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JUL - 6 2005

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

WARNING LETTER

Via Federal ExpressReynald G. Bonmati, President/CEO
Orthometrix, Inc.
106 Corporate Park Drive, Suite 102
White Plains, NY 10604

Dear Mr. Bonmati:

This Warning Letter informs you of objectionable conditions revealed during a Food and Drug Administration (FDA) inspection of your facility. This letter also requests that prompt corrective actions are implemented in response to the violations cited. L. Glenn Massimilla, PharmD, an Investigator from FDA's New York District Office conducted the inspection during the period of January 6 through March 4, 2005. The purpose of the inspection was to determine if your activities as a Sponsor of the study for the [REDACTED], [REDACTED], complied with applicable FDA regulations, published in Title 21, Code of Federal Regulations, Part 50-Protection of Human Subjects, and Part 812-Investigational Device Exemptions [21 CFR 50 and 812]. The clinical trial that was the subject of the inspection was: [REDACTED]. The products used in the study are devices as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321(h)].

The inspection was conducted under a program designed to ensure that data and information contained in applications for Investigational Device Exemption (IDE), Pre-Market Approval (PMA), and Pre-Market Notification [510(k)] submissions 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 investigation.

Our review of the inspection report and related documents submitted by the New York District Office revealed that you violated regulations governing the responsibilities of Sponsors, as published under 21 CFR Part 812 - Investigational Device Exemptions (available at <http://www.gpoaccess.gov/cfr/index.html>). At the close of the inspection, Dr. Massimilla issued a Form FDA-483, Inspectional Observations, and discussed the deviations noted during this inspection with Mr. Ralph G. Theodore, Vice President of Operations, and Mr. David R. Balzer, Jr., Director of Bio Medical Technology, Inc. The

deviations noted on the FDA 483, and our subsequent review of the inspection report and your written responses to those deviations, are discussed below:

1. You failed to secure the investigators' compliance with the investigational plan and applicable FDA regulations [21 CFR 812.46(a)].

Pursuant to 21 CFR 812.46, a sponsor who discovers that an investigator is not complying with the signed investigator agreement, the investigational plan, the requirements of applicable FDA regulation, or any conditions of approval imposed by FDA or the reviewing Institutional Review Board (IRB) must promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation.

An example of this failure to adhere to this regulation includes but is not limited to the following:

Our review of the inspection report for [REDACTED], one of the [REDACTED] clinical investigators who participated in this study, disclosed that, despite periodic clinical monitoring visits from your firm's designated monitors, violations were repeatedly committed at the site during the clinical investigation. The primary observation made at [REDACTED] site indicated that there were no records to demonstrate that your firm obtained prompt correction and subsequent compliance by [REDACTED], or that your firm was even aware of these violations. Specifically:

- a) Five of the [REDACTED] subjects enrolled in the [REDACTED] study by [REDACTED] signed the study informed consent form after the study procedure was performed.
- b) Two of the [REDACTED] subjects enrolled in the [REDACTED] study by [REDACTED] had no documentation in their study records that informed consent was obtained.

Your response to this observation in your letter to Dr. Massimilla, dated March 8, 2005, is inadequate. You stated that the original consent forms signed by the above referenced study subjects were misplaced or destroyed by a staff member after a new IRB-approved HIPAA authorization was signed by the subjects. Mr. Balzer's response letter to Dr. Massimilla, dated February 14, 2005, is also inadequate. Mr. Balzer stated that [REDACTED] has agreed to a plan for "tightening his SOPs in this area" which Mr. Balzer stated "should be sufficient to help avoid this situation in the future." Please provide us with the corrective and preventive actions that Orthometrix will take in order to prevent this situation from recurring at other clinical sites besides [REDACTED]

- c) At least four of the [REDACTED] subjects enrolled by [REDACTED] had no documentation that the mandatory pre-treatment x-ray had been performed to rule out other causes for heel pain, as required by the protocol.
- d) At least seven of the [REDACTED] subjects enrolled by [REDACTED] had no documentation that they met all the inclusion criteria.
- e) At least 21 of the 64 subjects enrolled by [REDACTED] had documentation in their study files that their [REDACTED] were less than 1.0, which was a criterion for exclusion from the study.

[REDACTED] has stated that the [REDACTED] were incorrectly calculated by his staff. Mr. Balzer's response letter noted that this was an oversight on his part as the contracted study monitor. He stated that his corrective actions will include adding a "pass/fail" box on the Case Report Form (CRF) for each assessment observation, and adding a new and separate checklist to the forms used by the study monitor. This response is inadequate. Please provide documentation that a corrective action plan has been implemented by Orthometrix, as the study sponsor, to prevent such occurrences .

- f) At least [REDACTED] subjects' records, of the [REDACTED] subjects enrolled by [REDACTED], showed that the specific treatment parameters of sonic wave frequency and/or treatment time were not met. [REDACTED] has stated that the treatment parameters were incorrectly documented by his staff.

Your responses to the above observations are inadequate. You have not addressed the fact that your designated study monitors failed to identify these deficiencies, and therefore failed to ensure investigator compliance. Please provide a corrective action plan that details the steps Orthometrix will take to identify and prevent clinical investigator non-compliance in the future. Include in the plan the measures that will be taken to address investigator non-compliance when it is identified.

2. Failure to ensure proper monitoring of the investigation, and ensure IRB review and approval are obtained. [21 CFR 812.40]

Pursuant to 21 CFR 812.40, responsibilities of Sponsors include ensuring proper monitoring of the investigation and ensuring that IRB review and approval are obtained. You failed to adhere to the above stated regulations. Examples of these failures include but are not limited to the following:

- a.) Your Standard Operating Procedure (SOP) [REDACTED] states that monitoring visits must occur "at an absolute minimum of once every four to six weeks." The interim monitoring visits for the three clinical study sites occurred at intervals much greater than six weeks. Specifically:

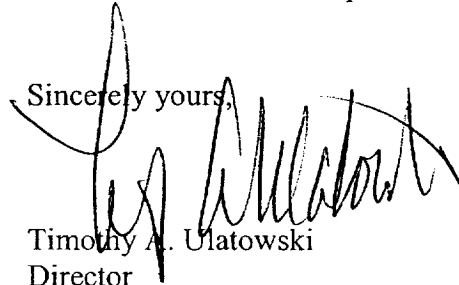
- i. [REDACTED] had [REDACTED] monitoring visits after his initiation visit on 8/6/02. The [REDACTED] visits occurred at intervals of 7 weeks, 17 weeks, 27 weeks, 25 weeks, and 14 weeks. As noted above, an FDA inspection at Dr. Weil's site resulted in numerous observations of failure to comply with the investigational plan and federal regulations.
 - ii. [REDACTED] had seven monitoring visits after his initiation visit on 8/2/02, five of which occurred at intervals of 16 weeks, 14 weeks, 33 weeks, 14 weeks, and 11 weeks.
 - iii. [REDACTED] had two monitoring visits after his initiation visit on 9/15/03. The two visits occurred at intervals of 31 weeks and 7 weeks.
- b.) Your SOP "[REDACTED]" states that monitors must "verify that an informed consent form has been obtained from each subject, and that informed consent forms are signed, dated, and properly executed prior to the subject's participation in the trial." As noted above, the study monitors did not discover the fact that [REDACTED] enrolled at least [REDACTED] subjects without documentation of the appropriate IRB-approved informed consent form.
- c.) Your SOP "[REDACTED]" states that the monitoring procedures presented in the document should be followed "during the review of every CRF by the study monitor." It is clear that the monitors did not adequately review every CRF, based on the number of discrepancies and deviations seen at [REDACTED].
- d.) Dr. [REDACTED] allowed his IRB approval to lapse from August 1, 2003, through September 15, 2003. During this time period, three subjects were enrolled in the study and received study treatment. In addition, three subjects who were enrolled before the IRB approval expired received the study treatment during the period in which IRB approval had lapsed.

The deviations presented in this letter are not intended to be an all-inclusive list of objectionable practices that may exist at Orthometrix, Inc. It is your responsibility to ensure adherence to each requirement of the Act and all pertinent Federal regulations. Please acknowledge receipt of this letter **within 15 working days**, including supporting documentation of the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies, along with a time frame for implementation of the corrective actions. Failure to respond to this letter and take appropriate corrective action could result in regulatory action without further notice. Please respond in writing to:

Food and Drug Administration
Center for Devices and Radiological Health, Office of Compliance
Division of Bioresearch Monitoring, Special Investigations Branch (HFZ-311)
2094 Gaither Road, Rockville, Maryland 20850
Attn: Ms. Doreen Kezer, Branch Chief.

A copy of this letter has been sent to FDA's New York District Office, Food and Drug Administration, 158-15 Liberty Avenue, Jamaica, NY 11433. We request that you copy the district on your response.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski". The signature is written in a cursive style with a large, sweeping initial "T".

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