Attachment 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 2 3 2006

ReGen Biologics, Inc.
c/o Mr. John Dichiara
Senior Vice President
Regulatory, Clinical and Quality
509 Commerce Street, East Wing
Franklin Lakes, New Jersey 07417

Re: K053621
Trade Name: ReGen Collagen Scaffold Surgical Mesh
Regulatory Class: III
Product Code: MPZ
Dated: December 28, 2005
Received: December 30, 2005

Dear Mr. Dichiara:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above. We have determined the device is not substantially equivalent to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to any device which has been reclassified into class I (General Controls) or class II (Special Controls). 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 [specifically a device marketed prior to May 28, 1976 or a device which has been reclassified from class III to class II or I (the predicate), or a device found to be substantially equivalent through the 510(k) process]. You may submit a new premarket notification if you have additional data you believe can demonstrate that your device is as safe and as effective as the predicate device.

Therefore, this device is classified by statute into class III (Premarket Approval), under Section 513(f) of the Federal Food, Drug, and Cosmetic Act (Act).

Section 515(a)(2) of the Act requires a class III device to have an approved premarket approval application (PMA) before it can be legally marketed, unless the device is reclassified.

Any commercial distribution of this device prior to approval of a PMA, Product Development Protocol (PDP), or the effective date of any order by the Food and Drug Administration re-classifying this device into class I or II, would be a violation of the Act. Clinical investigations of this device must be conducted in accordance with the investigational device exemptions (IDE) regulations.

The Food and Drug Administration Modernization Act of 1997 (FDAMA), in section 207, deals with the Evaluation of Automatic Class III Designation. Under this section a manufacturer, whose device is found to be not substantially equivalent to a predicate device, can request FDA to make a risk-based classification for their device. However, I believe that based on the review of your device, general controls would be inadequate and special controls difficult to develop, to provide reasonable assurance of the device's safety and effectiveness. However, you have the right to make such a request of this agency. For additional information on your options under Section 207, please refer to our guidance entitled, "New Section 513(f)(2) - Evaluation of Automatic Class III Designation, Guidance for Industry and Staff." This document is available on the World Wide Web/CDRH Home Page at: http://www.fda.gov/cdrh/modact/classiii.html.

If you wish to pursue the marketing of this device and need information or assistance for preparing investigational or premarket submissions, please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll free number (800) 638-2041 or (301) 443-6597, or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Mark N. Melkerson
Acting Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Attachment 5

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL 26 2006

ReGen Biologics, Inc.
% Mr. John Dichiara
Senior Vice President, Regulatory, Clinical
and Quality
509 Commerce Street, East Wing
Franklin Lakes, New Jersey 07417

Re: K053621
Trade Name: ReGen Collagen Scaffold Surgical Mesh
Regulatory Class: III
Product Code: MPZ
Dated: June 22, 2006
Received: June 22, 2006

Dear Mr. Dichiara:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above. We have determined the device is not substantially equivalent to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to any device which has been reclassified into class I (General Controls) or class II (Special Controls). 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.

Therefore, this device is classified by statute into class III (Premarket Approval), under Section 513(f) of the Federal Food, Drug, and Cosmetic Act (Act).

Section 515(a)(2) of the Act requires a class III device to have an approved premarket approval application (PMA) before it can be legally marketed, unless the device is reclassified.

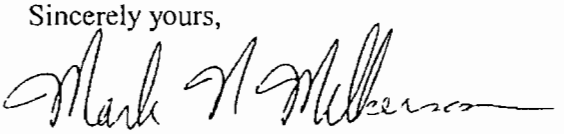
Any commercial distribution of this device prior to approval of a PMA, Product Development Protocol (PDP), or the effective date of any order by the Food and Drug Administration re-classifying this device into class I or II, would be a violation of the Act. Clinical investigations of this device must be conducted in accordance with the investigational device exemptions (IDE) regulations.

The Food and Drug Administration Modernization Act of 1997 (FDAMA), in section 207, deals with the Evaluation of Automatic Class III Designation. Under this section a manufacturer, whose device is found to be not substantially equivalent to a predicate device, can request FDA to make a risk-based classification for their device. However, I believe that based on the review

of your device, general controls would be inadequate and special controls difficult to develop, to provide reasonable assurance of the device's safety and effectiveness. However, you have the right to make such a request of this agency. For additional information on your options under Section 207, please refer to our guidance entitled, "New Section 513(f)(2) - Evaluation of Automatic Class III Designation, Guidance for Industry and Staff." This document is available on the World Wide Web/CDRH Home Page at: http://www.fda.gov/cdrh/modact/classiii.html.

If you wish to pursue the marketing of this device and need information or assistance for preparing investigational or premarket submissions, please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll free number (800) 638-2041 or (301) 443-6597, or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,



Mark N. Melkerson
Director
Division of General, Restorative
and Neurological Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Attachment 6

Mr. John Dichara
Senior Vice President
ReGen Biologics, Inc.
509 Commerce Street, East Wing
Franklin Lakes, NJ 07417

NOV 0 3 2006

Re: k053621
ReGen Collagen Scaffold Surgical Mesh
Appeal of Not Substantially Equivalent Decision
Dated: August 4, 2006
Received: August 7, 2006

Dear Mr. Dichara:

This letter is in response to your letter of appeal dated August 4, 2006, requesting that the not substantially equivalent (NSE) decision that was issued on July 26, 2006, from Mark N. Melkerson, Director, Division of General, Restorative, and Neurological Devices (DGRND), Office of Device Evaluation, be reviewed by the next level supervisor. I have reviewed this appeal under our regulations found in Title 21 of the Code of Federal Regulations Part 10.75 Internal agency review of decision, as the next level supervisor.

After reviewing your letter of appeal, meeting internally with DGRND 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 (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.

In response to my discussions with you, on September 28, 2006, you submitted suggested revised indications for use for this device as follows:

> The ReGen Collagen Scaffold (CS) is intended for use in general surgical procedures for the reinforcement and repair of soft tissues where weakness exists, including but not limited to, general soft tissue defects, hernias, and meniscus defects.
>
> The CS is not a prosthetic device and it is not intended to replace normal body structures. In repairing and reinforcing meniscal defects, the patient must have an

intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.

The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own tissue."

A new premarket notification (510(k)) may be submitted for the recently submitted indication for use. Please be advised that you should submit appropriate clinical data for this new indication. I encourage you work directly with Capt. Stephen Rhodes, Chief, Plastic and Reconstructive Surgery Device Branch, DGRND, to discuss a pre-IDE for this device with the revised indications for use.

If you have any questions regarding this letter, please contact Heather S. Rosecrans, Director, 510(k) Staff, at (240) 276- 4021.

Sincerely yours,

Donna-Bea Tillman, Ph.D., M.P.A.
Director
Office of Device Evaluation
Center for Devices and Radiological Health

Attachment 7

K053681 Indications for Use Statement (Statement 1)

The ReGen Collagen Scaffold is intended for use in general surgical procedures for the reinforcement and repair of soft tissue where weakness exists, including, but not limited to, general soft tissue defects, hernias, and meniscus defects. The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue. The CS is not intended to replace normal body structure.

K063827 Indications for Use Statement (Statement 2)

The ReGen Collagen Scaffold (CS) is intended for use in general surgical procedures for the reinforcement and repair of soft tissues where weakness exists, including, but not limited to, general soft tissue defects, hernias, and meniscus defects.

The CS is not a prosthetic device and it is not intended to replace normal body structure. In repairing and reinforcing meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.

The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own tissue.

K082079 Indications for Use Statement, as submitted (Statement 3)

The ReGen Collagen Scaffold is intended for use in surgical procedures for the reinforcement and repair of chronic soft tissue injuries of the meniscus (one to three prior surgeries to the involved meniscus) where weakness exists. In repairing and reinforcing meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.

K082079 Indications for Use Statement, as cleared (Statement 4)

The ReGen Collagen Scaffold is intended for use in surgical procedures for the reinforcement and repair of soft tissue injuries of the meniscus. In repairing and reinforcing meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization. The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue. The CS is not a prosthetic device and is not intended to replace normal body structure.

Attachment 8

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG 20 2007

ReGen Biologics, Inc.
c/o Mr. John Dichiara
Sr. Vice President
Regulatory, Quality and Clinical
509 Commerce Street, East Wing
Franklin Lakes, New Jersey 07417

Re: K063827
Trade Name: ReGen Collagen Scaffold (CS)
Regulatory Class: III
Product Code: FTM
Dated: June 22, 2007
Received: June 26, 2007

Dear Mr. Dichiara:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above. We have determined the device is not substantially equivalent to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to any device which has been reclassified into class I (General Controls) or class II (Special Controls), or to another device found to be substantially equivalent through the 510(k) process. This decision is based on the fact 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. Specifically, regarding device safety:

- Based on information we received by e-mail, dated June 21, 2006, from Ms. Margaret F. Crowe, there were 29 re-operations for the partial meniscectomy group, with none suggesting knee replacement, as compared to 32 re-operations and 7 explants for the CS group for a total of 38 second surgeries, with 1 re-operation recommending knee replacement. We also noted that the device explants were due to mechanical failure of the device (n=5), infection (n=1), and persistent pain (n=1). Therefore, the CS device had a 24% (38/162) second surgery rate, while partial meniscectomy patients had a 19% (29/151) second surgery rate;

- There were 49 serious adverse events in 29 of 162 (17.9%) CS patients compared to 38 events in 24 of 151 patients (15.9%) in partial meniscectomy patients. This results in a higher serious adverse event rate for the CS group, 0.30 events/patient, as compared to the partial meniscectomy group, 0.25 events/patient.

- Although we believe that the "second-look" arthroscopies are subjective in their evaluation and should have been supported with standardized standing knee radiographs for all patients, as outlined in the IDE protocol, and masking of the investigator to the treatment group, the one-year re-look arthroscopy results reported that 16% of the cases had devices that were "not firmly attached to the host rim" and 18% of the articular surfaces "worsened."

Based upon the increased risk associated with the use of the subject device, as outlined above, we believe that adequate effectiveness data to demonstrate a positive risk/benefit ratio is necessary as compared to the standard of care (i.e., partial meniscectomy).

- However, based on data provided in Appendix E, the average amount of native meniscal tissue remaining at surgery was 43% for the CS device and 50% for the partial meniscectomy control. Therefore, on average, at the time of surgery, less native tissue remained for the CS patients as compared to the partial meniscectomy patients; and

- Although there was 73% total tissue for the CS group at the one-year re-look arthroscopy as compared to 50% for the control group (Note: no re-look was performed on the control patients; therefore, the 50% value assumes that there is no additional tissue gain for the control group as compared to post-operative measurements of native tissue remaining after partial meniscectomy), there was no demonstrated clinical benefit associated with the 23% average additional total tissue for the CS group. Based on the clinical evaluation of pain, function, self-assessment or the radiographic findings, there was no demonstrated difference in outcome measures for those patients who were and were not implanted with the investigational device.

You may resubmit a new 510(k) if you have data you believe can show your device to be substantially equivalent.

Therefore, this device is classified by statute into class III (Premarket Approval), under Section 513(f) of the Federal Food, Drug, and Cosmetic Act (Act).

Section 515(a)(2) of the Act requires a class III device to have an approved premarket approval application (PMA) before it can be legally marketed, unless the device is reclassified.

Any commercial distribution of this device prior to approval of a PMA, or the effective date of any order by the Food and Drug Administration re-classifying this device into class I or II, would be a violation of the Act. Clinical investigations of this device must be conducted in accordance with the investigational device exemptions (IDE) regulations.

If you wish to pursue the marketing of this device and need information or assistance for preparing investigational or premarket submissions, please contact the Division of Small

Manufacturers, International and Consumer Assistance at its toll free number (800) 638-2041 or (240) 276-3150, or at its Internet address www.fda.gov/cdrh/industry/support/index.html.

If you decide to submit a new 510(k) you should submit a complete submission which includes the information identified in Title 21, Code of Federal Regulations (21 CFR), Section 807.87 and follows the formatting specified in 21 CFR, Section 807.90, and also refer to our document, titled Guidance for Industry and FDA Staff - Format for Traditional and Abbreviated 510(k)s which is available from the Internet at: www.fda.gov/cdrh/ode/guidance/1567.pdf. In addition, please ensure that any new 510(k) includes information that addresses the following issues:

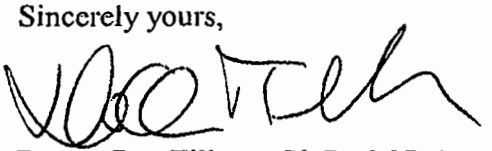
Please be advised that in addition to the issues outlined above which form the basis of the determination of "not substantially equivalent," we suggest that you contact FDA to discuss additional issues that you would need to address prior to submitting a new 510(k).

The information requested above represents the issues that we believe need to be resolved before our review of a new 510(k) submission can be successfully completed. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 513(i) of the Federal Food, Drug, and Cosmetic Act for determining substantial equivalence.

We also considered the burden that may be incurred in your attempt to respond to the deficiencies should you decide to submit a new 510(k). We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the document, "A Suggested Approach to Resolving Least Burdensome Issues". It is available on the Internet at www.fda.gov/cdrh/modact/leastburdensome.html

If you have any questions concerning the additional information that should be submitted in a new 510(k) submission, please contact Mr. John S. Goode at (240) 276-3676.

Sincerely yours,



Donna-Bea Tillman, Ph.D., M.P.A.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Attachment 9

MEMORANDUM OF MEETING
January 23, 2007
4:00 to 5:30 p.m.
Parklawn Building

Attendees:

FDA:

Andrew C. von Eschenbach, Bill McConagha, Daniel Schultz, Stephen Mason, and LaJuana Caldwell

ReGen Biologics:

Gary Bisbee, Ph.D., Chairman, President and CEO
John Dichiara, Senior Vice President,
Charles Beck M.D., an independent surgeon
Michael Hutton, DC lobbyist for ReGen, and
Philip Phillips, Becker & Associates

Subject: Marketing application for ReGen Collagen Scaffold, Menaflex

Highlights:

- Dr. von Eschenbach opened the meeting stating that his responsibility is to listen to ReGen's experience and ensure the integrity of the review process, but that the scientific assessment of the product remains with the scientific experts in CDRH. He introduced Bill McConagha and stated that he had appointed Bill to oversee the process and ensure its integrity.

- Dr. Brisbee briefly described ReGen's long history with the agency, dating back to the 1990's but wanted to talk about that the last 25 months. He asked Dr. Charles Beck to briefly describe the implant process for the resorbable collagen scaffold.

- Dr. Beck described the implant process and how it is used to restore the meniscus. He described the resorbable collagen scaffold as a surgical mesh. He further stated that the agency has cleared 225 surgical meshes in the last 5 years for repairs to Achilles tendons, biceps, quadriceps, etc.

- Dr. Dichiara described the procedural issues their firm had encountered when they submitted resorbable collagen scaffold for review. Dr. Dichiara stated that
  - 1) ReGen did not get an objective review of their product;
  - 2) in "Not Substantially Equivalent" letters, FDA provided a "moving target of objections";
  - 3) that the reviewers incorrectly compared their device to a surgical procedure rather than a predicate device;
  - 4) that FDA requested additional studies when the Center had approved comparable devices with less data than ReGen originally provided for this device;
  - 5) that the reviewers used data from ReGen's PMA submission that was not relevant to surgical mesh or the 510(k) review process; and

- 6) the Division Director and the reviewers did not agree on the classification of the device.

- Dr. von Eschenbach asked questions to clarify the intended use of the device as well as the endpoint or benefit of the device. He suggested that part of the problem is consensus on what the device is and its purpose. Dr. von Eschenbach acknowledged the human factor in the process and suggested that perhaps a review by an advisory committee with a fresh perspective might resolve the problem.

- ReGen expressed concerns about the level of expertise on the current panel, e.g., there are no orthopedists on the panel.

- Dr. Schultz stated that there is a process to appeal the Centers decisions (§ 10.75) that is available and provides for independent opinions and having a product reviewed in a public forum. He stated that he would have to have a reason to override the existing process. He further stated that he was committed to providing ReGen with a categorical and fair review and to resolve this issue quickly.

Action Items:

Dr. von Eschenbach agreed to look at the process going forward;
Dr. Schultz agreed to consider any proposal from ReGen for moving forward, but also reiterated that there is an appeals process at their disposal.
Mr. Phillips said he would submit ReGen's proposal to Dr. Schultz for his consideration.

LaJuana D. Caldwell
Office of the Executive Secretariat

Attachment 10

ReGen
Biologics

Daniel G. Schultz, MD
Director - FDA Center for Devices and Radiological Health
9200 Corporate Boulevard, HFZ-1
Rockville, MD 20850

Re: 10.75 Appeal of NSE decision on K063827

Dear Dr. Schultz:

We are writing under 21 CFR § 10.75(c) to request your review of the agency's not substantially equivalent (NSE) decision regarding K063827, and propose an appeal approach to resolve this matter. As you know, ReGen has great concern regarding how ODE handled the company's submissions, thus our request to exclude that organization from the appeal process. As a result, we are resorting to the normal 10.75 route of appeal used to consider premarket notification matters, with that exception. Resolution of this appeal is highly significant to the company's survival. Accordingly, we propose the following approach:

- An interactive review process with ReGen, including a meeting with you, your representatives, the company, and appropriate experts;
- Application to ReGen's 10.75 appeal of the same substantial equivalence standard and data and information requirements that were applied to numerous surgical meshes FDA found substantially equivalent to predicate devices;
- Expeditious review and determination of ReGen's appeal, hopefully within 60 days of its receipt;
- No participation by the Office of Device Evaluation; and
- No advisory committee participation,

Once we receive your agreement to this approach, we will submit our substantive appeal under 10.75(c). Please call me (203-321-5523) or John Dichiara (917-439-2597) to discuss any questions you have regarding this proposed approach.

We will greatly appreciate your consideration of this request.

411 Hackensack Avenue, 10th Floor, Hackensack, NJ 07601 Phone: (201) 651-5140 Fax: (201) 651-5141 www.regenbio.com

Sincerely

Gerald E. Bisbee, Jr., Ph.D.
Chairman and CEO, ReGen Biologics, Inc.

CC: Andrew C. von Eschenbach, M.D.
Robert Decheine
Ivan Zapien

Attachment 11

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

APR 25 2008

Gerald E. Bisbee, Jr. Ph.D.
Chairman and CEO
ReGen Biologics, Inc.
411 Hackensack Avenue
10th Floor
Hackensack, NJ 07601

Re: k063827
10.75 Appeal of NSE Decision

Dear Dr. Bisbee:

This letter is in response to your recent letter discussing your possible appeal of the "not substantially equivalent" (NSE) determination made by the CDRH Office of Device Evaluation on the 510(k) referenced above. You requested my agreement to certain limitations on my evaluation of the issues raised by such an appeal. Specifically, you proposed the following:

- "An interactive review process with ReGen, including a meeting with you, your representatives, the company and appropriate experts;
- Application to ReGen's 10.75 appeal of the same-substantial equivalence standard and data and information requirements that were applied to numerous surgical meshes FDA found substantially equivalent to predicate devices;
- Expeditious review and determination of ReGen's appeal, hopefully within 60 days of its receipt;
- No participation by the Office of Device Evaluation; and
- No advisory committee participation."

I have carefully considered your request. I am concerned that, were I to agree to the limitations you propose, I might not be able to evaluate fully the issues raised by an appeal.

An appeal under 21 CFR 10.75 contemplates a review of all aspects of the prior agency decision at issue. In this instance, that means the review would extend to CDRH's prior decisions with respect to both the intended use(s) and technological characteristics of the Collagen Scaffold (CS). An appeal under 21 CFR 10.75 also contemplates that the supervisor who performs the review should have access to the necessary resources and support. To that end, 21 CFR 10.75(b)(1) provides that the supervisor has discretion to

consult with the individuals responsible for the prior decision. In addition, 21 CFR 10.75(d) states that if any new information (information not in the file) is presented the matter will be returned to the appropriate lower level in the agency for reevaluation based on the new information.

Your proposed limitations could frustrate the review process, especially as it relates to the question of intended use. For example, if in reviewing the administrative file I were to have doubts about Dr. Tillman's prior decision about intended use, your proposed limitation would create a profound dilemma for me: On the one hand, you do not want me to consult with the orthopedic specialists in CDRH's Office of Device Evaluation (ODE) because you believe they are biased against the Collagen Scaffold (CS). On the other hand, however, you do not want me to consult with other orthopedic specialists outside the agency via an advisory committee review panel. The result is that I would be deprived of the opportunity to consult with orthopedic specialists necessary to perform a meaningful review. This is particularly confusing given that, during our recent meeting with the Commissioner of FDA, you argued that CDRH had failed in its prior decision by *not* consulting the proper orthopedic specialists on this matter. Please be assured that I am prepared to discuss some reasonable accommodation as part of my review process – indeed, I recognize your concern that ODE is biased against you -- but I am reluctant to agree to any terms that will compromise my ability to perform a thorough and meaningful review of the administrative file.

I wish to emphasize that I will assure that my review of any appeal in this matter will be full, fair, appropriately expeditious, and interactive. Nevertheless, I am disinclined to agree to the limitations proposed in your letter insofar as they preclude me from consulting with the appropriate experts, either within or outside FDA. In the event we wish to take your appeal to an advisory panel, we are willing to discuss with you the appropriate expertise to be represented in that panel. I understand that your consultant, Michael Hutton, is speaking with FDA's Bill McConagha about other ways to address your concerns, and I welcome and encourage that dialogue. I look forward to productive discussions in this matter, and to hearing from you soon. I hope this information has been helpful to you.

Sincerely,

Daniel G. Schultz, M.D.
Director
Center for Devices and
Radiological Health

Attachment 12

Memorandum to the Record
K082079 – ReGen Collagen Scaffold (CS)

Date: September 22, 2008

From: Donna-Bea Tillman, Ph.D
Director, Office of Device Evaluation

Brief Background

The ReGen Collagen Scaffold (CS, also referred to in places as the Collagen Meniscal Implant or CMI) is a collagen surgical mesh intended to be used for reinforcement and repair of meniscal defects. Although surgical meshes have been cleared for a wide variety of indications, this would be the first surgical mesh indicated for meniscal repair. On July 26, 2006, DGRND determined that 510(k) K053621 was Not Substantially Equivalent because:

> "...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".

ReGen appealed to me under 10.75, and in a letter dated November 3, 2006, I upheld the NSE decision for the original indications for use. However, I also noted that ReGen had proposed to modify the indications for use (see below), and that they could submit a new 510(k) for those indication. I also noted that clinical data would be needed to support the revised indication. Neither the review team nor the review division agreed with my decision to allow the sponsor to submit a 510(k) for the revised indications.

> The ReGen Collagen Scaffold (CS) is intended for use in general surgical procedures for the reinforcement and repair of soft tissues where weakness exists, including but not limited to, general soft tissue defects, hernias, and meniscus defects.
>
> The CS is not a prosthetic device and it is not intended to replace normal body structures. In repairing and reinforcing meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.
>
> The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own tissue."

ReGen submitted K063827, which included data from a clinical study that had been conducted under IDE. After two rounds of review, this 510(k) was found to be Not Substantially Equivalent on August 20, 2007, because "the performance data provided indicates that there is an increased

risk with the use of the device in the intended patient population and an uncertain benefit as compared to legally marketed predicate devices". Due to the history of this file, and the fact that the review team and the division had both disagreed with my decision to allow the sponsor to submit a 510(k) for the new indications, I signed this NSE letter.

The sponsor then began a series of appeals to the CDRH Center Director (Dan Schultz) and eventually the FDA Commissioner. During this process, ReGen claimed to have data that showed that the device produced a clinically meaningful benefit in the absence of increased risk in the "chronic" subgroup of patients in the IDE study, and that these results were to be published in the Journal of Bone and Joint Surgery (JBJS). Dr. Schultz agreed that ReGen could submit a new 510(k) with these data, and that it would be reviewed in an accelerated fashion.

The FDA review team was asked to conduct a preliminary review of a pre-publication copy of the JBJS article, and prepare a list of questions for the sponsor, with the intent of ensuring that the 510(k) would include the data necessary to allow an accelerated review. These questions were sent to ReGen in a letter signed by Dr. Schultz on July 8, 2008.

The new 510(k) (for the chronic indication) was received on July 23, 2008, and it was assigned to the same review team that had reviewed previous ReGen submissions. The administrative file contains detailed review memos from lead reviewer John Goode, clinical reviewers Roxy Horbowyj and Kevin Lee, and statistical reviewer Jianxiong Chu. It also includes supervisory memos from Joni Foy (branch chief of the Orthopedics Joint Branch) and Mark Melkerson (division director).

Discussion

The review team continues to believe that the proposed indications constitute a new intended use, even before they look at the clinical data. This is not consistent with my memo regarding the appeal of the first 510(k), where I found that ReGen had provided a plausible explanation for why a "repair and reinforce" indication was different than a "replace" indication for a surgical mesh intended to be used during partial meniscectomy, and that a 510(k) could be submitted for a such a "repair and reinforce" indication.

Note: The proposed indications are:

> "The ReGen Collagen Scaffold (CS) is intended for use in surgical procedures for the reinforcement and repair of chronic soft tissue injuries of the meniscus (one to three prior surgeries to the involved meniscus) where weakness exists. In repairing and reinforcing meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.

For the sake of brevity, I will refer to this indication as the "*repair and reinforce the meniscus in chronic patients*" indication.

The question that needs to be addressed in the current submission is therefore not one of "Is the new indication *repair and reinforce the meniscus in chronic patients* a new intended use on its face?", but rather, "Do the data demonstrate that the new indication *repair and reinforce the meniscus in chronic patents* is not a new intended use?"

The review team addresses this question as well, finding that the sponsor has failed to provide sufficient data to support the new indications for use, because the clinical data that were provided to support the new indication did not come from the indicated patient population. The lead reviewer notes that the device was used to replace significant amounts of meniscal tissue that were removed during partial meniscectomy, and NOT to augment tissue that had otherwise been adequately repaired. Since the sponsor has failed to provide clinical data that support the proposed indications for use, the lead reviewer finds that the 510(k) should be found NSE for lack of performance data.

> Note: To be more accurate from a regulatory perspective, the sponsor needs to provide data that demonstrate that the new indication for use is not a new intended use. The point made by the review team would still hold here – in the absence of any data on the proposed indications for use, FDA cannot determine if the new indications for use are in fact the same intended use.

The division director (Mark Melkerson) has over-turned the review team on this issue, finding that the clinical data provided **could potentially** be used to support the new indication for use. At this direction, the members of the review team have reviewed the results from the clinical study.

Clinical Study Results

In brief, the study is consists of two arms, both of which randomize patients to either the standard of care (partial meniscectomy) or standard of care plus the CMI device. Patients in the acute arm (n=157) had no prior meniscal surgery, while patients in the chronic arm (n=154) had either 1, 2, or 3 prior meniscal surgeries. The results from acute group did not show a clinical benefit, while the sponsor claims that the results from the chronic group do show a clinical benefit. Exactly what this benefit is, and to what extent it is accompanied by increased patient risk, is a matter of scientific dispute between the review team and the sponsor.

The pre-defined primary endpoints in the clinical trial were Visual analog pain score, Lysholm score, and Patient self-assessment score. As clearly depicted below in Table III of the JBJS article, there was no difference between control vs. CMI treated patients for either the acute or the chronic patients for ANY of these endpoints. It is not unreasonable to interpret these results as demonstrating that ReGen has failed to demonstrate a clinical benefit for the CMI device.

TABLE II Clinical Outcomes Data at Time of Most Recent Follow-up

	Acute Group		Chronic Group	
	Collagen Meniscus Implant (N = 75)	Control (N = 82)	Collagen Meniscus Implant (N = 62)	Control (N = 69)
Visual analog scale pain score *(points)*				
Mean change from preop. score	16	21	18	18
Mean score at time of last follow-up	5	6	19	21
Lysholm score *(points)*				
Mean change from preop. score	26	28	16	22
Mean score at time of last follow-up	90	87	79	78
Patient self-assessment score *(points)*				
Mean change from preop. score	0.9	1.1	0.7	0.9
Mean score at time of last follow-up	1.6	1.6	1.9	2.1

The sponsor has chosen to use a modified version of one of the 13 secondary endpoints identified in their IDE as a basis for supporting clinical benefit. The **Tegner Activity Score** was one of the additional endpoints (score of 0-10), identified in the IDE. The **Tegner Index** was not identified in the IDE protocol and was introduced in the JBJS paper. The JBJS paper states that:

> As demonstrated by the Tegner index, patients in the chronic group who had received a collagen meniscus implant regained significantly more of their lost activity than did the control patients in that group, thus returning closer to their preinjury activity levels. The patients in the chronic group who had received a collagen meniscus implant regained, on the average, 42% of their lost activity level at nearly five years whereas the controls in the chronic group regained only 29% ($p = 0.02$). Over the same period of time, the patients in the acute group (no prior surgery on the involved meniscus), regardless of whether they had been treated with a partial meniscectomy only or with the collagen meniscus implant, regained an average of 41% of their lost activity level. Ac-

The JBJS authors use this finding to hypothesize about the apparent lack of clinical benefit in the primary endpoint measures: "It therefore appears that the control patients in the chronic group had to reduce their activity levels in order to maintain pain levels similar to those in the patients who in the chronic group who received a collagen meniscus implant". However, the review team notes that the author's hypothesis is not supported by the higher mean change from pre-op Lysholm functional score for the control patients.

The sponsor has also highlighted the reoperation rate results as being an important measure of clinical benefit. They reported a statistically significant (p=.04) difference in cumulative survival out to five years between the CMI and control patients in the chronic arm. However, the review team notes that the sponsor has excluded 5 / 87 of the CMI

patients, and 17 reoperations for the CMI patients and 5 reoperations for the control patients. When these results were reanalyzed by the review team to include those reoperations that the team felt should have been originally include, the finding was reversed: the reoperation rate for the CMI patients (26%) was higher than that for the control patients (22%).

Finally, there is the important question of safety. As noted in the lead reviewer's memo, of the 87 CMI patients in the chronic group, 8 (9.2%) had Serious device-related Adverse Events. Additionally, the percentage of All Serious Adverse Events per patient was higher for the CMI group than the control group (43% vs 33%), although it is not reported if this difference is statistically significant.

After considering all of these results, I am left with the same concern I had during the review of the previous ReGen 510(k). The device appears to have an uncertain clinical benefit, and a potentially higher patient risk. However, the regulatory question that must be answered is "Are these data sufficient to demonstrate that the new indications for use fall into the same intended use as the predicate devices?"

CDRH Blue Book Memorandum "Guidance on the CDRH Premarket Notification program – K86-3" states:

> While a new device must have the same intended use as a predicate device in order to be SE, the Center does not require that a new device be labeled with precise therapeutic or diagnostic statements identical to those that appear on predicate device labeling in order for the new device to have the same intended use. Label statements may vary…Thus, a new device with the same intended use as a predicate device may have different specific indication statements, and, as long as these label indications do not introduce questions about safety or effectiveness different from those that were posed by the predicate device's intended use, the new device may be found SE.

Therefore, in order to determine if ReGen's proposed new indication for use *(repair and reinforce the meniscus in chronic patents)* falls into the previously cleared intended uses for surgical mesh, we have to look at how the safety and effectiveness profile (or risk/benefit profile) of the CMI compares to that of previously cleared surgical meshes.

Data used to support previous surgical mesh new indications

The "basic" indications for surgical mesh are to reinforce/repair soft tissue where weakness occurs. Specific types of soft tissues were called out in 510(k)s as early as K923657 ("defects of the abdominal and thoracic wall, gastric banding, muscle flap reinforcement, rectal and vaginal prolapse, reconstruction of the pelvic floor, urethral sling, and diaphragmatic, femoral, incisional, inguinal, lumbar, paracolostomy, scrotal, and umbilical hernias")

Over time, surgical mesh indications have been further expanded, as discussed in detail in Appendix E of John Goode's memo. In some cases clinical data have been provided to support these new indications for surgical mesh, and in other cases it has not. Mark Melkerson explains the basis for this difference as:

> "When it is determined that the "new" indication is quite different, the use of the device will change the standard practice of medicine, will be used in a much different manner, is made of a new material or design, and/or there are additional risks, different associated risks, or greater degree of risk; then, the information which was obtained for the predicate may be of limited value when evaluating the risk/benefit profile of the device for the "new" indication. In such cases, clinical data to support the submission is justified, falls within the same intended use as the predicates, and is consistent with our approach to previous clearances."

Both the sponsor and the review team have pointed to several key clearances of new indications for surgical mesh to support their position. I have reviewed the administrative record for these and offer my assessment below:

1. Rotator cuff repair surgery

The initial clearance for this "new indication" involved a single muscle group (K001738). In addition to bench testing demonstrating that the device mechanical properties were adequate for this new indication, the sponsor also provided some unpublished "case series" that showed a low adverse event rate and supported the effectiveness of the device for this new indication. The review team determined that because the device was indicated to be placed over the suture line to smooth the surface between the suture and the other muscles and NOT to provide any mechanical support, these data were sufficient for clearance.

When an expanded indication that included four different muscle groups was sought (K031969), the sponsor provided clinical data in the form of a retrospective review of the experience of three surgeons and 81 patients. Although there was a statistically significant reduction of pain ($p=0.005$) from the pre-op to post-op visits, it is likely that much of this improvement was due to the surgery itself. Safety did not appear to be a concern - there were few adverse events observed. Additional "case series" data from 148 patients also provided some support for effectiveness. Although these data provided some support for clearance, the clinical reviewer appears to have ultimately relied on the same rationale used for the initial clearance – namely that the device was not providing any real mechanical support.

How does this compare to the ReGen submission? For the predicate rotator cuff indication, the surgical mesh is not providing any mechanical support, and the potential risks of failure are minimal. Therefore, little or no clinical data are necessary to show that this indication falls into the more general reinforce/repair indication. For the ReGen "*repair and reinforce the meniscus in chronic patients*" indication, the same cannot be said. The CS device will be subject to significant mechanical forces,

and failure of the device could result in increased patient pain, loss of function, or need for a repeat surgery. Therefore, clinical data are needed to show that this indication does not raise issues of safety and effectiveness.

2. Anal, rectal and enterocutaneous fistula plug

For this indication, the device is provided in a "rolled" configuration rather than a flat sheet (K050337). In considering the way in which the device is used, the reviewer notes:

> "The use of this device, as indicated above, appears to be less as a reinforcement device but rather as a "plug" to heal the fistula. This action, however, over the period of time that the device is in situ in the fistula tract, does cause the same types of reactions as described for the predicates, and with that action, are equivalent. Healing the fistula is, in some regard, similar to reinforcement of soft tissue in that the presence of the device results in the support (repair)."

The clinical data provided to support this new indication consist of three "case series" for the repair of anal, rectal, and enterocutaneous fistulas respectively. The clinical reviewer noted:

> "As difficult it is to heal one of these complicated fistulas [ano-fistula repair and recto-vaginal fistula repair], the results seem very favorable that the use of this device will certainly benefit patients, with a "healed" rate to approximately 65-80%. This is better than could be achieved with the "standard of care" currently available, and it appears there are few complications. From my personal experience as a colo-rectal surgeon, it appears that, for severe rectal or anal fistulas, this device is acting like a seton, and it certainly causes less morbidity to the patients with a similar, if not better, success rate."

How does this compare to the ReGen submission? The decision to clear the anal fistula indication appears to be based on the finding that the device will provide a significant clinical benefit (compared to what is currently possible) with a low risk. Although the clinical data come from uncontrolled case series, the results are quite compelling. In the case of ReGen, while the data come from a well-controlled clinical study, the results are not compelling, and in fact, may suggest that the patient is at increased risk.

3. Sealing or reducing air leaks that occur during pulmonary surgery

The data provided to support this new indication came from an IDE study of 26 patients (with a total of 52 air leaks) at 4 clinical sites. Patients were treated with the surgical mesh only after conventional methods for sealing air leaks had failed. 96% of air leaks were successfully sealed, with no device-related complications.

How does this compare to the ReGen submission? The 'air leak' indication is in many ways similar to that of the anal fistula – the device appears to provide a significant clinical benefit and a low risk. Although the clinical data come from uncontrolled case series, the results are quite compelling. In the case of ReGen, while the data come from a well-controlled clinical study, the results are not compelling, and in fact, may suggest that the patient is at increased risk.

Conclusion

ReGen is requesting clearance for a new indication for surgical mesh, namely to "*repair and reinforce the meniscus in chronic patients*". Use of a surgical mesh in the intra-articular space potentially raises new questions of safety that have not needed to be addressed by predicate surgical mesh indications. In particular, is the device able to withstand the mechanical forces present in the joint, and what is the impact on joint function should the device fail? Clinical data are needed to address the questions, and to demonstrate that this new indication can be considered the same intended use as predicate devices.

ReGen has conducted a well-designed study intended to answer these questions. 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.

Attachment 13

Memorandum to the Record
K082079 – ReGen Collagen Scaffold (CS)
Post-Panel Recommendation

Date: December 15, 2008

From: Donna-Bea Tillman, Ph.D
Director, Office of Device Evaluation

Background

The ReGen Collagen Scaffold (CS) is a collagen surgical mesh intended to be used for reinforcement and repair of meniscal defects. Although surgical meshes have been cleared for a wide variety of indications, this would be the first surgical mesh indicated for meniscal repair.

From my September 22, 2008, memo:

> On July 26, 2006, DGRND determined that 510(k) K053621 was Not Substantially Equivalent because:
>
> > "…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".
>
> ReGen appealed to me under 10.75, and in a letter dated November 3, 2006, I upheld the NSE decision for the original indications for use. However, I also noted that ReGen had proposed to modify the indications for use (see below), and that they could submit a new 510(k) for those indication. I also noted that clinical data would be needed to support the revised indication. Neither the review team nor the review division agreed with my decision to allow the sponsor to submit a 510(k) for the revised indications.
>
> > The ReGen Collagen Scaffold (CS) is intended for use in general surgical procedures for the reinforcement and repair of soft tissues where weakness exists, including but not limited to, general soft tissue defects, hernias, and meniscus defects.
> >
> > The CS is not a prosthetic device and it is not intended to replace normal body structures. In repairing and reinforcing meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh.
> >
> > In addition the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.

The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own tissue."

ReGen submitted K063827, which included data from a clinical study that had been conducted under IDE. After two rounds of review, this 510(k) was found to be Not Substantially Equivalent on August 20, 2007, because "the performance data provided indicates that there is an increased risk with the use of the device in the intended patient population and an uncertain benefit as compared to legally marketed predicate devices". Due to the history of this file, and the fact that the review team and the division had both disagreed with my decision to allow the sponsor to submit a 510(k) for the new indications, I signed this NSE letter.

The sponsor then began a series of appeals to the CDRH Center Director (Dan Schultz) and eventually the FDA Commissioner. During this process, ReGen claimed to have data that showed that the device produced a clinically meaningful benefit in the absence of increased risk in the "chronic" subgroup of patients in the IDE study, and that these results were to be published in the Journal of Bone and Joint Surgery (JBJS). Dr. Schultz agreed that ReGen could submit a new 510(k) with these data, and that it would be reviewed in an accelerated fashion.

The FDA review team was asked to conduct a preliminary review of a pre-publication copy of the JBJS article, and prepare a list of questions for the sponsor, with the intent of ensuring that the 510(k) would include the data necessary to allow an accelerated review. These questions were sent to ReGen in a letter signed by Dr. Schultz on July 8, 2008.

The new 510(k) (for the chronic indication) was received on July 23, 2008, and it was assigned to the same review team that had reviewed previous ReGen submissions. The administrative file contains detailed review memos from lead reviewer John Goode, clinical reviewers Roxy Horbowyj and Kevin Lee, and statistical reviewer Jianxiong Chu. It also includes supervisory memos from Joni Foy (branch chief of the Orthopedics Joint Branch) and Mark Melkerson (division director). After reviewing the additional information, the review team continued to find that the data were insufficient to demonstrate substantial equivalence. In a memo dated September 22, 2008, I concurred with this recommendation.

Subsequent to this recommendation, and with input from the Office of the Commissioner, Dr. Schultz determined that an Advisory Panel meeting would be held to obtain expert input on the 510(k). Due to ReGen's concerns that the ODE review team was biased, OSEL Director Dr. Larry Kessler was selected to make the FDA presentation to the Panel. The Panel meeting was held on November 14, 2008. At that meeting, ReGen requested clearance, and the panel discussed, both a chronic indication (e.g., the indication submitted in K082079) and an acute indication.

In brief, the panel found that the clinical data demonstrated that the device was safe, and that there was some evidence of efficacy. To quote the FDA post-panel summary:

> "The Panel discussed and commented on FDA questions related to the mechanical integrity of the ReGen CS for its intended use, its ability to foster tissue ingrowth, specific clinical issues related to the use of the ReGen CS in the knee, its safety and effectiveness in comparison to the claimed predicate devices, and its appropriateness for acute soft tissue injury. The Panel generally believed that the ReGen CS was able to withstand physiological forces, would foster ingrowth of unorganized fibrocartilage tissue, was appropriate for both acute and chronic meniscal soft tissue injuries, and was as safe and effective as the predicate devices. However, the Panel cautioned that there will be confounding patient and operator factors that makes patient selection and operator training critical elements in the use of the ReGen CS. The Panel also recommended that a training course be offered for the device to evaluate surgical skills, and that the acute indication should be carefully defined."

After considering the Panel recommendations, the ODE review team continued to find that the data were insufficient to demonstrate substantial equivalence (see December 4 note to the record from John Goode). This recommendation was supported by a December 5 memo from DGRND division director Mark Melkerson.

Discussion

My initial recommendation regarding the 510(k) submission, which was only for the chronic indication, was that it be found Not Substantially Equivalent (see my Sept. 22 memo). In this memo I am revisiting that conclusion, taking into consideration the input from the Advisory Panel meeting. [Note: I was unable to attend the Advisory Panel meeting, but I have reviewed the transcript and spoken with FDA staff who did attend].

The experts on the Advisory panel were unanimous in their finding that for the chronic patient population, the CS device was safe.

> "(The) Panel generally believes that there is evidence of some soft tissue in-growth. However, it is not clear if the device is actually functioning like a meniscus. However, failure of the device appears to be no different from a simple meniscal tear, and, therefore, the device does not appear to carry any additional harm or risk."

They were less consistent in their finding regarding efficacy. They spoke a great deal about the potential benefits that the device could offer, and that the chronic patients had few other good options. They struggled with how to compare the device to predicate devices, and were also very concerned about appropriate patient selection and use of the device by physicians who were inadequately trained. When asked if ReGen had demonstrated substantial equivalence, the Panel Chair summarized their comments as:

> "(T)he 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."

The following dialog with the Panel Chair (Dr. Mabrey) and CDRH Center Director Dr. Schultz then ensued:

> 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 --
> 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 --
> 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 --

Most of the panel members were also generally supportive of including patients with acute injuries, with three exceptions:

- Dr. Kelly recommended the ReGen CS be reserved for patients with injuries involving at least 60% of the meniscus
- Dr. Shawen did not think there was enough date to support use in acute patients
- Dr. Endres recommended that the only acute patients who should be considered would be: "a young patient who has for whatever reason a subtotal meniscectomy and especially if they have any mal-alignment of the lower extremity".

Other important issues brought up by the panel included concerns about the need for proper training and patient selection.

Conclusion

ReGen is requesting clearance for a new indication for surgical mesh, namely to "*repair and reinforce the meniscus*". Use of a surgical mesh in the intra-articular space potentially raises new questions of safety that have not needed to be addressed by predicate surgical mesh indications. In particular, is the device able to withstand the mechanical forces present in the joint, and what is the impact on joint function should the device fail? Clinical data are needed to address the questions, and to demonstrate that this new indication can be considered the same intended use as predicate devices.

In my September 22, 2008 memo, I concluded that:

> *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.

I have revisited this recommendation after considering the input from the Advisory Panel, and discussing the submission extensively with members of the FDA review team and Dr. Schultz. The FDA presentation to the panel clearly presented the limitations of the clinical study, and the panel discussion indicated that the panel members understood these limitations. Even so, the panel members were very comfortable with the safety and effectiveness of the device. In terms of safety, they said on numerous occasions that the risks to the patient were very slight, especially when compared to allograft meniscus transplantation. In terms of effectiveness, the panel members believed that the device promoted growth of new tissue, and that this was a good thing. Although they acknowledged that there was no significant clinical benefit seen in the short term, many of the panel members spoke of the potential benefits in the long term.

The ReGen CS is a surgical mesh device with a new indication. A panel of qualified experts found it to be clinically safe, with histological data suggesting that it may promote tissue growth, and bench testing suggesting that it will withstand the mechanical forces that are present. Although strong evidence of clinical benefit is lacking, this level of evidence is similar to what has been accepted in previous 510(k)'s to add new indications for surgical meshes. Dr. Schultz and I have discussed this submission in detail, and he believes that ReGen has provide sufficient clinical data to demonstrate that the new indications for use has a similar risk/benefit profile to previously cleared indications for surgical mesh. Therefore, I have concluded that the ReGen CS device is substantially equivalent to predicate surgical meshes, in that the new indication does not constitute a new intended use.

On December 8, 2008, Dr. Schultz and I spoke with Panel members Dr. Kelly and Dr. Endres regarding appropriate labeling for the device (see attached minutes). I am making this recommendation with the condition that the labeling be modified as follows:

1. Indications should be limited to repair of the medial meniscus, since these are the only patients included in the clinical study.

2. The labeling include the following warnings:

    - Only qualified surgeons skilled and experienced in meniscus repair techniques and specifically trained in the use of the CS should use this device. Surgeons should be fully knowledgeable about proper patient selection, instruments and surgical techniques prior to performing surgery.
    - The surgical technique selected must be adequate to ensure proper fixation of the CS device.

3. The labeling include the following precautions:

- The use of the CS device should be limited to those patients with an irreparable medial meniscus injury necessitating the surgical removal of at least 20% of the meniscus.
- Removal of meniscus tissue that would not ordinarily be excised in a partial meniscectomy procedure should be avoided.
- The use of the CS device in patients with acute injuries should be considered with caution.
- Patients with isolated anterior horn tears are generally not appropriate candidates for the CS device
- Limit the use of the CS device in acute patients to those necessitating the surgical removal of at least 50% of the posterior half of the meniscus

These labeling changes were sent to ReGen on December 12. On December 15, Dr. Schultz and I had a teleconference with ReGen to discuss these changes. ReGen correctly noted that the 4th Precaution was already included in the Contraindications, so it was deleted. Although they argued about restricting the indications to medial meniscus, Dr. Schultz was quite firm about the fact that we could not clear the device for lateral meniscus when we did not have any data for this indication. They agreed to the rest of the labeling changes.

Therefore, I recommend that the 510(k) be found Substantially Equivalent.

Attachment 14

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 18 2008

Mr. John Dichiara
ReGen Biologics
411 Hackensack Avenue
Hackensack, NJ 07601

Re: K082079
Regen Collagen Scaffold
Regulation Number: 21 CFR 878.3300
Regulation Name: Surgical Mesh
Regulatory Class: Class II
Product Code: OLC
Dated: July 22, 2008
Received: July 23, 2008

Dear Mr. Dichiara:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Center for Devices and Radiological Health's (CDRH's) Office of Compliance at (240) 276-0120. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometrics' (OSB's) Division of Postmarket Surveillance at 240-276-3474. For questions regarding the reporting of device adverse events (Medical Device Reporting (MDR)), please contact the Division of Surveillance Systems at 240-276-3464. You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Daniel G. Schultz, M.D., F.A.C.S.
Director
Center for Devices and
Radiological Health

Enclosure

INDICATIONS FOR USE

510(k) Number (if known): K082079

Device Name: ReGen Collagen Scaffold (CS)

Indications for Use:

The ReGen Collagen Scaffold (CS) is intended for use in surgical procedures for the reinforcement and repair of soft tissue injuries of the medial meniscus. In repairing and reinforcing medial meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.

The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue. The CS is not a prosthetic device and is not intended to replace normal body structure.

Prescription Use X (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH

Attachment 15

Memorandum to the Record
K082079
Regen Collagen Scaffold

Date: December 20, 2008

From: Daniel Schultz, MD
Director, CDRH, FDA

This memo addresses my finding that the device is substantially equivalent to the predicate device, and records thoughts and analyses that I discussed with CDRH staff during my review of this application.

After careful consideration of the sponsor's application, the administrative record, the scientific opinions rendered by CDRH staff, the recommendations of the Orthopedic Advisory Panel at a meeting that I attended on November 14, 2008, and the memorandum from Dr. Donna-Bea Tillman dated December 15, 2008, I have reached the following conclusions which are consistent with conclusions reached by Dr. Tillman and the recommendations of the Orthopedic Advisory Panel:

- K082079 is Substantially Equivalent to cited legally marketed predicates for the treatment of acute and chronic injuries of the medial meniscus.

- 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.

- The panel was provided with, and asked to review, all of the data associated with this device and it was apparent to me from the depth of discussion at the panel meeting and the way in which the issues were addressed that they were extremely conversant with the data and very familiar with the clinical risks and benefits associated with this device, how the risk/benefit profile compared to the use of mesh in other orthopedic applications, and the risk/benefit profile of other treatment modalities currently used to treat injuries of the meniscus.

- The length of the review process associated with this submission is directly attributable to the sponsor's unwillingness to recognize and address the legitimate scientific concerns raised by CDRH. While surgical meshes may be classified from a regulatory standpoint under a single classification regulation, the question of how they affect clinical outcomes for new and different clinical applications is not only relevant, but central to our ability to determine substantial equivalence for this device.

This point was emphasized at the panel meeting by the sponsor's own mesh expert, Dr. Badylak:

"The last point that I want you to think about during the next few slides is that the microenvironment of the implantation site is an absolutely critical determinant in how well this surgical mesh is going to function."

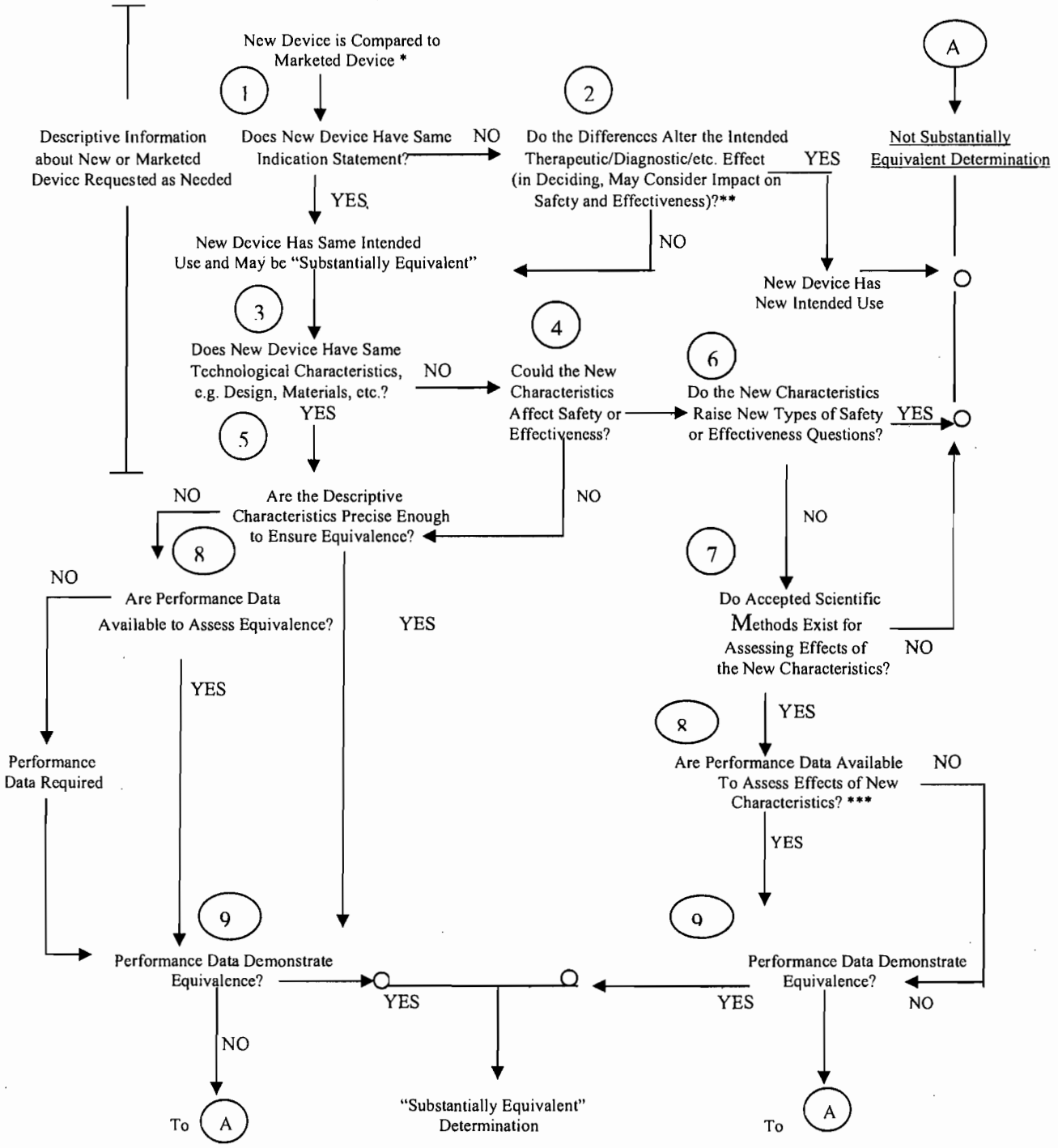
"So the individual sites are all different, and this is important because they define how well the surgical meshes are going to work."

"And, finally, microenvironmental factors including mechanical forces such as those that are seen in the knee are absolutely critical determinants in the remodeling process and the downstream results."

- Since the preclinical data alone were not able to predict the clinical performance of the CS device, it was absolutely imperative that a thorough and objective review of the available clinical data be performed. The sponsor requested and was granted a meeting at which their own clinical experts expressed their support of this device and their belief that it was in the best interest of patients for FDA to make it available for use in the U.S. I also met with the review staff including medical officers from the Office of Device evaluation and heard their concerns regarding lack of statistical significance for the primary endpoints of the IDE study and the very real safety issues associated with the placement of a foreign body like the CS device in the knee.
- The process by which FDA adjudicates scientific differences, particularly where those differences may have a significant impact on public health, is through an open public meeting utilizing an independent panel of experts in the field. The deliberations and recommendations of the panel are documented in the panel transcript and reflect both the complexity of the data as well as a clear conclusion that making this device available for use by surgeons who are capable of selecting appropriate patients in accordance with the labeling and individual patient characteristics and performing advanced arthroscopic procedures in the knee, is in the best interest of public health.
- Throughout the course of this review process, as reflected in the administrative record, there are multiple references by the sponsor to bias and application of inappropriate review standards to this application. The sponsor, and particularly their consultants, repeatedly expressed their disdain for the FDA review process and the individuals involved in the review of this application. The sponsor's efforts to demonize the staff and circumvent the process, the final decision notwithstanding, did nothing but complicate and delay this decision. In conclusion, I want to state for the record my belief that this application was reviewed without bias and in accordance with appropriate scientific and regulatory standards and with a single goal to protect and promote the public health.

Attachment 16

510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS



* 510(k) Submissions compare new devices to marketed devices. FDA requests additional information if the relationship between marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

** This decision is normally based on descriptive information alone, but limited testing information is sometimes required.

*** Data maybe in the 510(k), other 510(k)s, the Center's classification files, or the literature.