Bay Regional Medical Center IRB 12/20/11

Department of Health and Human Services

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

WARNING LETTER

December 2, 2011

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 12-HFD-45-12-01

Philip Incarnati
President & Chief Executive Officer
McLaren Health Care
G-3245 Beecher Road, Suite 200
Flint, MI 48532

Dear Mr. Incarnati:

Between June 22, 2011, and June 24, 2011, Ms. Nancy Bellamy, representing the U.S. Food and Drug Administration (FDA), inspected the Institutional Review Board (IRB) at Bay Regional Medical Center (BRMC) (IRB Registration Number 00003638). 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. We are aware that at the conclusion of the inspection, our investigator presented and discussed Form FDA 483, Inspectional Observations, with Ms. Alice Gerard, President and Chief Executive Officer, and her staff. From our review of the establishment inspection report, the documents submitted with that report, and BRMC's June 30, 2011, written response to the inspection findings, 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 follow FDA regulations regarding expedited review procedures [21 CFR 56.110(b)].

The 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. An IRB may use the expedited review process to review either or both of the following: (1) Some or all of the research appearing on the Federal Register list, "Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure,"[1] 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.

According to the Federal Register notice, the expedited review procedure may be used for continuing review as follows:

- 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
- Where no subjects have been enrolled and no additional risks have been identified; or
- Where the remaining research activities are limited to data analysis.

The BRMC IRB used expedited continuing review for research that was not eligible for approval through expedited review. Examples of this failure include, but are not limited to, the following:

a. On May 18, 2011, the IRB Chairman used the expedited review procedure for the continuing review and approval of study **(b)(4) "(b)(4)**." However, on March 21, 2011, the IRB was notified that one subject had been enrolled at BRMC, and the study was still open for subject accrual. Therefore, the **(b)(4)** study was not eligible for expedited continuing review.

b. On June 23, 2010, the IRB Chairman used the expedited review procedure for the continuing review and approval of study **(b)(4)** "**(b)(4)**." However, on June 14, 2010, the IRB was notified that one subject had been enrolled at BRMC, and the study was still open for subject accrual. Therefore, the **(b)(4)** study was not eligible for expedited continuing review.

c. On June 23, 2010, the IRB Chairman used the expedited review procedure for the continuing review and approval of study **(b)(4)**, "**(b)(4)**." Our inspection revealed that at the time of the expedited review for study **(b)(4)**, subjects had been enrolled at BRMC and the study was still open for subject accrual. Therefore, the **(b)(4)** study was not eligible for expedited continuing review.

The IRB inappropriately conducted expedited continuing review and approval of research that did not meet the requirements of 21 CFR 56.110(b). The **(b)(4)** studies were not eligible for expedited continuing review because the studies were open to subject accrual, and subjects had been enrolled in each study. These studies should have been reviewed and approved at a convened meeting with a majority of the IRB members present.

The BRMC's written response to the Form FDA 483, dated June 30, 2011, notes that written standard operating procedures (SOPs) on expedited review have been modified to address this violation. The written response indicates that the IRB staff and IRB members will be provided with educational material and training on the eligibility criteria for expedited review at the next convened IRB meeting. The written response further notes that the training presentation will be included in the meeting minutes, and a copy of the training material will be kept with the meeting minutes. This response is inadequate because the revised SOP does not address how the inappropriate use of expedited review, as noted above, will be avoided in the future. For example, the revised SOP does not describe any type of administrative review or provide tools to ensure that the use of expedited review is appropriate. As a result, the BRMC's written response is inadequate to correct the violation and prevent the recurrence of these or similar violations in the future.

2. The IRB failed to conduct continuing review of research at intervals of not less than once per year, and failed to follow written procedures for conducting its initial and continuing review of research [21 CFR 56.109(f) and 56.108(a)].

An IRB shall conduct continuing review of previously approved research at intervals appropriate to the degree of risk, but not less than once per year. In addition, an IRB is required to follow written procedures for conducting initial and continuing review of research. The written procedures for BRMC's IRB state, under Policy 7.00 of the IRB's Policy and Procedures Manual, that "BRMC's IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less frequently than once per year."

The BRMC IRB failed to conduct continuing review of research at least once per year, and failed to follow their written procedures for conducting initial and continuing review of research. Examples of this failure include, but

are not limited to, the following:

a. On September 11, 2009, the BRMC IRB met and approved the study **(b)(4)**, "**(b)(4)**." Continuing review for this study was due by September 11, 2010. However, continuing review was not conducted until November 12, 2010. As a result, the IRB failed to conduct continuing review within the required interval, and in doing so, failed to follow their written procedures. Our inspection revealed that one subject had been enrolled and followed up at BRMC, and the study was still open for subject accrual.

b. On September 11, 2009, the BRMC IRB met and approved the study **(b)(4)**, "**(b)(4)**." Continuing review for this study was due by September 11, 2010. However, continuing review was not conducted until November 12, 2010. As a result, the IRB failed to conduct continuing review within the required interval, and in doing so, failed to follow their written procedures. Our inspection revealed that five subjects had been enrolled and followed up at BRMC, and the study was still open for subject accrual.

The regulations require an IRB to conduct continuing review of research at least annually, which provides an IRB with the opportunity to substantively review research in progress and to determine that (1) risks to subjects are minimized, and (2) risks to subjects are reasonable in relation to anticipated benefits to subjects, if any, and the importance of the knowledge that may be expected to result. The BRMC IRB failed to conduct continuing review of research at least annually. As a result, the IRB failed to protect the rights and welfare of human subjects participating in research.

The BRMC IRB's failure to conduct continuing review at intervals of not less than once per year and its failure to follow written procedures for conducting initial and continuing review of research represent repeated occurrences of violations that were cited in the Warning Letter issued to the BRMC IRB on September 9, 2010. On September 24, 2010, Dr. Jay Summer, Vice President of Medical Affairs, submitted the BRMC IRB's written response to the September 9, 2010, Warning Letter. The response stated that BRMC had taken a number of steps to support the IRB and to ensure adherence to the procedures, including the following:

- BRMC assigned a different support person to the IRB and increased the support for a full-time IRB position staff. In addition, Dr. Summer assumed direct oversight of the new support person, so that the policies would be followed.
- BRMC implemented a simple tracking log for all studies, so that timely review of the studies can be achieved.

Our inspection revealed that the IRB has failed to properly implement and execute corrective and preventive actions in a manner that will prevent the recurrence of these violations in the future. As a result, the BRMC IRB has repeatedly failed to meet the regulatory requirements of 21 CFR Part 56. This issue was not addressed in your June 30, 2011, response to the Form 483.

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

An IRB shall 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; and the vote on these actions, including the number of members voting for, against, and abstaining.

The BRMC IRB maintains two sets of meeting minutes for November 12, 2010. One set of meeting minutes lists S.S. Ahmad, M.D., as Chairman, and the other lists M. Al-Qasmi, M.D., as Chairman. These two sets of minutes reflect inaccurate information, inaccurate numbers of votes, and inaccurate meeting attendance. As a result, the BRMC IRB failed to prepare and maintain adequate documentation of IRB activities. Examples of this failure include, but are not limited to, the following:

a. The November 12, 2010, meeting minutes, which list Dr. Al-Qasmi as Chairman, indicate that:

i. Ten (10) voting IRB members were present at the IRB meeting. However, the meeting minutes document the vote count for CRIRB renewals of studies **(b)(4)**: **(b)(4)** as having 5 votes for approval, 0 objections, and 0 abstaining. Thus, the vote counts documented in the minutes do not reflect an accurate number of IRB members present at the meeting.

ii. The November 12, 2010, meeting minutes list Dr. Al-Qasmi as the BRMC IRB Chairman. However, Dr. Al-Qasmi was not an IRB member until January 2011. As a result, listing Dr. Al-Qasmi as Chairman for this meeting reflects an inaccurate and inadequate record of IRB activities.

b. The November 12, 2010, meeting minutes, which list Dr. Ahmad as Chairman, indicate that ten (10) voting IRB members were present at the IRB meeting. The minutes document that Dr. **(b)(6)** and **(b)(6)** abstained from voting on studies **(b)(4)**; however, the minutes document that 9 of the 10 voting members present at the meeting approved the studies with two abstentions. As a result, the meeting minutes reflect an inaccurate account of meeting attendance or an inaccurate number of votes.

c. The January 14, 2011, meeting minutes indicate that seven (7) voting IRB members were present at the IRB meeting. The minutes document that Dr. **(b)(6)** did not participate in the voting process on studies **(b)(4)** and **(b)(4)**; however, the minutes document that 7 of the 7 voting members present at the meeting approved the studies. As a result, the meeting minutes reflect an inaccurate account of meeting attendance or an inaccurate number of votes.

The IRB failed to prepare and maintain adequate documentation of IRB activities. The November 12, 2010, and January 14, 2011, meeting minutes do not accurately reflect the IRB members present at the meeting or the vote on actions taken by the IRB, including the number of members voting for, against, and abstaining.

In addition, the discrepancies found in the November 12, 2010, meeting minutes make it difficult to determine whether a quorum was maintained throughout the convened meeting. If a quorum is lost during a convened meeting (e.g., those with conflicts being excused, early departures, 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)].

BRMC's written response to the Form FDA 483, dated June 30, 2011, notes that the IRB Chairman will remind members at the beginning of each convened IRB meeting of the voting rules, and they will be included in the meeting minutes. The written response indicates that a detailed documentation will be recorded to clearly signify the change in vote count during the IRB meeting, thereby tracking when members come and leave. This response is inadequate because it does not include any discussion of training of IRB staff on the requirements of IRB minutes or maintaining appropriate records of IRB operations, nor does it address how the IRB will prevent conflicting meeting minutes. As a result, BRMC's written response is inadequate to correct the violation and to prevent the recurrence of this or similar violations in the future.

FDA-Imposed Restrictions on the IRB:

This inspection has identified new violations in addition to the repeated occurrence of a violation cited in FDA's Warning Letter of September 9, 2010. The IRB has demonstrated a continuing pattern of deficiencies in the last three inspections. The IRB has failed to properly implement and execute corrective and preventive actions in a manner that will prevent the recurrence of these violations in the future. As a result, the BRMC IRB has repeatedly failed to meet the regulatory requirements of 21 CFR Part 56.

Given the seriousness of these violations and the risk to the rights and welfare of human research subjects, effective immediately, the FDA is placing the following two restrictions on the Bay Regional Medical Center IRB, according to 21 CFR 56.120 and 21 CFR 56.110(d), respectively:

1. **No new subjects will be added to ongoing studies subject to 21 CFR part 56.**

2. **FDA will suspend the BRMC IRB's use of the expedited review procedure.**

These restrictions will remain in effect until such time that you receive written notification from FDA that adequate corrections have been made. These restrictions do not relieve the IRB of its responsibilities to receive and respond to reports of unexpected and serious reactions and routine progress reports from ongoing studies. The restrictions state that no new subjects will be added to ongoing studies; however, this restriction would not affect any subjects already enrolled in ongoing studies, as long as it is in the best interest and safety of individual subjects to remain enrolled.

In addition, these restrictions would not affect those studies being conducted at BRMC but being reviewed and approved by the Community Research Institutional Review Board (CRIRB), which is organized and operated by Michigan State University.

Within fifteen (15) business days of your receipt of this letter, you are to notify this office in writing of the actions you have taken to bring the IRB into full compliance with FDA regulations. Your written response should address each citation in the letter and 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 adequately and promptly explain the violations noted above may result in regulatory action without further notice.

It is your responsibility to notify all affected sponsors and clinical investigators of the restrictions described above. Include with your response to the FDA a representative sample copy of the IRB's written communication(s) to affected sponsors and clinical investigators, notifying them of the current restrictions. Please also provide a complete list of all sponsors and investigators who were notified as a result of this action, and the date(s) on which they were notified.

Please provide a list of all studies currently being conducted that are affected by the above restrictions, and include the titles of the studies (with IDE or IND numbers, if applicable), the names of the test articles, the names of the clinical investigators, the dates of initial reviews and approvals, and the dates of continuing reviews. IND and IDE numbers can be obtained from the sponsors of the protocols affected by these restrictions. In addition, please provide a complete list of all studies being conducted at BRMC that are continuing under the oversight of CRIRB.

Failure to respond to this letter and to take appropriate corrective action could result in FDA's taking further regulatory actions, as authorized by 21 CFR 56.120, 56.121, and 56.124. These actions could include, but are not limited to, the continuation of the restrictions described above; the termination of ongoing studies subject to 21 CFR part 56 and approved by your IRB; and the initiation of regulatory proceedings for the disqualification of your IRB.

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

If you have any questions, please contact Patrick J. McNeilly, Ph.D., at 301-796-2941; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Patrick J. McNeilly, Ph.D.
Acting Branch Chief, Human Subject Protection Branch
Division of Safety Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 2266
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,
/S/
Leslie K. Ball, M.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Cc:
Alice Gerard
President & Chief Executive Officer
Bay Regional Medical Center
1900 Columbus Avenue
Bay City, MI 48708

Mohammed Al-Qasmi, M.D.
Chairman, Institutional Review Board
Bay Regional Medical Center
1900 Columbus Avenue

Bay City, MI 48708

Jay L. Summer, M.D.
Vice President of Medical Affairs
Bay Regional Medical Center
1900 Columbus Avenue
Bay City, MI 48708

Ashir Kumar, M.D.
Chairman, Community Research Institutional Review Board
Michigan State University
205 Olds Hall
East Lansing, Michigan 48824

J. Ian Gray, Ph.D.
Vice President for Research & Graduate Studies
Michigan State University
232 Administration Building
East Lansing, Michigan 48824

[1]□ A link to the Federal Register notice is located at: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm118099.htm

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)

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