DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MAY _ 5 2004

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Todd V. Swanson, M.D.
2800 East Desert Inn Road, Suite 100
Las Vegas, Nevada 89121

Dear Dr. Swanson:

Between April 11 and May 13, 2003, Food and Drug Administration (FDA) investigator, Mr. Anthony E. Keller, conducted an inspection of the [redacted] clinical study in which you participated. This inspection was conducted as part of the FDA's Bioresearch Monitoring Program which includes inspections designed to monitor the conduct of research involving investigational products.

Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products as published under Title 21, Code of Federal Regulations (CFR), Part 812, Investigational Device Exemptions (copy enclosed) and Part 50, Protection of Human Subjects (copy enclosed).

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational products as set forth under 21 CFR 812.119.

A listing of the violations follows. The applicable provisions of 21 CFR 812 and Part 50 are cited for each violation.

1. **You repeatedly and deliberately allowed subjects to participate in the study before obtaining approval from the reviewing institutional review board (IRB) (21 CFR 812.100 and 812.110(a))**

   According to investigational findings, you allowed [redacted] subjects to participate in the study before obtaining IRB approval. [redacted] granted approval on September 18, 2001. Between December 5, 2000 and July 17,

2001, the following subjects were implanted with the investigational device: [redacted], and [redacted] You did not have IRB approval prior to September 18, 2001.

An investigator is responsible for not allowing any subject to participate in an investigational study before obtaining IRB approval and may determine whether potential subjects would be interested in participating in an investigation but may not request the written informed consent of any subject to participate and not allow any subject to participate prior to obtaining IRB and FDA approval (21 CFR 812.100 and 812.110(a)).

2. **You failed to adhere to informed consent requirements (21 CFR 50.20, 50.25(a), 50.27(a), 21 CFR 812.100, 812.110(b), and 812.140(a)(3)(i))**

   a. You failed to ensure that written documentation of informed consent was obtained from subjects [redacted] and [redacted] An investigator is required to have written documentation of informed consent 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. Page three of the investigator agreement has a statement of certification that written informed consent will be obtained from subjects or their legal representatives. You signed this agreement and are obligated to follow it, as well as the regulations requiring written informed consent.

   b. The following subjects [redacted] and [redacted] signed the informed consent form after receiving the investigational device.

Subjects	Date of Informed Consent	Date of Implantation
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

   c. On August 16, 2002, subject [redacted] signed a draft informed consent form which had not been approved by the IRB. The draft informed consent form does not disclose the possibility of receiving the control device instead of the experimental device.

   d. Subjects [redacted] and [redacted] signed the September 18, 2001 version of the informed consent form which is outdated. The current, approved

version is dated December 23, 2002. The subjects signed the outdated form between the dates of January 16, 2003 through March 6, 2003.

e. You backdated subject [redacted] informed consent form. On November 30, 2002, subject [redacted] informed consent form was faxed from [redacted]. The faxed informed consent form has your original signature with a date of [redacted]. Your files contain evidence that the subject and witness signatures were on the form when it was faxed and your signature was added after the form was faxed in November.

f. Subject [redacted] informed consent forms are not dated.

g. On January 31, 2003, the [redacted] required your clinical site to have all subjects who signed an unapproved version of the informed consent to sign the approved version. Subjects [redacted] signed the approved version of the informed consent form; yet, there is no documentation showing that the other subjects signed the approved version.

An investigator is required to comply with the following: protect the rights, safety, and welfare of subjects, and ensure that informed consent is obtained (21 CFR 812.100 and 21 CFR 50.20). Further, an investigator is required to have written documentation of informed consent 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 (21 CFR 50.27(a)). Page three of the Investigator Agreement has a statement of certification that written informed consent will be obtained from subjects or their legal representatives. You signed this agreement and are obligated to follow it as well as comply with applicable FDA regulations and any conditions of approval imposed by an IRB or FDA (21 CFR 812.110(b)). The basic required elements for informed consent are set forth in 21 CFR 50.25(a). An investigator is responsible for providing a description of the procedures to be followed (21 CFR 50.25(a)(l)). In addition, an investigator is responsible for maintaining accurate, complete, and current records of informed consent (21 CFR 812.140(a)(3)(i)).

3. You failed to follow the approved investigational plan, including the protocol, and the investigator agreement (21 CFR 812.100 and 812.110)

a. You failed to follow the protocol and IRB requirements in that you did not notify the reviewing IRB of protocol revisions dated: [redacted] and [redacted]. Your clinical site has been using the [redacted] version. During the closing discussion, you mentioned that your study coordinator had not sent the revised protocols to the IRB and that your site needed to update the IRB.

b. You failed to follow the protocol's randomization procedures. You did not randomize all patients into the study. On November 1, 2001 and March 7, 2002, the sponsor sent randomization envelopes. In the protocol, section [redacted] Design, there is a description of how to randomize the subject into the study. Once the subject has agreed to participate and signed the informed consent form, the [redacted] group as determined by random selection. The envelopes are to be opened [redacted] and [redacted] The study has a ratio of [redacted] which means for every [redacted] patients receiving the control device (the control group), the [redacted] subject will receive the investigational device (the treatment group). At your site, [redacted] out of [redacted] subjects received the control device while the remaining [redacted] subjects received the investigational device. During the inspection, you and your co-investigators stated to Mr. Keller that there has been little or no attempt to randomize subjects into the study. In addition, you stated that the reason for getting into the study was to gain access to the investigational device and that you were sure your patients would not have accepted the control device after they knew of the investigational device's use in [redacted] and its history.

c. You failed to follow the protocol's inclusion/exclusion criteria by including subject [redacted] in the study despite the subject's failure to meet the inclusion/exclusion criteria. During the inspection you stated that subject [redacted] has a [redacted] problem and subject [redacted] should not have been enrolled in the study but you expected subject [redacted] to comply with follow-up visits.

d. You failed to follow-up with subjects within the required time frames in the protocol. For example, [redacted] had surgery on [redacted] and followed-up on [redacted] which was beyond the required [redacted] to [redacted] days for the immediate post-operative visit. Furthermore, subjects [redacted] and [redacted] were seen [redacted] months after their surgery also beyond the [redacted] to [redacted] day immediate post-operative visit protocol requirement.

An investigator is required to conduct an investigation in accordance with the investigational plan and applicable FDA regulations. The Investigator Agreement, page 3, includes a statement that any non-emergency deviation from the plan requires prior approval from the IRB, the sponsor, and FDA. You did not notify the reviewing IRB of the following: protocol revisions, failure to randomize all subjects into the study, and failure to follow-up with subjects within the required timeframes. Thus, you did not follow the Investigator Agreement. In order to protect the rights, safety, and welfare of subjects under an investigator's care, clinical investigators are required to ensure that investigations are conducted according to the signed agreement, the investigational plan, and applicable FDA regulations (21 CFR 812.100 and 812.110(b)).

4. You failed to report unanticipated adverse device effects (21 CFR 812.150(a)(1))

You failed to report to the reviewing IRB and the sponsor the following:

- On [redacted], subject [redacted] had a [redacted] replacement. From September 20 through October 16, 2002, Subject [redacted] experienced a feeling of coldness at the [redacted] and numbness with prolonged standing in the [redacted]
- On [redacted] subject [redacted] was treated with [redacted] due to "spitting" [*sic*] a stitch.

5. You failed to maintain accurate and complete records of receipt, use, and disposition of the device and subjects' case history documents (21 CFR 812.140(a)(2) and 812.140(a)(3))

A review of subject files revealed that records of use of the device and subjects' case history documents were incomplete or not properly maintained. Examples are as follows:

a. There were no records of receipt, use and disposition of the device for the [redacted] subjects implanted with the investigational device.

b. Subject [redacted] medical records were incomplete.

c. Records of subjects [redacted] and [redacted] case history files were missing.

d. There were no case report forms for subjects [redacted], and [redacted]

In addition, we are concerned that the case report forms for subjects [redacted] and [redacted] have results listed for body mass index, pre-operative [redacted] evaluation, pre-operative [redacted], pre-operative [redacted], or [redacted] data yet, the medical records or progress notes lack this documentation. Please provide copies of the original test or measuring results with your response.

During the inspection and closing discussion, Mr. Keller composed a list of subjects receiving the investigational device and showed the list to you and [redacted]. Both you and [redacted] stated that the list was incomplete and there were more subjects implanted than were on Mr. Keller's list. Also, you stated that you would retrieve the total number of investigational devices from your personal database. No such information to date has been received by Mr. Keller.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of investigational [redacted] It is your

responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, FDA asserts that you have repeatedly and deliberately failed to comply with the cited regulations and failed to comply with the conditions of the exempting regulations and it proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 812.119.

Within fifteen (15) days of receipt of this letter, write or call Michael E. Marcarelli, Pharm.D., at 301-594-4720 ext. 120 to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Michael E. Marcarelli, Pharm.D.
Director
Division of Bioresearch Monitoring, HFZ-310
Office of Compliance
Center for Devices and Radiological Health
Food and Drug Administration
2098 Gaither Road
Rockville, Maryland 20850

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents which include documentation of prescription use of the investigational device, and you may be accompanied by a representative of your choosing. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (enclosed) and 21 CFR 812.119. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a

general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational products. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,

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