United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

October 22, 2010

Via Electronic Transmission

The Honorable Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner Hamburg:

The United States Senate Committee on Finance (Committee) has jurisdiction over, among other things, the Medicare and Medicaid programs. As Ranking Member of the Committee, I have a responsibility to the more than 100 million Americans who receive health care coverage under these programs to oversee their proper administration and ensure that taxpayer dollars are appropriately spent on safe and effective drugs and devices.

The Food and Drug Administration (FDA) requires manufacturers that submit applications and clinical studies for drug, biologics, and device approvals to file disclosure statements regarding the financial interests of the clinical investigators who are not full-time or part-time employees of the manufacturers but are or were involved in conducting studies submitted to the FDA.[1] Specifically, a manufacturer is required to submit for each investigator, either a certification of no financial interest or disclosure of the amount and nature of the financial interest that meets any of the following criteria:

- Financial arrangements between the manufacturer and clinical investigator where the value of compensation to the investigator could be influenced by the outcome of the study.

- Significant payments from the manufacturer to the clinical investigator such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.

- Proprietary interest in the tested product held by the clinical investigator.

- Significant equity interest in the manufacturer held by the clinical investigator.

[1] 21 CFR §54.4.

In April 2010, I asked Medtronic, Inc. (Medtronic) to provide a copy of the financial disclosure forms the company filed with the FDA for 32 physicians who may have conducted studies on behalf of Medtronic during the period of January 2007 to the present. A review of the documents Medtronic provided to the Committee show that Medtronic filed financial disclosure forms for seven of the physicians and all seven had received "significant payments from the manufacturer." For example, the company reported consulting payments ranging from almost $40,000 to one physician to almost $2 million to another. Three of the physicians also received about $1 million in royalties, while another received several thousand in Medtronic stock.

Medtronic's production also included financial disclosure forms that were submitted to the FDA for more than 50 other clinical investigators. Almost all of these investigators received significant payments from Medtronic. Two of the investigators met three of the four criteria for disclosure to the FDA. Not only did they receive "significant payments of other sorts," but they also had a proprietary interest in the product tested and a financial arrangement where the value of compensation could be influenced by the outcome of the study. (See Attached)

In 2001, the Task Force on Financial Conflicts of Interest in Clinical Research established by the Association of American Medical Colleges (AAMC) issued guidelines for the oversight of financial interests in human subjects research. The following is one of the Task Force's recommendations for institutional policies concerning financial interests:

> Institutional policies should establish the rebuttable presumption that an individual who holds a significant financial interest in research involving human subjects may not conduct such research. The intent is not to suggest that every financial interest jeopardizes the welfare of human subjects or the integrity of research, but rather to ensure that institutions systematically review any financial interest that might give rise to the perception of a conflict of interest, and further, that they limit the conduct of human subjects research by financially interested individuals to those situations in which the circumstances are compelling. The presumption against significant financial interests in human subjects research should apply whether the research is funded by a public agency, a non-profit entity, or a commercial sponsor, and wherever the research may be carried out.[2]

In 2006, AAMC and the Association of American Universities (AAU) asked an advisory committee of senior officials at major research universities and medical schools to review the 2001 guidelines and provide further guidance on the management of conflicts of interest in human subjects research, among other things. In February 2008, the advisory committee issued its report reiterating the rebuttable presumption that an individual who holds a significant financial interest in research involving human subjects

[2] *Protecting Subjects, Preserving Trust, Promoting Progress—Policy and Guidelines for the Oversight of Individual Financial Interest in Human Subjects Research*, Task Force on Financial Conflicts of Interest in Clinical Research, Association of American Medical Colleges, December 2001.

may not conduct such research recommended in 2001 and clarifying the compelling circumstances exception.[3]

In light of the 2001 AAMC Task Force guidelines and the 2008 AAMC-AAU Advisory Committee report, I would appreciate FDA's response to the following questions:

1) While FDA regulations require a manufacturer to disclose to the FDA the significant financial interests of the manufacturer's clinical investigators, the regulations do not specify how FDA should treat financial interests that may present a conflict. Please describe in detail how FDA determines whether or not the financial interests reported to the agency adversely affect: (a) the rights and welfare of human subjects and/or (b) the integrity and reliability of the clinical studies submitted by manufacturers in support of the approval of their drugs, biologics and devices.

2) Assuming there are no compelling circumstances, are there financial interests that the FDA would consider too significant a conflict to be appropriate for a clinical investigator to be involved in a study? If yes, please describe those interests.

3) Does FDA advise manufacturers on specific steps that should be taken to minimize potential bias? Are there actions that FDA expects companies to take to manage potential conflicts of interest? Please be specific.

Thank you for your attention and assistance on this matter. I would appreciate your response to my questions by no later than November 12, 2010. Should you have any questions regarding this letter, please do not hesitate to contact Angela Choy or Brian Downey at (202) 224-4515. Any formal correspondence should be sent electronically in PDF searchable format to Brian_Downey@finance-rep.senate.gov.

Sincerely,

Charles E. Grassley
Ranking Member

Attachment

[3] *Protecting Patients, Preserving Integrity, Advancing Health: Accelerating the Implementation of COI Policies in Human Subjects Research*, A Report of the AAMC-AAU Advisory Committee on Financial Conflicts of interest in Human Subjects Research, February 2008.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

TO BE COMPLETED BY APPLICANT

The following information concerning [redacted] M.D. (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study [redacted] (*Name of clinical study*) is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☑ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☑ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☑ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
[redacted] M.D.	Vice President-Clinical & Medical Affairs
FIRM/ORGANIZATION: Medtronic Spinal and Biologics	
SIGNATURE: [redacted]	DATE: 10/27/09

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

FORM FDA 3455 (4/06)

PSC Graphics: (301) 443-1090 EF

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FIRM/ORGANIZATION Medtronic Spinal and Biologics	
SIGNATURE [redacted]	DATE 10/27/09

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