DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

OCT 7 2005

WARNING LETTER

VIA FEDERAL EXPRESS

Reynaldo F. Mulingtapang, M.D.
4 Columbia Drive
Tampa, Florida 33606-3589

Dear Dr. Mulingtapang:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at University of South Florida (USF), Division of Cardiovascular Disease. An investigator from FDA's Florida District Office conducted the inspection from June 7 through June 17, 2005. The purpose of the inspection was to determine if your activities as a clinical investigator for the [redacted] used in [redacted]" complied with applicable FDA regulations. The [redacted] is a device 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 written response dated June 24, 2005, to the noted violations and requests that you implement prompt corrective actions.

The FDA conducted the inspection under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. The program also ensures that human subjects are protected from undue hazard or risk during scientific investigations.

Our review of the inspection report prepared by the 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 Form FDA 483 and our subsequent inspection report review are discussed below:

Failure to obtain proper informed consent for 3 of 5 study subjects. [21 CFR 50.20, 812.100, and 812.140(a)(3)(i)]

Investigators are responsible for ensuring that informed consent is obtained and that records of informed consent are kept in accordance with FDA regulations 21 CFR 50.20,

812.100, and 812.140 (a)(3)(i). This includes obtaining signed new consent documents for subjects when the IRB approves changes in the protocol and accompanying consent document that alter the study procedures or may otherwise affect the subject's willingness to participate. Clinical investigators must include in each subject's case history documents evidencing that informed consent was obtained.

You failed to obtain subject signatures on the September 16, 2004, IRB-approved version of the informed consent document for 3 of 5 subjects. That updated informed consent document provides new information including:

- addition of follow-up diagnostic procedures at the 24 month visit:
  - Rutherford Classification,
  - Resting ABI's, and
  - Index extremity X-Ray.
- changes in the statement, "You will not be charged for any non-routine costs associated with the study. These costs will be covered by the sponsor." The new statement, "You or your insurance company will be charged for the [redacted]. Some insurance providers will not pay for the cost of the [redacted]."
- clarification of the statement, "The [redacted] is not FDA approved for placement in the [redacted] but it is FDA approved for use in the study." The new statement "The [redacted] is investigational, which means that it is not approved by the U.S. Food and Drug Administration (FDA) for placement in the [redacted]" and
- updated contact information for Dr. Mulingtapang.

In your response, you indicate that these three subjects were contacted by your study coordinator but declined to sign the new consent. You further indicate that they did not participate in the additional follow-up for which the new consent form attempted to solicit consent. However, there is no documentation of the subjects being contacted or withdrawn from the investigation in the case histories reviewed. Under the circumstances you describe, the subject files should have documentation of the efforts made to obtain consent, the subjects' refusals, and your subsequent steps to ensure that they were terminated from the study."

Please provide copies of policies, procedures, and training with expected completion dates, which are being developed and implemented to ensure informed consent is obtained and documented.

Failure to maintain accurate, complete, and current case histories. [21 CFR 812.140(a)(3)]

You failed to maintain complete, current, and accurate case history files regarding study activities required by the study protocol. Examples of this failure include, but are not limited to the following:

1) The nine month follow-up case report form (CRF) for [redacted] indicated the subject was contacted by phone, however the results of Ankle-Brachial Index (ABI) (requiring the subject be physically present) were recorded on the CRF.

In your response you state the subject had the follow-up testing performed but did not return for the outpatient visit and then withdrew from the study. You indicate that a narrative portion of the study records documented this situation. The CRF examined by the investigator for the nine month visit notes the subject was contacted only by phone. The results documented on that CRF could not be performed by phone contact. There is no source documentation that the subject actually had the tests performed. The narrative form you provided with your 483 response to support your explanation is dated September 17, 2004, nearly one year after the subject's scheduled 9-month visit and reported withdrawal from the study. These records were therefore not complete and current.

2) [redacted] baseline's history record indicates that the subject was "on Coumadin" however, the discharge CRF does not list Coumadin as a medication the subject is taking. There is confusion in the documentation as to whether the subject was or was not on Coumadin. In addition, the nine month follow-up visit CRF is missing values for blood pressure (B/P) in the left arm, left ankle systolic pressure, and left ABI.

In your response you state, the subject stopped his Coumadin 10 days prior to the procedure and restarted 2 days after, however, there was no source documentation noting this. The protocol requires subjects on Coumadin to have International Normalized Ratio (INR) performed. There is no documentation that INR's were performed on this subject, either in the immediate post-operative period or at his nine-month follow up visit. In addition, regulations require an investigator to 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 or of deviations that impact the scientific soundness of the investigation. See 21 CFR 812.150(a)(4). Failure to obtain these laboratory tests is a protocol deviation and would require notification of the sponsor and IRB, but there is no documentation of such notification. In addition, you did not address missing information in the case history and CRF. Specifically, values for nine month follow-up of left arm B/P, left ankle systolic pressure, and left ABI.

Your response is inadequate; it does not describe how you are going to ensure complete, accurate, and current documentation of clinical trial data. Documentation of all protocol related elements is a critical component to conducting clinical trials including, medications taken, diagnostic procedures. adverse events, and communications with the subjects. Please provide copies of policies and procedures, with expected completion dates that are being developed and implemented to ensure proper documentation of protocol related elements and the maintenance of complete, accurate, and current case histories.

Failure to conduct the investigation according to the signed agreement, the investigational plan, and applicable FDA regulations. [21 CFR 812.100 and 21 CFR 812.110(b)]

In accordance to 21 CFR 812.100 and 812.110(b), clinical investigators are required to ensure that investigations are conducted according to the signed agreement, the investigational plan, and applicable FDA regulations, as well as any conditions of approval imposed by the IRB or FDA. In addition, federal regulations require that clinical investigators obtain prior approval from the sponsor before implementing any deviations from the investigational plan, except for deviations to protect the life or physical well being of a subject in an emergency. (21 CFR 812.150(a)(4)). If these changes or deviations affect the scientific soundness of the plan or the rights, safety, or welfare of the subjects, FDA and IRB approval are also required. (21 CFR 812.150(a)(4), 812.35(a)).

Our investigation revealed several deviations from the signed agreement and investigational plan, including but not limited to the following:

1) Under the protocol in effect at the time, inclusion criteria #3 states, "Patient requires treatment of a [redacted]" However, [redacted] had [redacted] treated during the index procedure.

In your response you state that at the time of treatment of this subject, the protocol did not list treatment of both [redacted] during the index procedure as an exclusion criteria. You do not disagree that the inclusion criteria at the time referred to treatment of a [redacted] You state that you discussed enrollment of this subject with the sponsor and were given allowance to treat [redacted] as per standard of care and [redacted] as per the protocol. However, there is no documentation of this sponsor approval prior to enrolling this subject. You attached a letter from the sponsor dated January 28, 2003, clarifying treatment of additional [redacted] and stating they must be treated 24 hours prior to or after the index procedure, apparently to support your view that at the time of your enrollment and treatment of this subject, it was ambiguous as to whether or not subjects having more than [redacted] in need of treatment were to be excluded. You do not appear to rely on this letter as granting permission for the procedures done with regard to the subject in question, nor could you, as your subject was treated [redacted], six weeks prior to the date of the letter, and you treated both lesions at the same time, not 24 hours apart, as mandated in the sponsor's protocol clarification.

Treating this subject was a protocol deviation. There is inadequate documentation of notification of the sponsor and IRB of these deviations from the investigational plan.

Please provide copies of policies, procedures, and training with expected completion dates, which are being developed and implemented to ensure deviations from the investigational plan are reported in accordance with the FDA regulations and your IRB's policy.

2) The investigational plan requires anticipated and unanticipated adverse events and complications to be recorded on the Adverse/Serious Adverse Event CRF and reported to the local IRB and coordinating center. In addition, reporting of serious adverse events occurring in the study are to be reported within 24 hours of the investigator's knowledge to the coordinating center for the principal study investigator to review. However, you did not report serious adverse events in accordance with these requirements. For example, [redacted] complained of pain in the right leg during a non-scheduled study visit on 1/31/2005. In February, the subject was seen by Sub-Investigator [redacted], at which time he documented clotting of the superficial femoral artery, "probably in the area of the stent." The adverse event CRF was not completed until the FDA inspection on 6/28/2005. Please note, the adverse event CRF is missing the date of the event. Furthermore, there is no documentation of the event being reported to the IRB or sponsor.

In your response you note this event was inadvertently not documented on the CRF or reported to the sponsor and IRB due to the study staff attempting to contact the subject to set up the 24 month follow-up visit. In accordance with the protocol, this event should have been reported to sponsor and IRB within 24 hours of you becoming aware of this event. Your response is incomplete; it does not include a plan to ensure proper reporting of serious adverse events. Please provide copies of policies and procedures, with expected completion dates, that are being developed and implemented to ensure reporting of serious adverse device effects are in accordance with the investigational plan and IRB policy.

Failure to maintain investigational records for a period of two years after the latter of the date on which the investigation is terminated or completed or the date the records are no longer needed to support a PMA [21 CFR 812.140(d)]

You failed to maintain records of Duplex Flow Scans and Index Extremity X-Rays or Fluoroscopy for two years after the study completion. Examples of records not available for all subjects enrolled in trial the are the following:

1) Duplex Flow Scans at discharge, 9 months, 24 months, and non-scheduled visits: and
2) Index Extremity X-Rays or Fluoroscopy at baseline, 9 month, and 24 month.

In your response you state the records of the Duplex Flow Scans and the Index Extremity X-Rays for all subjects were not retained by the hospital. The originals were sent to the [redacted] and the original X-Rays were forwarded to the [redacted]. You also note you have contacted the labs to obtain the originals and will retain them with the study binders for at least two years. Your response is incomplete. Although you have requested the aforementioned records, you do not indicate what policies and procedures, with expected completion dates, are being developed and implemented to ensure proper maintenance of study-related source records in the future.

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in this clinical study. It is your responsibility as a clinical investigator to assure adherence to each requirement of the Act and all applicable federal regulations. **Within 15 working days** after receiving this letter please provide written documentation of the additional, 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. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings in accordance with 21 CFR 812.119. 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 311, 9200 Corporate Road, Rockville, Maryland 20850. Attention: **Doreen Kezer,** Chief, Special Investigations Branch.

We are sending a copy of this letter to FDA's Florida District Office and request that you also send a copy of your response to that office at 555 Winderley Place, Suite 200, Maitland, FL, 32751. If you have any questions, please contact Ms. Kezer by phone at 240-276-0125.

Sincerely yours,

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

cc

[redacted]