DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Blvd.
Rockville MD 20850

WARNING LETTER

Via Federal Express

AUG 30 2007

Pamela G. Grady, PhD
Director, Peripheral Vascular Clinical Trials
Boston Scientific Cardiovascular
4100 Hamline Avenue N
St. Paul, MN 55112-5700

Dear Dr. Grady:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your firm from May 9 through May 16, 2007, by an investigator from the FDA Minneapolis District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical studies titled *TriVascular AAA Stent-Graft System – a Phase I Evaluation of the Safety of the TriVascular Stent-Graft System in the Treatment of Abdominal Aortic Aneurysms* and *ENOVUS AAA Endograft – a Phase II Evaluation of the Safety and Efficacy of the ENOVUS AAA Endograft in the Treatment of Abdominal Aortic Aneurysms* under IDE # G020269, complied with applicable federal regulations. The AAA endograft used for each 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 requests prompt corrective action to address the violations cited and discusses your June 29, 2007, written response to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) 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 serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 812 -- Investigational Device Exemptions, and Section 520(g) (21 U.S.C. 360j(g)) of the Act. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report are discussed below. Please note that all the deviations listed are in reference to the study titled *TriVascular AAA Stent-Graft System – a Phase I Evaluation of the Safety of the TriVascular Stent-Graft System in the Treatment of Abdominal Aortic Aneurysms.*

1. **Failure to immediately conduct an evaluation of any unanticipated adverse device effect, and failure to prepare and submit complete, accurate, and timely reports of unanticipated adverse device effects evaluations to FDA and to all reviewing IRBs and participating investigators within 10 working days after first receiving notice of the effect [CFR 812.46(b)(1) and 812.150(b)(1)].**

   Sponsors are required to immediately conduct an evaluation of any unanticipated adverse device effect (UADE) [21 CFR 812.46(b)(1)] and then report the results of the evaluation within 10 working days to FDA, all reviewing Institutional Review Boards (IRBs), and all participating Clinical Investigators (CIs) [CFR 812.150(b)(1)]. Boston Scientific failed to adhere to the above noted regulations. For example:

   a.) At least 5 deaths have occurred in the study in the United States. At the time of the FDA inspection, 2 of these deaths (**subject 05-005** - died on 12/14/05, and **subject 04-501** - died sometime before 12/8/06) had not been evaluated to determine if there was a relationship between the deaths and the investigational device or to determine if they would be considered to be UADEs. In addition, there was no evidence that any follow-up information was requested or obtained from the study sites at which these 2 deaths occurred following the initial reports submitted by the study sites, and neither of these deaths are included in the current adverse event listing dated 6/8/07, which you included with your response letter.

   In your response, you stated that one of the corrective actions you have taken to address this observation was to provide a refresher training course with the AAA project team on adverse event reporting requirements. This response is inadequate. You have not addressed the underlying issue of ensuring timely follow-up with study sites when initial adverse event information is incomplete, and for ensuring evaluation of the events by Boston Scientific to determine if they are UADEs. Your response also noted that a study specific "Safety Plan utilizing the standard safety template has been drafted and will be implemented for the AAA TriVascular study on or before June 30, 2007." Please provide us with a copy of this plan, and include documentation of training that has been or will be performed to implement this plan.

   b.) Two UADEs occurred in which study subjects (**Subject 04-003** and **Subject 06-005**) contracted blood stream infections with *Pseudomonas aeruginosa* in 2004. These UADEs were evaluated by Boston Scientific and found to be a result of non-sterile, contaminated batch fill material used during the device implant procedure. Boston Scientific was notified of the events on 5/5/04 and 5/12/04, respectively. However, you did not notify all IRBs and CIs of the risk of non-sterile, contaminated product until 6/15/04, even though you had isolated the source of the contamination on 5/7/04. In addition, you did not notify FDA of these events as UADEs, but rather submitted a "Notice of IDE Change" to FDA on 5/21/04, which described "changes to TriVascular manufacturing and quality sampling processes, which were implemented as part of a corrective action related to a sterility failure of the fill material."

   Your response letter again noted that the AAA project team has been re-trained on

adverse event reporting, and that the study-specific Safety Plan will be implemented. You also stated that a CAPA (Corrective and Preventive Action) "will be opened to evaluate the effectiveness of our current UADE processes and implement appropriate actions to further improve in this area." This response is not adequate. Please provide us with documentation of the Safety Plan and training for applicable staff, and the CAPA that has been opened, as well as any actions that have been taken thus far to implement the CAPA.

c.) Boston Scientific first identified a stent fracture in a study subject on 10/20/05 and determined that stent fractures are UADEs. You notified FDA, all IRBs, and all CIs on 10/31/05. However, since that time, at least 24 additional stent fractures have been identified in study subjects. These events were not reported to FDA, IRBs, and CIs within 10 working days of Boston Scientific receiving notice of the events.

In Boston Scientific's response letter, dated June 29, 2007, you stated that you discussed this issue with the FDA reviewer in the Office of Device Evaluation (ODE) on 5/18/07. You stated that you both mutually agreed that stent fractures seen to date will not be submitted individually as UADEs, and that future stent fractures will be reported to FDA as UADEs only if they lead to further interventions or clinical events, or if there is a significant increase in the occurrence rate. Your response also noted that the study protocol was revised in August 2006 to list stent fractures as an anticipated adverse device effect. This response is not adequate, in that it does not address the underlying issue of UADEs that were not reported to FDA, all reviewing IRBs, and all participating CIs within 10 days of your receiving notice of the effect, as required by FDA regulation. Specifically, the 25 stent fractures observed up to the time of the FDA inspection occurred prior to the protocol change, and/or prior to your discussion with the ODE reviewer. Please provide documentation of a corrective action plan that will ensure that all UADEs observed in clinical studies sponsored by Boston Scientific will be appropriately evaluated and reported as required by federal regulation.

2. **Failure to provide Clinical Investigators with the information they need to conduct the investigation properly, and ensure that any reviewing IRB and FDA are promptly informed of significant new information about an investigation [21 CFR 812.40].**

Boston Scientific failed to ensure that all IRBs, CIs participating in the study, and FDA were promptly provided with significant new information about the clinical investigation for the AAA endografts. For example:

a.) Boston Scientific notified clinical investigators in a letter dated June 21, 2006, of the decision to cancel the endovascular aortic repair program. A second letter, dated September 15, 2006, included a sample addendum to the original informed consent form for study sites to use to notify subjects of a new follow-up schedule. The consent form addendum you advised the clinical investigators to use contained no mention of the cancellation of the study, and did not include accurate information on procedure changes regarding the requirement for quarterly or bi-annual x-ray evaluations, depending on the integrity of the stent. Most importantly, the addendum did not advise

subjects of the increased occurrence in stent fractures and possible associated risks, which was the reason for the increase in frequency of x-ray evaluations, as explained in your IDE Supplement 049 and submitted to the FDA.

b.) At least 14 serious adverse events occurred in subjects enrolled in the arm of the clinical study being conducted outside the US (OUS), including deaths, device migrations, occlusions, and device failures. These events have not been reported to CIs, IRBs, and FDA. During the FDA inspection, you told the FDA investigator no OUS study data have been reported to FDA, CIs, or IRBs, other than stent fractures.

In your response letter, you noted that you discussed this issue with the FDA reviewer in ODE on 5/18/07, and mutually agreed that Boston Scientific will include a summary of all safety data from the OUS study in future IDE annual reports, and that both US study and OUS study adverse event summaries will be provided annually to CIs and IRBs. This response is not acceptable in that you have not provided written documentation and a time frame in which you plan to provide this information to CIs and IRBs. In addition, the FDA Contact Report dated 5/18/07 and the IDE Supplement dated 6/13/07, which you included in your response, do not address providing US and OUS study summaries to CIs and IRBs.

3. **Failure to submit complete and accurate progress reports at least annually to all reviewing IRBs and to FDA [21 CFR 812.150(b)(5)].**

Boston Scientific failed to ensure that complete and accurate progress reports were submitted to all reviewing IRBs and to FDA at least annually. Specifically:

a.) Boston Scientific's January 2007 progress report to FDA states that only one death has occurred in the study. The safety report listing you provided in your response, dated 6/7/07, includes information on 2 deaths that occurred in the US study prior to January 2007. As noted above in **citation 1a**, 2 additional deaths were reported by CIs, and you did not report these deaths to FDA in the January 2007 annual progress report.

b.) Your Program Manager for the Vascular Program Clinical Trials told the FDA investigator that no study progress reports have been sent to the CIs or IRBs since 11/1/05.

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 study sponsor 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 and prevent the recurrence of similar violations in current or future studies for which you are the study sponsor. 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. Please send your response to:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Bioresearch Monitoring, HFZ-311
9200 Corporate Boulevard, Rockville, Maryland 20850
Attention: Ms. Doreen Kezer, MSN, Chief, Special Investigations Branch.

A copy of this letter has been sent to FDA's Minneapolis District Office, 212 3rd Avenue South, Minneapolis, MN 55401. We request that a copy of your response also be sent to that office.

If you have any questions, please contact Ms. Doreen Kezer at 240-276-0125 or at Doreen.Kezer@fda.hhs.gov.

Sincerely yours,

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

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