

510(K) MEMORANDUM

TO: K082079
FROM: John S. Goode, Biomedical Engineer, M.S., FDA/CDRH/ODE/DGRND/OJDB
DATE: August 14, 2008
SUBJECT: ReGen Collagen Scaffold (CS)
Proposed: FTM, Surgical Mesh; 21 CFR 878.3300; Class: II

Part 878 – General and Plastic Surgery
Devices:
Subpart D – Prosthetic Devices
Sec. 878.3300 Surgical mesh.

- (a) *Identification.* Surgical mesh is a metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples of surgical mesh are metallic and polymeric mesh for hernia repair, and acetabular and cement restrictor mesh used during orthopedic surgery.
- (b) *Classification.* Class II.

Note: In the sponsor's IDE G920211, FDA gave the device the Class III product code MPZ IMPLANT, RESORBABLE BOVINE COLLAGEN, MENISCAL REPAIR and a CMS reimbursement code of A1 (i.e., A (Experimental) and 1(Class III devices of a type for which no marketing application has been approved through the pre-market approval (PMA) process for any indication for use).

ADMINISTRATIVE INFORMATION:

Applicant/Sponsor: ReGen Biologics, Inc., 411 Hackensack Ave., 10th floor, Hackensack, NJ 07601
Contact Person: Mr. John Dichiaro, Sr. Vice President, Regulatory, Clinical and Quality
Phone Numbers: (201) 651-3505 Fax: (201) 651-5141 E-mail: jdichiaro@regenbio.com

RECOMMENATION:

My first recommendation is that additional time to review the file be given to the lead and consult reviewers. This file was requested to be reviewed in a total of three weeks. Taking into account other workload considerations, I believe that the consult reviewers and I had approximately 3 days to perform a complete review of this 510(k) and drafting of deficiencies. Because of this short time frame, there are no doubt additional analyses that could have been performed but were not; and, perhaps, additional deficiencies identified.

Based on the information reviewed, I recommend that this 510(k) be found NSE for new intended use.

Note 1: I have also been instructed by management to provide a review of the data contained in the 510(K), if Division or Office management decides to write a memo explaining why the subject device has the same intended use as legally marketed predicate devices; thereby overturning my recommendation of NSE for new intended use (per Blue Book memo titled "Documentation and Resolution of Differences of Opinion on Product Evaluations, December 23, 1993 (G93-1)". A review of the 510(k) data is outlined below, if necessary. 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 clinical data is not supportive of the proposed indications for use as the first "meniscal defect" criteria in the surgical technique for the IDE study was that the defect had to be an "Irreparable injury (same rationale for partial meniscectomy)" while the proposed indications for use in the 510(k) is for "reinforcement and repair of chronic soft tissues of the meniscus (one to three prior surgeries to the involved meniscus) where weakness exists." I believe that the subject device as used clinically (in the IDE study, feasibility study, in Europe and OUS) was not used to repair and reinforce a repair but to replace tissue that has been removed after partial meniscectomy. The sponsor reported that the average meniscus loss was 63%, 43% (37/87) of the tears in the CS group had 20% or less of the meniscus remaining, implying that there was 10% of the meniscus anterior and 10% posterior. My understanding of a device for the reinforcement and repair of soft tissue is that the device would act to augment tissue that has been adequately repaired using sutures, staples, etc. However, the subject device is being used to replace the meniscus in an area that cannot be repaired. Since the sponsor has not provided clinical data to support the proposed intended use, there is a lack of performance data.

Note 2: If management does not agree with the above assessment (i.e., that the clinical data is not supportive of the proposed indications for use/intended use), and write a memo to explain why the clinical data are supportive of the proposed indications for use; thereby overturning my recommendation of NSE for lack of performance data (again, per Blue Book (G93-1)), I have provided the following assessment of the clinical data provided. 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. We have already sent an AI letter dated July 9, 2008 after review of pre-submission materials, **Appendix C.**

Specifically, regarding the safety data provided, I have the following concerns:

- (a) In my analysis of the re-operations reported for the chronic group in Appendix J, there were 20 re-operations in 15 of 69 partial meniscectomy patients (22%), as compared to 27 re-operations in 23 of 87 CS patients (26%). This results in a higher re-operation event rate for the CS group, 0.31 events/patient, as compared to the partial meniscectomy group, 0.29 events/patient. The re-operations included 6 explants in 5 patients in the CS group with the device explants due to mechanical failure of the device (n=5) and infection (n=1). In the sponsor's analysis of the re-operations in Appendix J, they did not count 5 re-operations in the partial meniscectomy patients and 17 re-operations in the CS patients because they were either a re-operation on the same patient (n=4 in CS group, n=5 in control group), a procedure performed during the 1-year arthroscopic re-look (n=10 in CS group), or they stated that it was a re-operation not related to the meniscus (n=3, evaluation of saphenous nerve, excision of neuroma, and infection/device removal). However, I do not believe that it is appropriate to remove these re-operations from the analysis. I believe that all re-operations should be counted whether or not they are performed on the same patient. I believe that the 1-year re-look procedure was not intended to allow for additional procedures and by performing additional procedures (e.g., trephination of tear in CS device, removal of loose bodies, excision of scar tissue, debridement of edge of CS device, partial lateral meniscectomy, ACL repair, etc.) during the re-look, it cannot be determined whether or not these patients symptoms (e.g., pain, instability, redness, swelling) would have progressed to the point where another re-operation or device explantation were necessary. Finally, I believe that whether or not the re-operation was related to the meniscus or CS device, those re-operations related to the procedure should not be dismissed.
- (b) There were 37 serious adverse events in 21 of 87 (24%) CS patients compared to 23 events in 14 of 69 patients (20%) in partial meniscectomy patients. This results in a higher serious adverse event rate for the CS group, 0.43 events/patient, as compared to the partial meniscectomy group, 0.33 events/patient.
- (c) There were 14 serious device related adverse events in 8 of 87 (9.2%) CS patients compared to 2 events in 1 of 69 patients (1.4%) in partial meniscectomy patients. This results in a higher serious device related adverse event rate for the CS group, 0.16 events/patient, as compared to the partial meniscectomy group, 0.03 events/patient.
- (d) There were 51 non-serious device related adverse events in 29 of 87 (33%) CS patients compared to 5 events in 3 of 69 patients (4.3%) in partial meniscectomy patients. This results in a higher non-serious device related adverse event rate for the CS group, 0.59 events/patient, as compared to the partial meniscectomy group, 0.07 events/patient.

Based upon the increased risk associated with the use of the subject device, as outlined above, I 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, regarding the effectiveness data provided, I have the following concerns:

- (a) The clinical data failed to show that the CS device plus the control therapy was superior to the control therapy alone in these key effectiveness endpoints (pain (VAS), Lysholm function score, patient self-assessment);
- (b) Although the sponsor reported that "Chronic patients who received the CS regained more of their lost activity level (42% for CS patients) than did the controls (29% for controls; p=0.02)." According to the approved IDE G920211 protocol, Tegner index was not a pre-specified primary effectiveness endpoint and its related outcome "Tegner activity level" was actually collected as one of the thirteen "other information" endpoints in addition to the primary effectiveness endpoints. According to the protocol, a patient would be considered a success at 24 months if the Tegner activity score was at least one grade level higher than the pre-op activity level (unless this would require them to exceed their pre-injury level). Neither the sponsor nor the paper's author (Attachment A) provided the statistical analysis for the dichotomized Tegner activity level according to the study protocol. Therefore, the paper's analysis of Tegner Index should be considered as one of many possible post-hoc analyses for a scientific exploratory purpose and should not be used to support an indication claim for the investigative device because the Type I error rate would no longer be controlled at or below the pre-defined 5% level. Please be aware that, within the context of a confirmatory trial whose results will likely change the medical practice, such as in this case, if a confirmatory study failed on the primary endpoint, no further analysis for secondary endpoints or other endpoints of a lower order in clinical importance (e.g., Tegner activity level in this case) should be performed to support any labeling claim without a serious concern of Type I error rate inflation. Furthermore, the sponsor stated on p.29, the "clinical significance" of the Tegner index has not been reported in the literature. Therefore, it is not appropriate to rely on such a measure to establish clinical benefit of the CS device plus control therapy as compared to the partial meniscectomy control therapy alone;

- (c) Based on data provided on p.32, the average amount of native meniscal tissue removed for the CS patients was 63%, leaving 37% of the native tissue remaining; and the average amount of native meniscal tissue removed for the partial meniscectomy control patients was 60%, leaving 40% of the native tissue remaining. This data contradicts the sponsor's statement on p.14 that "because the CS provides reinforcement of the meniscal horns, the amount of tissue removed when using the device is usually less than when a partial meniscectomy is performed without the use of the CS." Therefore, the CS device plus control therapy leaves a patient, on average, with less native meniscal tissue as compared to the partial meniscectomy control therapy alone.
- (d) Although there was 73% total tissue for the CS chronic group at the one-year re-look arthroscopy as compared to 40% for the control group (Note: no re-look was performed on the control patients; therefore, the 40% 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 33% average additional total tissue for the CS group. Based on the clinical evaluation of pain, function, and self-assessment, there was no demonstrated difference in outcome measures for those patients who were and were not implanted with the investigational device. Furthermore, seven (7) of the evaluable 81 biopsies taken from acute and chronic CS subjects showed inflammatory tissue changes which were mild and non-specific consistent with a previous surgical intervention. The pictures you provided showed that there were trabecular fibrous tissues in the loose amorphous pink matrix, where a few mesenchymal cells were dispersed. These pictures also show that some synovial cells near the CS device show hyperplasia, with infiltrations of mononuclear cells, and perivascular mononuclear infiltration, with acute, subacute and chronic inflammation, and granulomatous reaction. Therefore, based on the pictures of the biopsy samples taken during the one year re-look arthroscopy for CS patients showed that there was no transformation of the CS material into a fibrous cartilage, e.g., meniscus, in any degree.

Therefore, based on the assessment of the data, I recommend NSE for higher degree of adverse events without a corresponding benefit – so, NSE – the data does not support SE.

Note 3: If the Division or Office writes memos overturning my recommendations of NSE for new intended use and lack of performance data and give the sponsor a chance to submit additional performance data (again, per Blue Book (G93-1)), **I have outlined some deficiencies to be put into an AI letter.** This would be the 8th time the sponsor would be allowed to present data to support the subject device. **Once the sponsor responds to these items, if there is disagreement with the review team/Division recommendation, my recommendation is to take this 510(k) to a panel meeting for an outside evaluation of the safety and effectiveness profile for this device.**

Note 4: We already have the sponsor's summary of data in IDE annual reports (see Attachment H of this memo for a summary) and, based upon data received; I believe it does not show the device is beneficial as compared to the standard of care – partial meniscectomy. Therefore, I don't believe there is much to be gained by asking for additional information.

BACKGROUND:

Prior 510(k) Decisions - Attachments for the following information are provided as background in Appendix A.

- The subject device has been the subject of two prior 510(k) submissions, K053621 and K063827, both found NSE.
 - K053621 was submitted on 12/28/05 and determined to be NSE for performance in a letter dated 2/23/06, which was rescinded in a letter dated 3/3/06 to allow the sponsor to provide additional information; and finally NSE for new intended use in a letter dated 7/26/06.
 - K053621 was then appealed and the NSE was upheld in a letter from Donna-Bea Tillman, ODE Director dated 11/3/06. In this letter, she also stated that a revised indication was proposed by the sponsor on 9/28/06 and that a new 510(k) may be submitted for this indication with clinical data. This decision was further explained in a memo from Donna-Bea Tillman to the file dated 8/13/07 that "given the large number of "reinforce and repair" indications that we have cleared for surgical mesh, it would be appropriate to review "reinforce and repair" indications for the meniscus as a 510(k) ... revised indications that more clearly define the use of the device for repair of the meniscus (as opposed to replacement), a new 510(k) could be submitted... clinical data would be necessary to support the revised indications." I don't agree with the assertion in the memo that because the indications for reinforcement and repair of soft tissue have become very broad over the past few years that it would be appropriate to review "reinforce and repair" indications for meniscus as a 510(k). I have clearly laid out the reasons why I don't agree with this assertion in my review memo below – 510(k) flowchart. In addition, in the Discussion section Donna-Bea stated that "ReGen noted... the CS material... allows preservation of more of the native tissue when compared to what would be removed during a partial meniscectomy." From the data provided for the

chronic group, the average amount of native tissue remaining at surgery was 37% for the CS device and 40% for the partial meniscectomy control (chronic group) – for the whole group [acute and chronic groups], these numbers are 43% for the CS device and 50% for the control group. This data disproves the sponsor's assertion in the 9/7/06 NSE appeal meeting with Donna-Bea.

- o K063827 was submitted on 12/22/06 and, after a round of questions, dated 3/26/07 and response in S1, was determined to be NSE because "the performance data provided indicates that there is an increased risk with the use of the device for the indicated patient population and an uncertain benefit as compared to legally marketed predicate devices." The ODE Director, Donna-Bea Tillman signed the NSE letter for K063827 on 8/20/07.

Commissioner Briefing Information - Attachments for the following information are provided as background in Appendix B.

- After the NSE decision for K063827, I was informed that ReGen was then in contact with the Ombudsman for CDRH, Les Weinstein, regarding next steps. Les granted the sponsor an extension to submit an appeal to proceed to the Medical Device Dispute Resolution Panel.
- On 12/14/07, I was requested to prepare briefing materials for the Commissioner of the FDA. Briefing materials were provided on 12/14/07.
- On 12/21/07, Ron Yustein, Clinical Deputy ODE Director, asked for the hard copy of the 510(k) for the Commissioner to look at.
- On 1/10/08, I received an e-mail from Ron Yustein requesting additional information regarding ReGen. I prepared a response that went through the Division on 1/11/08.
- On 1/17/08, the 510(k) K063827 was returned to me by Catherine Norcio.
- On 1/17/08, I received briefing information prepared by Ron Yustein for Dan Schultz, CDRH Director.
- On 1/17/08, a briefing meeting was held with Dan Schultz, CDRH Director including Ron Yustein, Les Weinstein, Mark Melkerson, Joni Foy, and John Goode. This was to prepare for a meeting with the sponsor and the FDA Commissioner. Dan requested a summary of the clinical data in the 510(k) to be prepared by 1/22/08.
- On 1/22/08, Mark Melkerson sent an e-mail containing a bulleted summary and a more complete summary of items which Dan Schultz requested for a 1/28/08 meeting. This information was prepared by the Division and the review team.
- On 1/24/08, received an e-mail from Donna-Bea Tillman through Joni Foy requesting a brief summary of clinical data for cleared surgical mesh (orthopedic) indications. This information was prepared and sent to Donna-Bea in an e-mail dated 2/6/08 and to Dan Schultz in an e-mail dated 2/8/08. This information was discussed in an internal meeting with Donna-Bea Tillman on 2/8/08.
- Attached to the file is a letter from Gary Bisbee, Ph.D., CEO ReGen to Dr. Von Eschenbach, FDA Commissioner dated 1/25/08.
- On 1/28/08, a briefing meeting was held with Dan Schultz, CDRH Director including Kate Cook OCD, Arnette Marthaler OCD, Mark Melkerson, Barbara Buch, Joni Foy, and John Goode. Dan summarized the meeting with ReGen and Commissioner for the Division.
- Attached to the file is a letter from Dr. Von Eschenbach, FDA Commissioner to Gary Bisbee, Ph.D., CEO ReGen, dated 2/12/08.
- Attached to the file is a letter from Dan Schultz, CDRH Director to Gary Bisbee, Ph.D., CEO ReGen, dated 4/25/08.

K082079 Pre-Submission Information - Attachments for the following information are provided as background in Appendix C.

- Attached to the file is a letter from Dan Schultz, CDRH Director to Gary Bisbee, Ph.D., CEO ReGen, dated 6/20/08. The letter stated in part that "if you believe that submitting a 510(k) for this indication [patients with chronic injuries] is appropriate, your submission would receive an expeditious and fair review."
- Prior to receiving the subject 510(k), K082079, a meeting was held with Dan Schultz, CDRH Director, on 6/26/08 to discuss the remaining issues with the ReGen CS device; whether the issues were all clinical or also preclinical. Those in attendance included Dan Schultz, Donna-Bea Tillman, ODE Director, Mark Melkerson, DGRND Director, Barbara Buch, DGRND Deputy Director, Joni Foy, Chief OJDB, and myself. Dan informed the group that ReGen came in with 4-5 orthopedic surgeons; some of whom were in the IDE trial and others that weren't. ReGen stated that there was no question that those patients in the revision group had a clinical benefit. The sponsor does not want to go to panel with the whole cohort and believe that the revision group has a positive risk/benefit compared to other meshes. Based on the internal meeting with Dan, it was my understanding that ReGen would be submitting a new 510(k) in July 2008. It was my understanding that the new 510(k) will be for a subset of those patients studied in their IDE – only those patients in

the study arm with 1-3 prior partial meniscectomies. Dr. Schultz agreed to have the sponsor, before their submission in July 2008 510(k), submit an "Executive Summary" of their data. Dr. Schultz asked for the review team to review the Executive Summary and provide feedback - noting any additional analyses, omissions, or any other deficiencies we would like to relay to the sponsor prior to their submission of the 510(k). When asked if a Panel meeting is still an option, it was stated that if the data wasn't clear, if not clear risk/benefit profile, other options are in play. Also, feedback on "Executive Summary" is to go through Dan/Les Weinstein, CDRH Ombudsman prior to going to sponsor.

- I received the sponsor's pre-submission "Executive Summary" containing a proof of a JBJS journal article titled, "Comparison of the Collagen Meniscus Implant with Partial Meniscectomy" and some additional figures and pictures in hard copy on 6/30/08. I requested consults from Roxolana Horbowyj and Kevin Lee. I was asked to prepare a response to the pre-submission in 4 days (by 7/3/08). In an e-mail dated 7/1/08, I requested that the sponsor provide an electronic version of the information. In an e-mail dated 7/1/08, Mr. Diciara provided a .pdf copy of a cover letter from Dr. DeHaven and the JBJS manuscript and a second .pdf to cut and paste for review purposes. I requested a statistical review of this information on 7/1/08 from Jack Zhou.
- I received a review from Kevin Lee and comments from Roxy Horbowyj on 7/1/08.
- On 7/2/08, Mark Melkerson, Director DGRND forwarded by e-mail two attachments containing a summary and outline of the sponsor's 510(k). This information was also to be reviewed by 7/3/08 (next day). This information was also forwarded on to Roxy, Kevin and Jack Zhou for consult. Additional comments from Kevin Lee and Roxy on the new information were provided on 7/2/08. I was sent an e-mail by Phyllis Silverman, OSB/Stats that I would not receive a review from Stats and that George (Jianxiong) Chu would now be reviewing this information in the future.
- On 7/2/08, I received a list of deficiencies on the pre-submission information from Donna-Bea Tillman, ODE Director.
- On 7/3/08, I sent an e-mail to Division management containing a list of deficiencies for review and approval that are recommended to be sent to ReGen Biologics, Inc. regarding a Future 510(k) Submission for the ReGen Collagen Scaffold (CS). In addition to my review, comments were received from Kevin Lee, Roxolana Horbowyj, and Dr. Donna-Bea Tillman and are based on review of pre-Submission information dated 6/23/08 and 7/1/08. I also requested statistical input but had not received any comments.
- I believe that there was additional input/modifications to the draft letter from the Division management while I was out of the office.
- On 7/21/08, I received an e-mail containing the final letter, dated 7/8/08, that was sent to ReGen regarding the pre-submission materials.

Subject 510(k) Submission, K082079 - Summary - Attachments for the following information are provided in Appendix D:

- ODE received 510(k) K082079 on 7/23/08. I received it on 7/24/08.
- As stated by the sponsor - the objective of this 510(k) is to demonstrate SE to other meshes; and, rely substantially on clinical data published in JBJS (attachment 1) to obtain a narrow indication for the CS device, i.e., that the device is indicated for use in patients with chronic meniscus injuries (one to three prior surgeries to the involved knee).
- In an e-mail dated 7/25/08 from Donna-Bea Tillman, ODE Director, she stated: "John: I just spoke with Dan - a few things to clarify: (1) All communication with the sponsor needs to come from Dan/Les; (2) Dan is asking that we complete our first round of reviews in two weeks - he will be setting up a meeting the beginning the week of August 11.
- When I asked for clarification about Donna-Bea's e-mail, both Mark Melkerson and Joni Foy informed me that I should be prepared to state where I am at in my review and the issues identified at that time.
- I assigned consults for the 510(k) to Kevin Lee, Roxy Horbowyj, and Jianxiong Chu on 7/28/08 to be provided by 8/8/08. I also provided the list of deficiencies we sent the sponsor regarding the pre-submission review on 7/8/08. On 7/29/08 I also provided the review team with the latest IDE protocols (Version 5) that were provided in G920211/S81 dated 11/20/06. Protocol 9601 starts on p.74/160 and Protocol 9602 starts on p.115/160.
- In an e-mail dated 7/30/08 from Mark Melkerson, I was asked to provide paper copies of the final clinical study protocol for the ReGen IDE to Dan Schultz, Director CDRH and Donna-Bea Tillman, ODE Director.
- In an e-mail dated 8/8/08 from Mark Melkerson, he stated that he has "spoken to Donna-Bea Tillman and have received clarification regarding her email below [dated 7/25/08]. "Complete our first round of reviews in two weeks" means completing a review with a signed memo with your recommendations and with a signed letter based on the recommendations with the appropriate branch or division level sign-off. As noted the two-week time frame is at the request of Dan Schultz." With this additional guidance, I had 2-3 working days to prepare a final memo for this 510(k).
- I received Kevin Lee's consult memo on 8/8/08, as requested. (Consult and deficiencies in Appendix D)
- I received a draft memo from Jianxiong Chu on 8/8/08 that was revised on 8/11/08. I requested additional information from Jianxiong (George) on 8/12/08 including a list of any deficiencies for the sponsor. Deficiencies were provided on 8/13/08. (Consult and deficiencies in Appendix D)

- I received an e-mail from Roxolana Horbowyj containing 6 bulleted concerns and a recommendation of AI. Four of the 6 bullets concerned either a change to the sponsor's indications or labeling. I don't believe that it is appropriate at this stage to request modifications to the sponsor's intended use, if the sponsor would like to change their intended use, a new 510(k) should be submitted. I also don't believe that it is appropriate, based on the identified issues with this file to request modifications to the labeling. Finally, the other two bulleted concerns are incorporated, for the most part, in the identified deficiencies. (Consult e-mail in Appendix D)
- I was informed by my branch chief, Joni Foy that she would like a final review memo with deficiencies by the morning of 8/13/08. This only gives me 2 days to perform a complete review of this 510(k) taking into account my other workload and due dates. I informed my branch chief that this deadline would be difficult to meet.
- On 8/13/08, there was a Division Briefing with Mark Melkerson, Barbara Buch, Joni Foy, Phyllis Silverman, Telba Irony and the review team including John Goode, Kevin Lee, Jianxiong (George) Chu, and Roxolana Horbowyj. Management was briefed on the status of the review.
- I prepared a NSE and AI letter for this file depending on the final decision on 8/14/08.
- A briefing meeting is scheduled with Dan Schultz, Director CDRH on 8/14/08.

Review Team, K082079:

John Goode:

Lead reviewer

Kevin Lee, M.D.:

Clinical and animal study review

Roxolana Horbowyj, M.D.:

Clinical review

Jianxiong (George) Chu:

Statistical review