DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

FEB 7 2006

WARNING LETTER

Via Federal Express

David M. Williams, MD
University of Michigan Health System, Radiology Department
1500 E. Medical Center Drive
Ann Arbor, MI 48109-0030

Dear Dr. Williams:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site from October 3 through October 26, 2005 by an investigator from the FDA Detroit District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study titled [redacted], sponsored by [redacted] complied with applicable federal regulations. The product used in the study is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also discusses your November 11, 2005, written response to the observations noted at the time of the inspection and requests that you promptly implement corrective actions.

The FDA conducted the inspection under a program designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), Product Development Protocols (PDP), or Premarket Notification [510(k)] submissions 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 the scientific investigation.

Our review of the inspection report prepared by the Detroit District Office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions and Part 50 - Protection of Human Subjects. At the close of the inspection, the FDA Investigator presented a Form FDA 483, "Inspectional Observations," to you for review, and discussed the listed deviations. The deviations noted on the FDA 483, our subsequent review of the inspection report, and your November 11, 2005, written responses to those deviations are discussed below:

1. Failure to ensure that informed consent was obtained in accordance with 21 CFR Part 50 and failure to document informed consent [21 CFR 812.100, 21 CFR 812.140(a)(3)(i), 21 CFR 50.20, and 21 CFR 50.27(a)].

You failed to ensure that the current, IRB-approved version of the informed consent was executed by each of the subjects enrolled as required by the above-stated regulations. Examples of this failure include but are not limited to the following:

a.) At least four subjects ( ) signed an unapproved version of the consent form.

b.) Two subjects ( ) were enrolled and treated before the IRB had approved the study and consent form.

c.) At least five subjects ( ) signed the consent form after the study procedure was performed.

You stated in your response to the Detroit District Director, that and were implanted with a study device from another clinical study as emergency treatment, and then you enrolled them into the . You also stated in your response that , and received the study device under emergency use, and that several of the devices used were from the other As a clinical investigator, you are responsible for ensuring that investigational devices are used only for the study for which they are designated. Subjects cannot be enrolled into a study before the IRB has reviewed and approved the study and the informed consent form. In addition, for emergency use of an investigational device, federal regulations require certification in writing by both the investigator and a physician who is not otherwise participating in the study that: (1) the subject is confronted by a life threatening situation necessitating use of the study device; (2) informed consent cannot be obtained because of the subject's inability to communicate; (3) time is not sufficient to obtain consent from the subject's legally authorized representative; and (4) there is no alternative method approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject. If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required, within 5 working days after the use of the article, its emergency use must be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation [21 CFR 50.23].

In response to the missing documentation, you provided one letter from another physician, dated 8/22/00, regarding , written one year after the study procedure was performed on 7/28/99. However, you did not address the missing documentation for the other four subjects.

Your response to these violations is not adequate in that you have not addressed the issue surrounding the majority of the examples shown above, in which subjects were not appropriately consented with the IRB-approved consent form before study enrollment, and you have not explained how you will ensure that study devices are adequately controlled. Your response notes that new administrative procedures will be implemented in the future,

that will address such things as "FDA rules on early and expanded access." Please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train study staff on the consenting process. This should include use of the correct IRB-approved version of the informed consent form, consenting subjects prior to study enrollment, ensuring IRB approval prior to study initiation, and compliance with emergency use regulations. Also, please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to ensure that use of investigational devices are controlled and used only for the designated clinical study.

d.) At least two subjects signed but did not date the consent forms, so it could not be verified that they had been appropriately consented prior to participating in the study. Specifically:

i. [redacted] signed but did not date the consent form. The study procedure was performed on 2/22/99 and you signed the form on 6/9/00. It should also be noted that the form used for this subject expired on 2/19/99 (prior to the study procedure).

ii. [redacted] initialed but did not sign or date the consent form. The study procedure was performed on 10/26/98.

Federal regulations require that informed consent shall be documented 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 at the time of consent [21 CFR 50.27]. In your response letter, you stated that you "will make every effort in the future to ensure complete documentation." Your response is not adequate in that you have not addressed how you will ensure that consent forms are correctly and completely signed and dated. Please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to ensure that informed consent is adequately documented, including timely completion of consent forms.

As a clinical investigator, you are responsible for ensuring that all study subjects are properly consented before any study-related procedures. This includes ensuring that the current IRB-approved version of the consent form is signed and dated by the subjects [21 CFR 50.27(a)]. Moreover, Federal regulations require that if an investigator uses a device without first obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within five (5) working days after the use occurs [21 CFR 812.150(a)(5)]. If you have not already reported this information to the sponsor and IRB, please do so now.

2. Failure to ensure that the requirements for exception from the general requirements for informed consent are met and documented, or that the responsible IRB approved the investigation for exception from informed consent requirements for emergency research. [21 CFR 50.23 and 21 CFR 50.24].

You failed to document conditions, for at least four subjects, under which a subject may be enrolled in a study without first obtaining informed consents. Specifically, for [redacted], [redacted], and [redacted], as noted above in citation 1(c), the study records did not contain appropriate certification to verify emergency use of the study device. You also failed to ensure that the conditions for emergency research were met, including: (1) approval by the IRB that informed consent of all subjects may be waived under specific conditions; and (2) procedures are in place to inform the subjects or the subject's legally authorized representatives, at the earliest

feasible opportunity, of the subjects' inclusion in the study. You also failed to notify the sponsor and the IRB within five (5) days of the use of the device without informed consent, as required by federal regulations [21 CFR 812.150(a)(5)] and [812.140(a)(3)(i)]. As previously requested above, please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train study staff on ensuring compliance with emergency use regulations.

3. **Failure to ensure an investigation is conducted in accordance with the signed agreement with the sponsor, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by FDA or the IRB [21 CFR 812.100, 21 CFR 812.110(b)].**

   You failed to adhere to the above-stated regulations. Examples of this failure include but are not limited to the following:

   a.) You failed to ensure the study was reviewed and approved by an IRB before enrolling subjects into the study. The IRB initially approved the study and consent form on 2/19/98. At least two subjects [redacted] were enrolled and treated in the study prior to obtaining IRB approval.

   b.) At least four ineligible subjects were enrolled and treated in the study. Specifically:
      i. The study protocol excluded potential subjects who were "under the age of 50."
         - [redacted] was 43 years old when enrolled and treated on 10/23/00.
         - [redacted] was 43 years old when enrolled and treated on 4/6/01.
         - [redacted] (no study number) was 14 years old when enrolled and treated on 6/19/01.

      You stated in your response letter that these subjects were enrolled under emergency use, so eligibility criteria were not followed. As noted above in citation 1(c), the study records did not contain appropriate certification to verify emergency use of the study device. In addition, federal regulations require that investigators must notify the study sponsor and the IRB of any deviations from the investigational plan no later than five (5) working days after the emergency use occurs if the deviation occurs to protect the life or physical well-being of a subject in an emergency, which you did not do [21 CFR 812.150(a)(4)]. Your response to this violation, that new procedures are being drafted to address "FDA rules on early and expanded access," is not adequate. Please explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train study staff on ensuring compliance with emergency use regulations.

      ii. The study protocol excluded potential subjects who were not surgical candidates. [redacted] had a note in the study record from another physician, dated 5/27/03, that clearly stated "any direct operative intervention...would be life-threatening...He is not considered an operative candidate." The subject was enrolled in the study and received the study procedure on 5/27/03. Your response letter states that "the subject would have undergone surgery even though the risks of surgery were significant. The surgical note...does not indicate anything to the contrary." Your statement does not appear to agree with the statement in the surgical note itself.

c.) You failed to report complications and adverse events to the study sponsor and the IRB as required by the study protocol. For example:

i. [redacted] experienced a pseudo-aneurysm on 2/23/99.
ii. [redacted] experienced post-operative sepsis on 9/28/99.
iii. [redacted] experienced dizziness, weight-loss, weakness, and dehydration on 1/25/01.

Your response notes that a tracking form has been implemented for radiological studies in order to document and track occurrence and reporting of complications and adverse events. Please provide an explanation of the methods or procedures that will be used to train study staff on the use of this document.

d.) The study protocol required that subjects return at specific times for follow-up visits for evaluations and assessments of adverse events and device efficacy. The protocol also required that procedures be performed at these follow-up visits in order to conduct the required evaluations and assessments. You failed to ensure that the protocol-required visits and procedures were performed as required. For example:

i. The records of at least eleven subjects indicated that 3-month, 6-month, and/or 12-month follow-up visits were not performed. In addition, there was no documentation in the study files that there had been attempts to contact the subjects to try to complete the required visits.
ii. The records of at least eight subjects indicated that protocol-required study procedures were not performed, including pre-procedure duplex scans, post-procedure duplex scans, 3-month duplex scans, and 3-month Doppler and segmental pressure tests.

You stated in your response that "the protocol did not contain explicit requirements for attempting follow-up, nor for designating subjects as lost to follow-up." However, the study protocol, section 2.15 – Follow-up Methodology, clearly states "all patients enrolled in the clinical study will be required to return for follow-up visits at 3 months, 6 months, 12 months, and yearly thereafter until FDA approval or completion of the study." The study visit timetable, which also includes the visit schedule and required procedures for each study visit, is clearly outlined in the protocol in section 2.9 – Overview of Study Patient Scheduling. The protocol also states "a patient may not be considered lost to follow-up or withdrawn unless efforts to obtain compliance are futile. Efforts must be documented in the patient's study file by copies of certified letters, phone logs, etc." As a clinical investigator, it is your responsibility to ensure that you and your study staff are familiar with the protocol and investigational plan.

You also told the FDA investigator that no follow-up visits were performed by you or your sub-investigators, and that subjects were followed at various clinics, by various clinical services. You also said you do not have clinic time to conduct follow-up visits. As a clinical investigator, it is your responsibility to ensure that subjects are seen at the intervals required by the protocol, and that all required procedures are performed. If subjects are seen by other physicians for follow-up visits, it is your responsibility to ensure that the correct procedures are performed so that the required study data are collected.

Your response, in which you note that new administrative procedures will be implemented in the future, is not adequate. Please explain and provide documentation of the particular

methods or procedures that will be used at your clinical site to train study staff on ensuring compliance with all requirements of the investigational plan.

4. **Failure to maintain accurate, complete, and current records relating to your participation in an investigation [21 CFR 812.140(a)].**

You failed to adhere to the above stated regulation. Examples of this failure include but are not limited to the following:

a.) At least thirteen subjects' records ([redacted] and [redacted]) contained no source documentation to verify that the subjects met the study eligibility criterion for a lesion 1.5 times the normal vessel size, or to verify the pre-stent and post-stent lesion characteristics. Your response noted that a new source record form was implemented in October 2002. However, at least two subjects, [redacted] and [redacted], were enrolled after that date, yet the new form was not utilized to verify the subjects' eligibility.

b.) The study record for [redacted] completed 6/23/03, states the subject died in August 1999, and that the death was not device- or procedure-related. However, the file contained no source documentation to verify the subject's cause of death. Your response contained a handwritten note explaining the cause of death for this subject, but the note was not signed or dated to signify the source of this information.

c.) There were numerous discrepancies between the dates of procedures reported on the Case Report Forms (CRFs) and the source documents. For example:

i. [redacted]: the assessment date on the CRF for the pre-procedure segmental pressures and the CT scan is 2/16/99, but the source record indicates the segmental pressures test occurred on 9/26/98, and the CT scan occurred on 9/15/98.

ii. [redacted]: the assessment date on the CRF for the pre-procedure Doppler and segmental pressures tests is 3/9/99, but the source record indicates the tests occurred on 8/18/97. The assessment date on the CRF for the 12-month follow-up visit is 5/23/00, but the source record indicates the visit occurred on 9/18/00.

iii. [redacted]: the assessment date on the CRF for the pre-procedure Doppler and segmental pressure tests is 9/13/00, but the source record indicates these tests occurred on 4/5/00. In addition, the information on the post-procedure CRF for Doppler and segmental pressure tests, with an assessment date of 9/14/00, is identical to that on the pre-procedure CRF.

iv. [redacted]: the assessment date on the CRF for the 12-month CT scan is dated 11/13/02, but the source record indicates this test occurred on 3/18/03.

You stated in your response that the protocol "did not establish a specific window for pre-procedure assessment; and did not require us to repeat assessments that had been performed clinically." However, by including data previously collected on a CRF with a later assessment date, it incorrectly implies that the data was collected on that date. Even if the protocol did not specifically prohibit use of data collected weeks or months before enrollment in the study, as a clinical investigator, you are responsible for ensuring that the data is correct, current, and applicable for the purpose. In addition, your response does not explain your decision to include on CRFs the results of tests that had not yet been performed. Your response letter also stated that, "In the future, we will make every effort to

identify potential sources of confusion in protocols and CRFs and bring these to the attention of the sponsor for written clarification." Please also explain and provide documentation of the particular methods or procedures that will be used at your clinical site to train study staff on ensuring that all study records and data will be accurate, complete, and current.

The regulations in 21 CFR Part 812 describe sponsor responsibilities as well as those of investigators. IRB responsibilities are spelled out in 21 CFR Part 56, Institutional Review Boards. These three sets of responsibilities overlap to ensure appropriate conduct of clinical studies and the protection of the rights and welfare of participating subjects. Therefore, though the sponsor and IRB involved in your study may have been remiss in fulfilling their responsibilities, you are still held responsible for knowing and following the regulations pertinent to your activities as a clinical investigator in FDA-regulated studies, ensuring adherence to each applicable requirement of the Act and all pertinent Federal regulations when conducting clinical research, and for ensuring that any staff or personnel who are delegated study tasks are knowledgeable regarding the Investigational Plan and are directly supervised by you.

Please explain and provide documentation of the particular methods or procedures that you will use to ensure that your duties and responsibilities as a clinical investigator will be adhered to for future studies.

The violations described above are not intended to be an all-inclusive list of deficiencies that may exist at your clinical site. It is your responsibility as a clinical investigator to ensure compliance with the Act and applicable regulations.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these violations in current or future studies for which you are the clinical investigator. Failure to respond to this letter and take appropriate corrective action could result in FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 812.119.

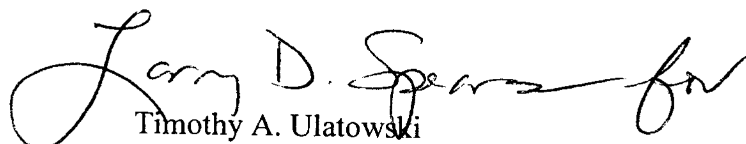
In addition, please provide a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study.

You will find information to assist you in understanding your responsibilities and planning your corrective actions in the *FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators*, which can be found at http://www.fda.gov/oc/ohrt/irbs/. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Please send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Special Investigations Branch, (HFZ-312), 9200 Corporate, Rockville, Maryland 20850; Attention: Ms. Doreen Kezer, Branch Chief.

A copy of this letter has been sent to the FDA's Detroit District Office, Food and Drug Administration, 300 River Place, Suite 5900, Detroit, MI 48207. We request that you copy the District Office on your response.

If you have any questions, please contact Ms. Doreen Kezer by phone at (240) 276-0125, or by email at doreen.kezer@fda.hhs.gov.

Sincerely yours,



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