not conducted until February 28, 2013.

We acknowledge that your September 14, 2015, written response states that PMC research staff has reviewed all research projects under the review of the PMC IRB and has determined that all projects are operating under current approval. We also acknowledge that your response indicates that the new committee of PMC’s Board of Directors will prepare and adopt new policies consistent with FDA regulations and will ensure the compliance of all research activities related to those policies, including appropriate continuing review of research. However, we are unable to perform an informed evaluation of the response for the following reasons:

- a. As noted in Item 1 above, we are unable to determine if the new committee will function as PMC’s IRB for any period of time, or if it will serve only to govern the current PMC IRB. We note that your response indicates that the new committee will prepare and adopt new policies consistent with FDA regulations, including policies for appropriate continuing review of research. We are unable to determine if the policies mentioned above are intended for the current PMC IRB or for the new

committee (if it is to function as an IRB).

b. The response does not contain a copy of any finalized written procedures related to continuing review, a description of any training provided to the IRB members and staff on such written procedures, and a list of IRB members and staff who have been trained or a projected timeline of planned training.

**Please submit the following:**

- a. A finalized copy of the written procedures to be followed by the entity that will serve as PMC's IRB (that is, either the current PMC IRB or the new committee of PMC's Board of Directors)
- b. A description of any training provided to the IRB members and staff on the new written procedures
- c. A list of IRB members and staff who have been trained on the new written procedures, or a projected timeline of planned training

Failure of the IRB to conduct continuing review at intervals of not less than once per year raises concerns about the adequacy of the IRB's oversight of ongoing research that the IRB had previously approved.

As noted above, we are unable to determine the roles of the current PMC IRB, the new committee, and the PMC Board of Directors. Please submit a written description explaining the respective roles of the three entities.

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

Within fifteen (15) working days of your receipt of this letter, the IRB should notify this office in writing of the actions that have been taken to prevent similar violations in the future. Failure to adequately and promptly address the violations noted above may result in regulatory action without further notice. If you believe you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

We recommend that the IRB visit the following FDA Web page for information on human subject protections that may assist the IRB in its efforts to come 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 the IRB has 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

-----  
This is a representation of an electronic record that was signed electronically and this  
page is the manifestation of the electronic signature.  
-----

/s/  
-----

DAVID C BURROW  
03/01/2016

**More in 2016**  
**[\(/ICECI/EnforcementActions/WarningLetters/2016/default.htm\)](http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/default.htm)**