



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

JUL -- 6 2005

WARNING LETTER

VIA FEDERAL EXPRESS

Mark A. Frankle, M.D.
13020 Telecom Parkway North
Temple Terrace, Florida 33637-0925

Dear Dr. Frankle:

The purpose of this Warning Letter is to inform you of objectionable conditions revealed during a Food and Drug Administration (FDA) inspection of your clinical site and to request prompt reply. During the period of February 22, 2005 through March 30, 2005, an investigator from FDA's Florida District Office inspected your site. The purpose of the inspection was to determine whether your clinical site activities and procedures relating to investigational studies of FDA-regulated products complied with applicable FDA regulations. The product used in [REDACTED] study 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)].

We have completed our review of the report submitted by the Florida District Office which described and documented deviations from the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 56 - Institutional Review Boards, Part 50 - Protection of Human Subjects, and Part 812- Investigational Device Exemptions. These deviations were listed on the Form FDA 483, "Inspectional Observations," that was presented to you and discussed with you and Mr. Derek Pupello, at the conclusion of the inspection.

The inspection was conducted under a program designed, in part, to ensure that data and information contained in applications for Investigational Device Exemptions (IDEs) are scientifically valid and accurate. Another objective of this program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

A description of FDA regulation deviations follows:

You implanted devices that did not have an FDA-approved IDE under § 520(g) of the Act.

Examples of failure to adhere to the regulations include, but are not limited, to the following:

1. Between March 13, 1998, and October 28, 2002, you implanted at least [REDACTED] patients with the [REDACTED] without prior FDA or IRB approval.

[REDACTED] is a medical device that requires a premarket approval (PMA) pursuant to section 515(a) of the Act, unless it has an approved investigational

device exemption (IDE) under § 520(g) of the Act. These devices did not have an FDA-approved PMA nor had an IDE been approved permitting their investigational use. By receiving and implanting these adulterated devices, you committed a prohibited act under § 301(c) of the Act.

During the inspection, you stated to our investigator that you believed the [REDACTED] devices were custom devices as suggested to you by the sponsor when you implanted at least [REDACTED] patients. These devices did not meet the definition of a custom device. The custom device exemption applies to devices that meet a narrow and specific set of statutory requirements as set forth in section 520(b) of the Act and further defined in 21 CFR 812.3(b). These devices did not meet the statutory or regulatory requirements for custom devices. Custom devices are limited to those intended for use by an individual patient named in a physician's order and made in a specific form for that patient or to meet the special needs of a doctor in his practice.[21 CFR 812.3(b)(5)] The [REDACTED] devices were not made to meet the need of an individual patient or to meet your individual needs as a physician (an example of the latter would be a device altered to meet the physical limitations of a doctor). Therefore, the [REDACTED] devices are not custom devices as defined by statute or regulation.

2. You implanted patients [REDACTED] and [REDACTED] with the [REDACTED] prior to IRB approval of the IDE.

An investigator may not allow any subject to participate in a study before obtaining IRB approval. 21 CFR 812.110(a). You informed our investigator that these patients were implanted on a compassionate use basis. If there is a patient or group of patients who do not meet the requirements for inclusion in the clinical investigation, for whom there is no alternative treatment, but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition, you should contact FDA before using a device on a "compassionate" basis in such patients. FDA regulations do not allow use of an investigational medical device without IRB approval of the study.

In addition to the violations listed above, the FDA investigator informed you that the [REDACTED] [REDACTED] you implanted in subject [REDACTED] on July 7, 2003 was not cleared or approved by FDA, nor did it have an approved IDE at the time of the implant. You should ensure before implanting medical devices that they are legally marketed devices with the required FDA approval or clearance.

Failure to adhere to the responsibilities of a clinical investigator. [21 CFR 812.100]

Pursuant to 21 CFR 812.100, an investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations. You failed to adhere to these regulations. In particular, between July 26, 2004 and January 17, 2005 you implanted at least [REDACTED] patients with [REDACTED] devices, specifically [REDACTED] or [REDACTED] corresponding [REDACTED]. These devices were not components identified in [REDACTED], therefore, you failed to ensure that the investigation was conducted according to the investigational plan.

You informed our investigator that you considered these implants to be custom devices. Again, these devices did not meet the definition of a custom device as already discussed. The custom device exemption applies to devices that meet a narrow and specific set of statutory requirements as set forth in section 520(b) of the Act. These devices did not meet these requirements nor those described in 21 CFR 812.3(b) for custom devices. Custom devices are limited to those intended for use by an individual patient named in a physician's order and made in a special form for that patient. [21 CFR 812.3(b)(5)]

A participating investigator must maintain all correspondence with another investigator, IRB, the sponsor, a monitor, or FDA, including required reports. In addition to the above violations, you should be aware that the FDA investigator noted instances when documentation of correspondence with the IRB and the sponsor was not maintained. For example, our investigator was informed that the request for use of the [REDACTED] for patients [REDACTED] and [REDACTED] was probably made over the phone. Your communication with [REDACTED], the sponsor, was completed primarily through telephone conversations. There was no documentation of these communications at your site. As an Investigator you are required to maintain records of correspondence with IRBs and the sponsor as described in 21CFR 812.140(a)(1). We recommend you maintain written documentation of your communication with the IRB and the sponsor.

Please submit a written response to this letter, identifying all human subjects who received the (1) [REDACTED] between March 13, 1998 to October 2002, prior to the IDE study, (2) unapproved [REDACTED] and (3) [REDACTED] and corresponding [REDACTED], or any other unapproved device by name, address and date of implantation. We reviewed the "CONSENT TO COLLECT INFORMATION" form you sent to patients implanted during the [REDACTED] Study and found it inadequate. To protect the rights and welfare of the human subjects you implanted, we recommend you develop a corrective action plan. At a minimum, the plan should include notification of each recipient by certified mail that they were implanted with an unapproved device, who to contact in the event of an emergency, and where to report adverse events. Your corrective action plan should be submitted to this office prior to implementation. Letters sent to the implant recipient should be reviewed and approved by all IRBs associated with the institutions where these patients were implanted prior to distribution. A sample copy of each IRB approved letter to be sent to implant recipients should also be submitted to this office. In addition, please provide a list of your current investigational studies and include the name of the study sponsor and the date of IRB approval.

The deviations cited above are not intended to be an all-inclusive list of deficiencies at your site. As a clinical investigator, it is your responsibility to ensure that investigations that you participate in are conducted in accordance with applicable FDA regulations.

Please notify this office in writing within fifteen (15) working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

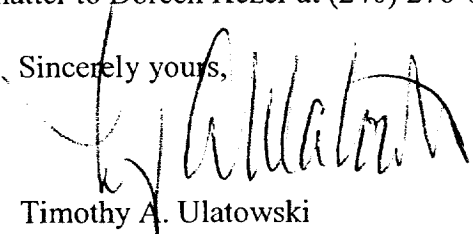
You should be aware that FDA considers your actions to be serious violations of the law and may result in FDA taking regulatory action without further notice to you. Failure to respond can result in further regulatory action, including initiation of disqualification procedures, without further notice.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Special Investigations Branch, 2098 Gaither Road, Rockville, Maryland 20850. Attention: Doreen Kezer, Chief, Special Investigations Branch.

A copy of this letter has been sent to the Food and Drug Administration, Florida District Office, 555 Winderley Place, Suite 200, Maitland, Florida 32751. We request that a copy of your response also be sent to FDA's Florida District Office.

Please direct all questions concerning this matter to Doreen Kezer at (240) 276-0125.

Sincerely yours,



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