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Inspections, Compliance, Enforcement, and Criminal Investigations

Herman A. Jenkins, M.D.



Department of Health and Human Services

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

WARNING LETTER

VIA UPS EXPRESS

AUG 16 2010

Herman A. Jenkins, M.D.
Professor & Chairman
Department of Otolaryngology
Mail Stop 8205
12631 East 17th Avenue, Room 3012
Aurora, CO 80045

Dear Dr. Jenkins:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site from April 21, 2010 to May 28, 2010 by investigators from the FDA Denver District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study "Fully-Implantable MET™ Ossicular Stimulator Clinical Trial," G040052 complied with applicable federal regulations. The Fully-Implantable MET™ Ossicular Stimulator is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also requests prompt corrective action to address the violations cited and discusses your June 11, 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 serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 812 -Investigational Device Exemptions. At the close of the inspection, the FDA investigator presented an inspectional observations 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 submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect (UADE) occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. [21 CFR 812.150(a)(1)]

An investigator shall prepare and submit complete, accurate, and timely reports of UADE's. You did not report several UADE's that occurred during the investigation to the sponsor or the reviewing IRB. You failed to adhere to the above stated regulation. Examples of the failure include, but are not limited to the following:

- In an email on February 21, 2009, to your Sub-investigator Audiologist Subject **(b)(6)** stated that while

the sponsor's representative was connecting the study device, "there was the loudest noise inside my head that I ever heard. I could not make it stop by pulling out the hearing aid. It's very difficult to describe the horrid pain and the fear that I felt."

- In the 3-Month Postoperative Evaluation Subject Questionnaire dated July 28, 2009, Subject **(b)(6)** stated the following in the comment section: "I need to turn up the volume 2 or 3 spots however if I do that I get a lot of feedback and pain with sound."
- In an email on September 24, 2009 to your study support coordinator Subject **(b)(6)** stated that after blowing her nose, "Immediately, the device made a sudden constant VERY loud high-pitched shrieking noise. It was far louder than any sound anyone would want to hear. It was a pain causing scream-level sound, obscuring any other sounds." The subject went on to state, "By the fourth time, the noise was making me nauseous and sweaty. I turned the device off."

In your response, you stated that on consultation with the research team that you did not view these events as having "serious adverse effects on the health or safety or welfare of the subjects," and that none of "these events met the WIRB reporting requirements for unanticipated problems that are adverse events," so they were not reported to the panel. Your response is inadequate in that it does not describe your corrective and preventive actions for properly reporting UADE's. Please explain how you will prevent recurrence of this failure.

2. Failure to ensure an investigation is conducted according to the signed agreement, the investigational plan, applicable FDA regulations, and any condition of approval imposed by an IRB or FDA. [21 CFR 812.100 and 21 CFR 812.110(b)]

A clinical investigator is responsible for ensuring that an investigation is conducted according to the signed agreement with the sponsor, the investigational plan, and applicable FDA regulations and any conditions of approval imposed by an IRB or FDA. You failed to conduct the investigation in accordance with the investigational plan. Examples of the failure include, but are not limited to the following:

- The protocol dated May 15, 2008 states in Section 5.3. Assessment of Safety that "Bone conduction will be measured using forehead placement of the bone oscillator. Both air-and bone-conduction threshold will be obtained at the initial evaluation for baseline measurement." However, for all subjects enrolled in this study, your site chose to continue to employ mastoid placement of the bone oscillator which was utilized in Phase I of this study. The protocol was revised prior to enrollment of the subjects at your site.
- **(b)(4)** subjects should have been excluded from participation in the study according to study protocol inclusion/exclusion criteria as follows:

Reason for exclusion from study

The subject had not used appropriate and optimally fitted hearing aids for at least 3 months and did not meet insertion gain prescriptive targets.

Subject had conductive or mixed hearing loss (air-bone gap greater than 10dB).

Affected study subjects

(b)(6)

(b)(6)

- The trial protocol dated May 15, 2008 states that "The evaluation of the safety of the fully implantable device will focus on air and bone conduction thresholds. For each subject, these measurements will be taken at specified times (baseline, post-surgery - 3, 6, and 12 months) for both the test (implant) and control (non implant) ears at specified time points during the course of the study." However, only one ear was tested for the following subjects:

(b)(6)

In your response, you acknowledge that you did deviate from the protocol, and that you did not feel it impacted the scientific validity of the study and that many of these deviations were consistent with standard clinical care. In addition, you stated that future protocol deviations will be avoided by implementation of a corrective action plan which includes training for yourself and your study staff as well as improved documentation for this study. Your response is inadequate in that the corrective action plan you provided does not clearly indicate how you will prevent these deviations from reoccurrence. Please explain fully how you plan to correct these failures and how you will ensure that all study staff will receive appropriate training specific to their individual duties.

Please note that the above deficiencies could significantly impact the Agency's review of the safety and efficacy of this device.

3. Failure to maintain accurate, complete, and current records of receipt, use, or disposition of a device. [21 CFR 812.140(a)(2)]

A clinical investigator is responsible for maintaining accurate, complete, and current records of receipt, use, or

disposition of an investigational device that relate to the type and quantity of the device, the dates of receipt, and the names of all persons who received, used, or disposed of each device. You failed to adhere to the above-stated regulation.

- Your site did not maintain any records that document study device receipt, use, and disposition.

In your response you stated that, "the Sponsor took responsibility for tracking all devices for the study. In any future study, a better logging of the devices will be maintained, as protocol inclusion and FDA requirements. Specifically our site will develop standard operating procedures for device tracking." Your response is inadequate as you have not included copies of these standard operating procedures or documentation of training on the procedures. Please provide these standard operating procedures and documentation of training on the procedures. Also, please note that you are ultimately responsible for maintaining documentation of device accountability at your clinical site.

The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a clinical investigator to ensure compliance with the Act and applicable regulations.

The inspectional report notes that you indicated that the sponsor was responsible for tracking the devices used in the study. The regulations in 21 CFR Part 812 describe sponsor responsibilities as well as those of investigators. IRB responsibilities are spelled out in 21 CFR Part 56, Institutional Review Boards. These three sets of responsibilities overlap to ensure appropriate conduct of clinical studies and the protection of the rights and welfare of participating subjects. Therefore, though the sponsor and IRB involved in your study may have been remiss in fulfilling their responsibilities, you are still held responsible for knowing and following the regulations pertinent to your activities as a clinical investigator in FDA-regulated studies. In addition, please note that informed consent should be obtained prior to any study related procedures not solely prior to implantation of the study device.

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 in current or future studies for which you are the clinical investigator. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 812.119.

You will find information to assist you in understanding your responsibilities and planning your corrective actions in the **FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators**, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>¹. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Your response should reference "CTS # EC1 00320/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 Denver District Office, Denver Federal Center, 6th Ave & Kipling St, Bldg 20, PO BOX 25087, Denver CO 80225. 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 Anne T. Hawthorn, J.D., 301-796-6561, Anne.Hawthorn@fda.hhs.gov.

Sincerely yours,

/S/

Timothy A. Ulatowski
Director
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cc:

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Links on this page:

1. <http://www.fda.gov/oc/ohrt/irbs/>
2. <http://www.fda.gov/Training/CDRHLearn/ucm162015.htm>