

Inspections, Compliance, Enforcement, and Criminal Investigations

Buettner, Craig M., MD 11/24/09



Department of Health and Human Services

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

WARNING LETTER

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Ref: 10-HFD-45-11-03

Craig M. Buettner, M.D.
100 Rice Mine Road Loop Suite 104
Tuscaloosa, AL 35406-2421

Dear Dr. Buettner:

Between May 4 and 6, 2009, Ms. Patricia Smith, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation [protocol **(b)(4)** entitled **(b)(4)** of the investigational drug **(b)(4)** performed for **(b)(4)**

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Smith presented and discussed

with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

Subjects were randomized postoperatively, as opposed to preoperatively, in violation of the protocol. Per Section 4.6.4.1 of the protocol, randomization was to take place following screening on Day 0, a day prior to surgery. In a Note to File dated April 8, 2009, your site staff notified the Institutional Review Board (IRB) that 44 subjects were randomized post-surgery, in violation of the protocol. The following are examples of subjects that were randomized postoperatively: Subjects 001, 002, 003, 004, 005, 006, 010, 011, 030, 031, 040, 058, 061, and 064.

In your June 3, 2009 written response, you stated that this violation occurred due to a misunderstanding of the protocol. You noted that you intended to randomize subjects only after verifying that all inclusion and exclusion criteria were met. You indicated that you understood that the protocol required subjects to have had a **(b)(4)** and as such, you mistakenly randomized subjects postoperatively to verify that they had indeed undergone the protocol-specified procedure. However, on May 11, 2007, your site was forwarded a monitor's email reiterating that subjects were to be randomized before surgery. Nonetheless, you continued to randomize subjects postoperatively until October 2007. Additionally, in your written response, you indicated that you notified the IRB of this protocol deviation. We note that under section 5.2 of the protocol, any protocol deviations were to be submitted to the IRB as soon as possible. However, you did not notify the IRB until April 8, 2009, almost a year following notification of your site's closure of the study on April 24, 2008, and almost two years after you were notified by the monitor that randomization was to occur prior to surgery. In your response, as corrective measures, you promised to randomize subjects as required by the protocol in the future, and to seek further clarification from the sponsor for any future ambiguities in protocol specifications.

We acknowledge your response. However, we are concerned that the response is not adequate to prevent future recurrence of the violation noted above because it provides no specific or detailed plans or procedures to prevent future recurrence of this or similar violations. In this case, not only did you fail to properly understand the protocol randomization procedure from the start of the study, and therefore did not ensure that the randomization procedure was carried out according to the protocol from the outset, but also you did not remedy the problem for more than four months after having received clarification of the protocol.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA 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 have any questions, please contact Constance Lewin, 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 Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division 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 yours,
{See appended electronic signature page}
Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

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

/S/

LESLIE K BALL
11/24/2009