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

NOV 15 2001

WARNING LETTER
Via Federal Express

Donald J. Hagler, M.D.
Mayo Clinic/Foundation
200 First Street SW
Rochester, MN 55905

Dear Dr. Hagler:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration inspection conducted at your clinical site and requests from you a prompt written reply informing us of your corrective actions. You participated as a clinical investigator in a study entitled, "[redacted]" sponsored by [redacted]. Data from the study conducted at your site was submitted to the FDA in support of the premarket approval application, [redacted]

During the period of June 26 through July 24, 2001, you were visited by Ronald R. Ruff, an investigator from the FDA's Minneapolis District Office. The purpose of Mr. Ruff's visit was to conduct an inspection to determine whether your activities and procedures as a clinical investigator for the [redacted] complied with applicable FDA regulations. This product is a device as that term is defined in section 201(h) of the Federal Food, Drug and Cosmetic Act (the Act).

The inspection was conducted under a program designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approvals (PMA), Product Development Protocol (PDP) or Premarket Notifications [510(k)] 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 scientific investigations.

Our review of the inspection report submitted by the Minneapolis District revealed significant violations of the requirements under Title 21, Code of Federal Regulations (21 CFR), Part 50 – Protection of Human Subjects, Part 56 – Institutional Review Boards, and Part 812 – Investigational Device Exemptions. These violations were

listed on the Form FDA 483, "Inspectional Observations," which was presented to and discussed with you at the conclusion of the inspection. The violations noted on the form FDA 483 and our subsequent review of the inspection report are not intended to be an all–inclusive list of deficiencies found at your site.

1. **Failure to conduct an investigation in accordance with the investigational plan, conditions of approval imposed by the Institutional Review Board (IRB), the signed agreement with the sponsor, and applicable FDA regulations [21 CFR 812.110(b) and 21 CFR 812.140(a)(4)]**

You failed to follow the study protocol in that follow-up visits for some subjects were not conducted on schedule or, for some, not conducted at all. For example, for at least eleven (11) patients, study records did not show that the 12-month follow-up visits required by the protocol were accomplished. In addition, an EKG follow-up test required at one year could not be found for at least three (3) subjects. The protocol states that in all cases, patients will be followed-up according to the protocol.

2. **Failure to prepare and submit complete, accurate, and timely progress reports including unanticipated adverse device effects [21 CFR 812.150(a)(1) & (3)]**

You failed to report complications/adverse events to the sponsor in a timely manner, often requiring prompting by the monitor before being reported. For example, review of study records indicated delayed reporting of 42 complication/adverse events involving 27 patients occurring between 9/23/99 and 12/27/00 and not reported until 4/01. In addition you also failed to report these adverse device effects to the institutional review board (IRB) as soon as possible but in no event later than ten (10) days after you first learned of the effect as required by the protocol. It is the responsibility of an investigator to report all procedural events and medical conditions and/or changes noted in a subject during the course of the study that would not have been expected to occur.

3. **Failure to maintain accurate, complete, and current records relating to the investigations [21 CFR 812.140(a)(1) and (3)(ii)]**

You failed to maintain records relating to your participation in an investigational study including documentation of IRB approval and continuing review. For example, there was no documentation that the IRB reviewed and approved the consent documents specific to study patients.

4. Failure to ensure that requirements for obtaining and documenting informed consent were met [21 CFR 812.100, and 50.20, and 50.27(a)]

You failed to provide numerous subjects with adequate informed consent prior to allowing them to participate in an investigational study. For example, consent documents for device subjects had not been revised to include changes such as a change in follow up visits from 3 months to 6 months starting in protocol revision #3. Other consents where not approved by the IRB and at least two patients signed a prospective consent following surgical procedures when the IRB approved protocol revision #7 was for retrospective patients.

It is the responsibility of the clinical investigator to ensure that informed consent is obtained in accordance with FDA regulations found at 21 CFR, Part 50, Protection of Human Subjects, and that a copy of the signed form is provided to the subject.

5. Failure to submit progress and final reports to the reviewing institutional review board (IRB) and the sponsor [21 CFR812.150(a)(3), and (6)]

You failed to prepare and submit to the sponsor annual progress reports. Also, there were no records documenting the submission of a periodic and/or final study summary report to the sponsor. You also failed to submit yearly progress reports to the IRB for continuing review consideration and there was no documentation to show that the IRB had approved continuation of the study. During the exit discussion with Mr. Ruff, you stated that you did not realize that submission of annual progress reports to the sponsor was required. The regulations state, "An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly."

Your participation in the study is based, in part, on the IRB approval. The reviewing IRB should be made aware of any changes to the study protocol that may affect scientific soundness of the plan, or the rights, safety, and welfare of the study subjects before you implement the changes.

EMERGENCY USE/COMPASSIONATE USE

The inspection revealed that four subjects were treated as "compassionate use" and/or "emergency use" patients. According to the report, there was no documentation of independent assessment by an uninvolved physician and/or no authorization from the IDE sponsor for at least two patients. We are concerned that while these four patients were treated under the "emergency use" or "compassionate use" provisions, all conditions for such use were not met.

FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious, albeit not life-threatening condition (hereinafter referred to as "compassionate use"). In these circumstances, FDA uses its regulatory discretion in determining whether such use of an investigational device should occur. Unlike emergency use of an unapproved device, prior FDA approval is needed before compassionate use occurs. In order to obtain Agency approval, the sponsor should have submitted an IDE supplement requesting approval for a protocol deviation under section 812.35(a) in order to treat the patient.

The compassionate use criteria and procedures can also be applied when a physician wishes to treat a few patients rather than an individual patient suffering from serious disease or condition for which no alternative therapy adequately meets the medical need. In this case, the physician should request access to the investigational device through the IDE sponsor. As with single patient compassionate use, a monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted in an IDE supplement after all compassionate use patients have been treated.

In the event that a device is used in circumstances meeting the criteria listed above, FDA would expect the physician to follow as many patient protection procedures as possible. These include obtaining:

- an independent assessment by an uninvolved physician;
- informed consent from the patient or a legal representative;
- institutional clearance as specified by institutional policies;
- authorization from the sponsor, if an approved IDE for the device exists.

Guidance on emergency and compassionate use is found in two (2) separate guidance documents, *Individual Patient Access to Investigational Devices Intended for Serious Diseases* and *Emergency Use of Unapproved Medical Devices* which can be viewed at http://www.fda.gov/cdrh/ode/idepolcy.html.

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan, and applicable FDA regulations. Your procedures and practices regarding clinical investigations for which you are the principal investigator need to include measures to assure that personnel responsible for the informed consent process are knowledgeable of all criteria of the study in

question and have access to pertinent information about the potential study subject. Moreover, the informed consent process needs to stress the importance of the subject adhering to the study requirements. While the subject always has the right to exit the study at any time, those with a high drop-out probability should not be recruited into the study. Once these procedures have been amended, a training program needs to be arranged for all personnel who have responsibilities with regard to investigational studies.

We have also been advised that the Mayo Foundation Institutional Review Boards (IRB) have formally suspended all your research activities. Please provide a written response to this letter within 15 working days stating what corrective action (s) you have initiated or plan to initiate to assure compliance with all applicable regulations and so that the IRB may consider your future participation in clinical trials. Failure to respond could result in further regulatory action without additional notice.

Because the inspection of your facility was not all-inclusive, other deficiencies may exist in your study. We recommend that you review your records for other deficiencies and correct them accordingly. It is your responsibility as an investigator to assure adherence to each requirement of the Act and regulations.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, HFZ-311, 2094 Gaither Road, Rockville, Maryland 20850, Attention: Liliane Brown, Consumer Safety Officer. A copy of this letter has been sent to our Minneapolis District Office, 240 Hennepin Avenue, Minneapolis, MN 55401. We request that a copy of your response be sent to that office as well.

Sincerely yours,

Larry Spears
Acting Director
Office of Compliance
Center for Devices and Radiological Health