DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

WARNING LETTER

VIA FEDERAL EXPRESS

Mr. Thomas Boden
Executive Director, Quality Assurance
Cordis Corporation
7 Powderhorn Drive
Warren, New Jersey 07059

Dear Mr. Boden:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at Cordis Corporation, and requests that you implement prompt corrective actions. This letter also addresses deficiencies in your written response to the objectionable conditions observed during that inspection.. Mr. Peter Lenahan and Ms. Deborah Nixon, investigators from FDA's New Jersey District Office, conducted the inspection from January 29 through February 26, 2004. The purpose of the inspection was to determine if your activities as a sponsor for the clinical study [redacted] comply with applicable FDA regulations. The [redacted] used in the study, the [redacted] are devices as defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321 (h)].

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), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another program objective is to ensure that human subjects are protected from undue hazard or risk during scientific investigations.

Our review of the inspection report prepared by the New Jersey District Office revealed serious violations of 21 C.F.R. part 812, Investigational Device Exemptions, and section 520(g) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 360j(g)]. At the close of the inspection, Mr. Lenahan and Ms. Nixon presented a Form FDA-483, "Inspectional Observations" to you for review and discussed the listed deviations.

The deviations noted on the FDA-483, your written response to those deviations and issues from our subsequent review of the inspection report are discussed below:

Failure to ensure that investigators comply with the signed agreement, the investigational plan, the requirements of part 812, or other applicable FDA regulations, or any other conditions of approval imposed by the reviewing IRB of FDA [21 C.F.R. 812.46(a)]

Under FDA regulations, a sponsor must ensure that investigators conduct the investigation in accordance with the signed agreement with the sponsor. Examples of your failure to satisfy this requirement include, but are not limited to, the following:

- Amendments numbers 1-6 to [redacted] protocol, dated: 8/16/2000, 1/18/2001, 3/30/2001, 4/25/2001, 6/11/2001, and 7/24/2001, were authorized by [redacted] however, there is no documentation that these amendments were signed off by the study review panel, as required by the Standard Operating Procedure OP 0026, section 3.4.4.

- In addition, [redacted] granted a waiver of the protocol for randomized patient # [redacted] at Site #3, during a telephone conversation, allowing the patient to undergo [redacted] at the same time as a [redacted] procedure; however, there is no documentation that the sponsor/monitor followed up with an investigation or noted the protocol deviation in the PMA.

- Furthermore, the firm does not have a Standard Operating Procedure to track the granting of waivers or protocol deviations or subsequent investigations.

In your response to these observations, you indicated that all ongoing studies are in the process of being reviewed for compliance with OP 0026 and that this review will be completed by March 17, 2004. Furthermore, you stated that although the deviation from the protocol was not annotated in the PMA that it was captured on the Case Report Forms. As a sponsor, it is also your responsibility to ensure appropriate procedures are in place for the granting and documentation of waivers and protocol deviations and that these procedures are followed by investigators.

Failure to monitor the progress of an investigation conducted under your IDE and failure to notify the FDA of the for cause termination of an investigator's participation in an investigation [21 CFR 812.40]

Under FDA regulations, a sponsor must ensure proper monitoring of each investigation and ensure that any reviewing IRB and FDA are promptly informed of significant new information about an investigation as specified in 21 CFR 812.40.

Examples of your failure to satisfy these requirements include, but are not limited to, the following:

- There were no existing Standard Operating Procedures for the internal review and investigation of deficiencies identified through the field clinical monitoring reports.
- The field monitor indicated that during visit dates of 11/29-30/01, Subject #[redacted] at Site #255 experienced a stroke during the procedure No additional information was requested from the clinical site to evaluate the status of this patient to verify whether a stroke had indeed occurred. Instead, you relied entirely on the clinical evaluation by the CRO.
- You failed to follow-up on the field clinical site monitoring report from site #3, dated 8/28-29/2002, which identified an unaccounted for [redacted]
- A second [redacted] was also observed to have been unaccounted for during a transfer at the same site.

Your response includes a "memo to file," dated January 13, 2004 which indicates only that [redacted] was opened, unused and discarded during the [redacted] To ensure compliance with FDA requirements, sponsors should take appropriate measures to instruct investigators concerning their responsibilities for recordkeeping and device disposition, as set forth in 21 CFR 812.140(a).

- The FDA was not notified that Dr. [redacted] the Co-Principal Investigator of Site #255 had his enrollment privileges suspended by his local IRB on 10/10/2001, "based on the IRB's findings of inadequacies in reporting and regulatory compliance." Dr. [redacted] was appointed by the IRB to act as interim Principal Investigator on 10/05/2001. On 11/21/2001, Dr. [redacted] Medical Monitor also suspended enrollment at that site. Dr. [redacted] is the other Co-Investigator; however, a clinical site monitoring visit report dated 11/29-30/2001 states that Dr. [redacted] also had left the study. There were no details concerning when or why Dr. [redacted] left the study, nor was FDA informed of Dr. [redacted] departure, as required by part 812..

Failure to obtain signed agreement from participating investigators [21CFR 812.43(c)]

For example, a new Principal Investigator, Dr. [redacted] did not sign the Statement of Investigator until 3/13/2002 even though the enrollment was re-opened on 12/14/2001.

Other findings noted but not reported on the FDA Form 483 include missing or inconsistent documentation of CRA training, failure to follow the protocol medication regimen, missing documentation of other protocol deviations, and inadequate documentation and review of device complaint records.

The above-described deviations are not intended to be an all-inclusive list of deficiencies found in your clinical study. When conducting clinical investigations of products regulated by FDA, it is your responsibility as a sponsor to adhere 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 corrective actions you have implemented or will implement to 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.

Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2094 Gaither Road, Rockville, Maryland 20850, Attention: Rachel Solomon.

A copy of this letter has been sent to FDA's New Jersey District Office, 10 Waterview Blvd., Third Floor, Waterview Corp Center, Parsippany, NJ 07054. We request that a copy of your response also be sent to that office.

If you have any questions, please contact Rachel Solomon by phone (301) 594-4723, ext. 123), or by email at res@cdrh.fda.gov.

Sincerely yours,

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