

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

# Oeyama-Moto Cancer Research Foundation IRB 4/7/16



Department of Health and Human Services

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

## **WARNING LETTER** APR 7, 2016

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

Ref: 16-HFD-45-03-04

Masao Wada, M.D.  
Chair  
Oeyama-Moto Cancer Research Foundation IRB  
3106 East Garvey Avenue South  
West Covina, California 91791-2344

Dear Dr. Wada:

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 11 and September 29, 2015, by Mr. Uttaniti Limchumroon, Mr. Greg K. Keshishyan, and Quynh-Van Tran, Pharm.D., 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. Limchumroon and Mr. Keshishyan presented

and discussed with IRB member Ms. Judy Fu Chuan Li the Form FDA 483, Inspectional Observations. We acknowledge receipt of the IRB's October 8, 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 October 8, 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 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 that are specified in the regulations. The IRB failed to adhere to this requirement. Specifically, the Oeyama-Moto Cancer Research Foundation IRB failed to prepare, maintain, and follow the written procedures 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 of changes in research activity [21 CFR 56.108(a)(3)].
- d. 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)].
- e. 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)].
- f. 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)].

The IRB's written response does not address this violation adequately because the response refers to written procedures for conducting the clinical investigation, rather than written procedures governing the functions and operations of the IRB, as required by 21 CFR 56.108(a), 21 CFR 56.108(b), and 21 CFR 56.115(a)(6).

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 finalized written procedures, or any draft procedures in development, and a projected timeline for the implementation of any new written procedures. In addition, please provide a description of any training provided to IRB staff and members on the new written procedures, and a list of staff and members trained, 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 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 the 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:

a. Minutes of the January 18, 2014, IRB meeting indicate that the IRB "reviewed, agreed on the protocol for IND (b)(4), in (b)(4) clinical trial." However, the minutes do not include documentation of a vote on this action, including the number of members voting for, against, and abstaining.

Regarding Item 2.a. above, we acknowledge that the IRB's written response to the Form FDA 483 indicates that all members of the IRB who voted, voted in favor of the action taken. However, the response is inadequate because it does not describe any actions taken to prevent similar violations in the future.

b. Minutes of the February 8, 2014, IRB meeting indicate that the IRB approved "of double arm study by coin toss, and agreed to transfer low dose group patients to high dose group for continuing treatment due to humanitarian reason." Minutes of the April 18, 2014, IRB meeting indicate that similar actions were taken during that meeting. The minutes do not include documentation of a vote on these actions, including the number of members voting for, against, and abstaining.

c. Minutes of the May 28, 2014, and August 28, 2014, IRB meetings indicate that the IRB approved "for newspaper soliciting of patients to participate" in the (b)(4) clinical trial. The minutes do not include documentation of a vote on this action, including the number of members voting for, against, and abstaining.

We acknowledge that Items 2.b. and 2.c. above were not included as observations on the Form FDA 483 that was issued to the IRB, and therefore, the IRB's written response to the Form FDA 483 did not address these violations.

Please submit a written description of the actions the IRB plans to take to ensure compliance with FDA regulations and the IRB's written procedures as they relate to meeting minutes. The response should include a description of any training provided to the IRB staff and members and a list of IRB staff and members trained, or a projected timeline of planned training, to address the violations described in Items 2.a. through 2.c. above.

Because of the IRB's failure to document vote counts in the minutes of IRB meetings held on January 18, February 8, April 18, May 28, and August 28, 2014, we are unable to determine if two IRB members, Dr. (b)(4) and Dr. (b)(4), who are subinvestigators for the (b)(4) clinical study, participated in the IRB's review of the study in any way, other than to provide information requested by the IRB.

Failure to prepare and maintain adequate documentation of IRB meetings raises concerns about the adequacy of the IRB's review process. Furthermore, inadequate documentation raises concerns about whether the IRB members maintained a quorum for the duration of the IRB meetings.

**3. The IRB failed to notify investigators and the institution in writing of its decision to approve or disapprove proposed research activities or of modifications required to secure IRB approval of the research activity [21 CFR 56.109(e)].**

The IRB is required to notify investigators and the institution in writing of its decision to approve or disapprove proposed research, or of modifications required to secure IRB approval. The IRB failed to adhere to this requirement. Specifically:

- a. The IRB did not notify the investigator in writing when it approved the "double arm study by coin toss" and "agreed to transfer low dose group patients to high dose group for continuing treatment due to humanitarian reason" on February 8, 2014. Similarly, the IRB did not notify the investigator in writing when it took the same action on April 18, 2014.
- b. The IRB did not notify the investigator in writing when it "discontinued for newspaper soliciting advertizement [*sic*] of patients to participate in this clinical trial" on December 8, 2014. Similarly, the IRB did not notify the investigator in writing when it took the same action on January 28, 2015.

The IRB's written response to the Form FDA 483 notes the IRB's understanding that a small "memorandum note" would serve as written notification; then it states, "Please see P.S. segment of the meeting minutes of each meeting." However, the meeting minutes provided during the inspection do not contain a "P.S. segment."

We acknowledge the IRB's written response; however, we are unable to undertake an informed evaluation of the response, because it does not contain copies of the memoranda that reportedly served as written notification of the IRB's decisions regarding the research activities noted in Items 3.a. and 3.b. above. Please submit copies of the memoranda referred to in the IRB's response regarding written

notification to investigators for the IRB's decisions reflected in Items 3.a. and 3.b. above.

If the IRB is unable to provide copies of the memoranda requested above, 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 procedures, or any draft procedures in development, and a projected timeline for the implementation of any new written procedures. In addition, please provide a description of any training provided to IRB staff and members on the new written procedures, and a list of staff and members trained, or a projected timeline of planned training.

Failure to notify investigators in writing of IRB decisions to approve or disapprove proposed research activities, or of modifications required to secure IRB approval, raises concerns about the adequacy of the IRB's communications with investigators.

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 the IRB's receipt of this letter, the IRB should notify this office in writing of the actions that will be 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. 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> (<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>).

We appreciate the cooperation shown to the FDA investigators 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. The IRB's 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  
Food and Drug Administration  
Building 51, Room 5354  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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DAVID C BURROW  
04/07/2016

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