

JUN 20 2003

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WARNING LETTER

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

VIA FEDERAL EXPRESS

Randolph C. Robinson, M.D., D.D.S.
President
Inter-Os Technologies, Incorporated
7430 East Park Meadows Drive, Suite 300
Lone Tree, Colorado 80124

Dear Dr. Robinson:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at Inter-Os Technologies, Inc., to discuss the written response to the deviations noted, and to request your prompt response to the remaining issues. Ms. Lori Medina, an investigator from FDA's Denver District Office conducted the inspection from February 18 to February 25, 2003. The inspection was conducted to determine if your activities as a sponsor and principal investigator of the [REDACTED] study complied with applicable FDA regulations. The [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)].

The FDA conducted the inspection under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another program objective is to ensure that human subjects are protected from undue hazard or risk during 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, Part 50-Protection of Human Subjects, and Section 520(g) of the Act [21 U.S.C. 360j(g)]. You received a Form FDA 483 "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed with you and others. We acknowledge receipt of a copy of your March 25, 2003, response to Mr. Howard Manresa, Director of the Compliance Branch, Denver District Office, and acknowledge that you voluntarily terminated the [REDACTED] Study until you receive an approved IDE. The deviations noted on the FDA 483, our subsequent review of the inspection report, and your response to the FDA 483 items are discussed below:

Failure to obtain informed consent [21 CFR 50.20]

You failed to obtain informed consent from two study subjects ([REDACTED]) prior to dental implant surgery.

Applicable federal regulations at 21 CFR § 50.20 provide that no investigator shall involve a human being as a subject in covered research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

Failure to obtain FDA and IRB approval prior to beginning the study [21 CFR 812.40, 812.42, 812.100, and 812.110(a) and (b)]

You failed to obtain an FDA approved IDE and IRB approval prior to enrolling and treating subjects under the protocol entitled "[REDACTED]"

During the inspection, the FDA investigator documented that you surgically implanted the [REDACTED], a significant risk medical device, in four patients without an approved IDE. Your written response states that you did not need an IDE to implant the first two patients with the [REDACTED] because you regarded the [REDACTED] as a custom device for these patients and, thus, exempt from IDE requirements. The custom device exemption applies to devices that meet a narrow and specific set of statutory requirements in section 520 (b) of the Act. The devices you implanted did not fully meet these requirements nor those described in 21 CFR 812.3(b) for custom devices. These devices also do not meet the IDE exemptions in 21 CFR 812.2(c) (7).

Custom devices are intended for use by an individual patient named in a dentist or physician's order and made in a special form for that patient. Two patients received implants of the same prototype [REDACTED] device. Although you "customized" the device to fit each patient, the [REDACTED] was the same design and not made specifically for each patient.

You also modified the prototype [REDACTED] and implanted a third patient as well as reimplemented one of the first two. You subsequently submitted an IDE application to the FDA. After receiving an IDE application disapproval letter from the FDA dated December 20, 2000, you also permitted a Sub-Investigator to implant the [REDACTED] in a fourth patient on November 2, 2001. The disapproval letter stated that "a sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application" and that "you must not place the [REDACTED] in any other human subjects until your IDE has been approved." The FDA disapproved the IDE, in part, because there were no animal data to demonstrate the device's safety and effectiveness.

Failure to adhere to the general and specific responsibilities of a clinical investigator [21 CFR 812.100 and 812. 110(a) and (b)].

You failed to conduct follow-up visits in accordance with the protocol. The protocol requires patient follow-up visits at 3 months and during the second year in the consolidation phase. There was no 3-month follow-up visit for one patient. Your response indicated that this individual must travel a long distance for follow-up and that he did receive a 2-year follow-up visit, but there is no documentation in his chart about the visit. Complete information on a subject is essential to support the IDE, and the

subject should not be unnecessarily exposed to the risks associated with an investigational device. During the informed consent process, the investigator is responsible for explaining to subjects the importance of meeting study requirements. Only subjects willing and able to meet the requirements should participate in the study.

Failure to carry out the responsibilities of a sponsor [21 CFR 812.40]

You failed to provide the Sub-Investigator with information needed to conduct the investigation and did not inform him that he was participating in a clinical trial. Consequently, the Sub-Investigator implanted a patient with an unapproved device and failed to obtain an appropriate, study-related IRB informed consent from his patient.

Your response indicated you did not realize that you needed both IRB approval and an IDE to conduct the study. However, as indicated above, the letter sent to you in December 2000, stated you needed both of these to conduct the study.

Failure to obtain signed agreements from participating investigators [21 CFR 812.43(c)]

There were no signed investigator agreements, including financial disclosure information, obtained from investigators participating in the study. The FDA disapproval letter informed you that the FDA requires signed investigator agreements. These agreements must contain the information specified in FDA regulations, including a statement of the investigator's commitment to conduct the investigation according to the investigational plan, FDA regulations, IRB requirements, and assurance that the requirements for obtaining informed consent are met. We acknowledge that you included a copy of your new Investigator Agreement in your response.

Failure to have written monitoring procedures as part of the investigational plan [21 CFR 812.25 (e)]

There were no written monitoring procedures for this study. The monitoring frequency is also not indicated resulting in infrequent, irregular monitoring intervals (15 to 16 months). Sponsors must monitor studies using written procedures, and at adequate intervals, to assure that investigators are complying with the signed agreement, investigational plan, and all applicable FDA regulations. We note that you included a copy of your new monitoring procedures and have established a monitoring interval of twice per year.

Failure to maintain device accountability records [812.140 (b) (2)]

There were no records to account for 3 of the 33 prototype [REDACTED] devices received from the manufacturer. FDA regulations require study sponsors to maintain records documenting shipping and disposition of study devices including information such as dates of shipment and batch number. We note that you developed a Device and Supply Disposition Log to correct this deficiency.

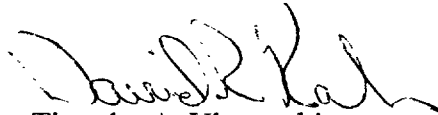
The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist at your facility. As a sponsor/investigator, you are responsible for ensuring that you conduct clinical trials according to FDA regulations.

Your response indicates that you have developed corrective measures and plans to ensure that these deviations are not repeated in the future. Your plans should also include notifying the four patients, by certified mail, that they received implants of an unapproved device. The other investigators (Drs. [REDACTED]) involved in the study should also receive notification, in writing, that they should not implant additional patients with the [REDACTED]. The monitoring plan should also state that the monitoring interval will be at least twice per year.

Please advise this office, in writing, within fifteen (15) working days after receiving this letter of the additional, specific steps you have taken to correct these violations and prevent the recurrence of similar violations. Failure to respond may result in the FDA taking regulatory action without further notice to you. Please direct your response to the following address: 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: Sybil Wellstood, Ph.D.

We are also sending a copy of this letter to FDA's Denver District Office and request that you also send a copy of your response to that office. If you have any questions, please contact Dr. Wellstood by phone at (301) 594-4723, ext. 140, or by email at saw@cdrh.fda.gov.

Sincerely yours,



For

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