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

AUG 31 2004

WARNING LETTER

Via Federal Express

Wendy J. Landow, MPH
Chief Executive Officer
Midwest Heart Foundation
1919 South Highland Avenue
Building B, Suite 201
Lombard, IL 60148

Dear Ms. Landow:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at Midwest Heart Foundation. This letter also discusses your written response to the noted violations and requests that you implement prompt corrective actions. Ms. Lisa Hayka, an investigator from FDA's Chicago District Office, conducted the inspection from March 17, 2004 through April 9, 2004. The purpose of the inspection was to determine whether your activities as a sponsor/monitor of the study entitled "[redacted]" complied with applicable regulations. The stent used in your study is a device 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 requests for Investigational Device Exemptions (IDE), Premarket Approval applications (PMA), and 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 scientific investigations.

Our review of the inspection report submitted by the district office revealed serious violations of requirements of Title 21, Code of Federal Regulations, (21 CFR), Part 812 - Investigational Device Exemptions. At the conclusion of the inspection Ms. Hayka presented a Form FDA-483, "Inspectional Observations," to you for review and discussed the listed deviations.

We acknowledge receipt of your letter dated April 16, 2004, addressed to Ms. Hayka. Your letter acknowledged the inspectional observations delineated on the Form FDA-483. It also briefly described plans to train investigators and research staff and to correct the observations described on the Form FDA-483. However, your proposed corrective actions were general in nature and lacked specific procedures for FDA to assess. We are therefore requesting additional information in order to evaluate the adequacy of your responses.

1. Failure to obtain FDA approval prior to initiating the [redacted] study [21 CFR 812.20(a)(1) & (2), and 812.42]

Pursuant to 21 CFR 812.20(a)(1), a sponsor shall submit an IDE application to the FDA if the sponsor intends to use a significant risk device, as defined in 21 CFR 812.3(m), in an investigation. Furthermore, a sponsor shall not begin an investigation for which an IDE is needed until the IDE application is approved by FDA and the clinical investigator obtains IRB approval. 21 CFR 812.20(a)(2) & 812.42.

The device under investigation in the [redacted] study is a stent used in the internal carotid artery. This is a significant risk device under 21 CFR 812.3(m) because it is intended as an implant, is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, and presents a potential for serious risk to the health, safety, or welfare or subjects. You failed to submit an IDE to FDA for the research study titled "[redacted]

This observation was not included on the Form FDA 483, but was discussed during the FDA inspection. We request that you include a corrective action plan for this observation in your written response to this letter.

2. Failure to ensure that IRB review and approval are obtained [21 CFR 812.40]

Under 21 CFR 812.40, a sponsor is responsible for ensuring that IRB review and approval are obtained for an investigation. You failed to ensure that IRB review and approval were obtained for the period from July 6, 2002 through May 2, 2003. Your records indicate that 40 investigational devices were implanted during that period. In addition, IRB review and approval were not obtained for the period from May 5, 2001 through July 6, 2001, and your records indicate that four investigational devices were implanted during that period.

3. Failure to ensure proper monitoring [21 CFR 812.40]

Under 21 CFR 812.40, a sponsor is responsible for ensuring proper monitoring of device investigations. A sponsor who discovers that an investigator is not complying with the investigational plan, signed agreement, applicable FDA regulations, or other conditions of approval imposed by the reviewing IRB or FDA must take steps to secure the investigator's compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the study. 21 CFR 812.46

You did not properly monitor the [redacted] study, as demonstrated by your failure to identify and/or address the following:

- The IRB-approved protocol for the [redacted] study specified the study device as the [redacted] There were approximately 168 procedures performed during this study, but, the [redacted] was used in only 9 of these procedures. The remaining procedures were conducted using various stents, including t[redacted] th[redacted] and the [redacted] This type of protocol change would require you to obtain FDA approval of a supplemental application, as well as IRB approval when appropriate, before implementing the change. 21 CFR 812.35.
- The research protocol required the placement of a venous sheath as a prophylactic measure in a case pacemaker was needed during the investigational procedure. The investigator reported, however, that he rarely, if ever, placed a femoral sheath before implanting the investigational device. As described above, a change to the study protocol to reflect this practice would require you to obtain FDA approval of a supplemental application, as well as IRB approval. 21 CFR 812.35.
- In a letter dated June 24, 1999 the IRB confirmed its understanding that the investigator would discontinue use of [redacted] because its use was not described in the informed consent materials or in the protocol. After the June 24 letter from the IRB, the investigator continued to use [redacted] during at least 18 surgeries to implant the investigational stent device. In order to change the protocol to reflect use of [redacted] you would be required to obtain FDA approval of a supplemental application, as well as IRB approval when appropriate, before implementing the change. 21 CFR 812.35.
- Subjects [redacted], and [redacted] all experienced unanticipated adverse device effects which the investigator failed to inform the IRB within 10 working days after learning of the effects.
- The clinical investigator did not properly obtain informed consent. At least two informed consents were not dated by the patients. This item is not on the Form FDA 483, but was discussed during the FDA inspection.

Your April 16, 2004 response to the FDA inspection states that you have planned additional staff training to address areas such as changes to research activity and adverse event reporting. In your written response to this letter, please provide an update on the status of your training plans. Your April 2004 letter also describes your plan to implement standard operating procedures (SOPs) for research that you sponsor. In your response to this letter, please provide an update on the development of these SOPs, including copies of the draft SOPs on monitoring, adverse event reporting, and changes in research activity.

The deviations described in this letter are not intended to be an all-inclusive list of deficiencies that may exist in your clinical study. It is your responsibility as a sponsor to assure adherence to each applicable requirement of the Act and FDA 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 recurrence of similar violations in current and future studies. Any submitted corrective action plan should 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: Ms. Marian J. Serge, R.N.

We are also sending a copy of this letter to FDA's Chicago District Office, 550 W. Jackson Street, Suite 1500, Chicago, IL 60611. We request that you also send a copy of your response to that office. If you have any questions about this letter, please contact Ms. Serge at (301) 594-4723, extension 139 or by e-mail at msl@cdrh.fda.gov.

Sincerely,

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