Inspections, Compliance, Enforcement, and Criminal Investigations

Satyaprakash N. Makam, MD 12/19/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

December 19, 2011

WARNING LETTER

VIA UNITED PARCEL SERVICE

Satyaprakash N. Makam, MD
10010 Donald S. Powers Drive
Munster, IN 46321

Dear Dr. Makam:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of your clinical site from September 7, 2011, to September 22, 2011, by an investigator from the FDA Detroit District Office. This inspection was conducted to determine whether activities and procedures related to your participation in the clinical study, "The US Study for Evaluating Endovascular Treatments of Lesions in the Superficial Femoral Artery and Proximal Popliteal by Using the Protege® EverFLex™ Nitinol Stent System II (DURABILITY II)" (Investigational Device Exemption (IDE) **(b)(4)**, complied with applicable federal regulations. The ev3 Protege EverFlex Self-Expanding Stent System 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), because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or function of the body. This letter requests prompt corrective action to address the violations cited.

The inspection was conducted under a program designed to ensure that data and information contained in requests for IDEs, Premarket Approval applications, and Premarket Notification submissions (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.

Our review of the inspection report prepared by the district office revealed several violations of Title 21, Code of Federal Regulations (21 CFR) Part 812 -- Investigational Device Exemptions, Part 50 -- Protection of Human Subjects, and Section 520(g) of the Act, 21 U.S.C. § 360j(g). At the close of th inspection, the FDA investigator presented an inspectional observations Form FDA 483 for your

review and discussed with you the observations listed on the form. The deviations noted on the Form FDA 483, your written response, and our subsequent review of the inspection report, are discussed below:

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

As an investigator, you are responsible for ensuring that informed consent is obtained in accordance with 21 CFR Part 50. No investigator may involve a human subject in research unless the investigator has obtained legally effective informed consent from the subject or the subject's legally authorized representative. In addition, an investigator shall document informed consent by the use of a written consent form approved by the Institutional Review Board (IRB) and signed and dated by the subject or the subject's legally authorized representative at the time of consent.

The sponsor, ev3 Endovascular, Inc., expressed concerns regarding your informed consent process during several monitoring visits. The sponsor communicated to you its concerns in writing on May 1 2009, June 15, 2009, and August 28, 2009, following the monitoring visits. However, you did not implement any corrective actions to address the sponsor's informed consent process concerns until September 30, 2009. This delay in implementing the appropriate corrective actions reflects a disregard for the safety and welfare of your subjects. Clinical investigators are required to follow applicable regulations and, if a deviation occurs, are expected to implement prompt corrective actions to protect the rights, safety, and welfare of the enrolled subjects. Examples of this failure include, but are not limited to, the following:

a. On the original informed consent documents (ICDs) for subjects **(b)(6)** and **(b)(6)**, and the revised ICD for **(b)(6)**, you only obtained the subjects' initials and printed name as documentation of their consent. A research subject's initials and printed name on the ICD do not constitute legally effective informed consent. FDA regulations require that the subject sign and date the form at the time of consent. Also, there is no indication that you attempted to re-consent the above subjects in order to obtain proper documentation, a signed and dated form, of informed consent.

b. **(b)(4)**. You did not obtain prescreening written Informed Consent for **(b)(4), (b)(6)**. For example, the "Note To File" dated 7/7/2009 for subject **(b)(6)** indicates that the subject underwent study-related testing, such as the **(b)(4)** on 4/9/2008, and that you did not obtain informed consen until 4/18/2008. Also, the "Note To File" dated 7/10/09 for subject **(b)(6)** indicates that the subject completed all screening assessments on 2/14/2008 and that you did not obtain informed consent until 2/15/2008.

In your October 5, 2011, Form FDA 483 response, you indicated that a corrective action plan (CAP) was put into place for the above deviations. You also provided documentation of staff training regarding this observation. Your response has been noted; however, the delay in the implementatior of the proper procedures is not acceptable. FDA expects prompt corrective actions for any similar violation in future FDA-regulated studies.

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

An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA. As a reminder, failure to adhere to these requirements may call into question the integrity and reliability of the data you obtained during the course of the study, and also increases the risk of harm to the participating subjects. Examples of these failures include, but are not limited to, the following:

a. The investigator agreement states that an investigator shall only use ICDs approved by the

sponsor and the IRB, and that an investigator may not modify or amend the ICD in any manner without the sponsor's written approval. The October 22, 2007, IRB-approved ICD indicates that subjects' insurance should be responsible for any expenses that the subjects incur for the study procedure. In addition, the approved ICD indicates that, if the subjects do not have any insurance o if their insurance does not cover any or all of the costs associated with the procedure, subjects are responsible for the costs.

It appears that **(b)(6)** was concerned about accepting responsibility for the cost of the research. Therefore, you revised ICD versions dated October 22, 2007 and August 14, 2008, for this subject with a hand-written note that states "any extra costs associated would be covered by **(b)(4), (b)(6)**." Although the FDA encourages amendments to the ICD that are in the best interest of the subjects, any amendment made to the ICD should apply to all subjects and you must obtain IRB and sponsor approval prior to implementing the amended ICD. Furthermore, unauthorized changes to the ICD related to financial expectations raise concerns about coercion in the consent process. Acquiring informed consent under coercion or undue influence is in direct violation of FDA regulations, 21 CFR 50.20 "General requirements for informed consent."

b. Section 4.13 of the protocol states that a written report will be provided to the sponsor within 10 business days after the investigator learns of a serious adverse event and that it must be provided to the IRB according to the board's reporting guidelines. The IRB policy/procedure number **(b)(4),** effective date 9/2009, indicates that events that are unexpected, of moderate or greater severity (but not fatal or life-threatening), and associated with the research interventions shall be reported to the **(b)(4), (b)(6).** Additionally, section 4.13 of the protocol states that all suspected adverse events (AEs) (defined as any undesirable medical occurrence in a study subject whether or not considered related to the study device, study procedures, or study requirements that is identified or worsens during the clinical study) must be recorded and reported to the sponsor.

On March 10, 2009, **(b)(4), (b)(6)** reviewed eight of your AEs and one protocol deviation for this study and noted that you were deficient in your reporting "mechanism." Consequently, the IRB requested submission of a written CAP to address your deficiencies prior to March 19, 2009. The IRB received your CAP on March 17, 2009. In your CAP, you stated that, "Study staff will follow all time submission guidelines," and **(b)(4)**. Our review of your documents indicates that **(b)(6)** experienced adverse events that should have been reported to the sponsor and/or the IRB within the **(b)(4)** reporting timeframe described above, but that you either reported late or never reported**.** The aforementioned events occurred after you submitted your CAP to the IRB. In addition, **(b)(6)** all experienced AEs that you never reported to the sponsor**.**

In your October 5, 2011, Form FDA 483 response, you indicated that you are implementing an electronic system to notify you of AE occurrences on a timely basis, and that your study staff is being educated on the protocol definition of AEs and the need to record and report all suspected AEs to the sponsor. This response is inadequate, in that you provided us with neither a timeframe delineating the implementation of the electronic notification system nor a standard operating procedure identifying your reporting mechanism to prevent these deviations from recurring in future FDA-regulated studies. Proper reporting of adverse events encountered during the clinical study is a critical step in ensuring the safety and welfare of study subjects. In addition, information gathered from these reports can potentially lead to changes in the study protocol; provide vital information to the reviewing IRB during its continuing review; and provide critical information to the FDA, which may affect the IDE and the final review of the device.

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

Please notify this office in writing within fifteen business days from the date you receive this letter of the specific *additional* actions that you have taken or will take to correct these violations and to prevent the recurrence of similar 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 the 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.

Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Please also include in your response a plan for monitoring the effectiveness of your corrective actions.

Your response should reference CTS # P110023/E002 and be sent to:

Attention: Kathy Weil
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room RM3566
Silver Spring, Maryland 20993-0002

A copy of this letter has been sent to FDA's Detroit District Office, 300 River Place, Suite 5900, Detroit, MI 48207. Please send a copy of your response to that office.

The Division of Bioresearch Monitoring has developed introductory training modules in FDA-regulated device clinical research practices, which are available on the FDA website. The modules are for persons involved in FDA-regulated device clinical research activities. These modules are located at the following website address: http://www.fda.gov/Training/CDRHLearn/ucm162015.htm[1].

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/[2]

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049864.htm[3]

If you have any questions, please contact Martin Hamilton directly at 301-796-5666 or by email at martin.hamilton@fda.hhs.gov.

Sincerely yours,
/S/
Steven D. Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

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Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
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1. http://www.fda.gov/Training/CDRHLearn/ucm162015.htm
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