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

OCT 3 2003

Via Federal Express
WARNING LETTER

David R. Lorenzi
President/CEO
Plus Orthopedics
6055 Lusk Boulevard
San Diego, California 92121

Dear Mr. Lorenzi:

The purpose of this letter is to inform you of objectionable practices and activities found during a Food and Drug Administration (FDA) inspection and to acknowledge your June 1, 2003, written response addressed to Alonza Cruse, Los Angeles District Director, FDA. Your letter was in response to the Form FDA 483 "Inspectional Observations" that was issued at the close of the inspection of Plus Orthopedics. The inspection took place during the period of April 14 through 23, 2003, and was conducted by Ms. Yvette E. Guillermo, an investigator from FDA's Los Angeles District Office. The purpose of the inspection was to determine whether your firm's activities as sponsor of an investigational study of the [REDACTED] comply with applicable FDA regulations. This product is a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act.

Our review of the inspection report prepared by the district office revealed serious violations of the requirements of Title 21 Code of Federal Regulations (21 CFR), Part 812 – Investigational Device Exemptions. You received a Form FDA 483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed with you; [REDACTED]

We acknowledge the corrective actions taken as indicated in your annual IDE report G010120/S6, dated January 20, 2003 – before FDA's inspection – and in your written response to the Form FDA 483, dated June 1, 2003. You also submitted a draft Audit/Corrective Action Operating Plan on July 21, 2003. However, some of your responses to date do not describe an adequate corrective action plan with specific times for completion and supporting documentation for corrections already made. The deviations noted on the Form FDA 483 and our subsequent review of the inspection report, and your responses are discussed below

Failure to obtain IDE and Investigational Review Board (IRB) approval before initiating the study. (21 CFR 812.20(a), 812.30(a), 812.40, and 812.42)

An investigation involving a significant risk device, such as the [REDACTED] cannot be conducted without an approved IDE. (21 CFR 812.20(a), 812.30(a), and 812.42.) The sponsor is also responsible for ensuring that necessary IRB approval is obtained. (21 CFR 812.40.)

You failed to submit an IDE application to FDA or obtain approval before shipping some of the investigational devices. You also failed to ensure that clinical investigators participating in the study obtained IRB approval prior to the use of the investigational device. As a result, thirty-one investigational devices were implanted without FDA and IRB approval of the study.

Failure to adhere to investigational device exemption (IDE) requirements including ensuring control of the investigational device, monitoring the study properly, and obtaining investigator agreements. (21 CFR 812.40, 812.43, and 812.45)

As the sponsor of an investigation, you are responsible for shipping the device only to qualified participating investigators (21 CFR 812.43(b)), monitoring the study properly (21 CFR 812.40), selecting qualified investigators and providing them with sufficient information to conduct the investigation properly (21 CFR 812.40 and 812.45), obtaining financial disclosure agreements from each investigator (21 CFR 812.43(c)(5)), and ensuring investigators' commitment to satisfy applicable informed consent requirements (21 CFR 812.43(c)(4)(iii)).

Your firm failed to do the following: ensure proper monitoring of the study; and obtain commitments that investigators would comply with the investigation plan and informed consent requirements. As a result:

- twelve investigational devices were implanted using a [REDACTED] that was not part of the test device and not included in the investigational plan;
- nine investigational devices were implanted in patients not enrolled in the study (five of the nine devices were implanted at unapproved clinical sites);
- some investigators participating in the investigation did not receive current copies of the investigational plan;
- the investigator agreement for one investigator was signed after implantation of four subjects with the investigational device;
- seventeen patients signed an informed consent form that deviated from the IRB-approved version; and
- subjects at four different clinical sites signed an informed consent form that failed to include randomization information.

In addition, you failed to obtain financial disclosure agreements for each investigator.

During the inspection, [REDACTED] indicated that [REDACTED] at the time of patient implants with the unapproved [REDACTED] resigned from Plus Orthopedics. [REDACTED] also stated that Plus Orthopedics received FDA approval on February 20, 2003 to use the [REDACTED] in the study. [REDACTED] stated that your company is currently ensuring compliance at the clinical sites through monitoring, and [REDACTED] stated that the [REDACTED] site closed its Orthopedic Department on April 1, 2003 and is no longer enrolling patients.

In your June 1, 2003 written response, you attributed some of the deficiencies noted above to a lack of understanding of FDA's IDE and device regulations by prior management. You stated that management was replaced, and you committed to temporarily suspend enrollment of new subjects while you work toward compliance with FDA regulations. You also committed to multiple corrective actions, including having the study audited by a third party auditor and notifying patients who received the investigational device outside of the study. You also stated that several corrective actions have already been implemented: unused investigational devices have been removed from investigation sites; employees have received training on the [REDACTED] and [REDACTED] study monitoring is currently being performed by an outside consultant; and all investigational sites have received the latest investigational plan.

Your responses to observations 1, 2, 3(a), 4 and 5 states the steps you plan to take or have taken to prevent future occurrences, but in most cases your responses do not adequately address how you will correct and prevent future deviations. For example, during the inspection close-out discussion, Ms. Guillermo discussed your failure to follow your new procedure for distributing the investigational device to investigators [REDACTED]. The discrepancies identified included the failure to ship some test devices in kits, the dates on some [REDACTED] forms not matching dates on the [REDACTED] log, and the completion of some [REDACTED] forms incorrectly by warehouse personnel. You must provide additional information to confirm that these problems have been addressed, such as the latest, approved SOP for this process, and copies of your device accountability log.

Your responses to Form FDA 483 observations 3(b) and 3(c) state that your procedures for monitoring the clinical trial have been revised, that your [REDACTED] has completed training in monitoring, and that an outside consultant is currently monitoring the study. Your response, however, does not specifically address how you plan to ensure that the study is adequately monitored. You must identify the specific steps you plan to take to ensure proper monitoring, submit documentation of the monitoring visits for each clinical site, and verify that the current consultant is adequately monitoring the study.

In addition, during the inspection close-out discussion and in your written response, it was stated that a modified investigator agreement, including a financial disclosure agreement, has been sent to all investigators. You also stated during the close-out discussion that the original investigator agreement for [REDACTED] was signed before

patients were enrolled, but that it was misplaced. You stated that [REDACTED] signed another agreement on December 20, 2001, and that a memo was placed in [REDACTED] file. Please submit copies of each of these signed investigator agreements.

Based on follow-up conversations with [REDACTED] and on your June 1, 2003 response, we also understand that the company is preparing a notification to be sent to patients who did not participate in the investigation but who were implanted with the investigational device. Please submit copies of this notification, including copies signed by the recipients, as well as the “re-signed” informed consent forms for the [REDACTED] site and the IRB-approved informed consent forms referenced in your response to observation 5 in the Form FDA 483. In addition, please submit copies of any IRB correspondence indicating approval of your revised informed consent forms and any other pertinent documentation.

During the inspection and close-out discussion, Ms. Guillermo discussed with you and [REDACTED] several protocol deviations, including the treatment of two patients not meeting the specified age criteria of 18-75 years, three patients above the maximum body mass index limit of 40, and three patients who received treatment of both [REDACTED] with the investigational device. [REDACTED] stated that there was confusion among clinical investigators concerning treatment of subjects for [REDACTED], and that the company intends to submit another IDE supplement to FDA. Please describe the steps taken to minimize such protocol deviations in the future, and any steps taken to address confusion regarding use of the device for [REDACTED].

Failure to maintain accurate, complete, and current records relating to the investigation (21 CFR 812.140(b))

It is the sponsor’s responsibility to maintain accurate, complete and current records relating to an investigation. 21 CFR 812.140. Your firm did not maintain adequate documentation of pre-study monitoring visits. For example, there is a lack of documentation of these visits for [REDACTED]. There is also incomplete documentation of pre-study monitoring visits at [REDACTED] since the clinical investigator did not sign the necessary documents to verify his presence at these visits.

The violations listed above are not intended to be an all-inclusive list of objectionable practices that may exist. The sponsor is responsible for adhering to each applicable requirement of the Federal Food, Drug, and Cosmetic Act (21 USC 321 *et seq.*) and all pertinent federal regulations.

We recognize that you have been working with the Office of Device Evaluation in FDA's Center for Devices and Radiological Health (CDRH) and the Institutional Review Boards to implement corrective actions, and that your efforts to complete your corrective action plan are ongoing. This letter does not supercede the obligations you previously

committed to take to solve data integrity problems. Plus Orthopedics should continue to work with FDA and the IRBs to satisfactorily complete the required auditing, implementation of the corrective action plan, and other responsibilities arising in connection with this study.

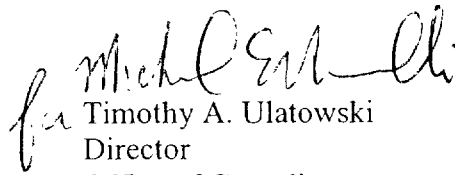
You must provide this office with written documentation of the additional specific steps you have taken or plan to take to correct these violations and bring your study activities into compliance with FDA regulations and to prevent recurrence of similar violations. Failure to do so could result in regulatory action without further notice.

Please address your correspondence to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Linda Godfrey.

A copy of this letter has been sent to FDA's Los Angeles District Office, 1990 MacArthur Blvd., Suite 300, Irvine, California 92612. We request that copies of your response be sent to FDA's Los Angeles District Office and the Office of Device Evaluation, Attention: Carl DeMarco, 9200 Corporate Boulevard, HFZ-400, Rockville, Maryland 20850.

If you have any questions, feel free to contact Linda Godfrey at (301) 594-4723 extension 134.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski". The signature is written in a cursive style and is positioned to the left of the printed name.

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