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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
2098 Gaither Road  
Rockville, Maryland 20850

**WARNING LETTER**  
**Via Federal Express**

JUN 23 2005

Dr. Michael Khoury  
25511 Little Mack Avenue  
Saint Clair Shores, MI 48081

Dear Dr. Khoury:

The purpose of this warning letter is to inform you of the objectionable conditions found during the FDA inspection conducted at your clinical site from January 18-27, 2005 by an investigator from the Food and Drug Administration (FDA), Detroit District Office. This letter also discusses your February 23, 2005, written response to the noted violations.

The purpose of the inspection was to determine whether activities and procedures relating to your participation in the [REDACTED] clinical study [REDACTED] Trial, IDE No. [REDACTED], PMA No. [REDACTED] complied with applicable federal regulations. The product under investigation is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(h). This letter also requests that prompt corrective actions be implemented in response to the violations cited.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and 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.

A description of deviations follows:

- 1. You failed to conduct the investigation according to the investigation plan and conditions of approval imposed by an Institutional Review Board (IRB). [21 CFR 812.110(b)]**

Pursuant to 21 CFR 812.110(b), clinical investigators are required to conduct investigations in accordance with the investigational plan. Examples of this failure include, but are not limited to, the following:

A. The pre-implantation case report form for Subject 4898- [REDACTED] noted the continuing use of medical oxygen by the subject at home, which is one of the exclusion criteria. The subject was implanted with the investigational device on May 16, 2000.

Your response states that the patient did not reveal this information to you until after the fact. However, the Pre-Implantation evaluation for this patient contains a handwritten entry stating: "patient on home oxygen PRN."

B. The study protocol required that five surgical control (SC) subjects be enrolled prior to enrollment of low risk (LR) subjects. However, 18 low risk subjects were enrolled after only four SC subjects were enrolled.

C. Subjects 807- [REDACTED] and 808- [REDACTED] were retrospectively enrolled as surgical control subjects. There is no study protocol or approved protocol amendment on file for the [REDACTED] Surgical Control Study to allow the retrospective enrollment of subjects.

Your response states that your communication with the sponsor indicated that enrollment of study group patients could proceed while continuing to enroll patients for the control group, as confirmed by the memo dated 12/8/98. However the 12/8/98 communication is a facsimile notification informing all IDE sites of the status of LR and SC enrollment to date and the need to enroll more surgical control subjects. In addition, a letter from the sponsor dated 11/30/98 informed you that patients could be enrolled retrospectively as surgical control subjects, however, it does not describe doing so prior to obtaining the initial 5 SC subjects required prior to enrollment of LR subjects.

D. You received approval from the [REDACTED] IRB for Emergency Use/Compassionate Use (EU/CU) for Subject 4400- [REDACTED] under the [REDACTED] protocol (IDE [REDACTED]). You implanted this subject with the [REDACTED] (IDE [REDACTED]), however, there was no approved protocol amendment for the use of the [REDACTED] device in this study.

Your response does not address the fact that you implanted this subject with a device that was not part of the approved protocol.

E. You requested compassionate use approval for Subject 6002- [REDACTED]. The IRB approved the enrollment of this subject in the "Emergency Use Protocol." The subject was implanted with a [REDACTED] device on 11/14/00 and an [REDACTED] device on 12/28/00. The approved EU/CU protocol only applied to the use of the [REDACTED] device and not the [REDACTED] device in this study.

Your response states that the subject was implanted after receiving approval from the IRB dated 10/24/00. However, the 10/24/00 letter states that the IRB approved your request to enroll a patient in the Emergency Use Protocol of the [REDACTED]. This protocol only applies to the [REDACTED] device.

In addition, the investigator noted that there was a single protocol that addressed both emergency and compassionate use. Please be advised that Emergency Use (EU) and Compassionate Use (CU) are not the same. EU is identified in 21 CFR 812.35(a)(2). EU does not require prior FDA approval but does require a report following device use. Specific reporting is required of the investigator and is described in 21 CFR 812.150(a)(4). Please refer to Information Sheet, Guidance for Institutional Review Boards and Clinical Investigators, "Emergency Use of Unapproved Medical Devices" available at the Internet web site [www.fda.gov/oc/ohrt/irbs/devices.html](http://www.fda.gov/oc/ohrt/irbs/devices.html). For compassionate use of a device in a patient or small group of patients who do not meet the requirements for inclusion in a clinical investigation, for whom there is no alternative treatment, and for whom the treating physician believes the device may provide a benefit in treating their disease or condition, you should contact FDA before using the device on a "compassionate" basis. In addition, you should note the availability of and requirements for treatment use of a device at 21 CFR 812.36.

**2. You failed to obtain IRB approval prior to allowing any subjects to participate in an investigation. [21 CFR 812.110(a)]**

Pursuant to 21 CFR 812.110(a), clinical investigators shall not allow any subject to participate in an investigation before obtaining IRB approval. For example, on 3/1/02, you implanted the [REDACTED] Subject 9095, under the EU/CU protocol two years after the IRB closed this study to enrollment due to concerns regarding an increased risk to human subjects.

Your response states that this patient was not enrolled in the study and was treated on an emergency use basis. Your response also does not address your failure to provide annual reports required by the IRB for continuing review of the study. For example, the 6/25/98 approval letter from the IRB for the [REDACTED] was for the period of one year as stated "The period of IRB approval is June 18, 1998 through June 17, 1999." The letter also stated that during the year you were required to report events such as significant adverse reactions, changes to the study protocol, and termination of the study. In addition, the IRB required, "at least, an annual review of all studies. As the principle investigator, you are responsible for reporting on the progress of each study."

**3. You failed to obtain proper informed consent in accordance with the regulations regarding the protection of human subjects. [21 CFR 50.20, 812.100 and 812.140(a)(3)(i)]**

Pursuant to 21 CFR 812.100 and 21 CFR 50.20, an investigator is responsible for ensuring that informed consent is obtained and may not 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. Pursuant to 21 CFR 812.140(a)(3)(i), clinical investigators are required to maintain the accurate, complete and current records of each subject's case history

including documents evidencing informed consent. Examples of failure to obtain adequate informed consent include, but are not limited to, the following:

A. Annual reports for the HR, LR and SC arms of the study were not submitted to the IRB for continuing review 1999. You failed to use the appropriate informed consent forms for Subjects 3446- [REDACTED], 4341- [REDACTED], 3292- [REDACTED], 4512- [REDACTED], 1483- [REDACTED], and 9095- [REDACTED]

Your response states that HR subject 4512 was originally consented with an emergency/compassionate use consent form and subsequently enrolled in the high risk study, but that the HR consent form was not used by oversight. You state that the only differences between the HR and EU/CU consent form deal with scope and duration of the clinical investigation and that the HR consent form identified the number of patients that will be enrolled in this clinical study. In fact, while similar to the EU/CU consent form in the bulleted list of risks, the HR consent form contains a lengthy discussion of scope and duration of the study, and numerous differences in follow-up treatment.

B. You failed to obtain informed consent prior to implantation for Subjects 807- [REDACTED], 808- [REDACTED] and 4877 [REDACTED]

Your response states that subjects 807 and 808 signed the SC consent as they were enrolled retrospectively. Regardless of when subjects are enrolled in a study, an investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, and for protecting the rights, safety, and welfare of subjects under the investigator's care. Your response regarding subject 4877 states that the device was placed during emergency surgery and that you were following the FDA Emergency Use Guidelines. However, you did not address the fact that there was sufficient time for you to request IRB pre-approval for this subject, inform the sponsor and FDA/CDRH reviewers of your intent to implant and wait for the device to be shipped to the hospital for implantation.

C. You failed to obtain the correct informed consent for two subjects:

1. Subject 4400- [REDACTED] signed an EU/CU [REDACTED] consent form on 3/20/00. The subject was implanted with a [REDACTED] device on 3/27/00.
2. Subject 6002- [REDACTED] signed an EU/CU [REDACTED] consent form on 11/22/00. The subject was implanted with a [REDACTED] device on 11/4/00.

Your response states that the EU consent form was signed at the request of the IRB as indicated in the approval letter as there was no protocol or informed consent that existed for a [REDACTED] repair. While it is correct that the letter from the IRB required the use of the consent form, please note that the letter from the IRB approved your request to enroll the patient in the Emergency Use Protocol of the [REDACTED]. This protocol applies only to the use of the [REDACTED]. The protocol states that the objective of the study is to determine the safety and effectiveness of the [REDACTED] to

treat abdominal aortic aneurysms in high surgical risk patients. The protocol does not mention the use of an alternate device.

**4. You failed to maintain accurate, complete and current records showing dates and reasons for each deviation from the protocol. [21 CFR 812.140(a)(4)]**

Pursuant to 21 CFR 812.140(a)(4), a clinical investigator shall maintain the following accurate, complete and current records relating to the investigation: the protocol, with documents showing the dates of and reasons for each deviation from the protocol. Examples of this failure to maintain complete records showing dates and reasons for deviations from the protocol include, but are not limited to, the following:

A. Subject 4898- [REDACTED] was enrolled and implanted even though the subject was receiving oxygen therapy at home. Home use of oxygen is one of the exclusion criteria listed in the protocol.

Your response states that the sponsor was informed of the deviation at the time it was identified by the sponsor monitor during record review on 6/7/04, as provided in attachment 6B-1. We acknowledge that attachment 6B-1, dated 6/10/04, does list the exclusion information regarding this subject. However, as stated previously, the Pre-Implantation evaluation for this patient contains a handwritten entry stating: "patient on home oxygen PRN." This deviation from the protocol should have been identified prior to surgery. The subject was implanted on 5/16/00. The deviation was discovered and reported four years later.

B. Four subjects were implanted with one or more approved devices at the time that the investigational device was implanted: Subjects 3653- [REDACTED], 4877- [REDACTED] and 9095- [REDACTED] were implanted with the investigational device and with an [REDACTED]. Subject 2519- [REDACTED] was implanted with the investigational device and with a [REDACTED]. The [REDACTED] and [REDACTED] are approved devices.

Your response states that a documentation error in the status report dated 11/04/04 regarding subject 3653 was discovered 2/14/05. Your response also states you intended to notify both the sponsor and the IRB. However, documentation of this notification was not included in your response. Please provide documentation that this notification has occurred.

Regarding subject 4877, your response states that the deviation was reported. However, we note that the documentation you provided was a letter to the file dated 3/18/02, two years after the implantation, and the deviation listed is that the informed consent form was not signed by the subject prior to implantation. The letter to file does not address the deviation of implanting this subject with three devices not covered by the protocol.

Regarding subject 9095, your response states the subject was implanted with the device and 2 [REDACTED] on 3/1/02, and that in June of 2002 the subject underwent repair of an endoleak. Your response states that both the sponsor and the IRB were notified post

operatively on July 8, 2002 of the serious adverse event. You acknowledge that the notification did not address the fact that [REDACTED] devices were used. Please provide documentation that this omission has been rectified.

Regarding subject 2519, your response states that the subject was implanted with [REDACTED] device and with a [REDACTED] graft on 4/22/99, and that this was reported to the sponsor on 4/26/99 via telephone, but omitted from the 11/4/04 status report provided to the IRB. Your response states that the IRB and sponsor will be notified of the corrections. Please provide documentation that the IRB and sponsor have been notified.

**5. You failed to prepare and submit progress reports on the investigations to the sponsor, the monitor, and the reviewing IRB at regular intervals. Progress reports must be submitted, at a minimum, on a yearly basis. [21 CFR 812.150(a)(3)]**

Pursuant to 21 CFR 812.150(a)(3), a clinical investigator is required to submit complete, accurate, and timely progress reports. You received approval by the IRB in June 1998. The 6/25/98 approval letter from the IRB for the LPS study was for the period of one year: "[REDACTED] with the [REDACTED] is June 18, 1998 through June 17, 1999." The letter also stated that during the year you were required to report events such as significant adverse reactions, changes to the study protocol, and termination of the study. In addition, the IRB required, "at least, an annual review of all studies. As the principle investigator, you are responsible for reporting on the progress of each study." You failed to submit annual progress reports to the reviewing IRB as required, even though you were enrolling subjects and implanting investigational devices. Examples of this failure include, but are not limited to, the following:

A. The LR/HR/SC arms of the [REDACTED] were approved by the IRB in June 1998. There were 18 LR, one HR and three SC subjects enrolled and implanted between August 1998 and March 1999, with at least 20 SAEs which included four deaths occurring during this period of which there was no 1999 annual report for these studies. Four additional HR subjects were enrolled and implanted from August 1999 to February 2000. You did not prepare and submit any annual report on the status of these arms of the clinical trial in 2001, 2002, or 2003, during which time the study was active for subject follow-up.

B. The LPS arm of the [REDACTED] was approved by the IRB in February 1999. There is no annual report for 2000 although there were 12 subjects enrolled and implanted from May 1999 to August 1999, with at least nine SAEs occurring during this period. There is no annual report for 2001 although there were 11 subjects enrolled and implanted from March 2000 to September 2000, with at least 11 SAEs (two deaths) and one protocol deviation during this period. In addition, there is no continuing annual review report for 2002 or 2003, during which time the study was active for subject follow-up.

C. The [REDACTED] was approved by the IRB in June 1999 and required an IRB annual continuing review. There were ten subjects enrolled and implanted from August 1999 to November 1999, with at least one SAE during this period. There was no documentation that annual status reports were submitted for 2000 or of continuing review for 2001, 2002, or 2003 during which time the study was active for subject follow-up.

D. The EU/CU study protocol was approved in July 1998. There were two subjects implanted under this protocol in 1998, six subjects implanted in 1999, five subjects implanted in 2000, and one subject implanted in 2002. Annual progress reports were not submitted for 2001, 2002, or 2003.

Your response states you understood that all documents required by the IRB including annual reports and adverse events were being reported in a timely manner. Upon learning that this was not the case, a status report dated 11/4/04 was compiled and sent to the IRB and sponsor. Your response is inadequate. As stated above, the 6/25/98 approval letter from the IRB for the LPS study was for the period of one year: "[REDACTED] with the [REDACTED] as June 18, 1998 through June 17, 1999." The letter also stated that during the year you were required to report events such as significant adverse reactions, changes to the study protocol, and termination of the study. In addition, the IRB required, "at least, an annual review of all studies. As the principle investigator, you are responsible for reporting on the progress of each study."

**6. Deviations to the investigational plan were noted, which could have affected the scientific soundness of the plan and the rights, safety, or welfare of human subjects. [21 CFR 812.150(a)(4)]**

Pursuant to 21 CFR 812.150(a)(4), a clinical investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than five working days after the emergency occurred. You implanted two subjects with a second investigational device during a subsequent implantation procedure. Implanting subjects with an additional device deviated from the investigational plan and could have affected the rights, safety, or welfare of the human subject. There was no sponsor or IRB prior approval or subsequent review of these deviations. Examples of this failure to obtain approval include, but are not limited to, the following:

A. You implanted Subject 3351-[REDACTED] with an investigational device on August 27, 1999. On May 22, 2001, you implanted this subject with a second investigational device which was originally issued for use in Subject 4898-[REDACTED]

B. You implanted Subject 1719-[REDACTED] with an investigational device on October 26, 1998. You implanted this subject with a second investigational device on December 2, 1999.

While your response provides a discussion regarding the implantation of additional devices into subjects 3351 and 1719, it does not address why the implantations took place in the absence of an emergency situation and without sponsor or IRB approval. Your response also states that the IRB was notified of protocol deviations in an addendum to the "[REDACTED]" We note that the addendum included in Attachment 9-AB is dated 2/14/05, which was several weeks after the inspection of your clinical site, and several years after the deviations occurred.

This letter is not intended to be an all-inclusive list of deficiencies at your site. It is your responsibility to ensure that you follow FDA regulations.

This letter also discusses your written response dated February 23, 2005, to the inspectional observations noted on the Form FDA 483. While the submission provides an explanation of events that occurred at your site, it does not discuss how you personally intend to address the deficiencies, nor does it provide a detailed explanation of system-wide corrective actions that will be taken to prevent these deficiencies from occurring in the future. It is recommended, at a minimum, that staff training be provided that includes retraining on Good Clinical Practice (GCP) guidelines with emphasis on safety. This will assist you and your staff in the protection of human subjects as it relates to the informed consent process and the federal regulations for investigational device exemption studies. In addition, we recommend that you establish specific Standard Operating Procedures (SOPs) for your research activities.

**Within 15 working days** after receiving this letter please provide written documentation of the 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. In addition, please provide a list of your current investigational studies and include the name of the study sponsor and the date of IRB approval. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action including initiation of disqualification procedures, without further notice.

Please respond in writing to:

Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Compliance  
Division of Bioresearch Monitoring  
Special Investigations Branch (HFZ-311)  
2094 Gaither Road  
Rockville, Maryland 20850  
Attention: Janet H. Cooper, Consumer Safety Officer

We are also sending a copy of this letter to FDA Detroit District Office, 300 River Place, Suite 5900, Detroit, MI 48207. We request that a copy of your response also be sent to that office.

If you have any question, please contact Doreen Keczor by phone at (240) 276-0125.

For further information concerning the Bioresearch Monitoring program, please visit our Internet homepage at <http://www.fda.gov/cdrh/comp/bimo.html>. Valuable links to related information are included at this site.

Sincerely yours,



Timothy A. Ulatowski  
Director  
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Center for Devices and  
Radiological Health

cc:

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