Inspections, Compliance, Enforcement, and Criminal Investigations

Centra Health Inc IRB 6/13/11

Department of Health and Human Services

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

June 13, 2011

WARNING LETTER

VIA UPS EXPRESS

George W. Dawson
President and CEO
Centra Health, Inc.
Centra Support Building
1920 Atherholt Road
Lynchburg, VA 24501

Dear Mr. Dawson:

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 February 3, 2011, to February 15, 2011, by an investigator from the FDA Baltimore 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 CFR) 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 and discusses your IRB's written response dated March 2, 2011, to the noted violations.

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 serious violations of 21 CFR Part 56-Institutional Review Boards, which requirements are prescribed under section 520(g)(21 U.S.C. 360j(g)) of the Federal Food, Drug, and Cosmetic Act (the Act). At the close of the inspection, the FDA investigator presented an inspectional observations Form FDA 483 for review and discussed the observations listed on the form with Mr. Thomas Jividen, Executive Vice President and IRB Chair, Mr. Juan DeLeon, Director, Corporate Compliance, and Ms. Elizabeth Burgess, IRB Secretary. The deviations noted on the Form FDA 483, your IRB's written response, and our subsequent review of the inspection report are discussed below:

Failure to conduct continuing review of research at least annually. [21 CFR 56.109(f)]

An IRB shall conduct continuing review of research covered by FDA regulations at intervals appropriate to the degree of risk, but not less than once per year. Examples of this failure to conduct continuing review at least annually include the following:

- The IRB did not conduct continuing review of the **(b)(4)**, which was due by January 13, 2011.
- The IRB did not conduct continuing review of the **(b)(4)** until January 13, 2011, although continuing review was due in January, 2010.

In 2009, your IRB was made aware of the need to conduct continuing reviews at least annually. In response, your IRB developed a spreadsheet and e-mail calendar to remind the IRB when a study is due for renewal. However, as documented during the 2011 inspection, the problems continue.

Your IRB's 2011 written response states that a new section in the IRB Policy and Procedure Manual, approved February 22, 2011, provides details concerning how reviews will be conducted and provides for written notice to the investigator **(b)(4)** days prior to the renewal date. This notice explains the possibility of a lapse in approval and corresponding procedures if the investigator or sponsor fails to submit the required renewal documentation. Your IRB's response also states that the IRB has established an **(b)(4)** Log that will be utilized to alert the IRB as to study review dates. This log will be **(b)(4)** at **(b)(4)**. Your IRB's response is inadequate in that it did not include a copy of the written notice and an example page from the log and related instructions. Please submit these documents for our review.

Failure to prepare, maintain, and follow required written procedures governing the functions and operations of the IRB. [21 CFR 56.108(a)(1), 21 CFR 56.108(b)(1)-(3), and 21 CFR 56.115(a)(6)]

As specified in 21 CFR 56.108 and 56.115(a)(6), an IRB must prepare, maintain, and follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of unanticipated problems involving risks to human subjects, instances of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB, or suspension or termination of IRB approval. An IRB must follow written procedures for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution. Examples of this failure to prepare or follow written procedures include the following:

- Your IRB Policy and Procedure Manual, approved on January 22, 2010, lacked 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; any instance of serious or continuing noncompliance; or any suspension or termination of IRB approval.

- Your IRB failed to follow your IRB Policy and Procedure Manual, which requires a "Request for Renewal of IRB Approval or Study Closure" **(b)(4)** in order to conduct continuing review. Your IRB failed to follow its written procedure by reviewing and approving at least three studies **(b)(4),** and **(b)(4)** without **(b)(4)** .

In 2009, your IRB was made aware of the need to have adequate written procedures and to follow them. In response, your IRB revised the IRB Policy and Procedure Manual and included forms for applying for IRB approval, requesting renewal, and modifying approved research. Yet, problems continue.

Your IRB's 2011 response states that the IRB Policy and Procedure Manual now includes the following:

- procedures for notifying the investigator and study coordinator of findings and actions;
- procedures for reporting serious adverse events (SAEs) and unanticipated problems (UPs) to the IRB chairman within **(b)(4)** business days;
- the IRB's assurance that SAEs and UPs will be reported to FDA; and
- information regarding study suspension and termination.

Your response is incomplete in that it does not specify the time frame in which your IRB will report terminations and suspensions of approvals to the FDA. Also, your response does not discuss reporting of serious or continuing noncompliance. Please submit revised policies and procedures, date of implementation, and proposed training to educate IRB members about the revised manual being implemented and FDA regulations.

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.

Within fifteen working days of receiving this letter, please provide written documentation of the additional actions your IRB has taken or will take to correct these violations and prevent the recurrence of similar violations. In addition, please notify this office of your availability to meet and discuss your IRB's corrective and preventive actions. 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 # EC100622/E001" and be sent to:

Attention: Anne T. Hawthorn
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3504
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to FDA's Baltimore District Office, 6000 Metro Dr., Suite 101, Baltimore, MD 21215. 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 [1].

If you have any questions, please contact Anne T. Hawthorn, (301) 796-6561, Anne.Hawthorn@fda.hhs.gov.

Sincerely yours,

/s/

Steven D. Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

Links on this page:

1. http://www.fda.gov/Training/CDRHLearn/ucm162015.htm