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Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

DEPARTMENT OF HEALTH & HUMAN SERVICES

DEC 21 2005



WARNING LETTER

Via Federal Express

David D. Dore, MD
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Celebration, FL 34747

Dear Dr. Dore:

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. An investigator from FDA's Florida District Office conducted the inspection from August 22 through September 2, 2005. The purpose of the inspection was to determine if your activities and procedures as a Clinical Investigator (CI) complied with applicable FDA regulations. The clinical trials that were the subject of the inspection were

[REDACTED] and [REDACTED], both of which were sponsored by [REDACTED] (formerly [REDACTED]). The products used in the studies are devices 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)]. This letter also discusses your September 22, 2005, written response to the observations noted at the time of the inspection and requests that you promptly implement corrective actions.

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), 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 Florida 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)). At the close of the inspection, the FDA investigator presented a Form FDA 483, "Inspectional Observations," to you for review, and discussed the listed observations. The deviations noted on the FDA 483, your written responses to those deviations, and our subsequent review of the inspection report 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 50.27(a)].**

You failed to ensure that the current IRB-approved version of the informed consent form was executed by each of the subjects enrolled in the studies as required by the above-stated regulations.

Examples of this failure include but are not limited to the following:

At least two study subjects were consented using an expired version of the consent form. Specifically:

- a.) For Protocol [REDACTED], Subject [REDACTED] signed the 9/13/99 version of the consent form, which expired on 3/8/00, on 3/31/00. The original version of the protocol, approved by the IRB on 9/13/99, specified that the [REDACTED] to be used for the study were the following: [REDACTED], the [REDACTED], the [REDACTED], and the [REDACTED]. The revised protocol, approved on 3/8/00, allowed use of the [REDACTED] in addition to the [REDACTED] listed above. Therefore, the version of the informed consent that Subject [REDACTED] signed also violated 21 CFR 50.25(a)(1) because it did not reveal this aspect of the study. This omission is very significant because Subject [REDACTED] in fact received the [REDACTED], despite not having given his consent to participate in a study that would employ it.
- b.) For Protocol [REDACTED], Subject [REDACTED] signed the 6/21/01 version of the consent form, which expired on 4/9/02, on 6/26/02.

You stated in your response letter to the Florida District Director, dated September 22, 2005, that you plan to have weekly meetings with your research team, at which time you will confirm that expired versions of IRB-approved consent forms are destroyed. Your response to these violations is not adequate in that you have not addressed the issue surrounding the examples shown above, in which subjects were not consented with the correct version of the consent form at the time of study enrollment. Please explain and provide documentation of the methods or procedures that will be used at your clinical site to train study staff on the consenting process, to include use of the correct IRB-approved version of the informed consent form, and consenting subjects when the consent forms are revised.

2. **Failure to ensure an investigation is conducted in accordance with the signed agreement with the sponsor, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by the FDA or the IRB [21 CFR 812.100, 21 CFR 812.110(b)].**

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

- a.) For Protocol [REDACTED]
 - i. The initial IRB approval for the study extended only until October 10, 2000 and required that you request renewed approval to continue your study after that time. You did not obtain IRB approval to continue the study until January 9, 2001. However, during the time the IRB approval had lapsed, you enrolled and/or performed study surgery on several subjects. Specifically:
 - At least five subjects ([REDACTED], [REDACTED], [REDACTED], [REDACTED], and [REDACTED]) were consented and enrolled into the study between October 11, 2000 and December 11, 2000.
 - At least six subjects ([REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], and [REDACTED]) had their study surgeries performed between October 16, 2000 and December 12, 2000.

You stated in your response letter that the IRB did not notify you that the study was due to expire. You also stated that the IRB now has a system in place for notifying clinical

investigators of IRB expirations, and that your research team “will be aware of when studies are due to expire.” Your response to these violations is not adequate. Please explain and provide documentation of the methods or procedures that will be used at your clinical site to ensure that you and your study staff are aware of the study renewal dates in order to ensure that there are no lapses in IRB approval during a study.

- ii. The original version of the protocol, approved by the IRB on 9/13/99, was revised and approved by the IRB on 3/8/00, to allow use of the [REDACTED] Subject [REDACTED] signed the 9/13/99 version of the consent form on 2/28/00 and received the [REDACTED] during surgery on 2/29/00, before the use of that component was approved by the IRB.

You stated in your response letter that you plan to have weekly meetings with your research team, at which time you will confirm that all protocol amendments are approved by the IRB. Your response to this violation is not adequate. Please explain and provide documentation of the methods or procedures that will be used at your clinical site to ensure that you and your study staff do not implement changes or revisions to study procedures before they have been approved by the IRB.

- iii. The protocol required that the [REDACTED] to be used for the study are “those with a [REDACTED].” However, you used a non-protocol [REDACTED] for at least eight subjects ([REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], and [REDACTED]).

You stated in your response letter that you contacted the sponsor and you were told that use of the [REDACTED] was acceptable. However, use of the [REDACTED] was noted as a protocol deviation by the study monitor on at least three separate monitoring reports over a period of several months. You also stated that, in the future, you will obtain written clarification from the sponsor for protocol deviations. Your response to these violations is not adequate in that it does not address what corrective actions you are planning to undertake. You should also understand that federal regulations require that investigators notify the study sponsor and the IRB of any deviations from the investigational plan within five working days, if the deviation occurs to protect the life or physical well-being of a subject in an emergency. If the situation is not an emergency, prior approval of the sponsor is required for changes or deviations from the investigational plan. [21 CFR 812.150(a)(4)] Such approval should be documented and included with the study records. [21 CFR 812.140(a)(1)] Federal regulations also require that investigator records contain documentation of the dates and reasons for each protocol deviation. [21 CFR 812.140(a)(4)]

Please provide an explanation of the methods or procedures that will be used at your clinical site to ensure that all protocol deviations are appropriately approved and documented.

- b.) The protocols for both studies required that subjects return at specific times for follow-up visits for evaluations and assessments of adverse events, device efficacy, and quality of life. The protocol also required that procedures be performed at these follow-up visits in order to perform the evaluations and assessments. You failed to ensure that the protocol-required visits and procedures were performed as required. For example:
 - i. For Protocol [REDACTED]:
 - The six-week visit was not performed for at least three subjects, and the six-week visit

- was performed outside the timeframe for at least three subjects.
- The three-month visit was not performed for at least three subjects, and the three-month visit was performed outside the timeframe for at least one subject.
- The six-month visit was not performed for at least nine subjects, and the three-month visit was performed outside the timeframe for at least five subjects.
- The twelve-month visit was not performed for at least nine subjects, and the twelve-month visit was performed outside the timeframe for at least three subjects.
- At least fourteen subjects who were seen at follow-up visits did not have the required post-surgical x-rays performed.

ii. For Protocol [REDACTED]:

- At least three subjects had visits that were not performed or were performed outside the timeframe.
- At least three subjects did not have the required post-surgical x-rays performed.

You stated in your response letter that you will meet with your research team before beginning any study to assess if there are sufficient assets for the safe and timely conduct of the study, and will meet weekly to review each study participant's status. Your response to these violations is not adequate. Please explain and provide documentation of the methods or procedures that will be used at your clinical site to ensure that your study staff is adequately trained and is aware of the requirements for each study, including follow-up visits, required procedures, and study documentation. Also, please include the procedures that will be used to ensure study subject compliance with the follow-up visit schedule.

- c.) You enrolled an ineligible subject into Protocol [REDACTED]. The protocol specifically excluded subjects who are under treatment for a psychiatric disorder. Subject [REDACTED] had documentation in the study files of an on-going treatment for depression and was on permanent disability for depression, but was enrolled and treated in the study.

You stated in your response letter that this subject was eligible for the study because the psychiatric treatment occurred three years ago and the subject was not currently under treatment for depression. However, your response to this violation is not adequate in that the study records indicate that the subject is currently on medications for treatment of depression and anxiety, and, as noted above, is on permanent disability for the condition. You also stated that, in the future, you would refer such a subject for psychiatric evaluation and clearance prior to enrollment. A subject who does not meet eligibility criteria cannot be enrolled into a clinical study without prior notification and approval of the study sponsor, and possibly of the IRB and the FDA. Please provide assurance that you understand your responsibilities as a clinical investigator regarding compliance with the study protocol and the investigational plan, and describe the methods or procedures that will be used at your clinical site to ensure that you and your study staff are aware of the eligibility requirements for each study.

3. Failure to maintain accurate, complete, and current records regarding the receipt, use, or disposition of a study device [21 CFR 812.140(a)(2)].

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

- a.) For Protocol [REDACTED]: There was no documentation of the total number of study devices you received, implanted, or returned to the sponsor. Although 93 subjects were enrolled into this study at your clinical site, the device accountability record in your study files, which was provided by the study sponsor, listed only 57 study devices implanted.
- b.) For Protocol [REDACTED]: There was no documentation of the total number of study devices you received, implanted, or returned to the sponsor. A record in your study files, which was provided by the study sponsor, listed only the eight devices implanted for the eight enrolled subjects at your site. A record was also observed in your files that reported 26 devices were shipped to your site, of which eight were used and four were returned. This record appears to indicate that there are fourteen unaccounted devices.

The files for both studies noted that a sales representative or distributor was delegated the responsibility of receiving and storing the devices. However, as a clinical investigator, you are responsible for ensuring that you maintain records of the type and quantity of devices received, the dates of receipt, the batch numbers or lot numbers, the names of all persons who received, used, or disposed of the devices, and how many devices were returned to the sponsor or otherwise disposed of. You also signed Investigator Agreements for both studies that stated the regulation indicated above. The agreements further state, "As you know, the FDA expects 100% of the experimental devices to be accounted for throughout the study and at its conclusion." Your delegation of a study task, such as device accountability, to another individual does not relieve you of the responsibility for ensuring that the study is conducted correctly and in accordance with the signed agreement, the investigational plan, and applicable federal regulations.

You did not address this violation in your response. Please explain and provide documentation of the methods or procedures that will be used at your clinical site to ensure that all study devices will be accurately and adequately documented and stored.

The violations described above are not intended to be an all-inclusive list of deficiencies that may exist at your clinical site. It is your responsibility as a clinical investigator to ensure compliance with the Act and applicable regulations when conducting clinical research, and to ensure that any staff or personnel who are delegated study tasks are knowledgeable regarding the Investigational Plan and are adequately supervised by you.

In addition to the items cited above, our review of the inspection results indicated that the IRB-approved consent form for Protocol [REDACTED] did not provide a description of all of the procedures that would be performed during the study, as required by 21 CFR 50.25(a)(1). Specifically, the form did not state that x-rays would be taken at all follow-up visits. You stated in your response that the informed consent was modeled after the sample consent form provided by the sponsor. As a clinical investigator, you are still responsible for ensuring that the consent form used for a study contains all the required elements as specified in the federal regulations. Your response stated that to prevent this problem from recurring, you and your research team will review the informed consents to ensure that they contain all the required elements prior to IRB submission. This is an acceptable corrective action. We suggest that you also review the consent forms for any on-going studies at your site to ensure that they contain all the required information.

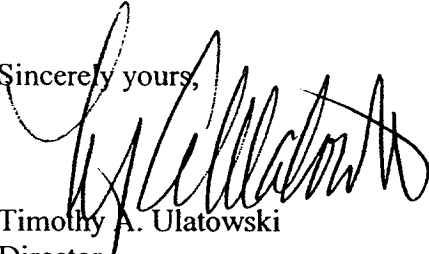
Within 15 working days after receiving this letter, please provide written documentation of the additional, specific steps you have taken or will take to correct the violations noted above and prevent the recurrence

of similar violations in current and future studies. You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. 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 the 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.

Please send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement, Program Enforcement Branch, HFZ-312, 9200 Corporate Boulevard, Rockville, Maryland 20850, Attention: Ms. Viola Sellman, Chief, Program Enforcement Branch.

We are also sending a copy of this letter to the FDA's Florida District Office, Food and Drug Administration, 555 Winderley Place, Suite 200, Maitland, FL 32751. We request that you copy the District Office on your response. If you have any questions, please contact Ms. Viola Sellman by phone at (240) 276-0125, or by email at vxs@cdrh.fda.gov.

Sincerely yours,



Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
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IRB/Purged Copy to:

Florida Hospital Institutional Review Board
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