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Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

WARNING LETTER

VIA FEDERAL EXPRESS

Bruce H. Ziran, MD
Director of Orthopaedic Trauma
St. Elizabeth Health Center
1044 Belmont Avenue
Youngstown, OH 44501

AUG 27 2008

Dear Dr. Bruce Ziran:

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 23 to May 2, 2008, by an investigator from the FDA Cincinnati District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study entitled, [redacted]

[redacted]

[redacted] complied with applicable federal regulations. [redacted]

[redacted] 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 written response dated May 12, 2008, to the noted violations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 C.F.R.) Part 812 -- Investigational Device Exemptions and Part 50 -- Protection of Human Subjects. 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:

You allowed subjects to participate in an investigation without FDA approval. [21 CFR 812.110(a)]

A physician that conducts an investigation, which is defined as a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device, 21 CFR 812.3(h), with a device for an indication that has not been FDA-approved or cleared shall not allow subjects to participate in the investigation. [21 CFR 812.110(a)]

The FDA approved indication for the [redacted] states, [redacted]
[redacted]

[redacted] Thus the approved indication is for use of the [redacted] alone. Your protocol entitled, [redacted]

[redacted] indicates that you were conducting an investigation to determine the safety and effectiveness of the [redacted] in combination with either an [redacted] or [redacted]. This clinical investigation of the safety and effectiveness of a new indication for the [redacted] requires an FDA-approved IDE. You allowed subjects to participate in the investigation without FDA approval.

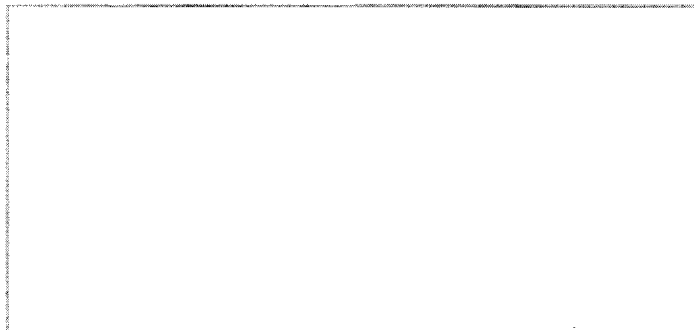
You [redacted] without an FDA-approved IDE in [redacted] subjects enrolled at your site. Examples include, but are not limited, to the following:

In your response you state upon recognizing the problem you took immediate action to suspend the study and sent a letter to the subjects involved informing them of the issue and provided them with an opportunity to contact you. In addition, your corrective action includes a statement that you will seek out education material/course regarding IDE/HUD issues before being part of an investigation that uses such devices. This response is incomplete in that you did not provide documentation of notification of all of the subjects. Please provide a copy of the letter sent to the subjects, the IRB approval of the letter, and documentation that all subjects were notified.

Failure to maintain accurate, complete, and current records relating to documents evidencing informed consent and failure to maintain case histories that document that informed consent was obtained prior to the subjects' participation in the study. [21 CFR 812.140(a)(3)(i)]

A participating investigator shall maintain accurate, complete, and current records relating to documents evidencing informed consent and the case histories shall include documentation that informed consent was obtained prior to the subjects' participation in the study in accordance with 21 CFR 812.140(a)(3)(i).

You failed to maintain case histories that document that informed consent was obtained from subjects prior to their participation in the study. Study consent forms for [redacted] subjects [redacted] enrolled in the study were dated after the study procedure was performed.



In your response you state your clinics were housed off the main campus temporarily and this required weekly transport of patients' charts of which some were misplaced or lost. You tried to find the lost consent documents and if they could not be found, re-obtained consent from the subjects; however, the re-obtained consent forms do not indicate that consent was obtained prior the subjects' participation in the study. As a result of possible loss, you instituted periodic checkpoints of source documents to ensure appropriate maintenance of the records, however, you acknowledged your periodic checks were insufficient. Your corrective action states you will recommend that the IRB institute a policy to avoid any investigational studies when patient records are subject to a risk of loss or misplacement. Your response is inadequate in that you as the principle investigator are responsible for maintaining accurate, complete, and current records relating to documents evidencing informed consent in accordance with 21 CFR 812.140(a)(3)(i).

Your corrective action further states that you will recommend that your office provide documentation that an informed consent discussion occurred and include the time and date of consent. This response is inadequate in that you did not provide the procedure and documentation of training of all applicable personnel for this policy. Please provide copies of policies, procedures, and trainings with expected completion dates that are being developed and implemented to ensure subjects' case histories contain documents evidencing informed consent. In addition, your corrective action lacks any policies and procedures to ensure all subjects have obtained informed consent prior to any study related procedures. Please provide copies of policies, procedures, and trainings with expected completion dates that are being developed and implemented to ensure informed consent is obtained with the most current IRB approved consent document prior to any study related procedures being performed.

Failure to ensure all required elements of informed consent were documented and provided to study subjects. [21 CFR 50.25(a) and 21 CFR 50.27(b)]

Although the IRB reviews and approves the informed consent document, it is ultimately the responsibility of the investigator to ensure the informed consent process meets the regulatory requirements. Your consent documentation does not include all the essential

elements listed in 21 CFR 50.25. Under 21 CFR 50.27(b), the written consent document must include the elements of informed consent required by 21 CFR 50.25. Research subjects voluntarily agree to participate in a clinical investigation. In order to make an informed decision to participate, they must be given all applicable information.

Examples of the failure to include essential elements in consent documents include:

- 1) The informed consent document does not identify that the implantation of [] combined with [] or [] is an experimental procedure. (See 21 CFR 50.25(a)(1)).
- 2) The investigational plan identifies risks to include [] reaction, [] []. However, the consent document lacks identification of any of these risks with this investigational device. (See 21 CFR 50.25(a)(2)).

In your response you state you discussed such issues verbally with patients and that you will make your best efforts to provide documentation of such discussions with the subjects and ensure it is present in written consents in future studies. This response is incomplete in that you did not provide documentation that you informed your subjects that this was an experimental procedure with additional risks, including [] reaction, [] [] that are identified in the investigational plan. Please provide documentation that subjects have been informed, and provide copies of policies, procedures, and trainings with expected completion dates that are being developed and implemented to ensure informed consent documents contain all the essential elements in accordance with 21 CFR 50.25.

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.

In your response you state you believed that since the study was vetted by the sponsor as well as every participating IRB, you would have been informed of the need for an IDE and there would not be any regulatory concerns. The regulations in 21 C.F.R. Part 812 describe sponsor responsibilities as well as those of investigators. IRB responsibilities are spelled out in 21 C.F.R. 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. You are held responsible for knowing and following the regulations pertinent to your activities as a clinical investigator in FDA-regulated studies.

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. In addition, please provide a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and

the current status of the study. 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 C.F.R. 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/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Send your response to: Attention: Doreen Kezer, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-310, Rockville, Maryland 20850.

A copy of this letter has been sent to Cincinnati District Office, 6751 Steger Drive Cincinnati, OH 45237. Please send a copy of your response to that office.

If you have any questions, please contact Doreen Kezer, (240) 276-0125 or e-mail doreen.kezer@fda.hhs.gov.

Sincerely yours,



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

