DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MAR 9 2004

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Richard R. Briggs, M.D.
Cathedral Rock Orthopaedic Surgery
7200 Cathedral Rock, Suite 170
Las Vegas, Nevada 89128

Dear Dr. Briggs:

Between May 2 and 21, 2003, Mr. Anthony E. Keller, a Food and Drug Administration (FDA) investigator, 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 and 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) prior to initiation of the study (21 CFR 812.100 and 812.110(a))**

   You implanted the [redacted], an investigational device, at two study sites: th[redacted] and [redacted]

- You allowed subjects to participate in the study before obtaining approval from the [redacted] IRB. The following subjects were implanted with the investigational device at the [redacted] prior to IRB approval:

Subject	Date of Implant
[redacted]	[redacted]/2001
[redacted]	[redacted]/2001
[redacted]	[redacted]/2000

- You allowed subjects to participate in the study at [redacted] before obtaining approval from [redacted] and [redacted] IRB, the IRB for [redacted] On December 4, 2002, the [redacted] and [redacted] IRB approved the [redacted] study. The following subjects received the investigational device at [redacted] prior to IRB approval:

Subject	Date of Implant
[redacted]	[redacted]/2000
[redacted]	[redacted]2001
[redacted]	[redacted]/2001
[redacted]	[redacted]/2001
[redacted]	[redacted]/2001
[redacted]	[redacted]/2001
[redacted]	[redacted]/2001
[redacted]	[redacted]/2001
[redacted]	[redacted]/2001
[redacted]	[redacted]/2001
[redacted]	[redacted]/2001
[redacted]	[redacted]001
[redacted]	[redacted]/2001

In addition to the above subjects, during the inspection, you indicated that you had implanted more subjects at [redacted] and possibly, a couple more subjects at [redacted] without approval from those hospitals' IRBs. 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 conduct the study in accordance with the investigational plan and protocol, and Investigator Agreement (21 CFR 812.100 and 812.110(b))**

- You failed to follow the protocol in that you did not notify the reviewing IRB of the

protocol revision [redacted] (April 2003 version). Currently, your clinical site is using Rev [redacted] April 2003 version. According to the IRB, the only protocol submitted for approval is the May 15, 2002 version.

- You failed to follow-up with subjects within the time frames required in the protocol. The requirements for follow-up after implantation include an [redacted] visit within [redacted] to [redacted] days, and visits at the following time intervals: [redacted] and [redacted] months. Subjects [redacted] and [redacted] were followed-up approximately [redacted] to [redacted] months after surgery.

Subjects	Date of Surgery	Date of Follow-up Visit Post-operatively
[redacted]	[redacted]01	[redacted]/01
[redacted]	[redacted]01	[redacted]01
[redacted]	[redacted]01	[redacted]01
[redacted]	[redacted]/00	[redacted]01
[redacted]	[redacted]/01	[redacted]/01
[redacted]	[redacted]/03	[redacted]/03

In addition to those patients listed above, subject [redacted] is an [redacted] patient who received the investigational device on [redacted], 2001 and whose last visit was [redacted] 2001. Subject [redacted] thus did not have the [redacted], and [redacted] month visits. Subject [redacted] received the investigational device on [redacted] 2003 and there is no record of any post-operative visits for subject [redacted].

In addition, you did not meet the protocol timeframes for pre-operative visits. The protocol requires a [redacted] visit prior to implantation. Subject [redacted] pre-operative visit was on [redacted] 2003, yet, subject [redacted] received the implant on [redacted], 2003. By failing to follow-up with subjects within the required timeframes, you did not follow the investigational plan.

The Investigator Agreement, page three, includes a statement that any non-emergency deviation from the investigational plan requires prior approval from the IRB, sponsor and FDA. You did not notify the reviewing IRB of the protocol revision and did not follow-up with subjects within the required timeframes, thus, you did not follow the Investigator Agreement and investigational plan. 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)).

3. **You failed to ensure informed consent was obtained from all study subjects and adhere to informed consent requirements (21 CFR 812.100, 21 CFR 50.20, 50.25(a)(l) and 21 CFR 50.27(a))**

- You failed to obtain the legally effective informed consent. For example, there was no written informed consent form for the following subjects treated with the

investigational device at your clinical site: [redacted] and [redacted]. This accounts for [redacted] of the [redacted] subjects. Although some records contained evidence that the subjects were informed verbally, not all records included documentation of the subjects being informed verbally of the investigational device status. For example, subjects [redacted] and [redacted] records did not contain any evidence that the subjects were even informed verbally of the investigational device status.

An investigator is required to protect the rights, safety, and welfare of subjects, and ensure that informed consent is obtained (21 CFR 812.100 and 21 CFR 50.20). For subjects [redacted] and [redacted] there is no evidence that you obtained any informed consent whatsoever (verbally or written). Further, an investigator is required to obtain and 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 the regulations requiring written informed consent.

- You failed to ensure that the [redacted] and [redacted] IRB approved the revised informed consent form, dated April 15, 2003 prior to using it at your clinical site. For example, the informed consent form for subject [redacted] was signed on [redacted] 2003. The IRB approved the informed consent form on [redacted] 2003. You did not have IRB approval to use the informed consent form prior to May 7, 2003.

- You failed to ensure the informed consent form approved by the [redacted] IRB on December 4, 2002 contained a description of the randomization procedures. Your site used the December 4, 2002 informed consent form to enroll subjects [redacted] and [redacted]. During the closing discussion, you stated that not including the randomization information in the informed consent form was an oversight.

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)).

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

You did not report to the reviewing IRB the following unanticipated adverse device effects:

- Subject [redacted] chronic pain since implantation; [redacted] received the investigational device on [redacted] 2001. Since implantation, [redacted] has experienced chronic pain.

- Subject [redacted] during recovery and revision of [redacted]
- Subject [redacted] development post-operatively of severe pain after [redacted] the [redacted]
- Subject [redacted] development of swelling and severe pain [redacted] through [redacted] days post-operatively; pain, burning and swelling on the [redacted] days after surgery; and
- Subject [redacted] development of mild erythema [redacted] days after surgery.

Page 2 of the Investigator Agreement requires the investigator to immediately notify the sponsor and IRB about any unanticipated adverse device effects within 48 hours by telephone and within 5 days in writing. In accordance with 21 CFR 812.150(a)(l), an investigator is required to report to the sponsor and to the reviewing IRB any unanticipated device effects as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

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))**

You failed to maintain records of receipt, use and disposition of the device and case history documents. Several case report forms (CRFs) had no data, missing information or a discrepancy in the data. For example, the following subject records were incomplete or non-existent:

- Subjects [redacted] and [redacted] records contained no exclusion documentation of [redacted], and no device batch number or code mark.
- Subjects [redacted] and [redacted] data was missing for [redacted] evaluation for the pre-operative visits.
- There were no operative notes for subjects [redacted] and [redacted].
- There were no CRFs completed for 17 subjects, subject [redacted] fourth and fifth pre-operative visit, and subjects [redacted] and [redacted] immediate post operative visit.
- Subject [redacted] documents show a discrepancy in the data. The pre-operative medical record has "[redacted]" and "[redacted]" The CRF has "[redacted]" and no data on [redacted].
- You failed to complete all CRFs. All subject CRFs were missing your signature and date.

An investigator is required to maintain accurate, complete, and current records of each subject's case history and exposure to the investigational device, as well as records of receipt, use and disposition of the device (21 CFR 812.140(a)(2) and 812.140(a)(3)).

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of the 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 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 the 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 Michael Marcarelli, Pharm.D.

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