

**ReGen Biologics, Inc.  
ReGen Collagen Scaffold (CS)  
510(k)**

**Orthopedic and Rehabilitation  
Devices Advisory Panel Meeting**

**November 14, 2008**

**FDA:**

**Larry G. Kessler, Sc.D.**

**Director Office of Science and Engineering  
Laboratories**

# ReGen CS Proposed Indications for Use 510(k) K082079

- The ReGen Collagen Scaffold (CS) is indicated 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.

# ReGen CS Proposed Indications for Use

## ReGen Executive Summary\*\*

\*\*FDA notes ReGen modified its proposed indication in its executive summary. **This indication not included in pending 510(k).**

The ReGen Collagen Scaffold (CS) 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 or provide full mechanical strength of the repair.

# Excerpt from JBJS Article – Acute Arm

1413

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## Comparison of the Collagen Meniscus Implant with Partial Meniscectomy

A Prospective Randomized Trial

**“The implant [ReGen CS] was not found to have any benefit for patients with an acute injury.”\***

soon after the original index partial meniscectomy. The implant supported meniscus-like matrix production and integration as it was assimilated and resolved. In the chronic group, the patients who had received an implant regained significantly more of their lost activity than did the controls ( $p = 0.02$ ) and they underwent significantly fewer non-protocol reoperations ( $p = 0.04$ ). No differences were detected between the two treatment groups in the acute arm of the study.

**Conclusions:** New biomechanically competent meniscus-like tissue forms after placement of a collagen meniscus implant, and use of the implant appears safe. The collagen meniscus implant supports new tissue ingrowth that appears to be adequate to enhance meniscal function as evidenced by improved clinical outcomes in patients with a chronic meniscal injury. The collagen meniscus implant has the utility to be used to replace irreparable or lost meniscal tissue in patients with a chronic meniscal injury. The implant was not found to have any benefit for patients with an acute injury.

**Level of Evidence:** Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

**Disclosures:** In support of their research for or preparation of this work, one or more of the authors received, in any one year, outside funding or grants in excess of \$10,000 from ReGen Biologics. In addition, one or more of the authors or a member of his or her immediate family received, in any one year, payments or other benefits in excess of \$10,000 or a commitment or agreement to provide such benefits from a commercial entity (ReGen Biologics). Also, a commercial entity (ReGen Biologics) paid or directed in any one year, or agreed to pay or direct, benefits in excess of \$10,000 to a research fund, foundation, division, center, clinical practice, or other charitable or nonprofit organization with which one or more of the authors, or a member of his or her immediate family, is affiliated or associated.

 A video supplement related to the subject of this article has been developed by the American Academy of Orthopaedic Surgeons and JBJS and is available for viewing in the video library of the JBJS website, [www.jbjs.org](http://www.jbjs.org). To obtain a copy of the video, contact the AAOS at 800-626-6726 or go to their website, [www.aaos.org](http://www.aaos.org), and click on Educational Resources Catalog.

 A commentary is available with the electronic versions of this article, on our web site ([www.jbjs.org](http://www.jbjs.org)) and on our quarterly CD-ROM (call our subscription department, at 781-449-9790, to order the CD-ROM).

J Bone Joint Surg Am. 2006;88(14):1413-26 • doi:10.2106/JBJS.G.00656

**\* From Conclusions:  
p.1413, JBJS Article**

# Reason for Panel Meeting

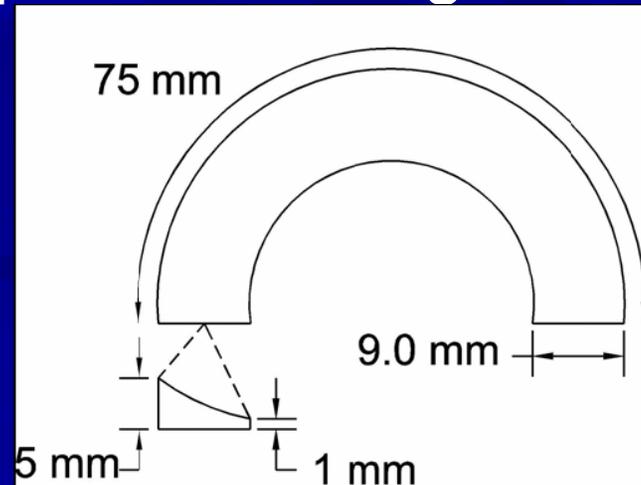
- ReGen CS has a new indication for use.
- To establish substantial equivalence (SE) FDA must consider effects new indication might have on safety and effectiveness for legally marketed predicate device(s).
- FDA considers why new indication does not affect safety and effectiveness of device when used as intended by the manufacturer in the predicate device's labeling.
- FDA must determine if data reasonably suggest new device is SE to predicate devices, when predicates are used in accordance with their labeled indications.
- FDA must rely on valid scientific evidence, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of the device under its conditions of use.
- Specific questions FDA has for the Panel are in Tab A of FDA Panel Pack.

# Outline

- Device Description
- Pre-Clinical Information
- Clinical Data
- Substantial Equivalence to a Predicate Device
- Predicate Device Information
- Panel Questions

# ReGen CS Device Description

- Resorbable matrix composed of Type I collagen
- Semi-lunar shape with a triangular cross-section for use in meniscus
- Surgeon trims device to size necessary for repair of damaged or weakened soft tissue
- Sutured in place through a minimally invasive arthroscopic procedure
- Shape of device is unlike predicate surgical meshes

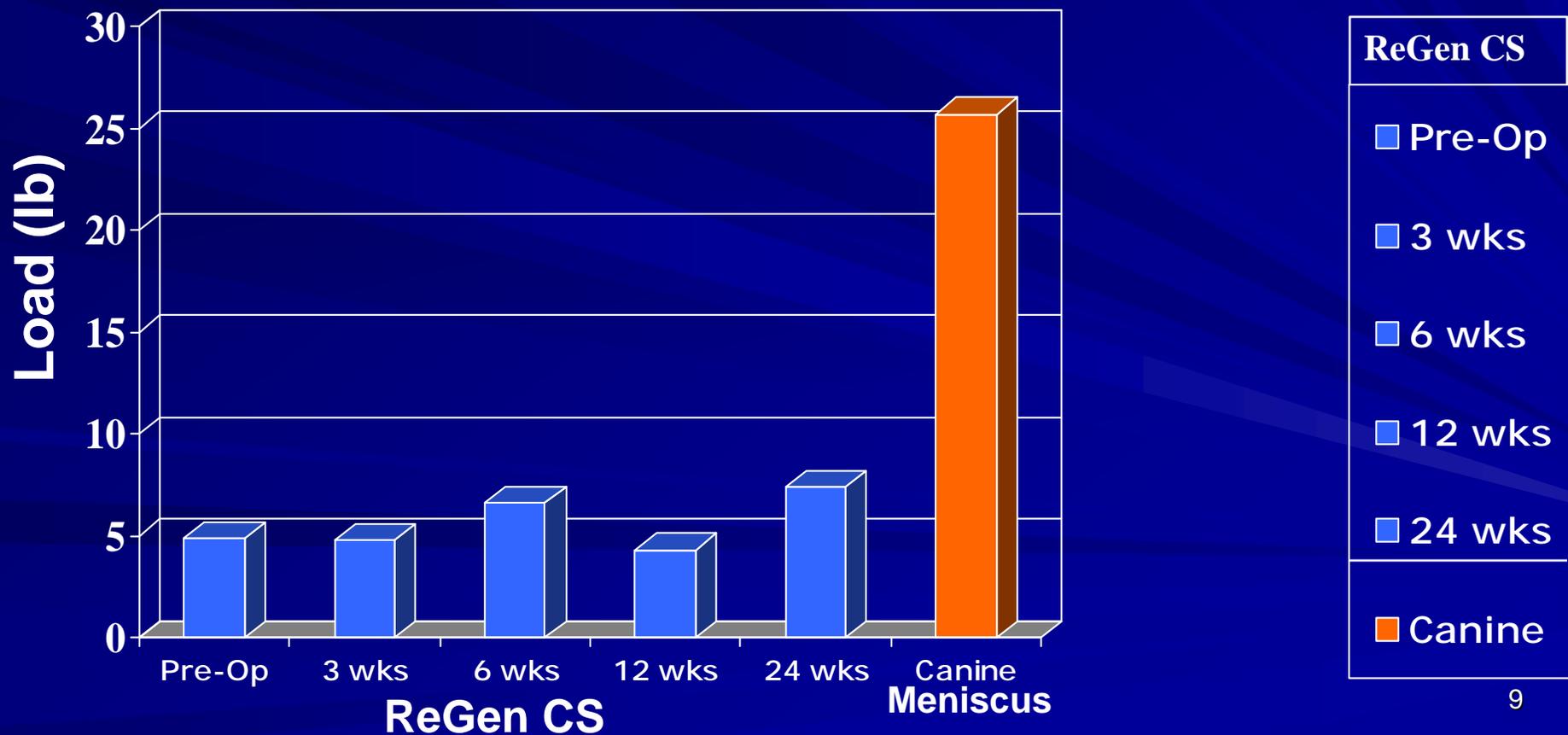


# Pre-Clinical Information

- **Bench: Suture Pull-Out Strength**
- **Animal Testing: Canine Model**
- **Biomechanics of the Meniscus compared to forces in the shoulder**
- Tensile Strength
- Biocompatibility
- Viral Inactivation
- Sterilization
- Packaging & Shelf Life

# Suture Pull-Out: Bench & Animal Study

- Bench: Suture retention strength similar to predicate meshes, which are not for meniscal repair
- Suture Pull-Out from Canine Native Meniscus 3-6x higher than from ReGen CS in Canine Model 0-24 weeks



# Clinical Data Sources

1. Feasibility Study – Single Center Published Results on 8 Patients
2. Published Results from Europe:
  - a. Case Study on Four (4) Patients
  - b. Case Study on Two (2) Patients
3. **IDE protocol and IDE data presented in 510(k)**
4. **Rodkey, W.G. et al., “Comparison of the Collagen Meniscus Implant with Partial Meniscectomy. A Prospective Randomized Trial,” *J. Bone Joint Surg Am.* 2008; 90: 1413-1426.**  
**(Note: “JBJS article” based on IDE Study, G920211).**

***FDA’s clinical data presentation will focus on the approved IDE protocol, JBJS article, and clinical data provided in the 510(k) submission***

# Study Overview

## ReGen's IDE Study:

- Randomized, controlled clinical trial of the ReGen CS
- Multi-center clinical trial approved 8/30/96. Enrollment completed April 2003 and follow-up continues
- **Sample Size chronic pts:** 144 patients (72 per group, minimum 64 evaluable)

## IDE study compares clinical outcomes of:

- partial meniscectomy (control group)
- partial meniscectomy followed by ReGen CS (ReGen CS treatment group)

## Two study arms (different protocols):

1. Acute (no previous meniscus treatment)
2. Chronic meniscal injury (1-3 previous meniscus treatments)

Only difference between arms is number of prior surgeries

510(k) requesting clearance for only **chronic patient group**

# IDE Protocol Study Endpoints

## Safety:

- Assessment of serum markers
- Adverse Events

## Effectiveness:

- Clinical Endpoints (pre-defined success: 2 out of 3)
  - VAS Pain Score
  - Lysholm Pain and Function Knee Score
  - Patient Self-Assessment
- Surrogate Endpoints – CS status assessment
  - Arthroscopy
  - Histopathology
  - Radiographs

# Additional Endpoints\*

- Synovial Fluid assessment
- Redness assessment
- Skin/superficial wound healing assessment
- Range of motion
- Thigh girth measurement
- Functional evaluation
- **Tegner activity level**
- Radiographic evaluation
- Gross appearance of regeneration
- Implant appearance
- Implant-Host stability
- Presence of loose bodies or fraying
- Implant-host junction
- Presence of inflammatory response

***\*Each endpoint had a predefined success/failure criteria in IDE protocol  
(See Tab G of FDA Executive Summary)***

# ReGen CS Surgical Technique

- Assessment of Meniscal Defect
  - Meniscus Defect Criteria
    - **Irreparable** injury (same for partial meniscectomy control group)
    - Traumatic or degenerative origin
    - Both attachment sites for the anterior and posterior horns intact
    - Site preparation must result in a full thickness defect
    - Defect site must extend into red/red zone or the red/white zone
    - Exclude unstable segmental defects in which the meniscal rim is not intact
- Partial meniscectomy
- Preparation of defect site and implantation

# Rehabilitation Protocol

- ReGen CS
  - Non-weightbearing with passive motion – 1 week
  - Partial-weightbearing with passive motion – 5 weeks
  - Slow progression to full activities by 6 months
- Control Group
  - Return to full activities – 2-3 weeks

# Patient Enrollment

- Chronic Arm:
  - Treatment: 85 subjects had partial meniscectomy + ReGen CS
  - Control: 69 subjects had only partial meniscectomy

*Note: Complete accounting of patient enrollment was provided in FDA Executive Summary (p.20) & in JBJS article*

# Patient Accounting – Chronic Arm\*

- The primary endpoints were evaluated at the 12 or 24-month endpoint.
- At the 3-7 year annual follow-up timepoints, there is approximately 50% of the data available.
- It is not clear how missing data at time-points later than 24 months impacts presentation of safety and effectiveness endpoints

*\* Information provided in 510(k), Appendix H*

# Clinical Data - Results

# Safety Results – Adverse Events

<b>Safety Results: Chronic Arm [510(k)]</b>	<b>ReGen CS</b>	<b>Control</b>
<b>Serum Analysis</b>	Not different	
<b>Adverse Events (AE)</b>		
<ul style="list-style-type: none"> <li>• Serious AE               <ul style="list-style-type: none"> <li>• Total events/total patients</li> <li>• Patients with events/total patients</li> </ul> </li> </ul>	37/87 (0.43) 21/87 (24%)	23/69 (0.33) 14/69 (20%)
<ul style="list-style-type: none"> <li>• Serious Device-Related AE               <ul style="list-style-type: none"> <li>• Total events/total patients</li> <li>• Patients with events/total patients</li> </ul> </li> </ul>	14/87 (0.16) 8/87 (9.2%)	2/69 (0.03) 1/69 (1.4%)
<ul style="list-style-type: none"> <li>• Non-Serious Device-Related AE               <ul style="list-style-type: none"> <li>• Total events/total patients</li> <li>• Patients with events/total patients</li> </ul> </li> </ul>	51/87 (0.59) 29/87 (33%)	5/69 (0.07) 3/69 (4.3%)
<ul style="list-style-type: none"> <li>• All AE               <ul style="list-style-type: none"> <li>• Total events/total patients</li> <li>• Patients with events/total patients</li> </ul> </li> </ul>	295/87 (3.39) 74/87 (85%)	240/69 (3.48) 54/69 (78%)

# Adverse Events (Knee Related: FDA)

Table 8: AE Chronic Study Arm	Serious AEs		Serious Device Related AEs		Non-Serious Device Related AEs	
	CS	Control	CS	Control	CS	Control
Surgery Op index knee:	1	1	1	0	0	0
Tear medial meniscus:	1	0	0	0	0	0
Intraarticular Swelling/Effusion:	4	2	3	0	9	1
Inflammation of Bone:	1	0	1	0	1	0
Instability of joint:	2	0	1	0	2	0
Pain	5	2	4	0	14	0
Loose bodies in the joint	0	1	0	1	0	0
Cyst	1	0	1	0	1	0
Synovitis/bursitis joint	0	1	0	0	0	0

# Adverse Events (Knee Related: FDA)

## Adverse Events – Chronic Study Arm (cont.)

### *Additional non-serious device-related AEs include:*

- Saphenous nerve injury
- Squeaking/creaking
- Stiffness
- Numbness lower extremity
- Patello-femoral complaints
- Locking/catching
- Torn implant
- Plica
- Lateral meniscus tear
- Implant fraying
- Popping/clicking of knee

### *Additional non-serious AEs include:*

- Reduced knee range of motion
- Worsening osteoarthritis of operative knee
- Tear at implant meniscus interface

# Safety Results - Explants

## Explants – Chronic Study Arm\*

There were 6 ReGen CS device explants in 5 patients

- 1 due to infection
- 5 due to mechanical failure

*\*Table 10 from FDA's Executive Summary*

# Effectiveness Results (JBJS)

Clinical Endpoints	Chronic Group	
	ReGen CS (n=82)	Control (n=69)
VAS pain score (points)		
•Mean change from pre-op	18	18
•Mean score at last follow-up	19	21
Lysholm score (points)		
•Mean change from pre-op	16	22
•Mean score at last follow-up	79	78
Patient self-assessment score (points)		
•Mean change from pre-op	0.7	0.9
•Mean score at last follow-up	1.9	2.1

# Effectiveness – 1 Year Re-Look

## Surrogate Endpoints:

- Outerbridge Score – Evaluation of Articular Cartilage Surface (Chronic Arm)
  - CS:
    - Mean Pre-Op = 1.5; Mean Score 1-year re-look = 1.3
  - Control
    - Mean Pre-Op = 1.7; No 1 year re-look performed
- Evaluation of ReGen CS Attachment to Meniscal Rim (Acute and Chronic Arms)
  - Firmly attached = 84% (119/141)
  - Not firmly attached = 16% (22/141)
- Changes in Knee Compartment for ReGen CS Subjects (Acute and Chronic Arms)
  - Improved = 23% (33/141)
  - Unchanged = 59% (83/141)
  - Worsened = 18% (25/141)

# Effectiveness – 1 Year Re-Look (cont.)

## Surrogate Endpoints:

- Cellular Ingrowth (Acute and Chronic Arms)
  - Marked with cells resembling fibro-chondrocytes = 45% (30/66)
  - Marked = 20% (13/66); Slight = 29% (19/66); None = 6% (4/66)
- Extracellular Matrix Organization (Acute and Chronic Arms)
  - Fibro-cartilagenous tissue = 68.8% (44/64)
  - Sections of continuous chondroid matrix = 1.6% (1/64)
  - Random organization = 26.6% (17/64)
  - No matrix organization = 3% (2/64)
- Inflammatory Response (Acute and Chronic Arms)
  - Minimal to none = 94.7% (124/131); Mild = 0.8% (1/131); Moderate = 0.8% (1/131); Severe = 1.5% (2/131); Missing = 2.2% (3/131)

# Effectiveness – Radiographic Evaluation

**Surrogate Endpoint\*: Radiographic Evaluation: Change from Pre-op for Combined Acute & Chronic Study Arms**

Parameter Evaluated	12 months			24 months		
	CS	Control	p-val	CS	Control	p-val
Osteophyte formation worsens $\geq 1$	15/64 (23%)	16/66 (24%)	1.00	19/72 (26%)	26/78 (33%)	0.38
Fairbank-Ridge Formation worsens $\geq 1$	5/64 (8%)	1/64 (2%)	0.21	10/71 (14%)	7/73 (10%)	0.45
Fairbank-Ridge Flattening of femoral condyle worsens $\geq 1$	16/64 (25%)	20/64 (31%)	0.56	25/71 (35%)	25/73 (34%)	1.00
Fairbank-Ridge Joint Space narrowing worsens $\geq 1$	21/64 (33%)	20/64 (31%)	1.00	30/71 (42%)	23/73 (32%)	0.23

*\*510(k) submission: Attachment C, pp 24-25, Info not provided only for chronic group* <sup>26</sup>

# Effectiveness – Amount of Tissue c15

Table 13: Meniscus Remaining and Defect Filling (Chronic Arm)

Surrogate Endpoint	Chronic Group	
	ReGen CS	Control
Percent meniscus remaining		
•Number studied	85	69
•Mean and standard deviation (%)	37 +/- 20	40 +/- 22
Percent defect filled		
•Number studied	76	
•Mean and standard deviation (%)	58 +/- 27	Not measured
Percent tissue surface area		
•Number studied	76	69
•Mean and standard deviation (%)	73 +/- 20	40 +/- 22

# Effectiveness – Tegner Index

Tegner Index:

- Not a pre-specified endpoint
- Related “Tegner activity level” : One of 14 “additional endpoints”

JBJS article:

- “Chronic CS patients regained more lost activity level (42% for CS patients) than did the controls (29% for controls;  $p=0.02$ ).”
- Information not provided in the JBJS article includes:
  - Mean scores at annual timepoints
  - Follow-up rates

# Effectiveness – Tegner (cont.)

## Tegner Activity Level (mean scores):

- Most recent report for both CS & Control chronic arm patients provided in IDE annual report in Feb. 2003
- Follow-up 70% at 12 months and 50% at 24 months
- No difference at 12 months
- 0.6 point difference at 24 months

Table 20: Tegner Activity Level (mean scores) – Chronic Arm\*

	N	Pre-Injury	N	Pre-operative	N	12 month	N	24 month
ReGen CS	83	6.5	82	2.9	60	4.1	45	5.0
Control	68	6.6	67	3.0	44	4.1	36	4.4

\*Data provided in IDE Annual Report, 2/2003

# Effectiveness – Tegner Index (cont.)

Tegner Index:

- “Clinical significance” not reported in literature
- Designed to complement other functional scores (e.g. the Lysholm knee score) for patients with ligamentous injuries; and Lysholm found not significantly different

# Effectiveness – Reoperations

JBJS article:

- Reoperations for patients in chronic arm
- 8 reoperations in CS group
- 15 reoperations in Control group

JBJS article did not include:

- 5 re-operations in the control group; and
- 17 re-operations in the CS device patients

Reasons for removing re-operations:

- Re-operation on the same patient (n=4 CS, n=5 Control)
- Procedure during the 1-year re-look (n=10 CS)
- Re-operation not related to meniscus (n=3, evaluation of saphenous nerve, excision of neuroma, and infection/device removal).

# Effectiveness – Reoperations (cont.)

FDA Analysis (cont.):

## FDA Reoperation Inclusion/Exclusion criteria

For control:

- Included anything that could be considered a failure of meniscectomy
- If procedure due to new trauma, excluded

For ReGen CS:

- Excluded if procedures was solely due second-look arthroscopy
- If during second look, additional procedures were performed and accompanying meniscal or medial symptoms/pain were noted, then, the patient/procedure was considered to have had an additional procedure or re-operation.
- All explants included as considered procedure or device related
- Procedures to repair or revise (smooth edges or repair tears in device) included
- If procedure due to new trauma, excluded

# Effectiveness – Reoperations (cont.)

c18

FDA Analysis:

Table 22: Number of additional procedures following index procedure for Chronic Study Arm patients

	CS		Control	
	# Procedures	# Patients	# Procedures	# Patients
<b>Included:</b> • Reoperations related to meniscal pathology or symptoms	15	14	11	11
<b>Included:</b> • Reoperations – procedure related	3	3	0	0
<b>Excluded:</b> • Reoperations related to protocol procedure only (2 <sup>nd</sup> look); and/or • Reoperations not procedure or device related	9	7 <sup>^</sup>	9	6 <sup>^</sup>
<b>Total Reoperations Included</b>	<b>18</b>	<b>17</b>	<b>11</b>	<b>11</b>

<sup>^</sup>Some patients had multiple operations

# **Substantial Equivalence to a Predicate Device**

# Comparison to Marketed Device

Sponsor stated that the ReGen CS is a surgical mesh

Surgical Mesh devices defined in 21 CFR 878.3300

- Title 21 – Food and Drugs
- Part 878 – General and Plastic Surgery Devices
- Section 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.

# Predicate Devices

As outlined in Table 1 of the FDA Executive Summary, current predicate surgical mesh devices are indicated for patients to reinforce soft tissue where weakness exists, including the following:

- rotator cuff
- hernia
- anal, rectal and enterocutaneous fistulas
- urethral and vaginal prolapse repair
- colon and rectal prolapse repair
- reconstruction of the pelvic floor
- bladder support
- soft tissue of the lung, etc.

**There are no legally-marketed surgical mesh devices indicated for the “reinforcement and repair of chronic soft tissue injuries of the meniscus”**

# Orthopedic Example – DePuy Restore Surgical Mesh

## DePuy Restore Surgical Mesh Indications for Use:

For use in general surgical procedures for reinforcement of soft tissue where weakness exists. In addition, the implant is intended for use in the specific application of reinforcement of the **soft tissues which are repaired by suture or suture anchors during rotator cuff repair surgery**. The Restore Implant is not intended to replace normal body structure or provide the full mechanical strength to repair the rotator cuff. **Sutures to repair the tear and suture or bone anchors to reattach the tissue to the bone provide mechanical strength for the rotator cuff repair**. The Restore Implant reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue.

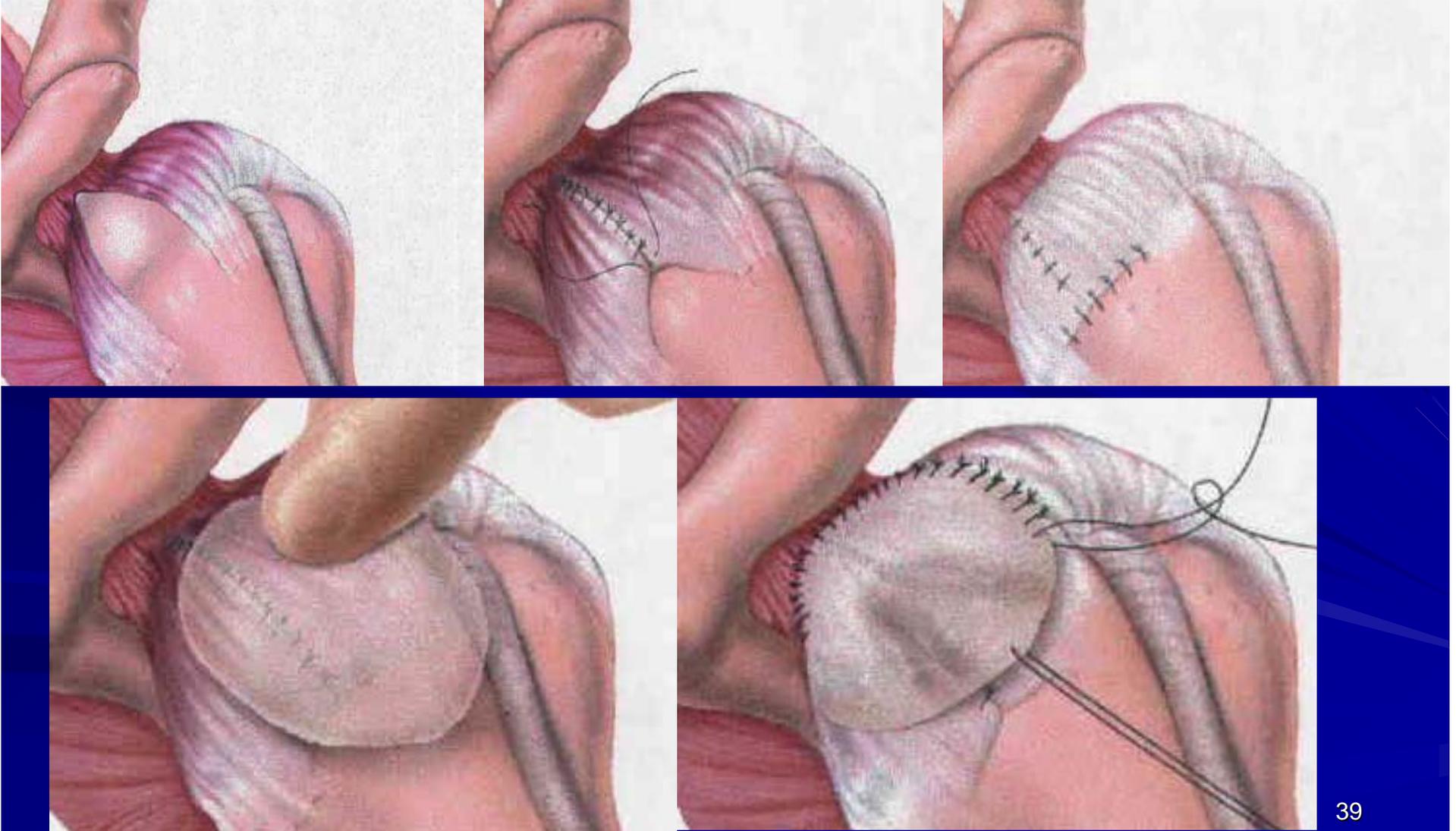
# Orthopedic Example – DePuy Restore Surgical Mesh (cont.)

## Comparing use of rotator cuff surgical mesh with ReGen CS

- The rotator cuff stabilizes and supports the shoulder joint
- The use of a surgical mesh in the rotator cuff creates a smooth area over a sutured repair

# Orthopedic Example – DePuy Restore Surgical Mesh (cont.)

Pictures from DePuy Restore Surgical Technique: (Copied with permission)



# ReGen CS Surgical Technique

- Assessment of Meniscal Defect

- Meniscus Defect Criteria

- **Irreparable** injury (same for partial meniscectomy control group)
- Traumatic or degenerative origin
- Both attachment sites for the anterior & posterior horns intact
- Site preparation must result in a full thickness defect
- Defect site must extend into red/red zone or the red/white zone
- Exclude unstable segmental defects in which the meniscal rim is not intact

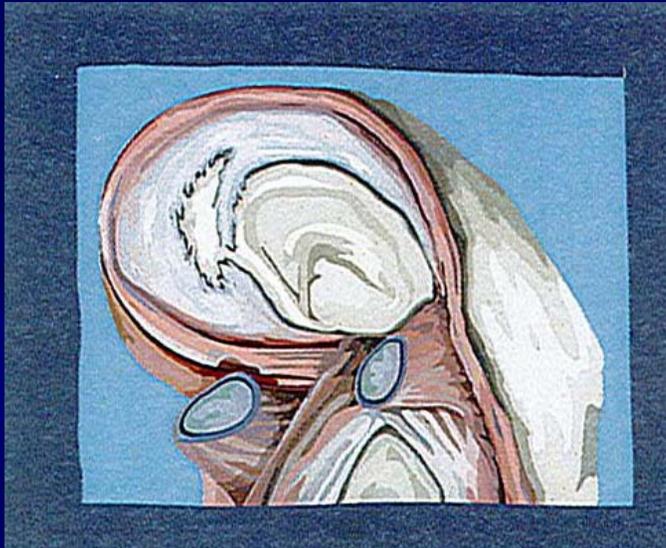
- Partial meniscectomy

- Preparation of defect site and implantation of CS

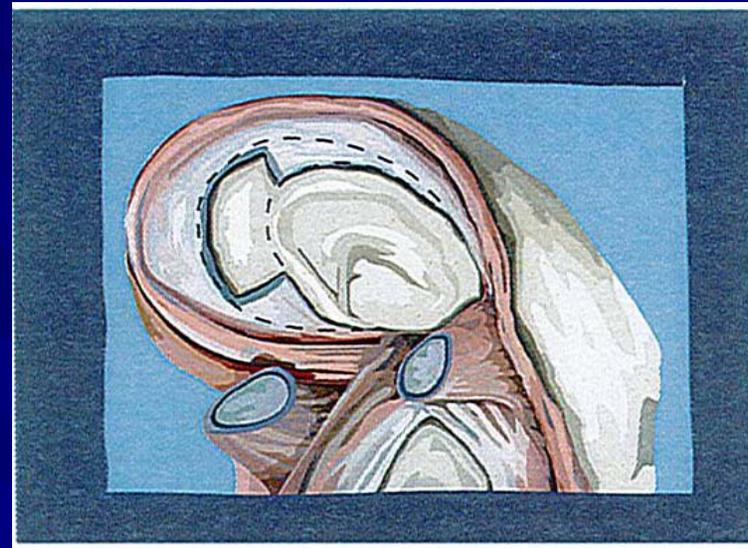
# ReGen CS Surgical Technique

*Illustrations from ReGen CS Surgical Technique:*

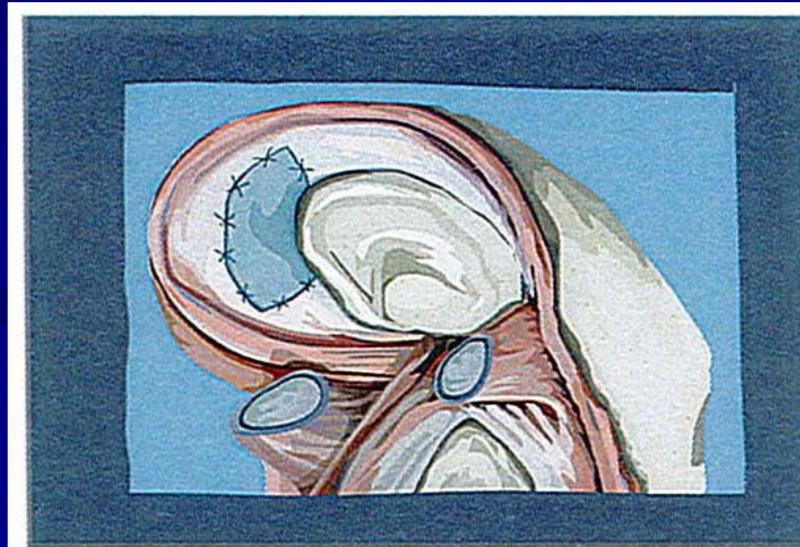
1.



2.



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# FDA 510(k) Review of Surgical Meshes with New Indications

Types of data vary depending on the new indication, for example, differences in clinical situation, specific indication, or product specifics:

- Biocompatibility, sterility, bench, and/or animal testing
- Varying degrees of clinical data may be necessary
- The sponsor's Executive Summary and 510(k) include statements concerning how FDA determined SE for legally marketed predicate devices.
- FDA disagrees with the characterization of FDA determinations: the firm is not privy to the information that FDA reviews for predicate products.

# Summary

- The clinical environment for this indication is one where there are weight bearing forces that will apply to the ReGen CS
- Safety
  - Treatment group with the ReGen CS device has device-related adverse events
  - Explants suggest mechanical failures of the device
- Effectiveness
  - ReGen CS did not attain significance in any primary endpoint
  - Analysis of two positive clinical endpoints
    - Tegner Index: post-hoc endpoint, analysis questionable
    - Reoperations: inclusion and exclusion criteria subjective