Inspections, Compliance, Enforcement, and Criminal Investigations

Independent Review Consulting, Inc

Department of Health and Human Services

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

July 19 2010

WARNING LETTER

VIA UPS EXPRESS

Erica J. Heath, President
Independent Review Consulting, Inc., IRB
100 Tamal Plaza, Suite 158
Corte Madera, CA 94925-1168

Dear Ms. Heath:

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 8 to February 25, 2010 by an investigator from the FDA San Francisco 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 March 17, 2010 written response 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 several violations of Title 21, Code of Federal Regulations (21 CFR) Part 50 -- Protection of Human Subjects, Part 56 -- Institutional Review Boards, and Section 520(g) (21 U.S.C. 360j(g)) of the Federal Food, Drug, and Cosmetic Act. At the close of the inspection, the FDA investigator presented an inspectional observation Form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the Form FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

1. Failure to use expedited review procedures only for certain kinds of research involving no more than minimal risk or for minor changes in approved research [21 CFR 56.110, 21 CFR 56.108(c)].

The IRB granted approval by expedited review of research for a significant risk study that did not meet the criteria provided for in 21 CFR 56.110. Examples of your failure include, but are not limited to the following:

- The **(b)(4)** was approved via expedited review rather than at a full board meeting. The **(b)(4)** is

a significant risk study, involving more than minimal risk, and is not within the categories of research on the list at: 63 FR 60353 (November 9, 1998). The study is, therefore, not eligible for expedited review.

Your written response states that the understanding of the board was that the device was not investigational and therefore, qualified for expedited review. Your response also states that the IRC Administration has determined that a more precise declaration of device status may aid in the prevention of future confusion, and increase the assurance of regulatory compliance and subject safety. In order to achieve this goal, you explain, revisions have been made to the Device Supplement Application Form 4.13B and training of staff and board members would occur no later than April 1, 2010. Your response is incomplete in that it does not describe how you will verify whether the study involves no more than minimal risk. Please submit your revised procedures pertinent to Form 4.13B, including procedures on how you will determine whether a study involves no more than minimal risk. Please also provide information regarding the dates when your staff and members of the board were trained on this revised procedure.

2. Failure to 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, the vote on these actions including the number of members voting for, against and abstaining, the basis for requiring changes in or disapproving research, and a written summary of the discussion of controverted issues and their resolution. [21 CFR 56.115(a)(2)].

Minutes of the IRB meetings are inaccurate and/or incomplete. Examples of this failure include, but are not limited to the following:

- The meeting minutes for both the February 10, 2009 and February 24, 2009 meetings regarding the **(b)(4)** should have included discussion regarding the controverted issues that ultimately prompted letters being sent to the principal investigators.

Your written response states that the existing format for meeting minutes failed to communicate as effectively as you prefer, therefore, the format for meeting minutes will be amended to include more descriptive language and explanation, and board members and staff would be trained no later than April 1, 2010. Your response is inadequate in that it does not describe the details of how you plan to change the minutes format or whether you plan to revise your written procedure for preparing minutes. Please provide FDA with this information, including a copy of the amended format for meeting minutes, and, if applicable, a copy of your revised written procedure for preparing minutes. Please also include information regarding the dates board members and staff were trained on the revised meeting minutes format and, if applicable, revised written procedure for preparing minutes.

3. The IRB failed to ensure the information given to subjects as part of informed consent is in accordance with 21 CFR 50.25. [21 CFR 56.109(b)].
This is a reoccurrence of a violation cited in the last IRB inspection and the last Untitled Letter issued to you in 2008.

The IRB shall require that information given to subjects as part of informed consent is provided in accordance with 21 CFR 50.25 (21 CFR 56.109(b)). The IRB failed to ensure that informed consent contained all the information required by 21 CFR 50.25 such as:

- **(b)(4)** the informed consent document utilized for this study did not contain a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records (21CRF 50.25(a)(5).

- **(b)(4)** the informed consent document utilized for this check did not contain an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject (21 CFR 50.25(a)(7)).

Your written response states that in order to ensure improved oversight, you are revising your processes to include more support of the board members' review through more staff involvement of screening the submission documents. In addition, your response states that training on these procedures was conducted on March 2, 2010. Your response is inadequate in that it did not describe how you will revise your processes to ensure subjects are provided informed consent in accordance with 21 CFR 50.25. Please also clarify how staff involvement in screening will ensure subjects are provided informed consent that is in

accordance with 21 CFR 50.25, e.g., an explanation of whom to contact for answers to pertinent questions about the research, the research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

4. In approving research covered by the regulations, the IRB failed to determine that risks to subjects are minimized, risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. [21 CFR 56.111(a)(1), (a)(2)]

In order to approve research, the IRB reviewed the protocol entitled "**(b)(4)** of the **(b)(4)**," version date 12/07/09 submitted by the study sponsor, **(b)(4)** However, during its review, the IRB did not determine that risks to subjects are minimized or reasonable in relation to anticipated benefit, if any, to subjects and the importance of the knowledge that may be expected to result. For example, the IRB did not review or determine that risks to subjects are minimized, risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may be expected to result regarding the risk of loosening of teeth or wear on dental enamel after long term exposure to the device or the risk of swallowing the dental appliance.

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 (15) working days of receiving this letter, please provide written documentation of the additional 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# BCI00202/E001 and be sent to

Attention: Anne T. Hawthorn, J.D.
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 the San Francisco District Office at 1431 Harbor Bay Parkway, Alameda, CA 94502-7070. 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 Hawthorn at (301) 796-5665 or via email at anne.hawthorn@fda.hhs.gov.

Sincerely yours,

/S/
Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

cc:
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Links on this page:

1. http://www.fda.gov/Training/CDRHLearn/ucmI62015.htm