



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
2098 Gaither Road  
Rockville MD 20850

MAY 12 1998

WARNING LETTER

VIA FEDERAL EXPRESS  
VIA FACSIMILE

Arthur D. Collins, Jr.  
President and Chief Operating Officer  
Medtronic, Inc.  
7000 Central Avenue, N.E.  
Minneapolis, Minnesota 55432

Dear Mr. Collins:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration has reviewed marketing materials that were distributed by Medtronic Inc., (Medtronic) in the promotion of its Freestyle® Aortic Root Bioprosthesis. The Freestyle bioprosthesis is a device within the meaning of section 201(h) of the Federal Food, Drug and Cosmetic Act (the Act). The materials have made inappropriate representations about Medtronic's product, as discussed below.

The Medtronic Freestyle Aortic Root Bioprosthesis was granted marketing approval on November 26, 1997. The sale and distribution of the device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Act under the authority of section 515(d)(1)(B)(ii) of the Act. FDA also determined that, to ensure the safe and effective use of the device, it was necessary to further restrict the device within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in the order and (2) insofar as the sale and distribution must not violate sections 502(q) and 502(r) of the Act.

On March 13, 1998, the Office of Device Evaluation sent your company a letter discussing its evaluation of Medtronic's December 1, 1997 amendment to the company's PMA for the product. That letter advised you that the final printed form of the labeling for the device is significantly different from the labeling approved by FDA with regard to the information about the AOA treatment and other issues upon which the agency and the company came to agreement during the deliberation process. That letter instructed Medtronic to, in addition to some other corrective actions, clarify in a footnote with bolded typeface that there are no clinical data available to evaluate the long-term impact of

the AOA treatment. The letter also advised you that promotion and advertising materials must be consistent with the approved labeling.

An advertisement in the January, 1998 issue of the Annals of Thoracic Surgery describes the Freestyle as the “only stentless bioprosthesis available in the U.S. to offer advanced processes in tissue preservation” and as “offer[ing] the potential for long-term durability and improved hemodynamics.” CDRH believes that this is a reference to the AOA™ anticalcification treatment that Medtronic has incorporated into its Freestyle valves. The description in the ad implies that the treatment preserves tissue in such a way as to be essential to the use of the product and that the treatment is known to provide long-term durability and improved hemodynamics. It also implies that other valves do not have “long-term durability.” Your materials do not define that term.

A piece of promotional literature that was distributed is entitled, “freestyle Technical Discussion Series.” It contains a discussion of the AOA treatment. The first paragraph includes a statement that calcification is a significant cause of valve failure. The following paragraph includes a statement that “research and *in vivo* animal studies indicate that this disadvantage can be potentially offset by using AOA anticalcification treatment.” These sentences, juxtaposed, create the impression that the AOA treatment can mitigate the disadvantages or reduce the frequency of valve failure caused by the calcification of the valves. It also implies that the treatment has current or immediate implications for the mitigation of valve failure. Nowhere in this document is there a statement of the extended period of time, about 15 years, that would be required to establish the clinical utility or efficacy of the treatment.

The discussion of “Efficacy in Animal Studies” implies that the efficacy demonstrated in animal and bench testing can be extrapolated to a benefit in humans. Statements such as “Although AOA anticalcification efficacy has not yet been proven clinically, the results of the animal implants appear very promising” and “This promise of increased resistance to calcification may extend the benefits of bioprostheses to more patients, and be beneficial to older patients in whom anticoagulation is particularly undesirable” also imply that the benefits for humans are more established than they are.

Section 502(q) of the Act provides that a restricted device is misbranded if its advertising is false or misleading in any particular. Section 502(r) provides that a restricted device is misbranded unless all advertisements and other descriptive printed matter pertaining to it contain a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

The Freestyle Bioprosthesis is misbranded within the meaning of sections 502(a), 502(o) and 502(r) of the Act and adulterated within the meaning of section 501(f)(1)(B). It is misbranded under 502(a) because the labeling for the device, as required by 21 CFR 801.109(d), does not include the required information about the device, including any relevant hazards, contraindications, side effects and precautions. It is misbranded under 502(r) because the advertising does not contain the required brief statement of the

device's intended use and relevant warnings, precautions, side effects and contraindications. It is misbranded under section 502(o) because no information or notice respecting the device has been submitted as required by section 510(k) of the Act. The agency's regulations at 21 CFR 814.39 require that, after FDA approval of a device, applicants submit a PMA supplement for review and approval by FDA before making a change affecting the safety or effectiveness of the device for which the applicant has an approved PMA, unless the change is of a type for which FDA has advised that an alternate submission is permitted. Your claims have changed the required labeling for the device.

The device is adulterated because it is a class III device for which there is no approved premarket approval application as required by section 515(a) of the Act and no investigational device exemption for the claims made for the device as required by section 520(g) of the Act. It is adulterated because you have made implied claims about the efficacy of the anticalcification treatment in the mitigation of clinical valve failures.

The agency has concluded that Medtronic has used unsubstantiated statements and representations in its promotion and advertising materials to indicate that use of the Freestyle® Aortic Root Bioprosthesis will improve patient outcome and should be used in patients where valve calcification would be considered a problem. Medtronic has used *in vitro* and animal studies to imply this benefit in direct contradiction to the agreements made with the agency. The official labeling of the product identifies the AOA treatment as a process that uses alpha-amino oleic acid. The approved labeling does not attribute any significance to the presence of the treatment.

This letter is not intended to be an all-inclusive list of deficiencies associated with your device. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter may also be reflected in other promotional and advertising materials used by your firm. You are responsible for investigating and reviewing all materials to ensure compliance with applicable regulations.

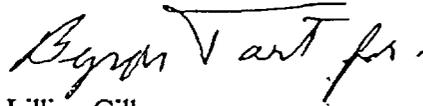
You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action being initiated by FDA without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office, in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations. Your response should also include steps being taken to address any misleading information currently in the marketplace and to prevent similar violations in the future. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to Deborah Wolf, Regulatory Counsel, Promotion and Advertising Policy Staff (HFZ-302), Office of Compliance, Center for Devices and Radiological Health, 2098 Gaither Road, Rockville, Maryland 20850.

A copy of this letter is being sent to FDA's Minneapolis District Office. Please send a copy of your response to the Director, Minneapolis District Office (HFR-MW340), Food and Drug Administration, 240 Hennepin Avenue, Minneapolis, Minnesota, 55401-1912.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Lillian Gill".

Lillian Gill  
Director  
Office of Compliance  
Center for Devices and  
Radiological Health