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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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. Mighell, M.D.
13020 Telecom Parkway North
Temple Terrace, Florida 33637-0925

Dear Dr. Mighell:

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 March 15, 2005, through March 30, 2005, Ernest Clausnitzer, 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 the [redacted] 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)].

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) and Part 812-Investigational Device Exemptions. These deviations were listed on the Form FDA 483, "Inspectional Observations," that was presented to 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.

Please note the following FDA regulation deviations:

Failure to adhere to the general and specific responsibilities of a clinical investigator. [21 CFR 812.100 and 812.110(c)]

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 for protecting the rights, safety and welfare of the subjects under the investigator's care. An investigator also is responsible for ensuring informed consent is obtained from all study subjects. Further, section 812.110 describes specific responsibilities of investigators, including the responsibility for ensuring that an investigational device is used only on study subjects within the investigator's supervision. Examples of failure to adhere to the regulations include, but are not limited to the

following:

1. On November 5, 2002, you signed an [redacted] Investigator's Agreement. Patient [redacted] was implanted with a [redacted] on November 15, 2002, but was not enrolled in [redacted] and no informed consent was obtained from patient [redacted]

   You informed our investigator that you believed this was a custom device for humanitarian need at the time of implantation and therefore the patient did not have an informed consent on file and was not enrolled into the study. Custom devices are defined at 21 CFR 812.3. Among other requirements, 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. In addition, please note that a custom device is not generally available in finished form for purchase or for dispensing upon prescription and it is not offered for commercial distribution through labeling or advertising.

   You informed our investigator that you did not have the custom device documentation showing the custom order but could obtain it from the [redacted] Sales Representative. Without this documentation, FDA cannot evaluate whether the device meets the criteria of a custom device as defined in 21 CFR 812.3. Please provide documentation showing that the [redacted] implanted in patient [redacted] on November 15, 2002 was custom ordered from [redacted] for this specific patient and in a specific form.

2. While you were the Principal Investigator for the [redacted] study conducted at Tampa General Hospital:

   Six patients were implanted with [redacted] components that were not components of [redacted] between July 26, 2004 and January 17, 2005. You and Mr. Pupello informed our investigator on March 31, 2005 that [redacted] just received FDA approval to add these components into the [redacted] study. This response is inadequate because the fact remains that at the time of the implantations, the components were not part of the approved study. You failed to adhere to the responsibilities of a principal investigator, in that you did not ensure the study was conducted according to the signed agreement, the investigational plan, and FDA regulations.

Receipt in Interstate Commerce of an Adulterated and Misbranded Device. [FDC Act 301(c)]

An [redacted] that did not have 510(k) clearance was implanted in study subject [redacted] on July 7, 2003. This device did not have an approved IDE at the time of implantation and was not part of the [redacted]; consequently, these devices are adulterated under § 501(f)(1)(B) of the Act in that they do not have an approved PMA and are misbranded under section 502(o) of the Act in that they are not the subject of a cleared 510(k). By receiving and implanting these adulterated devices, you committed a prohibited act under § 301(c) of the Act.

Throughout the inspection our investigator was informed that you believed that although you were the documented Principal Investigator, it was actually [redacted] who was overseeing the study. You stated that you were documented as the Principal Investigator due to a concern raised by the University of Southern Florida IRB, but it was your understanding that you were only the Principal

Investigator on paper due to your credentials being acceptable by the IRB.

You also informed our investigator that as the Principal Investigator for the [redacted] study conducted at Tampa General Hospital, you understood that you are responsible for the overall conduct of the study, including all of the activities of your co-investigator and your shared research manager. In your response to this letter, please address how you will fulfill your responsibilities as a Principal Investigator for this study and in future studies.

Please note that as a clinical investigator, you are responsible for every aspect of a research study conducted at your site. Failure to abide by an investigational plan and conditions imposed by the IRB or FDA or by Federal Regulations, may adversely affect the development of valid scientific evidence sufficient to support an application to FDA for marketing approval or clearance.

Findings obtained from our bioresearch monitoring inspections will be shared with the Office of Device Evaluation who will ultimately determine the applicability of your data in supporting the premarket applications.

In the future, in order to better understand investigational study practices, you might consider attending and having your staff attend training sessions that focus on the operations of investigational studies. Such programs are available from various professional associations. In addition, you will want to ensure that future studies in which you are involved have clearly identified the sponsor and clinical investigator responsibilities, have clearly identified protocols, and are well-monitored. There needs to be cooperation and communication between all participants of the study including the sponsor, the IRB, the investigator, and staff.

We would like to remind you that as a clinical investigator, it is your responsibility to ensure that investigations that you participate in are conducted in accordance with applicable FDA regulations. You should refer to the regulations relevant to device studies, some of which were referenced above, in 21 CFR Part 812. You can refer to the following web site for additional information: Investigational Device Exemptions - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm

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.

Within 15 days working days, you must respond to this letter in writing. Please include supporting documentation of the specific steps you have taken or will take to correct the violations identified and to prevent the recurrence of similar violations in current and future studies. 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.

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. 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, 2094 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 Florida District Office.

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

Sincerely yours,

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

age 5-Mark A. Mighell

cc: PURGED COPIES

[redacted]

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