For Immediate Release
Wednesday, December 3, 2008

Grassley seeks answers about the use of a heart device in clinical research at Northwestern Memorial Hospital

WASHINGTON — Senator Chuck Grassley is asking questions about an Edwards Lifesciences' device used in heart valve repair that was implanted in some patients at Northwestern Memorial Hospital. He is also asking the Food and Drug Administration whether or not the agency has reviewed this device for marketing. Grassley said he has received allegations that the device has not been approved for use in clinical research or cleared by the FDA.

The text of the letters sent today from Grassley to Edwards Lifesciences, Northwestern University/Northwestern Memorial Healthcare and the Food and Drug Administration follows here.

December 3, 2008

Henry S. Bienen, PhD
President
Northwestern University
633 Clark Street
Evanston, IL 60208

Dean M. Harrison
President and Chief Executive Officer
Northwestern Memorial Healthcare
251 East Huron Street
Chicago, IL 60611

Dear Dr. Bienen and Mr. Harrison:

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs. As a senior member of the United States Senate and as Ranking Member of the Committee, I have a special responsibility to the more than 80 million Americans who receive health care coverage under those programs to ensure that taxpayer and beneficiary dollars are appropriately spent on safe and effective drugs and devices.

I recently received troubling allegations that the Myxo ETlogix 5100 Ring (Myxo Ring), an annuloplasty ring used in heart valve repair, has not been approved and/or cleared for marketing by the Food and Drug Administration (FDA). At the same time it appears that the Myxo Ring has been, and perhaps continues to be, implanted in patients by Dr. Patrick McCarthy, a cardiothoracic surgeon at Northwestern Memorial Hospital. Furthermore, I was informed that the device is being implanted without an Investigational Device Exemption (IDE), which would allow the device to be used in a clinical study to collect data in support of an application to the FDA for approval. It is my further understanding that Dr. McCarthy invented this device, which is manufactured by Edwards Lifesciences (Edwards), and receives royalty payments from Edwards.

These allegations were brought to my attention by Dr. Nalini Rajamannan, Associate Professor and Valve Director of the Bluhm Cardiovascular Institute at Northwestern University's (Northwestern/University) Feinberg School of Medicine. In addition, Antonitsa Vlahoulis, one of the patients who received the Myxo Ring during her operation in April 2006, expressed concern to my Committee staff that this device had not been approved and/or cleared by the FDA when it was implanted in her without her informed consent.

Dr. Rajamannan and Ms. Vlahoulis also told my Committee staff that they have both brought their concerns to Northwestern. According to a letter that the University sent to Ms. Vlahoulis, dated September 18, 2008, Northwestern's Office for Research Integrity completed its own investigation of the allegations and concluded that the implantation of the device was "not research and did not require IRB approval." The letter also stated that Edwards confirmed in an email to Northwestern that the device was commercially available.

I am also aware of the fact that Edwards Lifesciences wrote in an email to Dr. McCarthy that "According to the FDA guidance document dated January 10, 1997…model 5100 is a minor modification of model 4200, GeoForm Annuloplasty Ring, cleared under K032250. The applicable 510(k) number for model 5100 is K032250." I cannot judge whether or not the Myxo Ring required FDA approval or clearance; however, Dr. Rajamannan told Committee staff that, in her opinion, the Myxo Ring is not a minor modification because, among other things, the shape of the ring is triangular whereas other annuloplasty rings are oblong. She also told my staff that after bringing this matter to Northwestern's attention, the University began to take action against her.

My Committee staff's own search for the Myxo Ring on FDA's website did not produce any information regarding the Myxo Ring other than 8 adverse event reports that were submitted to FDA's Manufacturer and User Device Experience Database (MAUDE).

In investigating these allegations, I would appreciate Northwestern's response to the following questions and requests for information. Please repeat the enumerated question and follow with the appropriate response.

1) Please provide the Committee with a copy of the report, memorandum, or any other documentation of the internal investigation completed by Northwestern's Office for Research Integrity.

2) Please provide a copy of all internal communications and correspondence regarding the Myxo Ring and the use of the device as part of an outcomes study. This request covers the period of January 2006 through the date of this letter.

3) Please provide a copy of all communications and correspondence with Edwards Lifesciences and FDA regarding the Myxo Ring. This request covers the period of January 2006 through the date of this letter.

4) What information regarding the Myxo Ring was provided to the Institutional Review Board during its review of the protocol and consent form for the

outcomes study entitled, "Early and Late Outcomes Following Surgical Intervention for Atrial Fibrillation Database"?

5) According to a July 24, 2008 letter to Dr. Rajamannan from Northwestern Medical Faculty Foundation, Inc., pursuant to the Foundation's request, Dr. Rajamannan "agreed not to provide clinical care at Northwestern Medical Faculty Foundation and Northwestern Memorial Hospital."

   a. Please explain why this request was made of Dr. Rajamannan.

   b. Did the University and/or Northwestern Memorial Hospital have concerns regarding her clinical performance?

   c. Prior to bringing her concerns regarding implantation of the Myxo Ring to the attention of the University, did Dr. Rajamannan receive any poor job performance evaluations? Has the University taken any disciplinary actions against Dr. Rajamannan in the past?

   d. Please provide the Committee with a copy of Dr. Rajamannan's personnel records. Dr. Rajamannan provided a signed authorization on October 28, 2008, for the release of her personal information.

6) Please provide a copy of any forms filed with the University and Northwestern Memorial Hospital detailing Dr. Patrick McCarthy's outside income and conflicts of interest from January 2004 through June 2008.

7) Because reporting practices vary widely from one institution to another, I would appreciate you also placing this income into a chart, detailing compensation from device companies to Dr. McCarthy. This request covers the period of January 2004 through June 2008. For each payment to Dr. McCarthy from a company, please provide the following information:

   a. Name of company;
   b. Date of payment;
   c. Payment description (CME, honorarium, research support, royalties, etc.); and
   d. Amount of payment.

In cooperating with the Committee's review, no documents, records, data or information related to these matters shall be destroyed, modified, removed or otherwise made inaccessible to the Committee.

I look forward to hearing from you by no later than January 5, 2009.

Sincerely,
Charles E. Grassley
Ranking Member

Attachments

*****

December 3, 2008

Michael A. Mussallem
Chairman and Chief Executive Officer
Edwards Lifesciences
One Edwards Way
Irvine, CA 92614

Dear Mr. Mussallem:

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs. As a senior member of the United States Senate and as Ranking Member of the Committee, I have a special responsibility to the more than 80 million Americans who receive health care coverage under those programs to ensure that taxpayer and beneficiary dollars are appropriately spent on safe and effective drugs and devices.

I recently received troubling allegations that Edwards Lifesciences' (Edwards) Myxo ETlogix 5100 Ring (Myxo Ring), an annuloplasty ring used in heart valve repair, has not been approved and/or cleared for marketing by the Food and Drug Administration (FDA). At the same time it appears that the Myxo Ring has been, and perhaps continues to be, implanted in patients by Dr. Patrick McCarthy, a cardiothoracic surgeon at Northwestern Memorial Hospital. Furthermore, I was informed that the device is being implanted without an Investigational Device Exemption (IDE). It is my further understanding that Dr. McCarthy invented this device and receives royalty payments from Edwards Lifesciences.

Antonitsa Vlahoulis, one of the patients who received the Myxo Ring during her operation in April 2006, expressed concern to my Committee staff that this device had not been approved and/or cleared by the FDA when it was implanted in her without her informed consent. Ms. Vlahoulis and her physician, Dr. Nalini Rajamannan, Associate Professor and Valve Director of the Bluhm Cardiovascular Institute at Northwestern University's (Northwestern) Feinberg School of Medicine, also informed my staff that they have brought their concerns regarding the Myxo Ring to FDA and Northwestern.

According to a letter that Northwestern sent to Ms. Vlahoulis, dated September 18, 2008, Northwestern's Office for Research Integrity completed its own investigation of the allegations and concluded that the implantation of the device was "not research and did not require IRB approval." The letter also stated that Edwards confirmed in an email to Northwestern that the device was commercially available.

I am also aware of the fact that Edwards Lifesciences wrote in an email to Dr. McCarthy that "According to the FDA guidance document dated January 10, 1997…model 5100 is a minor

modification of model 4200, GeoForm Annuloplasty Ring, cleared under K032250. The applicable 510(k) number for model 5100 is K032250." I cannot judge whether or not the Myxo Ring required FDA approval or clearance; however, Dr. Rajamannan told Committee staff that, in her opinion, the Myxo Ring is not a minor modification because, among other things, the shape of the ring is triangular whereas other annuloplasty rings are oblong.

My Committee staff's own search for the Myxo Ring on FDA's website did not produce any information regarding the Myxo Ring other than 8 adverse event reports that were submitted to FDA's Manufacturer and User Device Experience Database (MAUDE).

In investigating these allegations, I would appreciate Edwards' response to the following questions and requests for information. Please repeat the enumerated question and follow with the appropriate response.

1) Did Edwards submit information and/or a 510(k) application to the FDA regarding its Myxo Ring? If so, please provide a copy of what was submitted to the FDA.

2) On what date did the Myxo Ring become commercially available?

3) On what date was the first Myxo Ring implanted?

4) According to the company's email to Dr. McCarthy, "model 5100 is a minor modification of model 4200, GeoForm Annuloplasty Ring." On what basis did Edwards make that determination?

    a. Was the modification to model 4200 reported to the FDA?

    b. If so, on what date, to whom and how was that information communicated to the FDA?

    c. How many rings have been implanted by Dr. McCarthy?

5) Please provide a copy of all communications and correspondence with Northwestern and Northwestern Memorial Hospital and with the FDA regarding the Myxo Ring. This request covers the period of January 2006 through the date of this letter.

6) Please identify each payment Edwards made to Dr. Patrick McCarthy for the period of January 1, 2003 through October 31, 2008. Also, provide the annual amount paid to Dr. McCarthy. For each payment to Dr. McCarthy, please provide the following information:

    e. Date of payment;
    f. Payment description (CME, honorarium, research support, royalties, etc.); and
    g. Amount of payment.

7) Please provide all internal and external communications and/or documents in Edwards' possession regarding the outcomes study conducted by Dr. McCarthy entitled, "*Early and Late Outcomes Following Surgical Intervention for Atrial Fibrillation Database.*" This request covers the period of January 1, 2006 through October 31, 2008.

8) Please provide a detailed account of payments and/or benefits of any kind that Edwards provided to Northwestern University, Northwestern Memorial Hospital, and Northwestern Medical Faculty Foundation, Inc. for the period of January 1, 2003 through October 31, 2008. For each payment, please provide the following:

    a. Date of payment;
    b. Payment description (CME, honorarium, research support, etc.);
    c. Amount of payment; and
    d. Whether the payment was provided to Northwestern University, Northwestern Memorial Hospital, or Northwestern Medical Faculty Foundation, Inc.

9) Please also provide the total annual amount of payments and/or benefits Northwestern University, Northwestern Memorial Hospital, and Northwestern Medical Faculty Foundation, Inc. received from Edwards.

In cooperating with the Committee's review, no documents, records, data or information related to these matters shall be destroyed, modified, removed or otherwise made inaccessible to the Committee.

I look forward to hearing from you by no later than January 5, 2009.

Sincerely,
Charles E. Grassley
Ranking Member

*****

December 3, 2008

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner von Eschenbach:

As Ranking Member of the United States Senate Committee on Finance (Committee), I have a responsibility to the more than 80 million Americans who receive health care coverage under the Medicare and Medicaid programs to oversee the proper administration of these

programs and ensure that taxpayer dollars are appropriately spent on safe and effective drugs and devices.

I recently received troubling allegations that the Myxo ETlogix 5100 Ring (Myxo Ring), an annuloplasty ring used in heart valve repair manufactured by Edwards Lifesciences (Edwards), has not been approved and/or cleared for marketing by the Food and Drug Administration (FDA/Agency). At the same time it appears that the Myxo Ring has been, and perhaps continues to be, implanted in patients by Dr. Patrick McCarthy, a cardiothoracic surgeon at Northwestern Memorial Hospital. Furthermore, I was informed that the device is being implanted without an Investigational Device Exemption (IDE), which would allow the device to be used in a clinical study to collect data in support of an application to the FDA for approval.

These allegations were brought to my attention by Dr. Nalini Rajamannan, Associate Professor and Valve Director of the Bluhm Cardiovascular Institute at Northwestern University's (Northwestern/University) Feinberg School of Medicine. In addition, Antonitsa Vlahoulis, one of the patients who received the Myxo Ring during her operation in April 2006, expressed concern to my Committee staff that this device had not been approved and/or cleared by the FDA when it was implanted in her without her informed consent.

Dr. Rajamannan and Ms. Vlahoulis also informed the Committee that they have both brought their concerns to Northwestern. According to a letter that the University sent to Ms. Vlahoulis, dated September 18, 2008, Northwestern's Office for Research Integrity completed its own investigation of the allegations and concluded that the implantation of the device was "not research and did not require IRB approval." The letter also stated that Edwards Lifesciences confirmed in an email to Northwestern that the device was commercially available. According to that email from Edwards dated September 10, 2007, the Myxo Ring "has been marketed in the US since March 2006 pursuant to the FDA's 510K clearance process."

Edwards also wrote in an email to Dr. McCarthy that "According to the FDA guidance document dated January 10, 1997…model 5100 is a minor modification of model 4200, GeoForm Annuloplasty Ring, cleared under K032250. The applicable 510(k) number for model 5100 is K032250." I cannot judge whether or not the Myxo Ring required FDA approval or clearance; however, Dr. Rajamannan told Committee staff that, in her opinion, the Myxo Ring is not a minor modification because, among other things, the shape of the ring is triangular whereas other annuloplasty rings are oblong. The letter to Ms. Vlahoulis and the emails from Edwards Lifesciences are attached.

My Committee staff's search for the Myxo Ring on FDA's website did not produce any information regarding the Myxo Ring other than 8 adverse event reports that were submitted to FDA's Manufacturer and User Device Experience Database (MAUDE). I understand that at least 10 reports, however, have been submitted to MAUDE to date.

In investigating these allegations, I would appreciate FDA's response to the following questions and requests for information. Please repeat the enumerated question and follow with the appropriate response.

1) Has the FDA received any information and/or a 510(k) application from Edwards regarding the Myxo Ring? Has the FDA ever reviewed this device for marketing? If so, what was FDA's decision regarding this device?

2) According to Edwards' email to Dr. McCarthy, the Myxo Ring "is a minor modification of model 4200, GeoForm Annuloplasty Ring." Did Edwards report that modification to the FDA? If so, on what date, to whom and how was that information communicated to the Agency?

3) Based on the information the Committee has received to date, the Myxo Ring is not being used under an IDE. If it is in fact a device that has not been approved or cleared by the FDA, please explain whether or not implantation of this device should be conducted under an IDE.

4) According to an email from Ms. Vlahoulis to Don Workman at Northwestern, dated October 19, 2008, the patient stated that she sent a report to the FDA and the "FDA acknowledged to me that they never approved this ring and that they are investigating this situation." See attached. I would appreciate a briefing for my Committee staff as soon as the FDA concludes its investigation.

5) FDA's website states that a 510(k) is required when "There is a change or modification of a legally marketed device and that change could significantly affect its safety or effectiveness. The burden is on the 510(k) holder to decide whether or not a modification could significantly affect safety or effectiveness of the device.

    a. What type of reporting is required of 510(k) holders when they make modifications to their devices?

    b. How does FDA ensure that the 510(k) holder has made the appropriate decision regarding whether or not to submit a 510(k) when the holder makes modifications to a legally marketed device?

Thank you for your attention to this important matter. Please respond to the questions set forth in this letter by no later than January 5, 2009.

Sincerely,
Charles E. Grassley
Ranking Member
Attachment