Inspections, Compliance, Enforcement, and Criminal Investigations

Brookwood Medical Center 4/22/10

Department of Health and Human Services

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

WARNING LETTER

04/22/2010

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 10-HFD-45-04-02

Garry Gause

President and Chief Executive Officer
Brookwood Medical Center
2010 Brookwood Medical Center Drive
Birmingham, AL 35209

Dear Mr. Gause:

Between November 9 and 19, 2009, Ms. Patricia S. Smith, representing the Food and Drug Administration (FDA), inspected the Institutional Review Board (IRB) at Brookwood Medical Center. 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 with you a Form FDA 483, Inspectional Observations.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. We acknowledge your written response, dated January 6, 2010, to the Form FDA 483. However, because this response was received more than 15 business days after the Form FDA 483 was issued, the response has not been considered. We plan to evaluate your response to the Form FDA 483, along with any other written material provided, as a direct response to this Warning Letter.

We wish to emphasize the following:

1. The IRB failed to follow its written procedures for conducting continuing review of research [21CFR 56.108(a)(1)].

Our inspections revealed several instances in which the IRB failed to follow its written procedures for conducting continuing review of research. The IRB's written procedures state: "On-going research studies must be reviewed by the IRB at least annually, or more often if the IRB finds that the degree of risk to subjects warrants more frequent review. This renewal must take place prior to the approval expiration date noted on the approved protocol; otherwise, patient accrual must be suspended and, if the research is HHS-sponsored, the Agency must be notified. If a renewal is not received within 45 days, the study will be closed." Our review of the IRB records determined the following:

- There were two lapses in IRB approval for the **(b)(4)** protocol.

i. The initial approval for the **(b)(4)** protocol expired on May 31, 2007, but the study was not reapproved until July 2, 2007. Therefore, the study lapsed in IRB approval for more than one month.
ii. A subsequent continuing review was due by July 1, 2008; however, there was no documentation of another continuing review. The final report was not submitted until April 10, 2009, more than 10 months after the continuing review was due. It appears that IRB approval lapsed for a period of 9 months.

• Protocol **(b)(4)** was reapproved for an additional 6 months on July 3, 2008, and was due to expire on December 31, 2008. In our review of the records, FDA did not find any indication that continuing review was done between the expiration date and the time of our inspection 10 months later. Therefore, it appears that there was a lapse in IRB approval for almost 10 months.

• The initial approval for Protocol **(b)(4)** expired on June 30, 2009; however, the reapproval did not take place until August 27, 2009. As a result, IRB approval lapsed for almost two months.

This significant problem occurred in all three studies that FDA reviewed. Furthermore, this is an uncorrected problem that FDA had noted during our February 2003 inspection.

2. The IRB failed to follow its written procedures for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects [21 CFR 56.108(a)(4)].

The IRB's written procedures state: "The IRB must approve any protocol changes before they are instituted." Our review of the IRB meeting minutes, dated May 22, 2008, determined that the following protocol changes were noted by the IRB without being voted on and approved by a majority of the members present, as required by 21 CFR 56.108(c):

• Amendment 1 for Protocol **(b)(4)** included the addition of concomitant medications such as intravenous opioids, inhaled steroids, and Demerol.
• Amendment 2 for Protocol **(b)(4)** included substantial changes to the inclusion criteria, such as extending the upper age limit from 75 years to 80 years of age and allowing the inclusion of subjects with types of **(b)(4)** different from those indicated in the initial protocol.

3. The IRB failed to determine that risks to subjects are minimized [21 CFR 56.111(a)(1)].

In our review of the IRB meeting minutes dated April 28, 2008, FDA determined that the IRB requested a copy of the preceding two quarterly Data Safety Monitoring Board reviews along with a statistical summary, because they had concerns about reports of bleeding, embolus formation, and death occurring in the **(b)(4)** protocol. Despite this concern, there is no evidence that the IRB ever received the requested reports, and the study was permitted to continue until it closed on April 23, 2009.

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 Brookwood 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 adequately and promptly explain the violations noted above may result in regulatory action without further notice. If you believe that your January 6, 2010, written response to the Form FDA 483 fully explains the actions you have taken to prevent similar violations in the future, please communicate that to us in writing within fifteen (15) working days. As noted above, we plan to evaluate your written response to the Form FDA 483 along with any other written material provided as a direct response to this Warning Letter. You may reference the response dated January 6, 2010, in your response to this letter.

If you have any questions, please contact Kevin Prohaska, D.O., M.P.H., at 301-796-3707; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Kevin Prohaska, D.O., M.P.H.
Acting Human Subjects Protections Team Lead
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5356
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,
/S/

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

cc: Bradley Dennis, M.D.
Chief Medical Officer and Hospital Administrator
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Armand S. Schachter, M.D.
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(b)(4)

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