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United States Senate
COMMITTEE ON THE JUDICIARY
WASHINGTON, DC 20510–6275

April 28, 2014

VIA ELECTRONIC TRANSMISSION

Morton Schapiro
President
Northwestern University
633 Clark Street
Evanston, IL 60208

Richard J. Gannotta
President
Northwestern Memorial Hospital
251 East Huron Street
Chicago, IL 60611

Dear Mr. Schapiro and Mr. Gannotta:

On December 3, 2008, and September 30, 2009, I wrote to you about troubling allegations that the Myxo-ETlogix 5100 Ring (Myxo Ring), an annuloplasty ring used in heart valve repair, had not been cleared for marketing by the Food and Drug Administration (FDA) before it was implanted in patients as part of an outcomes study. However, the Myxo Ring was actually implanted as part of *two* outcomes studies.[1]

In October 2008, Edwards Lifesciences LLC – the manufacturer of the Myxo Ring – discontinued distribution of the device due to safety concerns.[2] Then, in March 2009, FDA found that the Myxo Ring was a "significant risk device" that required FDA approval.[3] Ultimately, in April 2009, the device was cleared with a new name, dETlogix Annuloplasty Ring. In my December 2008 letter, I asked you seven questions, including the following:

> 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.[4]

The request was not limited to a specific Institutional Review Board (IRB) Project Number. Rather, the request was for "*all* internal communications and correspondence regarding the Myxo Ring . . . ." However, in response to my December 2008 letter, you produced documents pertaining only to IRB 1532-003. You did not produce any documents pertaining to IRB 1532-004 — until my recent request by specific project number.

In your March 21, 2014 response to my March 4, 2014 letter, you claimed that my staff limited the scope of my December 3, 2008 request informally during conversations

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[1] "Early and Late Outcomes Following Surgical Intervention for Atrial Fibrillation Database" (IRB Project Number 1532-003) and "Mitral Valve Pathology: A Quantitative Assessment Pre- and Post-Repair" (IRB Project Number 1532-004).
[2] See attached letter from FDA, dated March 4, 2009.
[3] *Id*.
[4] Emphases added.

you had with them. However, you provided no documentation of any such agreement and my staff does not recall one. You also indicated in your March 21, 2014 letter as follows:

> [W]hen we responded to your [previous] inquiries . . . . *and even today*, it did not appear that . . . IRB Study 1532-004 was responsive . . . . 1532-004 . . . was terminated in 2007. Thus, the only relevant actual IRB study that was responsive to [your] request was, *and remains*, 1532-003.[5]

As you noted, IRB 1532-004 was terminated in 2007. My December 3, 2008 letter explained that "this request covers the period of January 2006 through the date of this letter." In addition, according to the documents you produced on March 21, 2014, a primary objective of IRB 1532-004 was to "evaluate results of myxomatous mitral valve repair using the Myxo ETlogix Annuloplasty Ring . . . ." My December 3, 2008 letter requested "*all* internal communications and correspondence regarding the Myxo Ring . . . ." Thus, by both subject-matter and time-frame, the documents pertaining to IRB 1532-004 fall squarely within the scope of my December 3, 2008 request.

Moreover, the IRB 1532-004 documents which you belatedly disclosed bear directly on the question that precipitated my investigation in 2008 and remains unanswered: did Northwestern implant an unapproved device — which it knew, or should have known, required approval — in patients without obtaining their informed consent?

Since September 18, 2008, Northwestern has repeatedly stated that it did not believe that such approval and consent were required because Dr. McCarthy was assured by Edwards in August 2007 that the Myxo Ring was only a "minor modification" of preexisting devices.[6] However, the documents produced thus far show that Dr. McCarthy was making statements that directly contradicted Edwards' assurances and that Northwestern would have known of these contradictory statements. Specifically, in a journal article submitted by Dr. McCarthy and ten Northwestern colleagues on behalf of its Bluhm Cardiovascular Institute in June 2007, Dr. McCarthy was promoting the Myxo Ring as "significantly larger than existing commercial remodeling rings."[7] In addition, in a protocol submitted to the University on June 7, 2006, Dr. McCarthy stated as follows:

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[5] Emphases added.

[6] September 18, 2008 is when Northwestern's Office for Research Integrity issued a memorandum summarizing the findings of its investigation of Dr. McCarthy's use of the Myxo Ring. On January 5, 2009, Northwestern produced this memorandum which cites and attaches emails through which Dr. McCarthy received assurances from Edwards on August 28, 2007 and September 10, 2007 (Bates Number NWU 00001-00013). As part of that production, Northwestern also provided the article referenced below in footnote seven, in which Dr. McCarthy indicated that he began implanting the Myxo Ring in patients on March 15, 2006. Subsequently, Northwestern Memorial Hospital (NMH) produced an email dated October 21, 2005, in which Edwards informed Dr. McCarthy that "[Edwards is] continuing to do [its] best to make [the Myxo Ring] available . . . and [is] in the process of ordering the rings needed to complete . . . in-house[] testing, which is required for FDA approval." However, Northwestern did not produce any document suggesting that it had confirmed with Edwards that this testing had been completed prior to March 15, 2006, when the Myxo Ring was first implanted in a patient at NMH.

[7] P.M. McCarthy, MD, E.C. McGee, M D, V.H. Rigolin, MD, Q. Zhao, MD, H. Subacius, MA, A. L. Huskin, RN, S. Underwood, RN, B. J. Kane, RDCS, I. Mikati, MD, G. Gang, MD, and R. O. Bonow, MD, "Initial clinical experience with Myxo-ETlogix* mitral valve repair ring," *The Journal of Thoracic and Cardiovascular Surgery*, Volume 136, Number 1 [received for publication on June 15, 2007; revisions received on December

> [R]epair with current ring systems do not address . . . excessive leaflet tissue . . . . The Myxo . . . [R]ing was specifically developed to help eliminate the need for the complex . . . sliding-plasty procedure. The Myxo ETlogix is *the first ring* . . . designed to reshape the annulus to accommodate the larger leaflets . . . by reshaping the . . . [annulus] . . . instead of cutting the . . . [leaflets.][8]

Given Dr. McCarthy's clear expertise in the field of heart-valve repair and his first-hand knowledge of the Myxo Ring and other devices used in that field, there is a genuine question as to how he could have believed that the Myxo Ring was only a "minor modification" of existing devices when he himself designed and promoted the Myxo Ring for a different purpose, with a different shape, and as "significantly" different in size. To determine how Northwestern could have reconciled these contradicting positions, an analysis of all relevant documents was required. To this end, your March 21, 2014 document production was helpful, as the protocol referenced above is from IRB 1532-004 and clearly relevant. However, your response raises new questions and leaves unanswered the central question of this investigation. Accordingly, please respond to the following:

1. Please provide documentation of any agreement to limit the scope of my December 3, 2008 request to IRB Project Number 1532-003. If you have none, please indicate that you have no such documentation.

2. Is it Northwestern's understanding that Dr. McCarthy believed that the Myxo Ring was "significantly larger than existing commercial remodeling rings" or that it was merely a "minor modification" of existing remodeling rings?

3. In light of the protocol referenced above, how did Northwestern reconcile Dr. McCarthy's description of the Myxo Ring as a groundbreaking design with Edwards' assurances that the device was merely a "minor modification?"

I would appreciate a response by May 16, 2014. Should you have any questions, please contact Jay Lim of my Committee staff at (202) 224-5225.

Sincerely,

Charles E. Grassley
Ranking Member

21, 2007; accepted for publication on February 12, 2008]: 79. In addition, as indicated in pages 80-81 of this article, Dr. McCarthy was gaining recognition for "making a major contribution" to the field of heart-valve repair by inventing the Myxo Ring, which was deemed "a tremendous advance." As noted on page 4 of this article, the Myxo Ring was implanted in patients from March 15, 2006 through November 19, 2007.

[8] Patrick M. McCarthy, et al., "Mitral Valve Pathology: A Quantitative Assessment Pre- and Post-Repair," at 4 (Bates Number NW/G000017). Emphasis added.

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

4 MAR 2009

The Honorable Charles E. Grassley
Ranking Member
Committee on Finance
United States Senate
Washington, D.C. 20510-6200

Dear Senator Grassley:

Thank you for your letter of December 3, 2008, concerning the status with the Food and Drug Administration (FDA or the Agency) of the model 5100 McCarthy Myxo ETlogix Annuloplasty Ring for use in heart valve repair, manufactured by Edwards Lifesciences LLC (Edwards). Below we have repeated the questions from your letter, followed by the Agency's responses.

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?**

As Edwards has revealed publicly, they submitted a 510(k) to FDA in October, notifying us of their intent to market the dETlogix (formerly called the Myxo ETlogix) Annuloplasty Ring. FDA received this submission on October 29, 2008. FDA is currently in the process of reviewing the submission.

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?**

In a letter dated August 15, 2008, Edwards notified the Agency that they were indeed marketing the Myxo ETlogix Annuloplasty Ring. The letter stated their belief that the Myxo ETlogix was substantially equivalent to the Edwards GeoForm, Model 4200, and Carpentier-Edwards Physio, Model 4450, Annuloplasty Rings, and that the Myxo Ring represented only a minor modification to the predicate rings. This letter was addressed to William MacFarland, Acting Chief of the Cardiovascular and Neurological Devices Branch in the Office of Compliance (OC) of FDA's Center for Devices and Radiological Health (CDRH).

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.

FDA has now determined that the Myxo ETlogix Annuloplasty Ring is not covered under any 510(k) clearance. A significant risk device such as the Myxo ETlogix Annuloplasty Ring that is not cleared or approved would be required to be studied under an investigational device exemption (IDE). Edwards has not yet received 510(k) clearance or IDE approval for the Myxo ETlogix Annuloplasty Ring. The sponsor came in for a regulatory meeting with CDRH's OC on October 14, 2008. At this meeting, the sponsor stated that their firm had discontinued distribution of the device. Shortly thereafter, Edwards submitted the 510(k), which FDA received on October 29, 2008. Edwards also stated publicly in October 2008 that the firm had discontinued distribution of the device.

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.**

The information provided to Ms. Vlahoulis did not, as the quotation suggests, include the clearance status of the Myxo ETlogix Annuloplasty Ring. As noted in our response to #1 above, the Agency received the 510(k) submission on October 29, 2008, and is in the process of reviewing it.

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?**

A 510(k) holder may make a modification to a device without filing a new 510(k) after concluding that the change does not significantly affect the safety or effectiveness of the device or constitute a major change in the intended use of the device. Sponsors may refer to FDA's 510(k) memorandum (dated January 10, 1997) "Deciding When to Submit a 510(k) for a Change to an Existing Device" for assistance in determining whether changes to a device require a new 510(k). This document (http://www.fda.gov/cdrh/ode/510kmod.html) includes a flowchart to help manufacturers through the logic scheme necessary to arrive at a decision on when to submit a 510(k) for a change to an existing device. The flowchart addresses labeling changes, technology or performance specifications changes, and materials changes. This document recommends that, if a sponsor concludes that a new 510(k) is not required, the sponsor should document the analysis and file it for future reference. The following text is taken from the definitions section of the FDA memorandum:

> For the purpose of this guidance, documentation means recording the results of applying the model to proposed changes in a device. Consideration of each decision point should be recorded, as well as the final conclusions reached. If testing or other engineering analysis is part of the process, the results of this activity should be recorded or referenced. A copy of this documentation should be maintained for future reference.

It should be noted that no formal reporting by the 510(k) holder to the Agency is required if the sponsor concludes that a given change does not require a new 510(k). However, a 510(k) holder is required to maintain the documentation and make it available to FDA during an inspection.

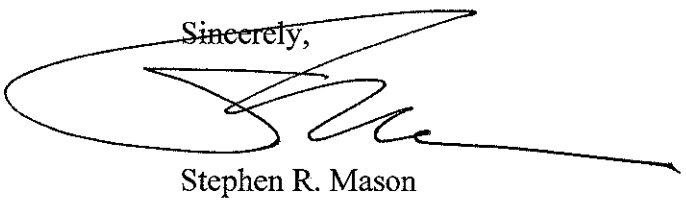
b. How does FDA ensure that the 510(k) holder has made the appropriate decision regarding whether or not to submit a 510(k) when the holder makes modifications to a legally marketed device?

As stated above, the 510(k) holder is not required to formally notify FDA after concluding that a given change does not require a 510(k). Therefore, the Agency does not have the opportunity to evaluate that decision in advance to determine if it was appropriate. However, the Agency educates sponsors about how to make the correct decision in this regard, e.g., the 510(k) memorandum referenced above. This document provides guidance and decision flowcharts for the sponsor to use when making these decisions. Furthermore, a 510(k) holder is required to maintain records and make them available during an inspection.

As mentioned in the FDA memorandum, there are bound to be some changes that fit into a "gray area" as to whether a new 510(k) submission is required. In these cases, sponsors are encouraged to contact the Agency if they have questions regarding the appropriateness of a 510(k). Lastly, although a sponsor may conclude that a particular change does not require a 510(k), the sponsor may subsequently make additional changes to the same device that do require a new 510(k). When this occurs, sponsors are required to submit a 510(k) incorporating <u>all</u> the changes that have been made to the device since clearance of the most recent 510(k) for the device.

Thank you again for your interest in this matter. If we can be of further assistance, please let us know.

Sincerely,



Stephen R. Mason
Acting Assistant Commissioner
for Legislation