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Via Federal Express

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WARNING LETTER

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

Lowell S. Weil, Sr., DPM
Weil Foot & Ankle Institute
1445 E. Golf Road
Des Plaines, IL 60016-1206

Dear Dr. Weil:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a recent Food and Drug Administration (FDA) inspection conducted at your clinical site. This letter also discusses your February 8, 2005 written response to the noted violations and requests that prompt corrective actions be implemented in response to the violations cited. Ms. Lisa Hayka, an investigator from FDA's Chicago District Office, conducted the inspection from January 10 through January 21, 2005. The purpose of the inspection was to determine if your activities as a Clinical Investigator (CI) of human research studies complied with applicable FDA regulations. The clinical trial that was the subject of the inspection was:

[REDACTED], sponsored by [REDACTED].
[REDACTED] The product used in the study is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 321(h)].

The FDA conducted the inspection under a program designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), Product Development Protocols (PDP), or Premarket 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 the scientific investigation.

Our review of the inspection report prepared by the Chicago District Office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions and Part 50-Protection of Human Subjects. At the close of the inspection, Ms. Hayka presented a Form FDA 483, "Inspectional Observations," to you for review and discussed the listed deviations. 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. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 and failure to document informed consent [21 CFR 812.100, 21 CFR 812.140(a)(3)(i), and 21 CFR 50.20].

A CI is responsible for ensuring that informed consent is obtained from all study subjects in accordance with 21 CFR Part 50. [21 CFR 812.100] Specifically, the investigator must ensure that informed consent is obtained from the subject or the subject's legally authorized representative prior to the subject's participation in the clinical study. [21 CFR 50.20] In addition, CIs are responsible for ensuring that each study subject's case history includes documents evidencing that informed consent was obtained prior to participating in a clinical study. [21 CFR 812.140(a)(3)(i)]

You failed to adhere to the above stated regulations. Examples of this failure include but are not limited to the following:

- a. Five of the [REDACTED] subjects enrolled in the [REDACTED] study at your site signed the study informed consent form after the study procedure was performed. Specifically:
 - i. Study subject [REDACTED] was treated with the study device on [REDACTED], but did not sign the study consent form until [REDACTED].
 - ii. Study subject [REDACTED] was treated with the study device on [REDACTED], but did not sign the study consent form until [REDACTED].
 - iii. Study subject [REDACTED] was treated with the study device on [REDACTED], but did not sign the study consent form until [REDACTED].
 - iv. Study subject [REDACTED] was treated with the study device on [REDACTED], but did not sign the study consent form until [REDACTED].
 - v. Study subject [REDACTED] was treated with the study device on [REDACTED], but did not sign the study consent form until [REDACTED].

Your response to this observation in your letter is inadequate. You stated that the original consent forms signed by the above referenced study subjects were destroyed by a staff member after a new IRB-approved HIPAA authorization was signed by the subjects. However, the version of the consent forms signed after study treatment by the five referenced study subjects was the original IRB-approved version, dated July 19, 2002. The "IRB-approved HIPAA authorization" you referenced in your response letter was actually a "consent form addendum" that was required by the IRB in April 2003. The IRB letter notifying you of the requirement for the addendum clearly stated "the signed document should be attached to the original consent form for each participant." The study records for these five subjects each contained an addendum signed prior to the study treatment. It appears that the addendum may have been used in lieu of the primary consent form at the time of enrollment of these subjects. As a CI, you are responsible for ensuring that all study subjects are properly consented before any study-related procedures. This includes ensuring that the current IRB-approved version of the consent form is signed and

dated by the subjects. [21 CFR 50.27(a)] You are also responsible for supervising personnel to whom you have delegated certain study tasks, such as obtaining informed consents and maintaining study files.

- b. Two of the [REDACTED] subjects enrolled in the study had no documentation in their study records that informed consent was obtained. Specifically:
 - i. Study subject [REDACTED] was treated with the study device on [REDACTED], but there was no documentation in the subject's file that informed consent for participation in the study was obtained.
 - ii. Study subject [REDACTED] was treated with the study device on [REDACTED], but there was no documentation in the subject's file that informed consent for participation in the study was obtained.

Your response to this observation in your letter is inadequate. You stated that the original consent forms might have been discarded by a staff member when the HIPAA authorizations were implemented. As stated above, you are responsible for ensuring that all study subjects are properly consented before any study-related procedures and you are responsible for supervising personnel to whom you have delegated certain study tasks. Please provide a written corrective action plan that will be implemented at your study site to ensure that potential study subjects are appropriately consented prior to participation in a clinical study, and how that consent will be documented. In addition, please provide us with an explanation of the consenting process used for study subjects at your clinical site.

Moreover, Federal regulations require that if an investigator uses a device without first obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs. [21 CFR 812.150(a)(5)] If you have not already reported this information to the sponsor and IRB, please do so now.

2. Failure to ensure an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations [21 CFR 812.100, 21 CFR 812.110(b)].

A clinical investigator is required to ensure that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations. [21 CFR 812.100; 21 CFR 110(b)] The study protocol is part of the investigational plan. [21 CFR 812.25(b)]

You failed to adhere to the above stated regulations. Examples of this failure include but are not limited to the following:

- a. The study protocol specifically excluded subjects with [REDACTED]. Of the [REDACTED] subjects you enrolled and treated for the study, at least [REDACTED] had documentation in their study files that [REDACTED]. Specifically:
 - i. Subject [REDACTED] - [REDACTED]
 - ii. Subject [REDACTED] - [REDACTED]
 - iii. Subject [REDACTED] - [REDACTED]

- iv. Subject [REDACTED]
- v. Subject [REDACTED]
- vi. Subject [REDACTED]
- vii. Subject [REDACTED]
- viii. Subject [REDACTED]
- ix. Subject [REDACTED]
- x. Subject [REDACTED]
- xi. Subject [REDACTED]
- xii. Subject [REDACTED]
- xiii. Subject [REDACTED]
- xiv. Subject [REDACTED]
- xv. Subject [REDACTED]
- xvi. Subject [REDACTED]
- xvii. Subject [REDACTED]
- xviii. Subject [REDACTED]
- xix. Subject [REDACTED]
- xx. Subject [REDACTED]
- xxi. Subject [REDACTED]

Your response to this observation in your letter is inadequate. You stated that "[REDACTED] had been [REDACTED] in error by staff when transmitting the data from the source documents to the case report forms." You also stated that you confirmed the errors of 20 subjects by reviewing [REDACTED] reviewing [REDACTED] and by noting that at subsequent visits, the patients' [REDACTED]. You should understand that the FDA investigator did not review all [REDACTED] study subjects' files, and the 21 questionable [REDACTED] found were from the sample of records that were reviewed. You also stated in your response letter that "the nurse responsible for the [REDACTED] is no longer employed by our Institute." In reviewing the records for the 21 subjects noted above, it appears that a number of different people entered data onto the forms, as evidenced by the variety of handwriting styles used.

You should also understand that the Case Report Forms (CRFs) are used as the means for recording data to be reported to the study sponsor, and subsequently to the FDA. As a clinical investigator, you are responsible for ensuring that all study subject records are accurate, complete, and current. [21 CFR 812.140(a)(3)]

Please provide us with the documentation to show that the [REDACTED] all [REDACTED] subjects noted above were actually [REDACTED]. In addition, please provide a written corrective action plan that will be implemented at your study site to ensure that study data collected during a clinical study are accurate and complete, and that source data are accurately transcribed onto the CRFs.

- b. At least four of the [REDACTED] subjects you enrolled had no documentation that the mandatory [REDACTED] had been performed to rule out [REDACTED], as required by the protocol. Specifically, the study records for Subjects [REDACTED], [REDACTED], [REDACTED], and [REDACTED] had "NA" recorded under the Mandatory [REDACTED] sections of the CRFs.

c. The study protocol stated that subjects must meet specific inclusion criteria in order to be eligible for the study. Of the [REDACTED] subjects you enrolled, at least seven had no documentation that they met all the criteria. For example:

i. Five subjects failed to meet the inclusion criteria in the protocol that stated that potential subjects must have [REDACTED]” Specifically:

- Subject [REDACTED] – Case report form for [REDACTED]
- Subject [REDACTED] – Case report form for [REDACTED]
- Subject [REDACTED] – Case report form for [REDACTED]
- Subject [REDACTED] – Case report form for [REDACTED]
- Subject [REDACTED] – Case report form for [REDACTED]
- Subject [REDACTED] – Case report form for [REDACTED]

Your response to this observation in your letter is inadequate. You stated that subjects [REDACTED] and [REDACTED] were questioned about [REDACTED] and it was determined that they [REDACTED]. You stated that “the subjects did not consider [REDACTED]

[REDACTED] As a clinical investigator, you are responsible for ensuring that all potential study subjects meet all eligibility criteria. The lack of information regarding [REDACTED] should have caused these subjects to be excluded, or at least should have prompted further questioning by you before approving them for the study. In addition, you are responsible for ensuring that any staff to whom you delegate study procedures, such as collection of screening data, are appropriately trained and qualified to perform that task.

Please provide a written corrective action plan that will be implemented at your study site to ensure that all study staff are trained in the study procedures, including collection of medical history data.

ii. One subject failed to meet the inclusion criteria in the protocol that stated that potential subjects must [REDACTED] Specifically:

- Subject [REDACTED] had [REDACTED] on the case report form.

Your written response does not address this observation. The verbal response you provided to the inspector -- [REDACTED] -- is inadequate.

d. The study protocol stated that treatment with the device must [REDACTED] including [REDACTED]. Of the [REDACTED] subjects you enrolled, at least 20 subjects’ records showed that these [REDACTED]

were not met. Specifically:

- i. Subjects [redacted] and [redacted] had [redacted]
- ii. Subject [redacted] had [redacted]
- iii. Subjects [redacted], and [redacted] had [redacted]
- iv. Subjects [redacted], [redacted], and [redacted] had [redacted]
- v. Subjects [redacted] and [redacted] had [redacted]

Your response to this observation in your letter is inadequate. You stated that, regarding [redacted] "the data are available from patient records, and a protocol deviation form has been completed with the correct information." As previously noted, as a CI, you are responsible for ensuring that all study subject records are accurate, complete, and current. If any data that were reported to the study sponsor are incorrect, the sponsor must be notified so that corrections can be verified and implemented. And, as noted above, the deficiencies and discrepancies observed by the FDA investigator were found in only the portion of the records he reviewed, and do not account for all the issues that may be present in other records for the [redacted] enrolled subjects.

Please provide copies of the missing data that you stated are available from patient records. In addition, please provide a written corrective action plan that will be implemented at your study site to ensure that study data collected during a clinical study are accurate and complete, and that source data are accurately transcribed onto the CRFs.

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist at your clinical site. It is your responsibility to ensure adherence to each requirement of the Act and all pertinent Federal regulations when conducting clinical research, and to ensure that any study staff or personnel who are delegated study tasks are knowledgeable regarding the Investigational Plan and are directly supervised by you.

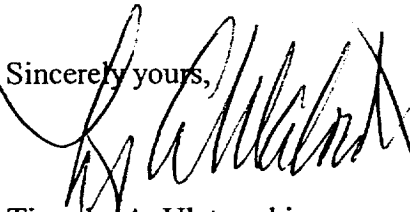
Please acknowledge receipt of this letter **within 15 working days**, including supporting documentation of the specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished.

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 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. Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch, (HFZ-312) 2094 Gaither Road, Rockville, Maryland 20850. Attention: Mrs. Viola Sellman, Chief, Program Enforcement Branch

We are also sending a copy of this letter to the FDA's Chicago District Office, Food and Drug Administration, 550 W. Jackson Street, Suite 1500, Chicago, IL 60661. We request that you copy the district on your response. If you have any questions, please contact Ms. Sellman by phone at (240) 276-0125, or by email at vx@cdh.fda.gov.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski". The signature is fluid and cursive, with a large initial "T" and "U".

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