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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

OCT 14 2004

Louis C. Rose, M.D.  
Throggs Neck Multi Care P.C.  
3058 E. Tremont Avenue  
Bronx, New York 10461

Dear Dr. Rose:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site. Mr. L. Glenn Massimilla, an investigator from FDA's New York District Office, conducted the inspection from June 7 through June 21, 2004. The purpose of the inspection was to determine if your activities as a clinical investigator for the [REDACTED] study complied with applicable FDA regulations. The [REDACTED] is a device as 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. The program also ensures 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, 21 CFR Part 50 – Protection of Human Subjects, and Section 520(g) of the Act. At the close of the inspection you were not available for discussion; therefore, Mr. Massimilla presented a Form FDA 483 “Inspectional Observations” to Joshua Falto, P.A.-C for review, and discussed the listed deviations with him. The deviations noted on the FDA 483 and our subsequent inspection report review are discussed below:

**(1) Failure to obtain Investigational Review Board approval (21 CFR 812.110(a)).**

Pursuant to 21 CFR 812.110(a), an investigator may determine whether potential subjects would be interested in participating in an investigation but shall not request the written informed consent of any subject and shall not allow any subject to participate before obtaining IRB and FDA approval.

Examples of your failure to comply with this requirement include but are not limited to the following:

Thirteen (13) subjects were enrolled from 7/27/2002 through 5/13/2003, and each subject had one or more devices [REDACTED] implanted from 7/27/2002 through 5/22/2003 at the [REDACTED] in [REDACTED]. However, you did not receive IRB approval until July 29, 2003, well after the dates of these implants. In addition, the study protocol and informed consent documents were reviewed by [REDACTED].

In our review of the inspection report, we also note that as of an April 6, 2004, Monitoring Visit, none of the subjects had yet signed an IRB-approved informed consent form.

**(2) Failure to obtain adequate informed consent (21 CFR 812.100 and 21 CFR 50.20, 50.25, and 50.27(a)).**

Pursuant to 21 CFR 812.100, an investigator is responsible for ensuring that informed consent is obtained in accordance with 21 CFR Part 50. In accordance with 21 CFR 50.20, "no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative." The informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. (21 C.F.R. 50.27(a)).

Examples of your failure to comply with the informed consent requirements include but are not limited to the following:

- Of the 13 subjects who had screening examinations/tests, 7 did not sign an informed consent document prior to these study-specific evaluations. Specifically, subjects [REDACTED] had pre-operative evaluations on 7/24/2002, 7/16/2002 and 7/26/2002, respectively, but did not sign informed consent documents until 7/27/2002. Subjects [REDACTED] had pre-operative evaluations on 8/5/2002 and 8/27/2002, but did not sign informed consent documents until 8/16/2002 and 10/2/2002, respectively. Subject [REDACTED] had pre-operative evaluations on 1/10/2003 and 1/13/2003, but neither signed an informed consent document until 2/19/2003.
- The informed consent document used to obtain consent from all 13 subjects enrolled in the study lacked required elements in that it failed to provide a contact for questions relating to the rights of research subjects, as required by 50.25(a)(7). In addition, the informed consent document contained incorrect or incomplete information. It incorrectly states that the subjects received the [REDACTED] when in fact the implant used at this site was planned to be, and was, the [REDACTED]. The informed consent document is also

incomplete in that it fails to include wording to complete the phrase “drug or device available to treat people with \_\_\_\_\_.” In addition, the informed consent document incorrectly identified the \_\_\_\_\_ Research Review Committee in the “confidentiality” section; in fact, there was no IRB involved at the time of consent. Any clinical investigation performed at \_\_\_\_\_ (the facility where surgery was performed) should have been submitted to the \_\_\_\_\_ IRB.

**(3) Failure to adhere to the investigational plan (21 CFR 812.100 and 812.110(b)).**

Pursuant to 21 CFR 812.100 and 812.110(b), clinical investigators are required to ensure that investigations are conducted according to the following: the signed agreement, the investigational plan, and applicable FDA regulations, as well as any conditions of approval imposed by the IRB or FDA. The study protocol is part of the investigational plan (21 CFR 812.25(b)). Our investigation revealed several deviations from the signed agreement and investigational plan, including but not limited to the following:

- The protocol required the exclusion of any “patient with \_\_\_\_\_” On 7/26/2002, the Preoperative assessment of \_\_\_\_\_ was conducted. The Inclusion/Exclusion case report form (CRF) for that visit indicated that a \_\_\_\_\_ was ineligible to participate in the study. However, on 7/27/2002, this subject had \_\_\_\_\_ though according to the protocol, patients enrolled in this clinical study who subsequently require surgery on \_\_\_\_\_ are acceptable only if \_\_\_\_\_ surgery is performed 9-12 months after the first surgery.
- Protocol-required follow-up was not conducted within the specified timeframes. For example, the following subjects had the specified evaluations conducted out of window: Subjects \_\_\_\_\_ (Early Post Op, 3 Months Post Op); \_\_\_\_\_ (Early Post Op, 6 Month Post Op); \_\_\_\_\_ (Early Post Op); \_\_\_\_\_ (Early Post Op); \_\_\_\_\_ (Early Post Op); \_\_\_\_\_ (Immediate Post Op); \_\_\_\_\_ (Early Post Op, 6 Months Post Op); \_\_\_\_\_ (3 Months Post Op); \_\_\_\_\_ (Immediate Post Op); \_\_\_\_\_ (Early Post Op).
- Protocol-required tests were not conducted. For example, \_\_\_\_\_ were not taken for the following subjects at the respective Post Op visit(s): \_\_\_\_\_ (12 Months); \_\_\_\_\_ (12 Months); \_\_\_\_\_ (12 Months); \_\_\_\_\_ (12 Months).

**(4) Failure to maintain accurate, complete, and current records (21 CFR 812.140(a)).**

Pursuant to 21 CFR 812.140(a), clinical investigators must maintain accurate, complete, and current records relating to the investigator's participation in an investigation. You failed to satisfy these requirements in that some patient records did not have the documentation necessary to support data collected in case report forms (CRFs). In addition, some subjects' CRFs did not contain complete information. Examples are as follows:

- Protocol-required data was not filled in on CRF #3 – [REDACTED] Evaluation for the following subjects at the respective visit(s): [REDACTED] (Pre Op, Early Post Op, 3 Months Post Op, 6 Months Post Op); [REDACTED] (Pre Op, Early Post Op, 3 and 6 Months Post Op); [REDACTED] (6 and 12 Months Post Op- and only one form for [REDACTED]); [REDACTED] (Pre Op, Early Post Op, 3 Months Post Op); [REDACTED] (6 Months Post Op); [REDACTED] (Pre Op, Early Post Op, 3 and 6 Months Post Op); [REDACTED] (6 and 12 Months Post Op); [REDACTED] (Pre Op, 3, and 6 Months Post Op); [REDACTED] (Pre Op, Early Post Op, 3 and 6 Months Post Op); [REDACTED] (Pre Op, Early Post Op, 3 Months Post Op); [REDACTED] (Early Post Op, 3 Months Post Op); [REDACTED] (Pre Op, Early Post Op, 3 Months Post Op); [REDACTED] (Pre Op, Early Post Op, 3 Months Post Op).
- Source documentation, such as a narrative report covering the operative procedure, were not contained in the following subjects' medical records: [REDACTED]
- Source documentation contained in the subjects' medical records is inconsistent with the data recorded in corresponding CRFs. For example, the medical record for subject [REDACTED] contains patient height and weight data of [REDACTED] and [REDACTED] lbs. (as of 8/22/2002). Physical Exams (CRF #4) for [REDACTED] dated 8/27/02 and 10/3/2002, contain patient height and weight data as [REDACTED] and [REDACTED] lbs. for each date. In addition, this subject had a medical history including [REDACTED] (per the medical record) but the (pre op) CRFs do not list these.

We recognize that you participated in a "control" arm of the study, which involved implantation of a device that has been cleared by FDA. However, because the study itself is being conducted pursuant to an IDE, you are subject to the regulations set forth at 21 CFR Part 812. We note that the Investigator Agreement you signed on July 26, 2002 explicitly states that "Pursuant to Food and Drug Administration regulations, 21 CFR, Section 812, [REDACTED] and Louis Rose, MD, do hereby agree that the following terms will apply to the proposed clinical study."

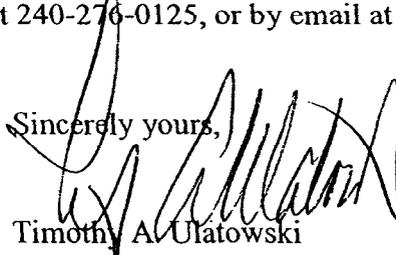
The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in this clinical study. It is your responsibility as a clinical investigator to assure adherence to each requirement of the Act and all applicable federal regulations.

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 these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. 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.

Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II, HFZ-312, 2094 Gaither Road, Rockville, Maryland 20850, Attention: Patricia L. Jahnes.

We are also sending a copy of this letter to FDA's New York District Office, and request that you also send a copy of your response to that office. If you have any questions, please contact Patricia L. Jahnes by phone at 240-276-0125, or by email at [plj@cdrh.fda.gov](mailto:plj@cdrh.fda.gov).

Sincerely yours,

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

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