



via Federal Express

M37901
Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

WARNING LETTER

MAY 24 2000

William W. George
President and Chief Executive Officer
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432

Dear Mr. George:

The purpose of this letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) sponsor-monitor inspection of Medtronic AVE (AVE), and to request a prompt reply from you informing us of your corrective actions. AVE sponsored a study to investigate the medical device, the AneuRx™ Endovascular Prosthesis (Bifurcated Stent Graft System). That product is a device as that term is defined under Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

During the period April 26 through April 28, 2000, Ms. Andrea P. Scott, a Supervisory Investigator with the Food and Drug Administration (FDA), San Francisco District Office, San Jose Resident Post, and Dr. L. Glenn Massimilla, a Consumer Safety Officer with the Center for Devices and Radiological Health (CDRH), Office of Compliance, Division of Bioresearch Monitoring, conducted an inspection at Medtronic AVE, a wholly owned subsidiary of Medtronic, Inc.

The purpose of that inspection was to determine whether Medtronic AVE's activities as the sponsor-monitor of investigational studies of the AneuRx™ Endovascular Prosthesis (Bifurcated Stent Graft System) complied with applicable FDA regulations. The inspection provided the FDA with information about AVE's activities as a sponsor-monitor of the Investigational Device Exemption [REDACTED] and its related Premarket Approval Application (PMA) P990020.

Our review of information from this inspection revealed violations of FDA regulations contained in Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions. The findings of FDA's inspection were listed on the form FDA-483, "Inspectional Observations," which, at the conclusion of the inspection, was presented to and discussed with Mr. Mel D. Schatz, Vice President and General Manager; Michel Letort, Ph.D., Director of Clinical Research; Rita Jacob, R.N., Clinical Research Manager; Ms. Meg Lannon and Ms. Susan Walton of Regulatory Affairs; and other individuals from Medtronic AVE's Peripheral Unit.

In addition, our review of FDA inspectional findings from clinical investigator (CI) sites of doctors [REDACTED] and [REDACTED] revealed repeated deviations from the requirements of the AneuRx™ clinical investigational plan. The deviations were listed on forms FDA-483, "Inspectional Observations," which were presented to and discussed with [REDACTED] on January 11, 2000, and to/with [REDACTED] on February 9, 2000. The extent of noncompliance observed at these and other participating CI sites resulted, in part, from your firm's failure to adequately monitor the clinical investigation at these sites. The following enumeration and discussion of violations and deviations from the regulations is not intended to be an all-inclusive list of problems encountered during our review.

1) Failure to ensure that FDA was promptly informed of significant new information about an investigation -- [21 CFR 812.40]

In the case of an (aneurysm) rupture that involved subject # [REDACTED] the sponsor (AVE) was notified by the CI on March 7, 1999; however, FDA was not notified by AVE until October 25, 1999. In the case of the rupture involving subject [REDACTED], AVE was notified on April 23, 1999; however, FDA was not notified by the sponsor until October 25, 1999. In the case of the rupture that involved subject [REDACTED], the sponsor was notified on June 18, 1999, but the sponsor did not notify FDA until October 25, 1999. In the case of the rupture involving subject # [REDACTED] the CI notified AVE on August 30, 1999; FDA was not notified by the sponsor until October 25, 1999. In the case of the rupture that involved subject [REDACTED] the CI notified the sponsor on September 21, 1999, but the sponsor did not notify FDA until October 25, 1999.

The significance of the sponsor's delays in reporting is that three rupture events which occurred prior to June 18, 1999 were not reported to FDA (in submissions related to this study) prior to the June 23, 1999 Circulatory System Devices Panel meeting during which this PMA was reviewed. Furthermore, the sponsor was aware of all five of the above-referenced ruptures prior to FDA's September 28, 1999 approval of the device but did not report those ruptures until approximately one month after PMA approval.

The failure to submit the reports in a timely manner resulted in submissions lacking data that may have been considered in reviews of safety and efficacy. FDA did not have the information that it expected to have been provided, in a timely manner, to conduct a full review of the safety and effectiveness of this investigational device in the above-referenced PMA.

2) Failure to maintain accurate, complete and current records relating to an investigation including all investigator correspondence -- [21 CFR 812.140(b)(1)]

The sponsor did not maintain records in a manner that would provide for or contribute to the timely reporting of significant clinical information. As a result of the failure to have effective policies and procedures, data was not properly managed. This resulted in significant delays in the reporting of significant events, including aneurysm ruptures, to FDA.

The status/disposition of source documentation from CI sites, used in the adjudication of adverse events, was not readily identifiable/retrievable. For example, there is no system, other than the mental recollection of one individual (the Senior Clinical Research Administrator), for determining what documents have been received and what adverse event investigations/reviews are pending receipt of documents.

3) Failure to ensure investigator compliance -- [21 CFR 812.46]

Our reviews have disclosed that, despite periodic clinical monitoring visits made by or on behalf of your firm, serious protocol violations were repeatedly made by several of the participating clinical investigators.

The "AneuRx Investigational Plan" states that the clinical investigator is responsible for the follow-up of study subjects including the appropriate imaging procedure. We note that follow-up imaging tests at 1-month, 6-months and 12-months post-treatment were required by the protocol. These tests were not always performed.

At Dr. [REDACTED], all Phase II and Phase III subjects' records were selected and audited for compliance with follow-up imaging tests during FDA's January 5-11, 2000, inspection. Of these, numerous subjects had not had required imaging tests performed. We note that the sponsor (Medtronic AVE) made over 12 monitoring visits prior to FDA's inspection and yet the compliance with this required test did not improve over the course of the study.

At [REDACTED], it was noted that none of the imaging procedures employed skin dose monitoring as required by the protocol. In addition, six subjects in the Phase III study had not had at least one of the required imaging tests performed at the 6-month post-treatment interval. It is notable that the sponsor, or their designated monitor, made over 30 monitoring visits between October 28, 1998 (date of initiation Phase III) and January 5, 2000 (the start of FDA's inspection) and yet the compliance rates did not improve over the course of the study.

4) Failure to ensure proper monitoring of the clinical investigation -- [21 CFR 812.40]

Based on the inspectional observations, FDA concludes that your firm failed to follow the monitoring procedures that were described in the PMA submission and that this failure contributed to the recurrent deviations observed at study sites.

We acknowledge the letter from Mr. Brian Sheehan, Vice President, Regulatory Affairs and Quality Assurance, Medtronic AVE, dated May 8, 2000, to Ms. Scott that responded to some of the observations made by FDA during the April 26-28, 2000 inspection. In this letter Mr. Sheehan asserts, "Medtronic AVE has been and remains committed to maintaining records and reporting clinical information on a timely basis per FDA requirements." FDA's inspection did not find this to be the case in the past and may verify your procedure for reporting clinical information in a timely manner in a future inspection.

The corrective actions that AVE states they have implemented may be verified during a future FDA inspection. We are concerned that our overall analysis of the inspectional findings, and their relationship to Medtronic's above-referenced submissions, indicates that the monitoring conducted by your subsidiary was deficient for the reasons described herein.

The significance of these observations is that these events were not reported to FDA in Medtronic's 1999 submissions related to this study. The failure to submit reports in a timely manner resulted in submissions lacking data that may have been considered in reviews of safety and efficacy. FDA did not have the information that it expected to have been provided, in a timely manner, to conduct a full review of the safety and effectiveness of the investigational device in the above-referenced PMA.

It is your responsibility to ensure adherence to each requirement of the Act and regulations. Within 15 days of receipt of this letter, please provide this office with written documentation of the specific steps you have taken or will take to prevent the recurrence of similar violations in current or future studies.

Your response should be directed to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring (HFZ-311), 2098 Gaither Road, Rockville, Maryland 20850. Attention: Mr. David R. Kalins. A copy of this letter has been sent to the Food and Drug Administration's Minneapolis District Office, 240 Hennepin Avenue, Minneapolis, Minnesota 55401. We request that a copy of your response also be sent to that office.

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Please direct questions concerning this matter to Mr. Kalins at (301) 594-4720, extension 137.

Sincerely yours,



for

Lillian J. Gill
Director
Office of Compliance
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Radiological Health

cc: Mr. Charles H. Swanson
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