ONE HUNDRED ELEVENTH CONGRESS

Congress of the United States

House of Representatives

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May 11, 2009

Dr. Joshua M. Sharfstein
Principal Deputy Commissioner
Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Sharfstein:

The Committee on Energy and Commerce and its Subcommittee on Oversight and Investigations, and its Subcommittee on Health are examining the process used by the Food and Drug Administration to ensure that medical devices are safe and effective.

As part of this ongoing investigation, numerous FDA scientists have raised concerns with a decision in December 2008 by Dr. Daniel Schultz, the Director of FDA's Center for Devices and Radiological Health, to approve a medical device manufactured by ReGen Biologics, Inc. This device, called a "collagen scaffold" (CS) and marketed as the Menaflex device, is used to reinforce and repair the meniscus, which is the natural cushion between the upper and lower leg bones in the knee.

Based on documents provided to the Committee, it appears that FDA has considered the company's applications three times over the past three years. Although the company attempted to demonstrate that its device was "substantially equivalent" to devices already on the market, FDA scientists and medical experts raised concerns about the safety and efficacy of the device. For example:

- In rejecting the company's first application, Mark Melkerson, the Acting Director of FDA's Division of General, Restorative, and Neurological Devices, sent a letter to ReGen on July 26, 2006, stating that "your device has a new indication ... that alters the therapeutic effect, impacting safety and effectiveness."

- In rejecting the company's second application, Dr. Donna-Bea Tillman, the Director of FDA's Office of Device Evaluation, sent a letter to ReGen on August 20, 2007, stating that "the performance data you have provided indicates that there is an increased risk with the use of your device for the indicated patient population and an uncertain benefit as compared to legally marketed predicate devices."

- In considering the company's third application, Dr. Tillman wrote a memorandum on September 22, 2008, stating that the data provided by the company "failed to meet its primary effectiveness endpoints," "was unable to show that patients who received the CS device experienced any benefit," and "raised some questions about the safety of the device, with CS patients potentially experiencing more serious adverse events and needing more operations."

Instead of accepting the recommendations of FDA scientists to reject ReGen's third application, Dr. Schultz sent a letter to ReGen on October 8, 2008, stating that he would seek input from an advisory panel of experts. Documents provided to the Committee also raise concerns about this advisory panel process, such as the exclusion of FDA experts who had raised concerns previously about the device, the propriety of ReGen's input into the selection of advisory committee members, and the failure to hold a formal vote on whether the device should be approved.

Nevertheless, on December 18, 2008, Dr. Schultz sent a letter to ReGen approving its application, concluding that the device is "substantially equivalent for both chronic and acute use for the medial meniscus."

We understand that you may be reexamining the decision to approve this device for marketing. Given the questions raised by FDA scientists about the lack of data on the safety and efficacy of this device, we believe this is a prudent course of action. To ensure that your review is complete, we are forwarding some of the key documents that have been provided to us, which are summarized below. Although we take no position on the ultimate outcome of your review, our paramount interest is in ensuring that all medical devices currently on the market are safe and effective, including the device manufactured by ReGen.

Background

Before approving a medical device to be marketed, FDA reviews a pre-market approval (PMA) application submitted by the device manufacturer. Under this PMA process, the company must provide data establishing both the safety and effectiveness of the device.[1]

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[1] 21 U.S.C. § 360e (premarket approval).

A PMA application is required for all "Class III" devices, which are devices "that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."[2]

For non-Class III devices, a company may bypass the PMA process by submitting an application for a "substantial equivalence" review. Under this process, known as the 510(k) process, the company must demonstrate that its device is at least as safe and effective as another device FDA has already approved for marketing.[3]

The review of applications is conducted by the Office of Device Evaluation (ODE) within FDA's Center for Devices and Radiological Health (CDRH). For orthopedic joint devices such as ReGen's device, recommendations from staff scientists are reviewed within ODE by the Chief of the Orthopedic Joint Devices Branch and the Director of the Division of General, Restorative, and Neurological Devices.

FDA also maintains advisory committees of experts that may be convened to provide independent, professional expertise. For example, CDRH has an Orthopedic and Rehabilitation Devices Panel that may review and evaluate data concerning the safety and effectiveness of orthopedic and rehabilitation devices. Additional or alternate members may be selected for this Panel when expertise is required that is not available among current standing members.[4]

On April 8, 1996, FDA determined that ReGen's device is a Class III device.[5] In 1997, ReGen began a clinical trial to establish the safety and effectiveness of its product. In 2004, ReGen submitted a PMA application that described the device as follows:

> The ReGen Biologics Collagen Meniscus Implant™ (CMI) is intended to function as an absorbable template to facilitate host tissue growth in patients who have an

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[2] 21 U.S.C. § 360c (classification of devices intended for human use). *See also* Food and Drug Administration, Center for Devices and Radiological Health, *Device Advice – Device Classes* (online at www.fda.gov/cdrh/devadvice/3132.html) (accessed May 5, 2009).

[3] *See, e.g.*, 21 C.F.R. § 870.92; Food and Drug Administration, Center for Center for Devices and Radiological Health, *Device Advice – Premarket Notification 510(k)* (online at www.fda.gov/CDRH/DEVADVICE/314.html) (accessed May 5, 2009).

[4] Food and Drug Administration, *Charter Amendment: Medical Devices Advisory Committee* (Aug. 18, 1999) (online at www.fda.gov/cdrh/panel/charter/charter-mdac.doc).

[5] Health Care Financing Administration, *Medicare and Medicaid Programs; Quarterly Listing of Program Issuances and Coverage Decisions; Third Quarter 1995,* 61 Fed. Reg. 15491, at 15501-15504 (Apr. 8, 1996) (online at http://fdsys.gpo.gov/fdsys/pkg/FR-1996-04-08/pdf/96-8623.pdf).

> irreparable tear or loss of meniscus tissue. The CMI provides a mechanically stable, functional replacement for the deficient tissue through the implant's absorption and replacement by the patient's tissue.[6]

After this PMA application was submitted, ReGen decided to submit an application for a review of its device under the 510(k) process, stating that its device was "substantially equivalent" to other medical devices FDA already approved for marketing.

ReGen's First 510(k) Application

On December 28, 2005, ReGen submitted its first 510(k) application. Although ReGen previously defined its device as an "implant" in its PMA application, it characterized the device in its 510(k) application as a "surgical mesh" designed to reinforce and repair the meniscus.[7]

On February 22, 2006, Mark N. Melkerson, the Acting Director of the Division of General, Restorative, and Neurological Devices, prepared a letter to ReGen rejecting its 510(k) application because it was "not substantially equivalent." The letter stated:

> We have determined the device is not substantially equivalent. ... This decision is based on the fact that your device has a new indication (i.e., the reinforcement and repair of soft tissue where weakness exists, including, but not limited to ... meniscus defects) that alters the therapeutic effect, impacting safe[ty] and effectiveness and is therefore a new intended use.
>
> Therefore, this device is classified by statute into class III (Premarket Approval), under Section 513(f) of the Federal Food, Drug, and Cosmetic Act.[8]

This letter was not sent to ReGen. Instead, the next day, Acting Director Melkerson sent a letter rejecting ReGen's application for a different reason. The letter stated:

> This decision is based on the fact that the performance data you have provided did not demonstrate your device to be as safe and effective as legally marketed devices. ... You may submit a new premarket notification if you have additional data you believe can demonstrate

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[6] ReGen Biologics, Inc., *Collagen Meniscus Implant Modular PMA Submission, PMA Shell No. M040013, Module 1* (July 7, 2004).

[7] ReGen Biologics, Inc., *Traditional Premarket Notification 510(k) Collagen Scaffold (CS)* (Dec. 28, 2005).

[8] Letter from Mark N. Melkerson, Acting Director, Division of General, Restorative, and Neurological Devices, Food and Drug Administration, to John Dichiara, Senior Vice President, ReGen Biologics, Inc. (Feb. 22, 2006) (unsent).

that your device is as safe and as effective as the predicate device.[9]

On March 2, 2006, after ReGen's counsel spoke to Miriam Provost, the deputy director of the Office of Device Evaluation, FDA rescinded the "not substantially equivalent" determination and converted it into a request for additional information.[10] The letter informing ReGen of this decision stated:

> We are unaware of any other legally-marketed surgical mesh indicated for use in reinforcement and repair of meniscus defects. In addition, we believe that the application of ReGen Collagen Scaffold in the repair of meniscus defects introduces new risks not normally associated with the general use of surgical meshes to reinforce soft tissue where weakness exists. ... Please identify a legally-marketed predicate device indicated for the repair or reinforcement of meniscus defects that has similar technological characteristics to ReGen Collagen Scaffold Surgical Mesh.[11]

On June 8, 2006, ReGen provided information on devices it believed were comparable. The letter stated:

> The [collagen scaffold] device is substantially equivalent (SE) to legally marketed surgical meshes, including the DePuy Restore® Orthobiologic Soft Tissue Implant, (K982330, K001738, K031969), the BioBlanket™ Surgical Mesh (K043259, K041923), and the Cook Biotech SIS Fistula Plug (K050337).[12]

On July 18, 2006, FDA's lead reviewer for this application, Charles Durfor, wrote a memorandum concluding that ReGen's device was "not substantially equivalent" to any other device FDA had approved for marketing that was intended to provide "reinforcement and repair of soft tissue where weakness exists, including, but not limited to, general soft tissue defects, hernia

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[9] Letter from Mark N. Melkerson, Acting Director, Division of General, Restorative, and Neurological Devices, Food and Drug Administration, to John Dichiara, Senior Vice President, ReGen Biologics, Inc. (Feb. 23, 2006).

[10] Food and Drug Administration, *Meeting Minutes: ReGen Collagen Scaffold Surgical Mesh, Regulatory, Clinical and Quality, ReGen Biologics, Inc.* (Mar. 2, 2006).

[11] Letter from Mark N. Melkerson, Acting Director, Division of General, Restorative, and Neurological Devices, Food and Drug Administration, to John Dichiara, Senior Vice President, ReGen Biologics, Inc. (Mar. 3, 2006).

[12] Letter from John Dichiara, Senior Vice President, ReGen Biologics, Inc., to Mark N. Melkerson, Acting Director, Division of General, Restorative, and Neurological Devices, Food and Drug Administration, and Charles N. Durfor, Ph.D., Food and Drug Administration (June 8, 2006).

and meniscus defects."[13]

On July 26, 2006, Acting Director Melkerson wrote a letter to ReGen rejecting its application. The letter stated:

> This decision is based on the fact that your device has a new indication (i.e., the reinforcement and repair of soft tissue where weakness exists, including, but not limited to ... meniscus defects) that alters the therapeutic effect, impacting safety and effectiveness, and is therefore a new intended use.[14]

ReGen appealed this decision in a meeting with Dr. Donna-Bea Tillman, the director of the Office of Device Evaluation, in September 2006. Following that meeting, Gerald E. Bisbee, Jr., the Chairman and CEO of ReGen, wrote to FDA to complain about the FDA staff scientists who concluded that ReGen's device was "not substantially equivalent" (NSE) to other approved devices. The letter stated:

> Because all three letters issued by the staff were intended as NSE letters, it is very hard for us to believe that such inconsistency reflects a thoughtful and careful review. Now, if you choose to send the 510(k) back to the same group of reviewers, I am very concerned that the review quality will not improve, that there is a closed-mindedness that may not be overcome, that opportunity for interactive discussions with review personnel will be severely limited, and that the outcome of the review will be no different.[15]

On November 3, 2006, FDA rejected ReGen's appeal. In a letter explaining the decision, Dr. Donna-Bea Tillman wrote:

> After reviewing your letter of appeal, meeting internally with DGRND [Division of General, Restorative, and Neurological Devices] and discussing your appeal with you and your associates on September 7, 2006, I find that I do concur with DGRND's NSE decision which was based on the fact that your device has a new indication ... that alters the

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[13] Memorandum from Charles N. Durfor, Ph.D., Food and Drug Administration, to File (July 18, 2006).

[14] Letter from Mark N. Melkerson, Acting Director, Division of General, Restorative, and Neurological Devices, Food and Drug Administration, to John Dichiara, Senior Vice President, ReGen Biologics, Inc. (July 26, 2006).

[15] Letter from Gerald E. Bisbee, Jr., Chairman and CEO, ReGen Biologics, Inc., to Dr. Donna-Bea Tillman, Director, Office of Device Evaluation, Food and Drug Administration (Sept. 25, 2006).

therapeutic effect, impacting safety and effectiveness, and is therefore a new intended use.[16]

ReGen's Second 510(k) Application

On December 22, 2006, ReGen filed its second 510(k) application, indicating that the device would be used in "repairing and reinforcing meniscal defects."[17]

On March 23, 2007, FDA's lead reviewer for the application, John Goode, wrote a memorandum recommending a rejection. The memorandum stated:

> K053621 [ReGen's first application] was found to be NSE for New Intended Use. I believe that the additional information in the indications for use in the subject 510(k) is just clarifying information regarding the indications (the patient population to receive the subject device) and it does not change the intended use of the device as identified in K053621 that was found to be NSE for New Intended Use – it is still for "reinforcement and repair of ... meniscal defects."[18]

On March 26, 2007, Mark N. Melkerson, Acting Director, Division of General, Restorative, and Neurological Devices, sent a letter to ReGen reiterating FDA's safety concerns and requesting additional information. The letter stated:

> Based upon the safety concerns outlined above, we believe that it is necessary for you to provide adequate effectiveness data to demonstrate a positive risk/benefit profile. ... However, it appears that the only effectiveness data provided in the 510(k) was for 8 patients in an uncontrolled feasibility study. ... Since the patient population in the feasibility study is small and does not have a control, we believe it is not sufficient to draw conclusions regarding device safety or effectiveness.[19]

In July 2007, after reviewing additional information provided by ReGen, FDA Medical

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[16] Letter from Dr. Donna-Bea Tillman, Director, Office of Device Evaluation, Food and Drug Administration, to John Dichiara, Senior Vice President, ReGen Biologics, Inc. (Nov. 3, 2006).

[17] ReGen Biologics, Inc., *Traditional Premarket Notification 510(k) Collagen Scaffold (CS)* (Dec. 22, 2006).

[18] Memorandum from John Goode, Food and Drug Administration, to File (Mar. 23, 2007) (emphasis in original).

[19] Letter from Mark N. Melkerson, Acting Director, Division of General, Restorative, and Neurological Devices, Food and Drug Administration, to John Dichiara, Senior Vice President, ReGen Biologics, Inc. (Mar. 26, 2007).

Officer Kevin Lee wrote a memorandum concluding that ReGen's device was still "not substantially equivalent" to any devices already approved by FDA. He also noted concerns with the safety and effectiveness of the device. The memorandum stated:

> Safety: Sixty-eight (41.97%) out of 162 CMI [Collagen Meniscus Implant] implanted subjects experienced multiple device related adverse events. ... I believe that the device is not safe, when compared to partial meniscectomy, upon the analysis of the adverse events from the data.
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> Effectiveness: There is no effectiveness data to support that the device is more effective than partial meniscectomy.[20]

Other FDA staff raised similar concerns. On August 3, 2007, FDA Medical Officer Roxolana Horbowyj wrote a memorandum stating:

> [D]ata as presented demonstrates no clinically or statistically significant different [*sic*] between investigational device ... and control.[21]

On August 15, 2007, FDA's lead reviewer, John Goode, wrote a memorandum recommending a rejection. The memorandum stated:

> I am recommending NSE: performance data do not demonstrate equivalence. ... I believe that there is an increased risk with the use of the CS device for the indicated patient population and an uncertain benefit as compared to legally marketed predicate devices.[22]

On August 20, 2007, Dr. Donna-Bea Tillman, the Director of the Office of Device Evaluation, sent a letter to ReGen rejecting its second application. The letter stated:

> We have determined the device is not substantially equivalent. ... This decision is based on the fact that the performance data you have provided indicates that there is an increased risk

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[20] Memorandum from Kevin Lee, Medical Officer, Food and Drug Administration, to File (July 23, 2007).

[21] Memorandum from Roxolana Horbowyj, Food and Drug Administration, to John Goode, Food and Drug Administration (Aug. 3, 2007).

[22] Memorandum from John Goode, Food and Drug Administration, to File (Aug. 15, 2007).

> with the use of your device for the indicated patient population and an uncertain benefit as compared to legally marketed predicate devices.[23]

ReGen again appealed the decision. The company wrote a letter to Dr. Daniel Schultz, the Director of FDA's Center for Devices and Radiological Health, requesting another review of its application and specifically requesting that there be "[n]o participation by the Office of Device Evaluation."[24]

On June 20, 2008, Dr. Schultz wrote back to assure ReGen that a third application would receive a fair review. The letter stated:

> I can assure you that, if you believe that submitting a 510(k) for this indication is appropriate, your submission would receive an expeditious and fair review.[25]

ReGen's Third 510(k) Application

On July 23, 2008, ReGen submitted its third application, stating that its device was "intended for use in surgical procedures for the reinforcement and repair of chronic soft tissue injuries of the meniscus."[26]

On July 31, 2008, FDA Medical Officer Kevin Lee wrote a memorandum citing deficiencies related to the safety and effectiveness of the device. The memorandum stated:

> I have a serious safety issue regarding this device. ... The results of your IDE G92021 1 showed that there was no effectiveness data. ... Please explain how you justify the safety of your device in the case that there were 36.8% incidence of device related adverse event from

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[23] Letter from Dr. Donna-Bea Tillman, Director, Office of Device Evaluation, Food and Drug Administration, to John Dichiara, Senior Vice President, ReGen Biologics, Inc. (Aug. 20, 2007).

[24] Letter from ReGen Biologics, Inc., to Dr. Daniel Schultz, Director, Center for Devices and Radiological Health, Food and Drug Administration (undated).

[25] Letter from Dr. Daniel Schultz, Director, Center for Devices and Radiological Health, Food and Drug Administration, to Gerald E. Bisbee, Jr., Chairman and CEO, ReGen Biologics, Inc. (June 20, 2008).

[26] ReGen Biologics, Inc., *Traditional Premarket Notification 510(k), ReGen Collagen Scaffold (CS)* (July 23, 2008).

> P9602, 9% of inflammation of implanted CMI, and 16% of subject having loose attached CMI from acute and chronic CMI implanted subjects.[27]

On August 11, 2008, FDA Statistician Dr. George Chu wrote a memorandum identifying a potential conflict of interest relating to the source of data provided to support ReGen's application. The memorandum stated:

> To my understanding, instead of a complete clinical report to allow an adequate review, the sponsor mainly relied on a recently published paper (William G. Rodkey et al: J Bone Joint Surg Am. (JBJS) 2008; 90: 1413-1426) to support the proposed indication claim. **Please note that the first author of this published paper is also a Vice President, Scientific Affairs of the sponsor firm.**[28]

Based on these assessments, on August 14, 2008, the lead reviewer on the application, John Goode, wrote a memorandum recommending a rejection:

> Based upon my review of the data, and the fact that there were multiple rounds of review of the previous 510(k)s K053621, K063827, and the sponsor's appeal, **I recommend NSE for lack of performance data**. ... I believe that the risk/benefit profile for the subject device is not comparable to the standard of care "partial meniscectomy" for the type of meniscal injury described in the IDE study.[29]

On September 10, 2008, Division Director Mark Melkerson wrote a memorandum concluding that ReGen's device was not substantially equivalent to other devices approved by FDA. The memorandum stated:

> [T]here appears to be an increased reoperation rate ... and increased adverse event profile. ... The sponsor also acknowledged the conclusions from JBJS article that the acute population demonstrated no positive risk/benefit ratio compared to partial-meniscectomy control.[30]

On September 22, 2008, Dr. Tillman, the director of the Office of Device Evaluation, wrote

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[27] Memorandum from Kevin Lee, Medical Officer, Food and Drug Administration, to File (July 31, 2008).

[28] Memorandum from Jianxiong Chu, Food and Drug Administration, to John Goode, Food and Drug Administration (Aug. 11, 2008) (emphasis in original).

[29] Memorandum from John Goode, Food and Drug Administration, to File (Aug. 14, 2008) (emphasis in original).

[30] Memorandum from Mark N. Melkerson, Director, Division of General, Restorative, and Neurological Devices, Food and Drug Administration, to the Record (Sept. 10, 2008).

a memorandum concurring with these recommendations and raising concerns with the safety and effectiveness of the device. The memorandum stated:

> Unfortunately, that study failed to meet its primary effectiveness endpoints, and thus was unable to show that patients who received the CS device experienced any benefit. Additionally, the study also raised some questions about the safety of the device, with CS patients potentially experiencing more serious adverse events and needing more operations. In comparison, the other "new" indications that FDA has previously cleared for surgical mesh have either been supported by more compelling clinical results or bench data that is sufficient to support the safety and effectiveness of the device for the new indication for use. Therefore, I find that the data currently provided by ReGen do not support a finding of Substantial Equivalence, because ReGen has failed to demonstrate that the proposed new indication for use can be considered as the same intended use as the predicate devices.[31]

Approval through Advisory Panel

On October 8, 2008, Dr. Daniel Schultz, the Director of FDA's Center for Devices and Radiological Health, sent a letter to ReGen stating that, instead of rejecting the company's third application based on the recommendations of FDA scientists, he would "seek input from the Orthopedic and Rehabilitation Devices Advisory Panel of the Medical Devices Advisory Committee."[32] The advisory panel met on November 14, 2008. Several concerns have been raised about this advisory panel meeting, such as the exclusion of FDA experts who had raised concerns previously about the device, the propriety of ReGen's input into the selection of advisory committee members, and the failure to hold a formal vote on whether the device should be approved.

A. Exclusion of FDA Experts

Documents provided to the Committee indicate that FDA scientists who previously raised concerns about the safety or effectiveness of the device were not permitted to present their views at the advisory panel meeting. Instead, Dr. Schultz selected the Director of the Office of Science and Technology, Dr. Larry Kessler, to present information about ReGen's application, after receiving briefings from other FDA staff.

On November 4, 2008, the day before the advisory panel meeting, the lead reviewer on the

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[31] Memorandum from Dr. Donna-Bea Tillman, Director, Office of Device Evaluation, Food and Drug Administration, to the Record (Sept. 22, 2008).

[32] Letter from Dr. Daniel Schultz, Director, Center for Devices and Radiological Health, Food and Drug Administration, to John Dichiara, Senior Vice President, ReGen Biologics Inc. (Oct. 8, 2008).

application, John Goode, sent an e-mail to colleagues expressing concern with the short amount of time allotted to prepare Dr. Kessler. The e-mail stated:

> I believe that it is **ridiculous** to believe that we can properly brief Larry in 2 hours to make such an important presentation to the Panel, especially if most of this time will be answering his questions. As you know, this device has been in front of the FDA for 16 years with multiple types of submissions including an IDE, PMA, and 3 510(k)s. I wonder how much time Larry and his team have devoted to the review of the various submissions. I guess we'll find out tomorrow.[33]

Nevertheless, after Dr. Kessler made his presentation to the advisory panel, he also recommended rejecting the application. On December 15, 2008, Dr. Kessler sent an e-mail to Dr. Schultz. The e-mail stated:

> First, as you know, the company did not achieve statistical significance for any of its effectiveness endpoints in the clinical study and as such, there is no statistical basis demonstrating effectiveness for this product. There appears limited evidence clinically supporting effectiveness. In the face of device failures that represent a potential safety risk, OSEL would not recommend placing an ineffective product on the market. Second, the device will be placed in a region of the body that will undergo weight bearing forces that are not comparable to those experienced by the mesh products with which we are familiar. We believe this sets a precedent that concerns us.[34]

B. Input from ReGen on Panel Members

Documents provided to the Committee indicate that ReGen was asked to provide input into the selection of members of the advisory panel, and certain voting members may have been excluded in favor of outside consultants.

On October 13, 2008, Gerald Bisbee, the Chairman and CEO of ReGen, e-mailed Dr. Schultz in response to a request for input about potential advisory panel members. The e-mail stated:

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[33] E-mail from John Goode, Division of General, Restorative, and Neurological Devices, Food and Drug Administration, to Jonette Foy, Chief, Orthopaedic Joint Devices Branch, Food and Drug Administration, *et al.* (Nov. 4, 2008) (emphasis in original).

[34] E-mail from Larry Kessler, Director, Office of Science and Engineering Laboratories, Food and Drug Administration, to Daniel Schultz, Director, Center for Devices and Radiological Health, Food and Drug Administration (Dec. 15, 2008).

> You asked for criteria that we had developed to characterize a sports medicine surgeon expert. We considered a number of criteria and believe that the following three are required:
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> - Experienced in arthroscopic knee surgery as evidenced by performing a minimum of fifteen (15) meniscus repairs and/or meniscus allografts annually;
> - In practice for a minimum of five (5) years of practice since becoming board-certified by the American Board of Orthopaedic Surgery (ABOS);
> - Practices arthroscopic surgery for sports medicine-related patients, with a specific emphasis on knee and shoulder arthroscopy.
>
> Many thanks for the opportunity to provide input.[35]

On October 27, 2008, Jonette Foy, the Branch Chief for Orthopaedic Joint Devices, sent an e-mail to Mr. Goode raising concerns with this panel selection process. The e-mail stated:

> [T]he determination regarding the makeup of the Panel has been determined by individuals outside of the Division. As you mentioned, voting members who were available for participation, specifically orthopaedic surgeons & a statistician (Dr. Propert) were specifically excluded from participation in the Panel (according to informal dialogue with Dr. Ronald Jean, Executive Secretary for the Ortho Panel). It has also been informally mentioned that Dr. Jean may not actually serve as the Exec Sec at the upcoming panel & that role may be assumed by another individual, which is another deviation from our normal procedures.[36]

On the same day, October 27, 2008, William McConagha, FDA's Assistant Commissioner for Accountability and Integrity, wrote an e-mail to Jeffrey Senger, Deputy Chief Counsel, stating that FDA planned to bring in five consultants in response to ReGen's request. The e-mail stated:

> The panel will have 3 standing members plus 5 consultants who have backgrounds

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[35] E-mail from Gary Bisbee, Chairman and CEO, ReGen Biologics, Inc., to Daniel Schultz, Director, Center for Devices and Radiological Health, Food and Drug Administration, *et al.* (Oct. 13, 2008).

[36] E-mail from Jonette Foy, Chief, Orthopaedic Joint Devices Branch, Food and Drug Administration, to John Goode, Division of General, Restorative, and Neurological Devices, Food and Drug Administration, *et al.* (Oct. 27, 2008).

consistent with Bisbee's requested specs.[37]

On November 1, 2008, Mr. Senger responded by raising concerns about ReGen's input into this process. The e-mail stated:

> Bill, we are concerned about the draft's statement that "FDA welcomed your input into the structure and composition of this advisory committee." I understand (see below) that we do not give others this opportunity, so it would document special treatment for ReGen.[38]

C. Lack of Formal Vote

FDA guidance for advisory committees requires that "members cast a formal vote on issues related to the approvability of a product submission."[39] Dr. Schultz failed to call a vote, however, despite the fact that the chair of the advisory panel, Dr. Jay D. Mabrey, stated that panel members were having difficulty comparing ReGen's device to other devices previously approved by FDA. The transcript of the meeting includes the following exchange:

> DR. MABREY: Dr. Schultz, it is the — with regards to Question 4 on safety and efficacy, the Panel generally believes that the device is safe and that its effectiveness may remain to be seen. There does seem to be some holes in the data with regards to efficacy, but there does not appear to be any outright problems with the device. Is that adequate for FDA?
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> DR. SCHULTZ: Well, I think, you know, I guess I'd like to hear more specifically CS device is at least as safe and effective as predicate devices. So, again, the way you said that, I think I would like to —
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> DR. MABREY: Well, I think I'm also trying to reflect that we're having trouble with comparing this with predicate devices because they really aren't used in the same way --

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[37] E-mail from William McConagha, Assistant Commissioner for Accountability and Integrity, Food and Drug Administration, to Jeffrey Senger, Deputy Chief Counsel, Food and Drug Administration, *et al.* (Oct. 27, 2008).

[38] E-mail from Jeffrey Senger, Deputy Chief Counsel, Food and Drug Administration, to William McConagha, Assistant Commissioner for Accountability and Integrity, Food and Drug Administration, *et al.* (Nov. 1, 2008).

[39] Food and Drug Administration, *Guidance for FDA Advisory Committee Members and FDA Staff: Voting Procedures for Advisory Committee Meetings* (Aug. 2008) (online at www.fda.gov/oc/advisory/GuidancePolicyRegs/ACVotingFINALGuidance080408.pdf) (accessed May 5, 2009).

DR. SCHULTZ: Are different, right.

DR. MABREY: But as far as one can make those comparisons, I think it's the sense of the Panel that, yes, it is as safe and effective —

DR. SCHULTZ: Thank you.[40]

On December 18, 2008, Dr. Schultz sent a letter to ReGen approving its application, concluding that the device is "substantially equivalent for both chronic and acute use for the medial meniscus."[41] In a decision memorandum two days later, Dr. Schultz explained his decision. The memorandum stated:

> The basis of my decision is the preclinical and clinical data in the submission considered in the context of the target population and the interpretation of the data by a panel of independent experts in the field who clearly and unanimously found the device to be at least as safe and as effective as the other surgical mesh products currently used in orthopedics.[42]

Conclusion

Documents provided to the Committee raise questions about whether FDA scientists and medical experts believe ReGen's device is in fact safe or effective. We hope that your review will examine these documents and address the questions that have been raised. We request that you keep us apprised of the status of your review. We also look forward to your cooperation as we continue our inquiry into FDA's medical device review process.

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[40] Food and Drug Administration, *Transcript of FDA Orthopedic and Rehabilitation Devices Panel Meeting* (Nov. 14, 2008) (online at www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4400t03.pdf) (accessed May 5, 2009).

[41] Letter from Dr. Daniel Schultz, Director, Center for Devices and Radiological Health, Food and Drug Administration, to John Dichiara, Senior Vice President, ReGen Biologics (Dec. 18, 2008).

[42] Memorandum from Dr. Daniel Schultz, Director, Center for Devices and Radiological Health, Food and Drug Administration, to the Record (Dec. 20, 2008).

If you have any questions regarding this letter, please contact Theodore Chuang or Paul Jung of the Committee staff at (202) 226-2424.

Sincerely,

Henry A. Waxman
Chairman

Bart Stupak
Chairman
Subcommittee on Oversight and Investigations

Frank Pallone, Jr.
Chairman
Subcommittee on Health

cc: The Honorable Joe Barton
Ranking Member
Committee on Energy and Commerce

The Honorable Greg Walden
Ranking Member
Subcommittee on Oversight and Investigations

The Honorable Nathan Deal
Ranking Member
Subcommittee on Health