DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

WARNING LETTER

MAR 2 5 2004

VIA FEDERAL EXPRESS

Mark Reisman, M.D.
Director of Cardiovascular
Research Department
Swedish Medical Center
1221 Madison Street
Arnold Pavilion, Suite 1020
Seattle, WA 98104

Dear Dr. Reisman:

The purpose of this letter is to inform you of violative conditions and activities found during a Food and Drug Administration (FDA) inspection at your clinical site, and to request that prompt corrective actions be taken. During the period of November 5-7, 11, 12, 20-21, and 25, 2003, Ms. Lori Silverstein, Ms. Catherine Laufmann and Ms. Deborah Nebenzahl, investigators from the FDA, Seattle District Office, conducted an inspection of your clinical investigation which used significant risk devices to treat migraine headaches by [redacted] The purpose of the inspection was to determine whether your activities as a sponsor and principal investigator of an investigational study involving significant risk devices complied with applicable FDA regulations.

The inspection included a review of the protocol and other materials submitted to your Institutional Review Board (IRB) in connection with this study. Your patient consent form, which was approved by the IRB, states that the study was being conducted "to look at the safety of [redacted] in patients who have frequent migraine headaches with or without aura and see what effects" this treatment has on their headaches. The products used in this study to close the [redacted] is approved for use in patients with [redacted]

[redacted]. Both of these products are devices within the meaning of section 201(h) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 321(h).

The inspection was conducted under a program designed, in part, to ensure that data and information contained in applications for Investigational Device Exemptions (IDEs) and Humanitarian Device Exemptions (HDEs) 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.

Our review of the inspection report submitted by the district office revealed serious violations of requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812 – Investigational Device Exemptions, and Part 50 – Protection of Human Subjects. At the conclusion of the inspection, the FDA Investigators held a discussion with you detailing the objectionable conditions found. The violations observed by the investigators and during our subsequent review of the inspectional report are discussed below.

- **Failure to obtain FDA approval prior to beginning the study [Section 520(g) (21 U.S.C. 360j(g)) and 21 CFR 812.40, 812.42, 812.110(a)]**

The Act and its implementing regulations set out a scheme for the study of investigational medical devices. 21 U.S.C. 360j(g) and 21 CFR Part 812. In February 2002, you submitted an application to FDA for an IDE for a study entitled, "[redacted]" for closure of [redacted] in the treatment of migraine headaches using [redacted]. This application was disapproved on March 28, 2002, by FDA's Office of Device Evaluation (ODE) in the Center for Devices and Radiological Health (CDRH). In their disapproval letter, ODE stated that the risk of device placement for [redacted] outweighs the potential benefit of the proposed treatment for migraine headaches.

Subsequently, you applied to your IRB for approval to conduct the "[redacted]" and that organization approved your study on December 5, 2002. You enrolled the first patient on January 21, 2003, almost ten months after ODE had disapproved your IDE application. Between January 21 and September 17, 2003, [redacted] devices were implanted in nine (9) patients at the Swedish Medical Center to treat migraine headaches. Of the nine subjects implanted, six received the device approved for the [redacted] and two received the device approved through the HDE process solely for the stroke indication. It is unclear which device the first patient received because the device label was not found in the records for this subject.

All of the subjects enrolled in your study were implanted with significant risk devices without prior FDA approval of an IDE. Because your study was conducted to determine the safety and effectiveness of using these devices in a manner not approved by FDA, you were required to have an FDA-approved IDE application before you could legally conduct such studies.

FDA acknowledges your affidavit dated November 25, 2003. While it provides a sequence of events and your acknowledgement of the proceedings related to the "[redacted]," it does not diminish the seriousness of the violations outlined in this letter. As an experienced clinical investigator of device protocols, and with full knowledge of the disapproval letter from the FDA regarding [redacted], you were aware that you needed FDA approval before conducting a clinical investigation using the [redacted] devices to treat migraines.

- **Failure to obtain adequate informed consent [21 CFR 50.25(a) and 812.100]**

Investigators are responsible for ensuring that informed consent is obtained in accordance with FDA regulations at 21 CFR Part 50 and 812.100. The basic elements of informed consent are set forth at 21 CFR 50.25(a) and include a description of the procedures to be followed. Section 50.25(a)(1) requires the informed consent to include, among other things, a statement that the study involves research and an explanation of any of the procedures that are experimental.

The letters sent to potential study patients from your cardiovascular research nurse dated December 17, 2002 and February 5, 2003, stated that, "The device used [redacted] is NOT investigational; it has been approved by the FDA." Because these letters do not alert potential patients to the experimental nature of the study procedures when the device is used for the treatment of migraine headaches, these documents fail to comply with the requirements for informed consent.

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

You must immediately cease conducting clinical investigations in which you implant the [redacted] devices to treat migraines. Conducting clinical investigations without an approved IDE application is prohibited under Section 301(q)(1) of the Act [21 U.S.C. 331(q)(1)]. Continued study of these devices for unapproved uses without an IDE will be considered by FDA to be a knowing violation of the Act.

Before continuing your research study, you must receive approval of an IDE application. The information to be included in an IDE application and the procedures for submitting an IDE application are set forth in 21 CFR Part 812, Subpart B - Application and Administrative Action.

Within 15 days, you must respond to this letter in writing. You should be aware that FDA considers your actions to be serious violations of the law and your failure to respond may result in FDA taking regulatory action without further notice to you. These actions include, but are not limited to, investigator disqualification, seizing product inventory, obtaining an injunction to prevent further violations of the law, assessment of civil money penalties, and criminal prosecution.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ-311), 2098 Gaither Road, Rockville, Maryland, 20850. Attention: Doreen Kezer, MSN, Consumer Safety Officer.

A copy of this Warning Letter was sent to the Food and Drug Administration's Seattle District Office, HFR-PA-350, 22201 23 rd Dr. SE, Bothell, WA 98021, Attention: David A Pettenski. We request that a copy of your response also be sent to this office.

Please direct all questions concerning this matter to Ms. Kezer at 301-594-4718.

Sincerely yours,

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