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Inspections, Compliance, Enforcement, and Criminal Investigations

North Memorial Medical Center 6/24/10



Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

June 24, 2010

WARNING LETTER

VIA UPS EXPRESS

David W. Cress
President and Chief Executive Officer
North Memorial Medical Center
3300 Oakdale North
Robbinsdale, MN 55422

Dear Mr. Cress:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB) from March 23, 2010 to March 30, 2010 by investigators from the FDA Minneapolis District Office. The purpose of this inspection was to determine whether your IRB is in compliance with applicable federal regulations. IRBs that review investigations of devices must comply with applicable provisions of Title 21, Code of Federal Regulations (21 C.F.R.) Part 56-Institutional Review Boards, Part 50-Protection of Human Subjects, and Part 812-Investigational Device Exemptions. This letter also requests prompt corrective action to address the violations cited.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and Premarket Notification submissions (510(k)) are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the district office revealed several violations of Title 21, Code of Federal Regulations (21 C.F.R.) Part 56 -- Institutional Review Boards. At the close of the inspection, the FDA investigator presented an inspectional observation Form FDA 483 for review and discussed the observations listed on the form with Gary D. Hanovich, M.D., IRB Chair. The deviations noted on the Form FDA 483 and our subsequent review of the inspection report are discussed below:

Failure to have adequate written procedures governing the functions and operations of the IRB. [21 CFR 56.108(a) and (b)]

The IRB has no written procedure for ensuring prompt reporting to appropriate institutional officials and the Food and Drug Administration of any instance of serious or continuing noncompliance with FDA regulations or the requirements or determinations of the IRB. Serious and unexpected adverse events were repeatedly not reported promptly to the IRB for the study entitled "Genentech AVF 4096g: A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination with Carboplatin and Paclitaxel Chemotherapy for the First-Line Treatment of Patients with Metastatic Melanoma. (03/07/55)."

- a) Serious and unexpected adverse events that occurred on 6/26/2009 and 9/3/2009 were not reported to the IRB until 1/27/2010.
- b) Serious and unexpected adverse events that occurred on 5/1/2008, 9/21/2008 and 10/9/2008 were not reported to the IRB until 04/14/2009.
- c) Serious and unexpected adverse events that occurred on 7/28/2008 and 1/12/2009 were not reported to the IRB until 03/09/2009.

Failure 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 is in nonscientific areas. [21 CFR 56.108(c)]

The IRB reviewed and voted on FDA-regulated research when less than a majority of the members were present and granted initial approval. Examples of this failure include, but are not limited to, the following:

- a) The IRB roster for 2009 consists of 14 voting members. Minutes for the IRB meeting held on September 9, 2009, identified seven (7) members present, in which the IRB approved continuation the FDA regulated study entitled, "(b)(4)."
- b) The IRB roster for 2008 consists of 15 voting members. Minutes for the IRB meeting held on April 9, 2008, identified six (6) members present, in which the IRB reviewed the FDA regulated study entitled, "Protocol GOG 0214, Phase II Double-Blind, Randomized Trial Evaluating the Biologic Effect of Levonorgestrel on the Ovarian Epithelium in Women at High Risk for Ovarian Cancer."
- c) The IRB roster for 2007 consists of 20 voting members. Minutes for the IRB meeting held on December 12, 2007, identified seven (7) members present, in which the IRB reviewed the FDA regulated study entitled, "Protocol GOG 0209, Randomized Phase III Trial of Doxorubicin/Cisplatin/Paclitaxel and G-CSF versus Carboplatin/Paclitaxel in Patients with Stage III & IV or Recurrent Endometrial Cancer."

Failure to prepare and maintain adequate documentation of IRB activities. [21 CFR 56.115(a)(2) and (5)]

An IRB must prepare and maintain adequate documentation including minutes of IRB meetings which shall be in sufficient detail to show the number of members voting for, against, and abstaining on actions taken by the IRB. Such documentation also must include 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. Examples of this failure include, but are not limited to, the following:

- a) The IRB meeting minutes for 2007, 2008, 2009 and 2010 describe voting actions as "passed unanimously" and do not identify the number of members voting for, against, and/or abstaining.
 - Minutes for the IRB meeting held on January 13, 2010 indicate that the IRB reviewed and approved the FDA regulated study entitled "TAXUS Liberte Post-Approval Study: A U.S. Post-Approval Study of the TAXUS Liberte Paclitaxel-Eluting Coronary Stent System." However, the minutes lack details of the votes on its actions, including the number of members voting for,

against, and/or abstaining.

b) The list of IRB members for 2010 shows only the member's name, place of employment and phone number. The list does not adequately identify scientific, non-scientific, and community members; voting members from non-voting members; or whom each alternate is designated to represent and in what capacity.

The violations described above are not intended to be an all inclusive list of problems that may exist at the IRB. The IRB is responsible for ensuring compliance with the Act and applicable regulations.

During the inspection it was noted that the IRB has used compassionate use review for some FDA regulated studies. Please note that information with reference to compassionate use of devices can be found in Chapter III of the guidance document entitled *Guidance on IDE Policies and Procedures*. This guidance document can be found at the following website address:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm>¹.

Please note your response dated April 21, 2010 was received, however, it was not received within the established timeframe for submission of post-inspection responses. The Agency will review your written response and will respond to you in a subsequent letter.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the actions you have taken or will take to correct these violations and prevent the recurrence of similar violations. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you.

Your response should reference "CTS# EC100214/E001" and be sent to:

Attention: Kathy Weil
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3451
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to the Minneapolis District Office, 250 Marquette Ave., Suite 600, Minneapolis, MN 55401. Please send a copy of your response to that office.

The Division of Bioresearch Monitoring has developed introductory training modules in FDA regulated device clinical research practices, which are available on the FDA website. The modules are for persons involved in FDA regulated device clinical research activities. These modules are located at the following website address:

<http://www.fda.gov/Training/CDRHLearn/ucm162015.htm>².

If you have any questions, please contact Kathy Weil at (301) 796-6054 or via e-mail at Kathy.Weil@fda.hhs.gov.

Sincerely yours,

/S/

Michael E. Marcarelli, Pharm.D., M.S.

Director

Division of Bioresearch Monitoring

Office of Compliance

Center for Devices and Radiological Health

Links on this page:

1. <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm>
2. <http://www.fda.gov/Training/CDRHLearn/ucm162015.htm>