

PREMARKET NOTIFICATION [510(k)]

REGEN COLLAGEN SCAFFOLD (CS)

Applicant:

**ReGen Biologics, Inc.
411 Hackensack Ave. – 10th Floor
Hackensack, NJ 07601**

Official Correspondent:

**John Dichiara
Telephone: (201) 651-3505
Fax: (201) 651-5141
jdichiara@regenbio.com**

TABLE OF CONTENTS

MEDICAL DEVICE USER FEE COVER SHEET	
CDRH PREMARKET REVIEW SUBMISSION COVERSHEET	
510(K) COVER LETTER	
510(K) COVER PAGE	
TABLE OF CONTENTS	
510(K) SCREENING CHECKLIST	

1.0	EXECUTIVE SUMMARY	1
1.1	OBJECTIVES.....	1
1.2	BACKGROUND.....	1
1.3	BASIS FOR SUBSTANTIAL EQUIVALENCE.....	3
1.4	REGULATORY PRECEDENTS.....	6
1.5	CONCLUSION.....	7
2.0	INDICATIONS FOR USE	9
3.0	510(K) SUMMARY FOR COLLAGEN SCAFFOLD	10
4.0	TRUTHFUL AND ACCURATE STATEMENT	13
5.0	DEVICE DESCRIPTION	14
5.1	DEVICE NAME AND OVERVIEW.....	14
5.2	MATERIAL COMPONENTS.....	14
5.3	PRODUCT CHARACTERIZATION.....	14
5.4	DRAWINGS OF DEVICE.....	15
5.5	DEVICE MANUFACTURING.....	15
6.0	PROPOSED LABELING, PACKAGING	16
6.1	PACKAGING AND SHELF LIFE.....	16
6.2	DRAFT PACKAGE LABEL.....	16
6.3	INSTRUCTIONS FOR USE.....	16
7.0	STERILIZATION INFORMATION	17
7.1	METHOD OF STERILIZATION.....	17
7.2	VALIDATION METHOD.....	17
7.3	VIRUS INACTIVATION.....	17
8.0	BIOCOMPATIBILITY TESTING	18
8.1	SPECIFICATION FOR LEAD.....	17
8.2	REPORT ON HUMORAL IMMUNE TESTING IN U.S.....	17

CONFIDENTIAL

9.0	PERFORMANCE TESTING	20
9.1	BIOMECHANICAL TESTING	20
9.2	BIOMECHANICS OF THE MENISCUS	20
9.3	ANIMAL TESTING	22
9.4	CLINICAL EXPERIENCE	21
10.0	SUBSTANTIAL EQUIVALENCE	55
10.1	BACKGROUND.....	55
10.2	PREDICATE DEVICES	54
10.3	THE CS HAS THE SAME INTENDED USE AS FDA CLEARED SURGICAL MESHES	54
10.4	PRINCIPLES OF OPERATION AND TECHNOLOGICAL CHARACTERISTICS	57
10.5	CS DEVICE SAFETY PROFILE IS COMPARABLE TO ITS PREDICATE SURGICAL MESHES	59

LIST OF APPENDICES

- A – JBJS Article
- B – Data used for Cleared Surgical Meshes
- C – Substantial Equivalence Table
- D – Predicate Device Labeling
- E – Dr. Tillman Letter
- F – Draft Instructions for Use for CS
- G – Immunology Report
- H – Patient Accountability Table for Chronic CS Patients
- I – Line Listing of Tissue Loss/Gain
- J – Reoperations
- K – Serious Adverse Event Tables
- L – Device Related Adverse Event Tables
- M – Non- serious Adverse Event Tables
- N – All Adverse Event Tables
- O – Explant Narratives
- P – Diagram Showing Mesh Placement in Shoulder vs. Meniscus
- Q – Risks Associated with Predicate Meshes

LIST OF ATTACHMENTS

- A – Volume I [redacted] Appendices A-J)
- B – Volume II [redacted] (Appendices K-W)
- C [redacted] Additional Information Response [redacted]
- D – May 19, 2008 Communication to Dr. Daniel Schul [redacted]

**SCREENING CHECKLIST
FOR ALL PREMARKET NOTIFICATION [510(k)] SUBMISSIONS**

510(k) Number: _____

The cover letter clearly identifies the type of 510(k) submission as (**Check the appropriate box**):

- Special 510(k) Do Sections 1 and 2
- Abbreviated 510(k) Do Sections 1, 3 and 4
- Traditional 510(k) or no identification provided Do Sections 1 and 4

Section 1: Required Elements for All Types of 510(k) submissions:

	Present or Not Applicable	Inadequate or Missing
Cover letter, containing the elements listed on page 3-2 of the Premarket Notification [510] Manual.	YES, see Cover Letter	
Table of Contents.	YES	
Truthful and Accurate Statement.	YES, see Section 4.0	
Device's Trade Name, Device's Classification Name and Establishment Registration Number.	YES, see Cover Letter	
Device Classification Regulation Number and Regulatory Status (Class I, Class II, Class III or Unclassified).	YES, see Cover Letter	
Proposed labeling including the material listed on page 3-4 of the Premarket Notification [510] Manual.	YES, see Section 6.0	
Statement of Indication for Use that is on a separate page in the premarket submission.	YES, see Section 2.0	
Substantial Equivalence Comparison, including comparisons of the new device with the predicate in areas that are listed on page 3-4 of the Premarket Notification [510] Manual.	YES, see Section 10.0	
510(k) Summary or 510(k) Statement.	YES, see Section 3.0	
Description of the device (or modification of the device) including diagrams, engineering drawings, photographs or service manuals.	YES, see Section 5.0	
Identification of legally marketed predicate device.*	YES, Cover Letter and Section 10.0	

CONFIDENTIAL

	Present or Not Applicable	Inadequate or Missing
Compliance with performance standards.* [See Section 514 of the Act and 21 CFR 807.87 (d).]	N/A	
Class III Certification and Summary. **	N/A	
Financial Certification or Disclosure Statement for 510(k) notifications with a clinical study. * [See 21 CFR 807.87 (i)]	N/A	
510(k) Kit Certification.***	N/A	

* May not be applicable for Special 510(k)s.

** Required for Class III devices, only.

*** See pages 3-12 and 3-13 in the Premarket Notification [510] Manual and the Convenience Kits Interim Regulatory Guidance.

Section 4: Additional Requirements for ABBREVIATED and TRADITIONAL 510(k) submissions (If Applicable):

	Present or Not Applicable	Inadequate or Missing
a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation:	YES, See Section 8.0	
b) Sterilization and expiration dating information:	YES, See Section 7.0	
i) sterilization process	See Section 7.1	
ii) validation method of sterilization process	See Section 7.2	
iii) SAL	See Section 7.1	
iv) packaging	See Section 6.1	
v) specify pyrogen free	See Section 7.3	
vi) ETO residues	N/A	
vii) radiation dose	See Section 7.1	
c) Software Documentation:	N/A	

Items with checks in the "Present but Deficient" column require additional information from the sponsor. Items with checks in the "Missing" column must be submitted before the substantive review of the document.

Passed Screening _____ Yes _____ No

Reviewer: _____

Concurrence by Review Branch: _____

Date: _____

CONFIDENTIAL

1.0 EXECUTIVE SUMMARY

This Executive Summary was prepared and is being provided in consideration of the Food and Drug Administration ("FDA" or "the Agency") guidance document entitled *Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s.* 



1.1 Objectives



1.2 Background

1.2.1 The Device

The ReGen Collagen Scaffold (CS) is a resorbable collagen-based surgical mesh composed primarily of bovine type I collagen. Like predicate surgical meshes, it serves to reinforce damaged or weakened soft tissue and provides a resorbable scaffold for replacement by the patient's own soft tissue. The CS is not a prosthetic device and it is not intended to replace normal body structures or functions.

The device is provided in a semi-lunar shape which is intended for use in the meniscus. In each instance, the surgeon assesses the defect and trims the device to the size necessary for repair of the damaged or weakened soft tissue in the meniscus. The device is designed to be sutured in place through a minimally invasive arthroscopic procedure to reinforce a defect in the human meniscus, thus

¹ ODE and OIVD, CDRH. *Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s.* August 12, 2005. <<http://www.fda.gov/cdrh/ode/guidance/1567.html>>.

decreasing the amount of trimming and shaping required by the surgeon at the time of surgery. This is not unlike the pre-shaped three dimensional configuration of the Cook Fistula Plug, the strand configuration of the Cook SIS Facial Implant, or the pre-configured meshes used in specific types of hernia repair (such as for inguinal or paraesophageal hernia repair). Furthermore, their use of the CS in the meniscus is similar to other devices cleared by FDA for use in meniscus repair.

In repairing and reinforcing meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh and must have a chronic meniscus injury (one to three prior surgical treatments to the involved meniscus). 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. Neither its labeling nor indications for use suggest the device should be used to replace healthy tissue or tissue that can be repaired.

Simply put, a partial meniscectomy, the standard of care for meniscus injuries, would be performed whether or not the CS device is used. Because the CS provides reinforcement of the meniscal horns, which are typically removed during surgery, the horns do not have to be removed as part of the partial meniscectomy, allowing the surgeon to leave more structurally important native tissue.

The CS device for use in the meniscus has historically been referred to as the Collagen Meniscus Implant (CMI). For consistency throughout this submission, the device will be referred to as the CS.

1.2.2 Regulatory History

The CS, referred to as the Collagen Meniscus Implant, or (CMI) has been the subject of a randomized clinical trial conducted under an FDA-approved investigational device exemption [redacted] the CS was the subject [redacted]

[redacted]

The clinical data presented in [redacted] and included patients with acute injuries to the involved meniscus combined with patients with chronic injuries to the meniscus (one to three prior surgical treatments). These clinical data supported substantial equivalence of the CS to predicate devices in terms of safety and effectiveness by showing a statistically significant increase in tissue surface area in patients receiving the CS,

[redacted]

[redacted] and no difference in types or incidence of adverse events or complications as compared to predicate devices. T [redacted]

[redacted] as been provided for ease of review as [redacted]

[REDACTED]
[REDACTED] s that this submission presents clinical data on the study arm for patients with chronic meniscus injuries. This submission provides appropriate clinical data, from a peer reviewed publication, to support the proposed intended use of the surgical mesh for the chronic patient population (Appendix A).

1.3 Basis for Substantial Equivalence

The ReGen CS has the same intended use and similar technological characteristics to predicate surgical mesh devices, including the following:

- Restore Orthobiologic Implant (K031969, K001738 and K982330);
- SIS Fistula Plug (K050337);
- TissueMend, OrthoMend (K031188 and K051766);
- Surgisis Mesh (K974540, K980431, K992159, K034039);
- BioBlanket Surgical Mesh (K043259 and K041923);
- ZCR Patch, Permacol (K992556, K013625, K021056, K043366, K050355);
- IMMIX Film (K024199 and K032673);
- SIS Plastic Surgery Matrix (K034039)
- Sportmesh (K052830)
- Optimesh (K014200)
- Marlex Mesh (Pre-amendment).

The proposed indication for use statement for the ReGen CS is as follows:

[REDACTED]

Surgical mesh is intended for use to reinforce soft tissue where weakness exists. Specific soft tissue indications throughout the body for surgical meshes have been cleared by the Agency. The surgical mesh category includes devices that are indicated to seal or reduce air leaks in the lungs (K961440), treat urinary incontinence (K992159), provide a bridging material to obtain the desired surgical result in the repair of hernias or other fascial defects (K024199), provide a resorbable tissue scaffold for rotator cuff repair (K031969), provide a plug for anal and rectal fistulas (K050337) and to provide a means for containing bone graft material in vertebral body defects in the spine (K014200). All of these devices expanded the indications within the intended use set forth in the surgical mesh classification, each having no prior predicate with the same indication. Each was found SE based on addressing safety and effectiveness through bench testing, animal data and sometimes limited clinical data (See **Appendix B** for a discussion of the type of data provided for other cleared surgical meshes with new indications for use). Importantly what made each of these meshes substantially equivalent to their predicates is that each had the same intended use, not the same indication for use, as its predicates.

As a result, none of these so called “new” surgical meshes was found substantially equivalent based on the specific indications for use, each of which differed from their predicates. Although each device’s indications related to a specific anatomic site not common with its predicate, the broad surgical mesh intended use, and not the intended anatomic site of the new device, defined the 510(k) review. In this context, all of the safety and effectiveness questions were the same. In other words, a surgical mesh in the meniscus is no more distant from its predicate than a surgical mesh indicated for use in an anal fistula, the spine, a rotator cuff, or in lung repair. All of these uses employ surgical mesh and that is what they have in common with their predicates. FDA must compare the meniscus indication to its predicates in the same manner as the Agency compared other new indications for surgical mesh to legally marketed devices.

CONFIDENTIAL

The regulatory standard for substantial equivalence requires that the device be compared to a legally marketed predicate device. Risk benefit assessments in the context of premarket notifications are inherent in the statutorily defined comparison to determine substantial equivalence. Specifically, the risk/benefit comparison between new devices and their predicates is determined by the statutory definition of substantial equivalence, i.e., "new" devices must have the same intended uses and technologies, or differing technologies that have equivalent safety and effectiveness, as their predicate devices. By definition, therefore, if they are equivalent in these respects, they have equivalent risk benefit profiles.

ReGen has provided extensive data supporting the substantial equivalence of the CS to predicate surgical meshes, as well as the safety and effectiveness of its CS mesh for use in the meniscus. These data far exceed the amount and type of data provided by the sponsors of predicate meshes identified by ReGen, to support their respective premarket notifications (**Appendix B**). Testing of the CS in canine models demonstrates that the matrix is biocompatible and is replaced by the animals' own tissue. Extensive clinical experience in humans, in which relook arthroscopies and biopsies were performed, confirm the conclusions from the canine studies, that the device reinforces meniscus defects and provides an absorbable scaffold for replacement by the patient's own tissue.

In evaluating the use of surgical mesh in the meniscus, a review was undertaken of the risks associated with the general use of surgical mesh for the previously cleared indications, as well as those associated with the use of the CS in the meniscus. This evaluation included data from the following sources:

[REDACTED] published data. It was clear from these comparisons that the complications associated with the use of the CS in the meniscus are the same as those associated with other surgical mesh soft tissue indications and no new types of safety or effectiveness questions are raised. In addition, the rates of complications and reintervention were comparable to those of predicate surgical meshes.

The company's bench testing, animal studies and human clinical trials establish the substantial equivalence of the device. A table that summarizes the substantial equivalence based on intended use, materials, technological characteristics and performance data of the CS in comparison with the predicate devices is included as **Appendix C**.

In addition to demonstrating substantial equivalence of the CS to predicate surgical meshes, the data from a controlled multicenter clinical trial on patients with chronic meniscus injuries show that at approximately 5 years post-implantation CS patients experience statistically significant improvements in pain, function (Lysholm), self-assessment, satisfaction and activity level (Tegner) from their preoperative status. These patients have the additional clinical benefit of a statistically significant increase in tissue within the meniscal defect. Furthermore, though not required for a substantial equivalence determination, these CS patients with chronic meniscus injuries have statistically superior clinical outcomes to partial meniscectomy patients in regaining lost activity levels and requiring fewer reoperations related to meniscus symptoms.

The extensive clinical data on patients with chronic meniscus injuries demonstrate that the CS device has a safety profile comparable to partial meniscectomy even though the CS patients in the trial had an additional relook surgery and biopsy that the partial meniscectomy patients did not. This is surprising because partial meniscectomy does not involve a relook surgery or the use of an implant or suturing but merely excises the damaged tissue and makes no attempt to treat the permanent loss of meniscus tissue. The placement of all surgical meshes is additive to the complications associated with surgery alone (e.g., partial meniscectomy) and this fact is supported by the complications noted in the labeling of predicate devices (**Appendix D**).

1.4 Regulatory Precedents

The Food and Drug Modernization Act of 1997 ("FDAMA") amended the Act to require that the Agency employ the "least burdensome" means of bringing new devices to market. In considering the least burdensome regulatory pathway to market for the CS, ReGen thoroughly researched precedents to identify the relevant FDA requirements that the Agency has applied to devices presenting similar safety and effectiveness issues.

FDA has cleared numerous 510(k)s for resorbable implanted surgical mesh devices that are used in multiple medical specialties, including general surgery and orthopedics, for the same intended use as the CS, i.e., to reinforce and repair soft tissue, and with similar technological characteristics. The legally marketed predicate devices that are cited in the 510(k) are classified under Class II Surgical Mesh (21 CFR 878.3300). This classification regulation describes surgical mesh as "a metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists." These devices are class II, subject to the 510(k) requirements. Over time, FDA has cleared numerous devices under this classification regulation with varying specific indications for use statements and with materials other than metallic or polymeric screens.

Although not cited as predicates for this device, the Agency has also cleared absorbable and non-absorbable meniscus repair devices (darts, arrows and all-inside devices) for use in repair of the meniscus. These devices are regulated in Class II under 21 CFR 888.3030, *Single/multiple component metallic bone fixation appliances and accessories*. These meniscus repair devices were found SE to metal bone plates and screws, and are more distant from their predicates than any surgical mesh, including the CS, from its respective predicates. While the intended use of these devices may differ from the CS, there are similarities to the CS with respect to the use of absorbable implants to repair the meniscus in the articulation of knee. In addition there is similarity in the treatment goals of both devices to conserve tissue within the meniscus.

Furthermore, bone void filler devices and dental bone grafting material have characteristics and functions similar to surgical meshes, like the CS, and these type of devices are classified into Class II. Both bone void fillers and dental bone graft fillers are subject to

Class II Special Controls Guidance Documents. These guidances identify criteria for clearance (e.g., composition, material properties, performance testing, biocompatibility, etc.), many of which are common to the surgical mesh submissions cleared by FDA in the past. The classification of these types of devices and surgical mesh demonstrate that Class II controls are adequate to provide reasonable assurance of safety and effectiveness. Bone void fillers have the same breadth of use as surgical meshes including as “a resorbable implant intended to fill bony voids or gaps of the extremities, spine, and pelvis that are caused by trauma or surgery and are not intrinsic to the stability of the bony structure” (21 CFR 888.3045).

In sum, FDA understands that collagen-based products may be readily controlled in Class II to ensure safety and effectiveness. In other words, collagen-based scaffolds used in the meniscus and intra-articular space of the knee can be controlled in Class II. Use of Class II devices within the meniscus and in the articulation of the knee is not new to the FDA, as demonstrated by meniscus repair devices cleared by the Agency.

1.5 Conclusion

The CS is substantially equivalent to other legally marketed class II surgical mesh devices cleared for use in various medical applications. It has similar composition, technological characteristics and intended use of cleared predicate surgical mesh devices

The indication for use of the CS in the treatment of meniscus injuries presents no new types of safety and effectiveness questions as demonstrated by bench testing, animal studies, extensive clinical data and a review of adverse events associated with the use of the device compared to known complications associated with its predicates. Class II special controls have been used in the regulation of other devices intended for use in the meniscus, as well as devices used to fill voids or defects in orthopedic and dental applications. The CS, therefore, should be classified as a surgical mesh under 21 CFR 878.3300, and regulated by Class II controls, which will provide reasonable assurance of safety and effectiveness.

In addition to the demonstration of substantial equivalence, data reported in the peer reviewed literature from well controlled clinical studies has been presented which demonstrates that the CS has a serious adverse event rate that is not statistically different from that of partial meniscectomy, a surgical procedure that does not involve the use of an implant and does not treat the permanent loss of meniscus tissue. This evidence also

demonstrates that CS patients with chronic meniscus injuries experience statistically significant improvements in pain, function (Lysholm) and self-assessment from their preoperative status. Use in this patient population also shows superiority to partial meniscectomy in regaining lost activity levels and fewer reoperations related to meniscus symptoms.

2.0 INDICATIONS FOR USE

510(k) Number (if known): _____ Device Name: ReGen Collagen Scaffold
(CS)



Prescription Use _____
(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 IF
NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Page 1 of ____

CONFIDENTIAL

3.0 510(K) SUMMARY FOR COLLAGEN SCAFFOLD (CS)

Submission Prepared: July 22, 2008

Applicant Information

John DiChiara
Senior Vice President
Regulatory, Clinical, and Quality
ReGen Biologics, Inc.
411 Hackensack Avenue, 10th floor
Hackensack, NJ 07601

Device Information

Device Name: ReGen Collagen Scaffold (CS)
Common Name: Surgical Mesh
Classification Name: Surgical Mesh, 21 CFR 878.3300
Classification Code: FTM
Reviewing Panel: Orthopedic Devices

Predicate Devices

- Restore Orthobiologic Implant, DePuy Orthopaedics, Inc. (K031969, K001738 and K982330);
- SIS Fistula Plug, Cook Biotech, Inc. (K050337);
- TissueMend, OrthoMend, TEI Biosciences, Inc. (K031188 and K051766);
- Surgisis Mesh, Cook Biotech, Inc. (K974540, K980431, K992159, K034039);
- BioBlanket Surgical Mesh, Kensey Nash, Corp. (K043259 and K041923);
- ZCR Patch, Permacol, Tissue Science Laboratories PLC (K992556, K013625, K021056, K043366, K050355);
- IMMIX Film, OsteoBiologics, Inc. (K024199 and K032673);
- SIS Plastic Surgery Matrix, Cook Biotech, Inc. (K034039);

CONFIDENTIAL

- Sportmesh, Artimplant (K052830);
- Optimesh, Spineology, Inc. (K014200);
- Marlex Mesh, Davol, Inc. (Pre-amendment).

Device Description

The ReGen Collagen Scaffold (CS) is a resorbable collagen matrix comprised primarily of bovine type I collagen. The CS is provided in a semi-lunar shape with a triangular cross section to be used to reinforce weakened meniscal soft tissue and provide a resorbable scaffold that is replaced by the patient's own tissue. The surgeon trims the device to the size necessary for repair of the damaged or weakened soft tissue.

Intended Use



Substantial Equivalence

The ReGen Biologics Collagen Scaffold (CS) has the same intended use and similar technological characteristics to the predicate surgical mesh devices, including; the DePuy Restore® Orthobiologic Soft Tissue Implant (K982330, K001738, K031969), the Cook Biotech SIS Fistula Plug (K050337), the TEI Biosciences TissueMend and OrthoMend (K031188, K051766), the Cook Biotech Surgisis Mesh, the Kensey Nash BioBlanket™ Surgical Mesh (K043259, K041923), the Tissue Sciences Laboratories' Permacol and ZCR Patch (K992556, K013625, K021056, K043366, K050355), the Organogenesis CuffPatch (K042809), the Cook Biotech SIS Plastic Surgery Matrix (K034039), the Artimplant Sportmesh (K052830) and the Spineology Optimesh (K014200). The device has been shown to be as safe and effective for its use in the meniscus as predicate surgical meshes for their cleared indication. Any differences identified have been shown to not raise new types of safety or effectiveness questions. The questions common to all resorbable surgical meshes have been addressed in this submission by biomechanical, biocompatibility, animal testing, as well as clinical experience with the device. Safety of the CS for use in the meniscus has been demonstrated through peer reviewed literature reporting extensive clinical data allowing comparison of use of the device to predicate surgical meshes used in other anatomic locations and to partial meniscectomy.

Conclusion

The CS device has the same intended use, comparable materials of composition and technological characteristics as its predicates; therefore, it is SE to those predicate devices.

4.0 TRUTHFUL AND ACCURATE STATEMENT

As Required per 21 CFR 807.87(k)

I certify that, in my capacity as Senior Vice President of ReGen Biologics, I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.

John Dichiara

CONFIDENTIAL

5.0 DEVICE DESCRIPTION

5.1 Device Name and Overview

The ReGen Collagen Scaffold (CS) is a resorbable collagen-based surgical mesh composed primarily of bovine type I collage. Like predicate surgical meshes, it serves to reinforce damaged or weakened soft tissue and provides a resorbable scaffold for replacement by the patient's own soft tissue. The CS is not a prosthetic device and it is not intended to replace normal body structure or function.

The device is provided in a semi-lunar shape which is intended for use in the meniscus. The semi-lunar meniscus configuration is sutured in place through a minimally invasive arthroscopic procedure. The surgeon trims the device to the size necessary for repair of the damaged or weakened meniscal soft tissue.

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. Neither its labeling nor indications for use suggest the device should be used to replace healthy tissue or tissue that can be repaired. Simply put, a partial meniscectomy, the standard of care for these injuries, would be performed whether or not the CS device is used. 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.

5.2 Material Components

The data regarding material components of the CS was presented in premarket notification K063827 on pages 14 and 15. A complete study report on GAG concentration was presented in Appendix E of K063827. The letters of access to the device master files for chondroitin sulfate and sodium hyaluronate are included in Appendix F of K063827. A copy of this premarket notification is included as **Attachment A** to this premarket notification.

5.3 Product Characterization

5.2.1 Physical Dimensions

This information was presented on (**Attachment A**). Please note that the flat sheet configuration for K063827 is not being pursued in this submission.

5.2.2 Physical Characteristics

This information was previously presented on
(Attachment A).



5.4 Drawings of Device

Representative device drawings were previously provided on pages 16 and 17 of K063827
(Attachment A).



ReGen seeks clearance of the semi-lunar Configuration of the CS
mesh intended for use in the meniscus.

5.5 Device Manufacturing

Information regarding device manufacturing was previously presented on
(Attachment A).



6.0 PROPOSED LABELING, PACKAGING

6.1 Packaging and Shelf Life

Information regarding packaging and shelf life for the CS device was included on [REDACTED]
[REDACTED] The shelf life test report was included in [REDACTED]
premarket notification is included as **Attachment A** to this submission.

6.2 Draft Package Label

A sample package label was included in [REDACTED]
(**Attachment A**).

6.3 Instructions for Use

The draft Instructions for Use are included in **Appendix F**.

7.0 STERILIZATION INFORMATION

7.1 Method of Sterilization

This information was provided on Attachment A).

7.2 Validation Method

This information was provided on Attachment A).

7.3 Virus Inactivation

Data regarding virus inactivation was presented on page
Complete study reports were included in Attachment A).

8.0 BIOCOMPATIBILITY TESTING

Biocompatibility testing was summarized on [REDACTED] [REDACTED] Biocompatibility test reports were included in [REDACTED] Attachment B).

Formaldehyde residual testing and genotoxicity testing were included in [REDACTED] the [REDACTED] additional information submission [REDACTED] is submission is included as Attachment C.

USP Heavy Metal testing results were presented in Appendix J of [REDACTED] additional information submission [REDACTED] This submission is included as Attachment C.

8.1 Specification for Lead

8.2 Report on Humoral Immune Testing in U.S. IDE Multicenter Clinical Trial

This study examined sera from subjects in a multicenter clinical trial (MCT) of the Collagen Meniscus Implant (CMI), conducted under [REDACTED] for antibodies against the CS. The study was completed by an independent laboratory at the University of Arizona College of Medicine. The MCT included a 1:1 randomization to a control group (partial meniscectomy only, no CS placement) or to the CS treatment group. Serological follow-up of subjects was for 12 months post-surgery. The protocol excluded subjects

CONFIDENTIAL

previously exposed to CS or collagen. Sera were collected at the investigational sites, frozen and shipped directly to the laboratory where they were assayed in an ELISA modified for human immunoglobulin detection using CS as the antigen. The laboratory was blinded to the treatment group at the time of assay.

The results demonstrated no significant differences between the control and CS treated groups that could not be accounted for by normal assay variability. There was no evidence of significant antibody formation to the CS. Analysis of results from individual subjects demonstrated few with elevated antibody levels in this assay. Of the individuals having reactive sera, some were in the control group and some in the CS treatment group. In addition, the clinical course of subjects with the highest levels of antibody reactivity against the CS using ELISA was normal, with the individuals showing no evidence of a significant inflammatory response or impaired healing.

The results indicate that there were no relevant elevations of antibodies against CS in treated subjects and there was no evidence of clinically significant humoral immunity to the implant.

A complete report of the results of this study appears in **Appendix G**.

9.0 PERFORMANCE TESTING

This information was previously presented on [REDACTED] (Attachment A).

9.1 Biomechanical Testing

9.1.1 Suture Retention Strength in Range of Predicate Devices

This testing was discussed on page [REDACTED]. The complete test report was presented in [REDACTED] (Attachment B).

9.1.2 Tensile Testing

Tensile testing was discussed on [REDACTED]. The complete test report was provided in [REDACTED] (Attachment B).

9.1.3 CS Can Withstand Functional Demands of the Knee

[REDACTED]

Like predicate resorbable surgical meshes, the CS is not intended to function as a prosthetic meniscus and therefore is not designed to have the mechanical strength of the native human tissue. Each of these devices, including the CS, is a scaffold that is designed to be resorbable and to be replaced by the patient's own tissue. As such, the mechanical properties of the device are only relevant at the time of initial implantation because over time the mechanical properties of the construct change as tissue fills the scaffold, the scaffold resorbs and the tissue remodels. Therefore, the only way to assess the ability of the CS to withstand the mechanical forces of the knee is through animal testing and human clinical studies.

To serve as a template for new tissue formation, the CS is a porous scaffold that may only be attached to an intact meniscus rim with intact anterior and posterior horns. It is the intact meniscus rim and horns that continue to distribute load within the joint while new tissue replaces the scaffold. The CS alone is not a substitute for meniscus tissue or function, and therefore should not be compared to meniscus tissue. During the first 6 months following implantation, the patient's activity level is restricted to reduce the stress on the mesh-reinforced meniscus, and to allow tissue in-growth and maturation to take place.

The mechanical strength of the CS is within the range of the predicate resorbable scaffolds which are designed for the same purposes of soft tissue repair and reinforcement. These scaffolds are similarly sutured to soft tissue defects, including use in orthopedic applications (e.g., the shoulder where the primary forces are an order of magnitude higher than in the knee).

The CS has been validated for use in the knee through animal testing presented in this and previous submissions and extensive clinical experience, having shown adequate mechanical strength to remain in place while providing a template for new tissue formation. Results from 141 relook arthroscopies performed in the IDE Study and detailed histological evaluation of biopsies from 135 patients have shown that the CS functions adequately to remain attached to the host rim and provide a scaffold that results in a significant increase in tissue within the meniscal defect.

The Company has presented clinical data to show that the device has adequate strength to remain adhered to the host tissue, by the fact that [REDACTED] as a result of mechanical failure. Ultimately, the clinical data proves that the device has sufficient strength to function as a surgical mesh and the feasibility data show that the resulting tissue maintains its volume even past 6 years based on a second relook arthroscopy procedure.⁴ While not all patients in the trial have the same amount of tissue filling the meniscal defect, the device still allows the surgeon to preserve more of the native meniscal horns and provides a mean increase in meniscus tissue volume of [REDACTED] for all patients in the study and [REDACTED] increase for patients with chronic meniscus injuries.

9.2 Biomechanics of the Meniscus

9.2.1 Introduction

The ability of a resorbable mesh to function adequately to reinforce soft tissue and provide a scaffold for new tissue growth is dependent on its ability to remain adequately adhered to the host tissue and resist the forces exerted on it. In the section above, we discussed the suture retention strength as a primary factor in assessing this ability. This section describes the forces to which the CS is subjected, bench testing performed to demonstrate that the CS provides initial reinforcement of the defect repair, and how forces on a surgical mesh within the meniscus are no greater, and likely less, than those on a surgical mesh used in the shoulder, another articulating joint.

9.2.2 CS Provides Reinforcement of the Meniscus

These issues were discussed on [REDACTED] Attachment A).

9.2.3 Tensile Stress is Key Force in the Meniscus

These issues were discussed on [REDACTED] Attachment A).

9.2.4 Bench Testing Demonstrates CS Provides Reinforcement

These issues were discussed on [redacted] (Attachment A).

9.2.5 Bench Testing Demonstrates CS Provides Reinforcement

Bench testing was described on [redacted] (Attachment A).

9.2.6 Tensile Forces in the Shoulder: Same or Greater than in the Meniscus

This information was provided on [redacted]
(Attachments A and B).

9.2.7 Surgical Techniques are Similar in the Shoulder and Meniscus

This information was provided on [redacted] detailed diagrams
were provided in [redacted] (Attachments A and B).

9.2.8 Summary: Mesh Used Similarly in the Shoulder and Meniscus

This discussion appeared [redacted] (Attachment A).

9.3 Animal Testing

9.3.1 Canine Study

A discussion of the canine study was presented on [redacted] A
full technical report appears in [redacted] (Attachment B).

9.3.2 Canine Study to Evaluate Strength of CS Over Time: Suture Pull-Out

A discussion of this testing appears on [redacted] full technical
report was provided in [redacted] (Attachment B).

9.4 Clinical Experience

9.4.1 Introduction

Clinical experience with the CS for use in the reinforcement and repair of soft
tissue injuries of the meniscus is available from a number of sources as follows:

1. An IDE Multicenter Clinical Study (Multicenter Safety and Effectiveness Study of the Collagen Meniscus Implant) with two arms, one each for patients with acute and chronic meniscus injuries – which has been audited and certified by an independent third party [redacted] Four analyses of the study are presented in this submission, as follows:
 - a. An analysis representing data pooled from both the chronic and acute arms is presented to demonstrate the effectiveness of the CS in serving as a scaffold for growth of the patient's own tissue and to assess overall safety of the device.
 - b. An analysis of data from patients in the CS group of the chronic study arm is presented to demonstrate the clinical benefit of the device through a comparison of clinical outcomes pre-operatively and 4.9 years post-operatively
 - c. Published results (**Appendix A**) comparing patients in the CS group and partial meniscectomy control group in the chronic arm of the IDE multicenter clinical study are presented. The data demonstrates clinical superiority to partial meniscectomy in certain outcomes measures.
 - d. An analysis of adverse event data from the chronic arm of the IDE study demonstrates the overall safety of use of the CS in the chronic patient population.
2. Feasibility Study – single center published results^{3,4}
3. Published results from a case study on four patients from Europe by Reguzzoni et al.⁵
4. Published results from a case study on two patients from Europe by Ronga et al.⁶

These clinical data are consistent with the conclusions from the bench testing and animal studies that the device is biocompatible, resorbable, provides a scaffold for tissue growth, and that there are no adverse effects on the joint attributable to the device. Furthermore, the risks and complications associated with the use of the CS include those associated with any surgical procedure and placement of surgical

² Study conducted under IDE # G920211 – Certification Letter included in Attachment A.

³ Rodkey, WG, Steadman, JR, Li ST. 1999. A clinical study of collagen meniscus implants to restore the injured meniscus. *Clin Orthopedics* 367: S281-S292

⁴ Steadman JR, Rodkey W. 2005. Tissue-engineered collagen meniscus implants: 5 to 6 year feasibility study results. *Journal of Arthroscopic and Related Surgery* 21: 515-525.

⁵ Reguzzoni M, Manelli A, Ronga M, Raspanti M, Grassi F. 2005. Histology and ultra structure of a tissue-engineered collagen meniscus before and after implantation. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* 74B: 808-816.

⁶ Ronga M, Bulgheroni P, Manelli A, Genovese E, Grassi F, Cherubino P. 2003. Short-term evaluation of collagen meniscus implants by MRI and morphological analysis. *Journal of Orthopaedics and Traumatology* 4:5-10.

mesh for the various cleared indications; there were no reported adverse events that occurred in the IDE study related to the device or device placement that were of a different type than those that have been reported for other surgical meshes. Patients with chronic meniscus injuries benefit from the use of the device by statistically significant improvements from pre-operative levels in pain, function (Lysholm), self-assessment, satisfaction, and activity levels. In addition, CS treated patients had a statistically significant increase in tissue volume in the meniscus. Chronic patients have the added benefit of superiority to partial meniscectomy in regaining lost activity level and reduced reoperations related to meniscus symptoms.

9.4.2 IDE Multicenter Clinical Study (MCT) – Introduction

ReGen Biologics is conducting a long-term randomized, controlled clinical trial of the Collagen Meniscus Implant under [REDACTED]. Enrollment is complete and follow-up information continues to be collected in order to obtain long-term data on clinical outcomes of the device through seven years. The CMI and CS devices are identical in terms of physical and chemical characteristics. The data from this IDE study is applicable to the function of the CS as a surgical mesh because the hypothesis in the IDE states that the device functions to repair the damaged meniscus and provides a resorbable scaffold for replacement by the patient's own tissue. This is the same assumption as is made by the proposed indication for the CS in this 510(k) submission.

Under [REDACTED] patients were enrolled into an acute treatment arm (no previous surgeries to the involved meniscus – protocol 9601) or a chronic treatment arm (1 to 3 previous surgeries to the involved meniscus – protocol 9602). The mean patient follow-up of this study is 4.9 years. The IDE study was designed as two separately controlled and randomized study arms. Analysis of data from the chronic treatment arm was therefore built into the study design, and did not result from a systematic analysis leading to the identification of a chronic patient population. This design also lends itself to allow pooled analyses of the acute and chronic arms because the two treatment arms differed only in terms of whether the patient underwent previous meniscus surgery. The following sections provide results from safety and effectiveness analyses of the data from the pooled patient populations (acute and chronic arms) which was presented in [REDACTED] [REDACTED] as well as analyses focusing on data from the chronic study arm which were recently reported in a peer reviewed scientific journal (Appendix A).

The pooled data from the acute and chronic study arms was initially presented in [REDACTED]

These data demonstrated the safety and effectiveness of the device by showing a

statistically significant increase in tissue surface area in patients receiving the CS, no difference in safety performance between the CS treatment group and partial meniscectomy control group, no difference in types or incidence of adverse events or complications as compared to predicate devices and clinical benefit in improved clinical outcomes from pre-operative to post-operative status.

The recently published data from the chronic treatment arm demonstrate that patients receiving the CS had the same benefits noted above for the pooled patient population and in addition showed superiority to partial meniscectomy in regaining lost activity levels and requiring significantly fewer reoperations related to meniscus symptoms. This publication and the additional safety and effectiveness data provided in this submission form the basis for the substantial equivalence of the CS device to predicate surgical meshes for the indication for use in patients with chronic meniscus injuries.

9.4.4.1 IDE MCT – Pooled Data on Acute and Chronic Patients

Clinical data from 162 patients receiving the device, with a mean follow-up of 4.9 years, confirm the findings from ReGen's bench and animal studies that the CS has sufficient mechanical strength to remain in place and serve as an effective scaffold for growth of the patient's own tissue. Results from this clinical study included observations on 141 patients at re-look arthroscopy at approximately 12 months that showed patients had a mean gain of [redacted] in tissue surface area due to device placement, and in [redacted] of evaluable biopsies, extracellular matrix organization was seen. Clinical data from both published studies and a US Multicenter Clinical Trial indicate that neither the device itself nor the resultant new tissue causes any damage to the joint or the apposing articular surfaces. The CS has the same intended use and technology as predicate surgical meshes and has been demonstrated to be as safe and effective for its indication for use; it is therefore substantially equivalent to its predicates.

A comprehensive discussion of the clinical data on the pooled patient population of acute and chronic patients appears on pages [redacted]

[redacted] Copies of the relook arthroscopy results appear in [redacted]. A copy of the report on histological evaluation appears in [redacted]. Copies of the tables on additional histological results appear in [redacted]. Copies of the tables on adverse events appear in [redacted]. This premarket notification is included as **Attachments A and B**.

Additional information regarding adverse events for the combined acute and chronic patients was presented in Appendix C of the [redacted]. This submission also contains a line listing of tissue loss/gain for the combined populations (Appendix E); histology

report (Appendix F); narratives for patient explants (Appendix G); and a line listing of all adverse events for both groups. This amendment is included as **Attachment C** to this submission.

Additional discussion of the clinical data regarding the pooled population was also included in a May 19, 2008 submission to the Agency. This submission is included as **Attachment D** to this submission.

9.4.4.2 IDE MCT - Clinical Benefit Seen for Patients with Chronic Meniscal Injuries

Data analysis was performed to assess patients in the chronic study arm of [redacted] who had one to three prior surgeries to the involved meniscus and received the CS device. There were a total of 87 patients who were consented and treated under the study protocol and received the CS device. Two of these patients were later found to have received more than three surgeries to the involved meniscus; however, they were included in this analysis for completeness. **Appendix H** shows the patient accountability for the analyses in this section of the document.

Enrollment is complete and follow-up information continues to be collected in order to obtain long-term data on clinical outcomes of the device through seven years. Data regarding clinical endpoints of pain (VAS score at three levels of activity), function (Lysholm score), self-assessment, Tegner score (a measure of activity), and satisfaction were collected at physical visits through the 2 year post-operative time point, and via questionnaire at time points from 3-7 years. The mean term of follow-up for these patients was approximately 4.9 years.

The potential clinical benefit of the CS in this patient population was analyzed by comparing the pre-operative data regarding the variables listed above to the data collected at the longest follow-up time period. The differences between the mean pre-operative and post-operative values are presented, along with their statistical significance.

9.4.4.2.1 Pain

Subjects were asked to rate their pain level during the previous 48 hours on a visual analog scale (VAS) under three conditions: 1) during the highest level of activity; 2) during routine activities of daily living; and 3) at rest. The scale was the standard 100 mm VAS scale, where the left side (minimum 0 mm) corresponded with no pain and the right side (maximum 100 mm) corresponded with the worst possible pain.

For analysis purposes a composite pain score was derived by combining the values from the three separate conditions noted above.

Figure 2 below presents the mean composite pain score for the chronic CS patients at the pre-operative time point, the mean composite score at longest follow-up, the difference between those score, and the p-value for this difference.

Figure 2. Comparison of Pain at Pre-operative and Longest Follow-up

Group	Mean Pain Score Pre-operative	Mean Pain Score Longest Follow-up	Change in VAS Mean Pain	p-Value
Chronic CS N=87	[Redacted] N=86	[Redacted] N=77	[Redacted] N=76	[Redacted]

This data shows that the CS patients experienced a clinical benefit of decreased pain in the operative knee at the longest follow-up time point. This reduction in pain is statistically significant at th [Redacted]

9.4.4.2.2. Knee Function (Lysholm Score)

Subjects were asked to rate knee function in specific categories using the Lysholm scale. This validated scoring system, based on subscale weights published by Tegner and Lysholm (1985), has eight domains (subscales) and an overall score calculated as the sum of the domains. Each domain contributes to the overall score; however, the weight of each domain ranges from maximal 5 to 25 points. The maximum overall score ranges from 0 – 100, with 0 representing the worst possible knee function, and 100 representing the best possible knee function.

Figure 3 below presents the mean Lysholm score for the chronic CS patients at the pre-operative time point, the mean Lysholm score at longest follow-up, and the difference between those scores, and the p-value for this difference.

Figure 3. Comparison of Lysholm score at Pre-operative and Longest Follow-up

Group	Mean Lysholm Score Pre-operative	Mean Lysholm Score Longest Follow-up	Change in Lysholm at longest follow-up	p-Value
Chronic CMI N=87	[Redacted] N=87	[Redacted] N=77	[Redacted] N=77	[Redacted]

At their longest term follow-up, the chronic CS patients experienced a clinical benefit of improved knee function as demonstrated by a statistically significant increase in function from their pre-operative status as measured by the Lysholm scale.

9.4.4.2.3 Patient Satisfaction

Patient satisfaction was measured by asking patients how satisfied they would be if they had to live with the current condition of their knee for the rest of their lives. The response choices were very dissatisfied, somewhat dissatisfied, neutral, somewhat satisfied, or very satisfied. This evaluation provided patients the opportunity to assess their overall level of satisfaction prior to treatment, and to assess the outcome after meniscal treatment.

At the pre-operative time point [redacted] of chronic CS patients were very dissatisfied or somewhat dissatisfied with the condition of their knee. Only [redacted] were somewhat satisfied at the pre-operative time point. At the longest-term follow-up, the number of patients who were satisfied or somewhat satisfied had increased to [redacted] and the number of cases somewhat or very dissatisfied had decreased to [redacted].

This change in satisfaction for the chronic CS cases is statistically significant at the [redacted] level. More patients felt satisfied with the condition of their knee after the use of the CS than before.

9.4.4.2.4 Tegner Activity Level

The Tegner activity scale has been the most widely used activity scoring system for patients with knee disorders and has been validated for use in patients with meniscus injuries.^{7,8,9,10} It is a numerical scale ranging from 0 to 10. Each value indicates the ability to perform specific activities. An activity level of 10 corresponds to participation in competitive sports; an activity level of 6 points corresponds to participation in recreational sports;

⁷ Paxton EW, Fithian DC, Stone ML, Silva P. The reliability and validity of kneespecific and general health instruments in assessing acute patellar dislocation outcomes. *Am J Sports Med.* 2003;31:487-92.

⁸ Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res.* 1985;198:43-9.

⁹ Marx RG, Stump TJ, Jones EC, Wickiewicz TL, Warren RF. Development and evaluation of an activity rating scale for disorders of the knee. *Am J Sports Med.* 2001;29:213-8.

¹⁰ Briggs, KK, Mininder SK, Rodkey, WG, Steadman, JR. Reliability, Validity, and Responsiveness of the Lysholm Knee Score and Tegner Activity Scales for Patients with Meniscal Injury of the Knee. *JBJS.* 2006; 88A:698-705

and an activity level of 0 is assigned if a person is on sick leave or receiving a disability because of knee problems.

Tegner activity scores were obtained pre-injury (retrospectively, on the basis of patient recall), preoperatively, and postoperatively. Thus, we could calculate the percentage of the lost activity level that was regained as a result of the treatment intervention. This measurement is the Tegner index, and it normalizes the return to activity across a diverse patient population. For example, a Tegner index of 1.0 indicates that the patient regained 100% (all) of the activity level that had been lost as a result of the injury, whereas a Tegner index of 0.25 shows that the patient regained only 25% of lost activity.

Figure 4. Change in Tegner Activity Level (Pre-operative to Longest Follow-up)

Group	Pre-Injury Tegner Activity Level	Pre-operative Tegner Activity Level	Longest Term Follow-up Tegner Activity Level	Longest Term Follow-up Tegner Index
Chronic CS N=87	[redacted]	[redacted] N=87	[redacted] N=77	[redacted] N=74

At the longest term follow-up chronic patients who received the CS regained [redacted] of their lost activity level. This gain from pre-operative is statistically significant with a p-value of [redacted]. Chronic CS patients therefore saw a clinical benefit of increased activity as compared to their pre-operative activity level.¹¹

9.4.4.2.5 Patient Self-Assessment

Patients were asked to rate their knee function at the pre-operative visit, and at subsequent follow-up visits. The response choices were “normal”,

¹¹ In the JBJS article, the Tegner index was used, not the raw Tegner scores because the Tegner index normalizes return to activity across a patient population of the type we report here. However, in a recent publication³ the standard error of the measurement was 0.4, and the minimum detectable change with a 95% confidence interval was 1.0 for meniscus lesions. Therefore, any changes in raw Tegner scores from preoperative to post intervention with a change equal to or greater than 1.0 can be considered detectable by the instrument and not due to error. Although “clinical significance” of the Tegner index has not been reported in the literature, the data from this study show that patients in the CMI treatment group regained significantly more of their lost activity than did patients in the control group, and therefore returned closer to their pre-injury activity levels. This finding is statistically significant and has obvious clinical merit as the raw change score from pre-op is 1.4.

“nearly normal”, “abnormal”, and “severely abnormal”. At the pre-operative time point [redacted] of patients rated their knee as normal or nearly normal, while [redacted] of patients rated their knee as abnormal or severely abnormal. It should be noted that this is a group of patients with chronic knee injuries – it is possible that they have grown to accept the level of impaired function in their knee as normal or nearly normal.

At the longest term follow-up [redacted] of patients felt their knee was normal or nearly normal, while the number of cases who felt their knee was abnormal or severely abnormal had decreased to [redacted]. This change in self-assessment was statistically significant with a p-value of [redacted].

9.4.4.2.6 Re-Look Arthroscopy Results – Tissue Gain

The mean percentage meniscal loss for the 87 patients in the chronic group who received the CS was [redacted]. At the one year time point, [redacted] chronic CS cases [redacted] underwent protocol required second look arthroscopy for the purpose of evaluating the CS and the surrounding joint space. At this relook procedure, surgeons documented that the CS patients had a mean total meniscus tissue surface area of [redacted] of native meniscus. This would mean a gain in tissue surface area of [redacted] relative to the [redacted] of meniscal tissue remaining at the time of implantation. (Figure 5 below)

Figure 5. Tissue Gain

Initial Surgery		Relook Surgery		
N	% Meniscus Remaining (SD)	N	% Total Tissue (SD)	% Tissue Gain
87	[redacted]	76	[redacted]	[redacted]

A line listing of all chronic CS cases that indicates percent meniscus loss at time of device placement, percent of defect filled, and total meniscal tissue is included as **Appendix I**.

9.4.4.2.7 Conclusions – Clinical Benefit

Like predicate resorbable surgical meshes, the CS device reinforces the soft tissue defect in the meniscus and provides a scaffold that results in a statistically significant increase in tissue within the meniscus defect. In addition to this increased tissue, patients with chronic meniscus injuries who received the CS device showed improved clinical outcomes as demonstrated by statistically significant improvement from their pre-operative status in pain, function, self-assessment, satisfaction and activity level at a mean of 4.9 years.

9.4.4.3 Published Results on Patients with Chronic Meniscus Injuries - Demonstrating Clinical Superiority

Published results of the outcomes associated with the use of the CS in ReGen's IDE study appear in the July 2008 edition of the *Journal of Bone and Joint Surgery* (Appendix A). This article corroborates ReGen's assessment of the data and discusses the superior clinical outcomes observed in patients with chronic meniscal injury who have received the CS device versus patients who have received partial meniscectomy alone. This section of the 510(k) will refer to this article.

9.4.4.3.1 Overview

Both the CS implantation and control procedures were performed through the use of minimally invasive arthroscopic surgery. As described in the JBJS publication, the postoperative rehabilitation program was specific to each treatment group, with control patients prescribed standard physical therapy and CS patients receiving a brace and undergoing more prescribed rehabilitation protocol for up to six months.¹²

The mean duration of follow-up was 59 months (range, 16 to 92 months). Repeat arthroscopies at one year post-implantation on the CS patients demonstrated that the CS device resulted in a significant increase in total tissue within the meniscal defects for all CS patients. In addition, the chronic injury CS patients regained significantly more of their lost activity level and experienced significantly fewer non-protocol required reoperations related to meniscus symptoms than the partial meniscectomy control group.

¹² While the rehabilitation protocols were different, these differences were not expected to have a profound effect on the two or five-year results reported. As stated in the AI response dated March 26, 2007, greater pain and more limited knee function was seen early (up to six months) in the CS group due to surgery associated with device placement and restriction of activity per protocol, but no differences were evident beyond 6 months. Thus, it was concluded that the initial differences in rehabilitation had no effects on the long-term outcomes.

The Chronic Study Arm includes a total of 156 patients¹³. There were 87 patients in the treatment group who had the CS sutured into the defect after partial meniscectomy, and 69 patients in the control group who did not receive the CS placement after partial meniscectomy. Two patients in the CS group were excluded from the data analysis because they had more than 3 prior surgeries to the involved meniscus leaving a total of 85 CS patients for analysis.

Baseline operative data indicate an average [redacted] meniscus tissue was removed during the partial meniscectomy in the CS patients, leaving [redacted] of their original meniscus surface area remaining. For the 69 control patients, the average amount of meniscus tissue removed in the partial meniscectomy procedure was [redacted] leaving [redacted] their original meniscus surface area remaining. Please refer to Figure 6.

Repeat arthroscopies at one year post-implantation on the CS patients demonstrated that the CS device resulted in a significant increase (97% gain) in total tissue within the meniscal defect. In addition, the chronic injury CS patients regained significantly more of their lost activity level and experienced significantly fewer non-protocol required reoperations related to meniscus symptoms than the partial meniscectomy control group.

9.4.4.3.2 Re-Look Arthroscopy Results – Tissue Gain

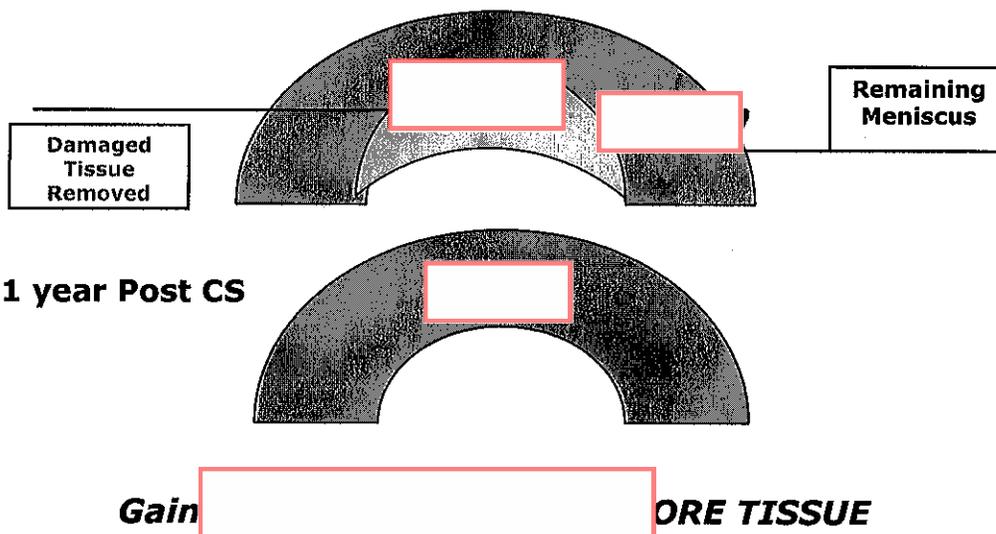
Of the 85 patients receiving the CS [redacted] underwent second-look arthroscopy at approximately 12 months for the purpose of evaluating the status of the CS and the surrounding joint space. The remaining [redacted] [redacted] were either lost to follow-up, explanted, or refused to allow the additional surgery. At the one-year relook, the surgeon documented that the CS patients had, on average, a total meniscus tissue surface area of [redacted] native meniscus, indicating a gain in tissue surface area [redacted] relative to the [redacted] original meniscus remaining at the time of CS placement). See Figure 6 below.



Figure 6. TISSUE GROWTH FOR CHRONIC PATIENT GROUP

Treatment	Initial Surgery		Relook Surgery		
	N	% Meniscus Remaining (SD)	N	% Total Tissue (SD)	% Tissue Gain
CS	85	[REDACTED]	76	[REDACTED]	[REDACTED]
Control	69	[REDACTED]	0	[REDACTED]	[REDACTED]

CS Patients after Partial Meniscectomy



Because the intended use of the CS as a resorbable surgical mesh is to reinforce the remaining meniscus and provide a scaffold for replacement by the patient's own tissue, these data clearly demonstrates that the device fulfills that function. In addition, the use of the CS generally allows the surgeon to preserve more of the meniscal horns than would be possible when performing a partial meniscectomy alone, because without the reinforcement of the CS, leaving the meniscal horns could cause further meniscal damage. The CS provides the same clinical benefit as any cleared predicate surgical mesh intended to reinforce and repair damaged soft tissue.

Appendix I presents a line-by-line listing of all patients with chronic injuries in the CS treatment group with the respective percent tissue loss and percent tissue remaining at baseline, as compared to the percent total tissue and percent tissue gain at 12 months. This listing shows that all patients in the chronic CS group experienced some tissue gain with the use

of the device. The majority of the patients experienced a substantial increase in tissue quantity which they would not have had with partial meniscectomy alone.¹⁴

9.4.4.3.3 Re-Look Arthroscopy Results – Evaluation of Chondral Surfaces

Surgeons were asked to evaluate the articular surfaces of the knee using the Outerbridge scale at the time of study surgery.^{15,16,17} The Outerbridge score ranges from 0 to 4, with 4 representing the most extensive damage to the articular surfaces. Surgeons were asked to repeat this evaluation at the time of the protocol required relook arthroscopy on the CS patients. At the index surgery, the mean Outerbridge score was [redacted] for the patients in the chronic group who received the CS device [redacted] for the controls in the chronic group. This difference was not significant.

At the time of the one-year relook arthroscopy, the mean Outerbridge score had improved to [redacted] for the patients in the chronic group who received the CS device. With the numbers studied, the slight improvement in the patients in the chronic CS group was not significant. Since the control patients did not undergo relook arthroscopy, similar comparisons were not possible. Articular cartilage changes following knee injury are progressive and the fact that there was no statistically significant difference in the mean Outerbridge scores supports the conclusion that surgeons did not report any damage to the joint as a result of CS placement in the 141 relook surgery patients. See Figure 7 below for Outerbridge scores.

Figure 7. Mean Outerbridge Scores for Chronic Patient Group

Treatment	Pre-operative	1 Year Relook Surgery
CS	[redacted]	[redacted]
Control	[redacted]	[redacted]

The data presented indicate that the CS device did not cause damage to the adjacent articular surfaces. A complication noted in the literature and labeling of cleared surgical meshes used in various types of soft tissue

¹⁴ See references 1-6 and 28-36 in JBJS publication included in **Appendix A**.

¹⁵ Baratz ME, Fu FH, Mengato R: Meniscal tears: The effect of meniscectomy and of repair on intraarticular contact areas and stress in the human knee. *Am J Sports Med* 1986; 14:270-275.

¹⁶ Hede A, Larsen E, Sandberg H: Partial versus total meniscectomy. A prospective, randomised study with long-term follow-up. *J Bone Joint Surg* 1992; 74B:118-121.

¹⁷ Andersson-Molina H, Karlsson H, Rockborn P: Arthroscopic partial and total meniscectomy: Long-term follow-up study with matched controls. *Arthroscopy* 2002; 18:183-189.

repair is damage to surrounding anatomic structures, specifically erosion, as a result of the use of the mesh.^{18,19,20,21}

9.4.4.3.4 Biopsy and Histology Results

Biopsy samples of tissue in the area where the CS was placed were obtained in 131 of the 141 patients undergoing re-look arthroscopy in both arms of the study. The remaining 10 patients did not have biopsies either because they refused them or because the surgeon was unable to obtain an adequate biopsy specimen. Needle biopsies were performed under direct visual observation using a 14 to 15 gauge soft tissue biopsy needle, yielding a specimen for examination of approximately 1.3mm in diameter and varying lengths.

Of 131 cases, all underwent histological evaluation; however [redacted] [redacted] CS and were therefore evaluated to determine the direct cellular response to CS placement. Histologic examination of a [redacted] lies in both chronic and acute CS patients showed evidence of infiltration of the pores within the CS with maturing connective tissue, best described as a fibrous connective tissue differentiating toward a fibrochondrocytic (meniscal-like) tissue. Most evaluable cases demonstrated some degree of CS assimilation into a newly developing fibrochondrocytic matrix. This assimilation was varied in type. Most often the CS became embedded in a benign fashion and was resorbed or assimilated without obvious surface cellular resorption. In some cases resorbing cells were noted on the surface of the CS.

When an interface between the CS and host meniscus rim could be identified, incorporation of the new tissue generated by the implant into the host tissue was consistently present and characterized by an angiogenic tract connecting the implant matrix into the host tissue. An incidental, rare finding was inflammation of the synovium in the biopsy specimen, but none of these cases were associated with any clinical findings of synovitis at the time of relook arthroscopy. There were no clinically relevant negative findings such as severe inflammation or a giant-cell response in any of the biopsy specimens examined. A complete report of the descriptive histology

¹⁸ Nygaard IE, McCreery R, Brubaker L, *et al.* Abdominal sacrocolpopexy: a comprehensive review. *Obstet Gynecol* 2004;101(4):805-23.

¹⁹ Amrute KV and Badlani GH. Female incontinence: a review of biomaterials and minimally invasive techniques. *Curr Opin Urol* 2006; 16(2):54-9.

²⁰ Griffith PS, Valenti V, Qurashi K, *et al.* Rejection of goretex mesh used in prosthetic cruroplasty: a case series. *Int J Surgery* 2008;6(2):106-9.

²¹ Riaz AA, Ismail M, Barsam A, *et al.* Mesh erosion into the bladder: a late complication of incisional hernia repair. A case report and review of the literature. *Hernia* 2004;8(2):158-9.

of evaluable specimens from all patients in the IDE study was included as [redacted] Attachment B).

With a combination of both new tissue ingrowth and new matrix production as a marker of success, the chronic patient population analyzed in the publication constituted [redacted] s. Ninety-seven percent of these cases were considered successes.

In summary, the second look arthroscopy and biopsy evaluations indicate that the CS provides a scaffold for meniscus-like matrix production by the host. There appeared to be no damage to the joint or adjacent articular surfaces attributed to the use of the device. Like predicate absorbable surgical meshes, tissue integrates into the device as the device is assimilated and resorbed. The lack of any clinically significant inflammatory reaction, and the presence of new tissue, indicate the CS is biocompatible in this location, and performs the function for which it was intended.

9.4.4.3.5. Tegner Activity Level

As stated previously in Section 9.4.4.2.4, the Tegner activity scale has been the most widely used activity scoring system for patients with knee disorders and has been validated for use in patients with meniscus injuries.^{22,23,24,25} It is a numerical scale ranging from 0 to 10. Each value indicates the ability to perform specific activities. An activity level of 10 corresponds to participation in competitive sports; an activity level of 6 points corresponds to participation in recreational sports; and an activity level of 0 is assigned if a person is on sick leave or receiving a disability because of knee problems.

Tegner activity scores were obtained pre-injury, preoperatively, and postoperatively. The pre-injury values were collected at the time of the initial patient screening. Thus, we could calculate the percentage of the lost activity level that was regained as a result of the treatment intervention.²⁶

²² Paxton EW, Fithian DC, Stone ML, Silva P. The reliability and validity of kneespecific and general health instruments in assessing acute patellar dislocation outcomes. *Am J Sports Med.* 2003;31:487-92.

²³ Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res.* 1985;198:43-9.

²⁴ Marx RG, Stump TJ, Jones EC, Wickiewicz TL, Warren RF. Development and evaluation of an activity rating scale for disorders of the knee. *Am J Sports Med.* 2001;29:213-8.

²⁵ Briggs, KK, Mininder SK, Rodkey, WG, Steadman, JR. Reliability, Validity, and Responsiveness of the Lysholm Knee Score and Tegner Activity Scales for Patients with Meniscal Injury of the Knee. *JBJS.* 2006; 88A:698-705

²⁶ Tegner Index = (Gain during study*) / (Loss due to Injury**)

* Gain during Study = (Tegner at time) - (Tegner at Pre-surgery)

** Loss due to Injury = (Tegner Pre-Injury) - Tegner at Pre-surgery)

This measurement is the Tegner index, and it normalizes the return to activity across a diverse patient population. For example, a Tegner index of 1.0 indicates that the patient regained 100% (all) of the activity level that had been lost as a result of the injury, whereas a Tegner index of 0.25 shows that the patient regained only 25% of lost activity.

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 pre-injury activity levels. The patients in the chronic group who had received a collagen meniscus implant regained, on the average, [redacted] of their lost activity level at nearly five years whereas the controls in the chronic group regained only [redacted]

As noted by the authors of the JBJS article, the possibility of recall bias associated with the scoring of pre-injury activity levels to calculate the Tegner Index exists; however, if patients overestimated their pre-injury activity level, in most instances this overestimation would have resulted in an underestimation of the Tegner Index. Furthermore, within this study, both the control and the CS patients would have had equal probabilities of experiencing any recall bias as this data was prospectively collected under the IDE study protocol. Additional support for lack of recall bias comes from the fact that the mean pre-injury Tegner Scores for both the CS and partial meniscectomy patients were essentially the same [redacted] or the CS patients and [redacted] (for the partial meniscectomy patients) indicating that the patient's recall of their pre-injury Tegner scores were essentially equivalent.

The authors of the JBJS publication believe that the benefits of being able to account for the pre-injury activity levels in the Tegner Index outweigh this potential weakness. It is very different for one patient to gain 3 points in activity level as a result of injury, when they have lost only 3 points and another to gain 3 points when they have lost 6. This sort of difference is accounted for with the Tegner Index. The fact that the paper was published with a discussion of this limitation indicates that the reviewers and editors of the *Journal of Bone and Joint Surgery* felt the use of the Tegner Index was a clinically acceptable method of reporting changes in activity level in this study.

²⁷ The 42% regain of activity level reported in the paper differs from the 39% regain reported in Section 9.4.4.2.4 due to two patients who were excluded from the analysis in the JBJS. One of these two patients was a protocol violation that was excluded because they had more than 3 surgeries to the involved meniscus. The other patient that was excluded is a patient who had an explant at 4 months. Data collected after the explantation was in the database and should not be used in calculating the Tegner, so it was excluded from this analysis.

9.4.4.3.6. Reoperation and Survival Rates

Reoperation and survival rates were determined through five years of follow-up. As described in Figure 1 of the JBJS paper the patient population excluded 5 of the 87 CS patients enrolled and treated under the protocol. This includes 2 patients who were protocol violations with more than 3 prior surgeries to the involved meniscus, 2 deaths and 1 early skin infection that tracked to the implant site and resulted in explantation at 3 weeks post implantation. In addition, 69 patients in the partial meniscectomy control group were included in the patient population for analysis.

The Kaplan-Meier method was used to analyze time to an endpoint to assess durability of the index surgical procedures, in this case reoperation. The Kaplan-Meier method estimates the probability of the proportion of patients with reoperations at a particular time. Because of the low number of patients with follow-up past five years, survival results were estimated at five years. Furthermore, five years was the average time for the clinical outcomes results reported in the article; hence, this fact was further reason to use five years as the cut-off for the survivorship analysis. Thus, the survivorship analysis included patients through their sixtieth month after their index surgery, but patients who were into their sixty-first month or greater were not included in this analysis.

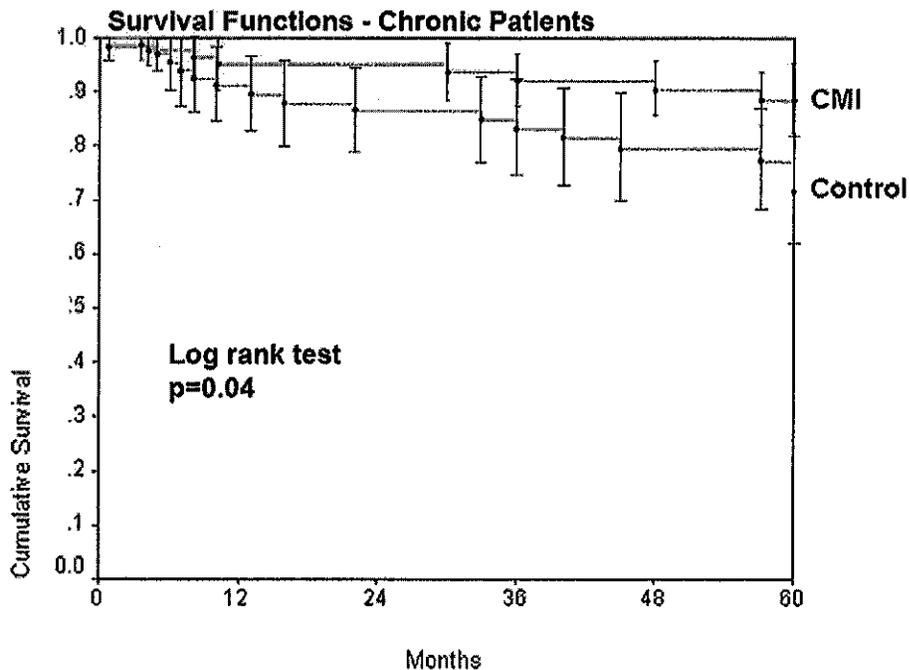
Because the study protocol required the CS patients to have an additional relook surgery and biopsy that was not required of the control group, it was necessary to develop, *a priori*, a scientifically valid analysis plan. As part of this plan, the authors therefore developed a clinically relevant definition of a reoperation. A reoperation was defined as an unplanned additional operation (outside of the protocol) on the study knee as a result of disabling or persistent pain and/or mechanical symptoms that could possibly involve the meniscus. A reoperation was performed when it was the surgeon-investigator's professional judgment that such an intervention at that time was in the patient's best interest.

Survivorship analysis was calculated to assess the durability of the result of the surgical procedure (CS implantation or partial meniscectomy). It was defined *a priori* as no unplanned (outside-the-protocol) second operation on the study knee as a result of disabling or persistent pain and/or mechanical symptoms that could possibly involve the meniscus. It is also important to realize that once a patient underwent a "reoperation" as defined above, that patient was eliminated from further consideration for survivorship. That is, for example, if a patient underwent a reoperation at eighteen months, they were considered a "non-survivor" or failure for the purpose of this analysis. Even if that same patient then underwent yet another reoperation at thirty

months, that reoperation would not have further effect on the survivorship analysis because that patient already was a “non-survivor”. Therefore, the survivorship analysis should not be confused with an overall reoperation rate.

In this study, chronic CS patients had about half as many unplanned reoperations on the involved knee as did the controls for disability or persistent pain and/or mechanical meniscus symptoms as noted above in the discussion of the survivorship analysis. The odds for the requirement of an additional such surgery within the survivorship analysis were 2.7 times greater for the controls than the chronic CS patients (95% confidence interval = 1.2 to 6.7; $p = 0.04$). The reoperation rate was 9.5% for the patients who had received a collagen meniscus implant and 22.7% for the control patients. At five years, with a reoperation as the end point, the survival rate was 89% for the patients who had received a collagen meniscus implant and 74% for the controls, which was a significant difference ($p = 0.04$). The Kaplan-Meier survivorship curve is presented in Figure 8.

Figure 8. Kaplan-Meier survivorship curve



[Redacted] includes all reoperations [Redacted]
[Redacted] y and biopsy) and
[Redacted] patients within the 152 patient cohort of patients with chronic meniscus

injuries through the 5 year time frame. The table lists the surgical procedures performed, the reason for surgery, the time point of surgery, whether the surgery was considered by the authors as a reoperation that met the definition previously stated and thereby included in the analysis as described in the publication, and a further explanation of why any surgery was included or excluded from being considered a reoperation. For example, certain findings noted at the time of the scheduled and protocol-required relook arthroscopy were incidental findings. In and of themselves, these findings did not equate to any or at least significant clinical findings that would have led the surgeon-investigator, in his professional judgment and in the patient's best interest, to have an additional surgical intervention. Therefore, such incidental findings would not/did not lead that patient to become classified as a "non-survivor" for the purpose of the survivorship analysis presented in the JBJS article.

It is especially noteworthy that although the CS patients were required to have relook arthroscopy with biopsy at one year, the reported non-protocol reoperations for the CS patients were a result of clinically significant pathology; hence, we do not believe that the protocol-required repeat arthroscopies biased the overall survivorship and reoperation rates. These findings from the survivor analysis based on reoperations suggest that in chronic patients the new CS-generated tissue appears to have replaced or reproduced at least some of the functions of the original meniscus tissue, and this new tissue, similar to the function of native meniscus tissue, may slow the progression of degenerative joint changes that otherwise would lead to decreased functional capacity and require further surgical intervention.

9.4.4.3.7. Pain

Subjects were asked to rate their pain level during the previous 48 hours on a visual analog scale (VAS) under three conditions: 1) during the highest level of activity; 2) during routine activities of daily living; and 3) at rest. The scale was the standard 100 mm VAS scale, where the left side (minimum 0 mm) corresponded with no pain and the right side (maximum 100 mm) corresponded with the worst possible pain. For analysis purposes a composite pain score was derived by combining the values from the three separate conditions noted above.

Based on the hypothesis in the publication, the study population for assessment of pain was all patients who had a minimum two year follow-up as of the date of database closure and excluded deaths and explants. This provided an available population for analysis of 66 CS patients and 57 partial meniscectomy controls.

Figure 9 summarizes the changes from baseline in the composite pain scores for both the CS treatment group and control group and the mean composite pain scores at the longest follow-up evaluations. There was no statistically significant difference between the CS and control patients for either measurement. Based on the superiority of the CS patients in regaining lost activity, it would appear that the control patients in the chronic group had to reduce their activity levels in order to maintain pain levels similar to those of the patients in the chronic group who had received a collagen meniscus implant.

Figure 9. Composite Pain Scores

	Change from Pre-op	Score at Last Follow-up
CS		
Control		
p-value		

9.4.4.3.8. Knee Function (Lysholm Knee Score)

Subjects were asked to rate knee function in specific categories using the Lysholm scale. This validated scoring system, based on subscale weights published by Tegner and Lysholm (1985), has eight domains (subscales) and an overall score calculated as the sum of the domains. Each domain contributes to the overall score; however, the weight of each domain ranges from maximal 5 to 25 points. The maximum overall score ranges from 0 – 100, with 0 representing the worst possible knee function, and 100 representing the best possible knee function.

Based on the hypothesis in the publication, the study population for assessment of Lysholm knee function was all patients who had a minimum two year follow-up as of the date of database closure and excluded deaths and explants. This provided an available population for analysis of 66 CS patients and 57 partial meniscectomy controls.

Data for assessment of knee function based on the Lysholm knee score for both the CS treatment group and control group are shown in **Figure 10**. The data show that there is no statistically significant difference between the CS patients and partial meniscectomy control patients in either the mean change from baseline or the mean score at longest follow-up.

Figure 10. Mean Lysholm Function Scores

	Change from Pre-op	Score at Last Follow-up
CS		
Control		
p-value		

9.4.4.3.9. Patient Satisfaction

Patient satisfaction was measured by asking patients how satisfied would they be if they had to live with the current condition of their knee. The response choices were very dissatisfied, somewhat dissatisfied, neutral, somewhat satisfied, or very satisfied. This evaluation provided patients the opportunity to assess their overall outcome after meniscal treatment.

In the chronic group, [redacted] of the patients treated with a collagen meniscus implant [redacted] the controls were very or somewhat satisfied with the outcome [redacted]. While [redacted] more of the CS patients than the control patients were satisfied with their clinical outcome following surgery, this difference is not statistically significant.

9.4.3.3.10. Safety – Published Results

Safety was assessed by an examination of serious or clinically relevant complications in the study knee that required some form of treatment. The severity of each event and whether it was related to the implant was determined

by the surgeon-investigator at the time of the report of the event. A serious or clinically relevant complication was identified in twelve patients (7.5%) who had received a collagen meniscus implant and eleven (7.3%) in the control group. Of the twelve documented serious complications in patients with a collagen meniscus implant, seven were classified as probably or at least possibly related to the collagen meniscus implant.

The rates of serious complications were essentially equal for the patients treated with the collagen meniscus implant and the control patients. Although seven of the twelve complications in the group with the collagen meniscus implant were classified as being probably or at least possibly related to the implant, it appears that placement of the collagen meniscus implant did not lead to any more serious complications than did partial meniscectomy, the current standard of care. We believe that this finding is noteworthy especially because the patients who had received a collagen meniscus implant were required to undergo a second surgical procedure with a biopsy of the meniscal tissue but the controls were not.

Safety of the device was also supported by the fact that there were no comments noted during any of the relook surgeries indicating that the chondral surfaces appeared to be damaged by the device or the new tissue resulting from the use of the device. No exuberant tissue growth was

observed in any of the 141 patients who had relook arthroscopies. Histologically there were no clinically relevant findings such as severe inflammation or giant cell response in any of the biopsy specimens examined.

A more comprehensive analysis of adverse events and safety is presented in Section 9.4.5 of this submission as this was not the primary focus of the publication.

9.4.4.3.11. Conclusions

The CS supports significant new tissue ingrowth that appears to be adequate to enhance meniscal function as evidenced by statistically significant improvements over partial meniscectomy in regaining lost activity (Tegner Index) and in the reoperations related to meniscus symptoms. The new tissue is stable and appears safe and biomechanically competent. Consistent with the data presented, the CS has the utility to reinforce and repair soft tissue defects of the meniscus and provide a suitable scaffold that is replaced by the patients own tissue resulting in improved clinical outcomes for patients with chronic meniscus injuries.

9.4.5 Safety Results – IDE Multi-Center Clinical Trial – Chronic Patient Population

Safety of the CS was monitored by the collection and analysis of adverse events reported by patients during physical examinations through the two-year follow-up. The protocol defined an adverse event very broadly. "...as any unintended or abnormal clinical observation that is not of benefit to the patient. This includes any event not present prior to exposure to study treatment or any event already present which worsens in either intensity or frequency following exposure." Note that this definition is quite broad and includes non knee-related events as well as knee-related events that would be viewed by a clinician as part of the normal post injury course for patients with meniscus injuries.

The protocol further defined a serious adverse event as an, "...event which is fatal, life-threatening, permanently disabling, unexpected, or results in hospitalization and is at least possibly related to study treatment." In addition to collecting specific adverse event information to 24 months, patients from 2-7 years post-operatively received a mailed questionnaire asking them to report on patient self assessed clinical outcomes and comments regarding their treatment. All patients were at a minimum of 2 years post-surgery with a mean follow-up of 4.9 years. Adverse events were reported and analyzed for the total number of patients enrolled in the chronic arm of the study (156 patients – 87 CSs and 69 controls) through the entire duration of follow-up for each patient. Note that for completeness, the two patients

excluded from effectiveness analyses due to having more than 3 prior surgeries to the involved meniscus have been included for the safety analysis.

9.4.5.1 Serious Adverse Events – IDE Multi-Center Clinical Trial - Chronic Patient Population

Overall [redacted] in the chronic arm of the study had adverse events designated as serious on the case report form. These included [redacted] in the CS group, and [redacted] in the control group. Serious adverse events that could be considered fatal, life-threatening or permanently disabling were reported for [redacted]. Two of these [redacted] unrelated to [redacted] developed a [redacted] most likely attributed to the surgery. The remaining adverse events included [redacted].

All of these are anticipated adverse events and consistent with the types of adverse events noted for cleared indications for surgical mesh.

There is no statistically significant difference at any time point in either the rate of serious adverse events (events per patient), or the percentage of patients experiencing serious adverse events. This is remarkable considering that the CS patients are being compared to a control of partial meniscectomy that did not involve the addition of an implant and were not subjected to the additional relook surgery and biopsy. Please refer to **Appendix K**, listing the incidence of patients with serious adverse events by post-operative time period, and by category.

In addition, the [redacted] device is within the range of complications reported in the literature for hernia mesh of 7% to 57% and for the reintervention rate (a subset of total complications) of 16% reported for the Restore device used in the shoulder.²⁸

²⁸ Heniford reported in 2003 that the patient complication rate for laproscopic ventral hernia repair ranged between 7% and 23% and for open ventral hernia repair the rates were 31% to 57%. Kingsworth reported a patient complication rate of 34.6% for hernia repair with polypropylene mesh. Malcarney reported in 2005 a reintervention rate of 16% following use of the Restore surgical mesh for rotator cuff repair.

Heniford BT, Park A, Ramshaw BJ, *et al.* Laparoscopic repair of ventral hernias: nine years' experience with 850 consecutive hernias *Ann Surgery* 2003 238(3):391-400.

Kingsnorth AN, Sivarajasingham N, Wong S, *et al* Open mesh repair of incisional hernias with significant loss of domain. *Ann R Coll Surg Engl* 2004; 86:363-6

9.4.5.2 Device Related Adverse Events

During the course of the clinical trial the treating physician was asked to evaluate the relationship of the device to the adverse event being reported. The physician could report that an event was “definitely”, “probably”, “possibly”, or “not related” to the device. If the physician was not able to make a determination, “unknown” could be entered.

9.4.5.2.1 Serious Device Related Adverse Events

[redacted] serious device related adverse events. [redacted]
[redacted] who experienced [redacted] of the serious events are those
patients who went on to have [redacted]. These patients are
listed below:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The other three patients reported [redacted]
[redacted] who experienced [redacted] The patient
[redacted] the second patient who

□



For purposes of substantial equivalence, the rate of serious device related adverse events can be compared to the complication rates reported in the literature for predicate surgical meshes used in other anatomic locations. [redacted]

[redacted] compares favorable with those reported for hernia mesh of 1% to 57% for hernia mesh and 16% for the Restore mesh used in shoulder repair.²⁶

9.4.5.2.2 Non-Serious Device Related Adverse Events

During the 24 month period of physical visits to the treating physicians, [redacted]

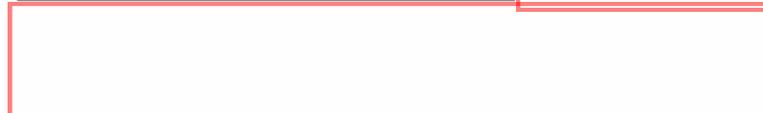


During the 24 month period, the following symptoms reported were most often noted to have some relationship to the device. [redacted]



[redacted] These events are similar to those seen with other surgical meshes.

At the greater than 24 month time period, [redacted]



These events are similar to those seen with other surgical meshes.

Because the definition of an adverse event in the IDE study includes any observation that is not of benefit to the patient, most events reported as non-serious would be considered by the surgeons to be expected as part of the post-operative course following meniscus surgery or ACL reconstruction. These non-serious events would not

be considered to be complications that would be reported in a scientific publication.

Please refer to **Appendix L** for a listing the incidence of patients with device-related adverse events by post-operative time period, and by category.

9.4.5.3 Non-serious Adverse Events – IDE Multi-Center Clinical Trial – Chronic Patient Population

Overall, a total of [REDACTED]

[REDACTED]

There was a [REDACTED]

[REDACTED]. This difference would be expected, given the definition of an AE and due to the difference in surgical procedures where the CS patients received a surgical mesh that required sutures, while the control patients underwent only partial meniscectomy. At the 24 month and greater than 24 month time point, the non-serious adverse event rate was statistically significantly higher for the control patients. This indicates that once the patients' healing period is completed and they are over any negative consequences associated with the one year relook and biopsy, they have a safety profile that is actually better than the standard of care treatment which is partial meniscectomy.

Overall, there was no statistically significant difference in the event rate, or the percent of patients experiencing non-serious adverse events. Please refer to **Appendix M**, listing the incidence of patients with non-serious adverse events by time period.

9.4.5.4 All Adverse Events – Chronic Patients

All adverse events include serious adverse events, non-serious adverse events, and those events where a serious/non-serious determination was not made by the treating physician. This lack of serious/non-serious determination generally occurred in situations where the adverse event was self-reported by the patient, and the physician did not have enough information to judge the seriousness of the event.

Overall [REDACTED]

[REDACTED] There is no statistically significant difference in [REDACTED]

terms of adverse event rate or the percent of patients experiencing adverse events overall.

At the 1-7 day time period and the 3 month time period [redacted]

[redacted] As previously noted, this is not unexpected given the more extensive nature of the operative intervention in the CS group. However, at the 24 month and greater than 24 month time periods, the adverse event rate for the control group is statistically significantly higher than the rate seen in the CS group. This indicates that the use of the CS does not appear to be related to any long-term clinical problems, and indicates no long term safety issues.

The fact that the long-term adverse event profile of the CS is better than that of partial meniscectomy could indicate an additional long term benefit associated with the use of the device and is consistent with the reoperation results presented in the JBJS publication.

Please refer to **Appendix N** for tables listing the incidence of patients with all adverse events.

9.4.5.5 Explants of the Device – Chronic Group

[redacted]
of the device as reported previously in Section 9.4.5.2.1, "Serious Device Related Adverse Events." In [redacted] the device was removed approximately three weeks after implantation [redacted]

[redacted] These explantations occurred at [redacted]

[redacted] the patient violated the rehabilitation protocol; in a [redacted] and in a [redacted]

[redacted] A summary of information on the explant patients in the chronic group appears in **Appendix O**.

The [redacted] reoperation rate reported in the survival analysis and the [redacted] explant rate are comparable to complication rates reported for surgical

meshes in other applications. Brockman, et al²⁹ reported early recurrence rates requiring reintervention after laparoscopic hernia repair from 3.4% to 15.7%. Malcarney, et al.³⁰ reported an explant rate of 16% in patients undergoing rotator cuff repair with the Restore device. Helton, et al.³¹ reported a ventral hernia recurrence rate of 9% using the Surgisis product. LeBlanc, et al.³² reported a recurrence rate of 6% for various types of surgical meshes in hernia repair. Heniford, et al.³³ reported a 4.7% recurrence rate for various types of surgical meshes used during laparoscopic repair of ventral hernias, and Lawson-Smith, et al.³⁴ reported a recurrence rate of 2.9% when using surgical mesh and fascia to repair incisional hernias.

As evidenced by the literature, the explant and reoperation rates of the CS are within the complication ranges reported for the cleared indications of predicate devices for various types of soft tissue repair.

9.4.5.6 Summary of Adverse Events

Overall, the type and extent of adverse events noted for the CS patients are similar to those for the control patients, when the difference in surgical mesh placement and the 12 month relook procedure and biopsy are considered. Serious adverse event rates are comparable at all time points, while non-serious and all adverse event rates are higher for the CS group at the 1-7 day and 3 month time period. This difference can be attributed to the difference in surgical procedure and rehabilitation for the two groups.

At longer time points (24 months, and greater than 24 months), there is a higher event rate in the control group. This would indicate that there are no significant long-term safety issues associated with the use of the CS. This is remarkable considering that partial meniscectomy does not involve the use of an implant, does not involve suturing of the meniscal defect but merely excises the damaged tissue, and does not treat the permanent loss of

²⁹ Brockman JB, Patterson NW and Richardson WS. Burst strength of laparoscopic and open hernia repair. *Surg. Endosc.* 2004;18: 536-539

³⁰ Malcarney H, Bonar F, Murrell G. Early inflammatory reaction after rotator cuff repair with a porcine small intestine submucosal implant. *American Journal of Sports Medicine* 2005;33:907-911.

³¹ Helton WS, Fisichella P, Berger R, Horgan S, Espat N, Abcarian H. Short-term outcomes with small intestinal submucosa for ventral abdominal hernia. *Archives of Surgery* 2005;140:549-562.

³² LeBlanc KA. Complications associated with the plug and patch method of inguinal herniorrhaphy. *Hernia* 2001;5:135-138.

³³ Heniford BT, Park A, Ramshaw B, Voeller G. Laparoscopic repair of ventral hernias: Nine year's experience with 850 consecutive hernias. *Annals of Surgery* 2003;238:391-400.

³⁴ Lawson-Smith MJ, Galland RB. Combined fascia and mesh repair of incisional hernias. *Hernia* 2006; [epub].

meniscus tissue associated with long term degenerative changes in the knee joint. This lower long-term adverse event rate for the CS patients is also consistent with the improved reoperation rate related to meniscus symptoms and indicates a positive safety profile for the device when used in patients with chronic meniscus injuries.

The types of adverse events noted are not unexpected, are consistent with those associated with the cleared indications for use of surgical mesh (**Appendix P**), and are described in the CS product labeling (**Appendix F**). The rate of serious adverse events is also comparable to complication rates reported in the literature for hernia mesh and shoulder mesh. In addition, the [redacted] is within the recurrence or reintervention rates reported for hernia mesh from 2.9% to 15.7% and for shoulder mesh reported at 16%.

9.4.6 Feasibility Study – Published Results

A clinical feasibility study under IDE G920211 was conducted at a single investigational site in 8 patients between the ages of 18 and 60 years old. The objectives of the feasibility study were to confirm that the device was implantable arthroscopically, that there were no significant adverse reactions associated with the use of the device, and that the device remained adequately attached to the host tissue to support host tissue growth.

Eight patients, coincidentally all of whom were male, were enrolled in the study. The average amount of meniscus loss was 62%. After surgery, subjects underwent a rehabilitation program that lasted 6 months. Clinical follow-up and blood collection were performed at 1, 6, and 12 weeks, and at 6 and 12 months. Six patients underwent a relook arthroscopy and biopsy at 6 months and two underwent these procedures at 12 months. The protocol was approved to extend the follow-up period to 6 years. MRIs were taken at 6 and 12 weeks, and at 6 and 12 months.

There were no significant complications attributed to the CS in any of the eight patients and no untoward effects on the joint as a result of the device or the tissue replacing it. One patient had an additional relook arthroscopy at 9 months to debride excessive scar tissue formation. All patients returned to activities of daily living by 3 months and were fully active by 6 months. By two years, all patients had improved Lysholm scores compared to their preoperative scores. Seven (7) patients had an improved Tegner score at 2 years. For patient self-assessment at 2 years, 5 patients rated their knees as improved compared with preoperatively.³⁵

³⁵ Refer to footnote 11

Immunology testing (ELISA assays) showed no significant increase in antibodies at any time point. Relook arthroscopy at 6 or 12 months follow-up revealed remodeled tissue in all patients. The average filling of the defect was estimated to be 77% at the time of the relook arthroscopy. Histologic analysis confirmed new fibrocartilage matrix formation. MRIs showed that the implant did not shrink and the decreasing signal intensity suggested that the new tissue was undergoing maturation.

All Feasibility Study patients returned for clinical, radiographic, magnetic resonance imaging, and arthroscopic examinations an average 5.8 years (range 5.5 to 6.3 years) after CS implantation.³⁶ Lysholm, Tegner, and patient satisfaction scores remained improved significantly compared to pre-operative values. From pre-operative to 5.8 years, pain scores were still improved, but had declined from the 1 and 2-year post-operative values. The meniscus-like tissue that developed in the scaffold presented no complications for more than 5 years. There were no signs of joint damage as a result of the treatment. The amount of the defect remaining filled was similar from the initial re-look at 6 to 12 months to the amount seen at the second re-look at a mean of 5.8 years post-operatively (77% vs. 69%). The hypothesis was affirmed that these patients significantly improved, on average, at 2 years compared to preoperative status, and remain improved at 5.8 years.

Copies of the referenced articles appeared in
(Attachment B).

9.4.3 Published Clinical Experience - Reports from Europe

Clinical experience with the CS used in the meniscus has been published by Reguzzoni et al.³⁷ and Ronga et al.³⁸ These reports are based on European clinical experience with the semi-lunar configuration of the CS device for use in the meniscus [referred to as the Collagen Meniscus Implant (CMI)].

Ronga and colleagues reported on two patients who received the CS and underwent biopsy via a second look arthroscopy at 6 months after implantation. MRI was performed prior to the second look arthroscopy at 6 months, and also at 12 months. Light microscopy and SEM were used to evaluate the 6 month biopsy specimens as compared to pre-implant CS devices.

³⁶ Refer to footnote 12

³⁷ Reguzzoni M, Manelli A, Ronga M, Raspanti M, Grassi F. 2005. Histology and ultrastructure of a tissue-engineered collagen meniscus before and after implantation. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* 74B: 808-816.

³⁸ Ronga M, Bulgheroni P, Manelli A, Genovese E, Grassi F, Cherubino P. 2003. Short-term evaluation of collagen meniscus implants by MRI and morphological analysis. *Journal of Orthopaedics and Traumatology* 4:5-10.

At the re-look arthroscopies, macroscopic examination demonstrated continuity of the CS with the native residual meniscus. The stability of the CS as well as tissue consistency similar to fibrocartilage were shown through probing the implant area. The biopsy specimens demonstrated invasion of the scaffold by connective tissue and blood vessels, indicating viable tissue, with the newly synthesized collagen fibrils clearly distinguishable from the pre-implant CS device. No phagocytomacrophagic cells or inflammatory reactions were observed within the implant. MRI findings confirmed CS biocompatibility, showed evidence of the evolution of the integration process between the CS and the host meniscal rim from 6 to 12 months, and evidenced changes over time that may reflect initial resorption of the device or further organization of new tissue within the scaffold.

Reguzzoni and co-authors published a case series in which the CS was implanted in four patients affected by traumatic irreparable tears of the posterior horn of the medial meniscus. All procedures were carried out arthroscopically. Patients had a mean age of 38 years. The meniscus tear was the sole intrarticular lesion detected, and the chondral surfaces of the medial compartment were intact.

The study included harvesting of biopsy specimens at 6 months after implantation of the CS. The biopsies were performed at the time of a re-look arthroscopy to evaluate the function of the device. No patients complained of pain or other symptoms in the operated knee. All patients were evaluated before CS surgery and at the time of biopsy with the use of the Lysholm score and Tegner activity scale.

No complications occurred in the postoperative period. All patients returned to activities of daily living by 3 months and were fully active at 6 months. The Lysholm score and Tegner activity scale increased in all operated knees during the 6 month follow-up period. At the re-look arthroscopy, meniscus-like tissue formation was noted and the CS was healed to the capsule and host meniscus rim. One implant showed a small area of fragmentation that did not require debridement. There were no signs of synovitis or damage to the joint or apposing cartilage surfaces at 6 months post-operatively.

Six months after implantation, light microscopic and SEM examinations revealed that the multi-lamellar structure typical of the CS scaffold is less evident due to tissue invasion into the pores of the scaffold. These pores were filled by connective tissue, where many cells, either spindle-shaped or round, were surrounded by newly formed extracellular matrix and blood vessels. No phagocytes were observed.

No adverse events occurred in this series of patients after CS implantation. The authors reported a general improvement in the clinical status postoperatively, but that this trend could also be related to the partial meniscectomy. At 6 months post-op, there was no damage to the apposing cartilage surfaces. The invasion of the

scaffold by fibroblast-like cells and connective tissue matrix, as well as the absence of phagocytes and macrophages, confirmed the biocompatibility of the CS. The authors concluded that the morphological findings of this case series demonstrate that the CS provides a three-dimensional scaffold for colonization by precursor cells and vessels leading to the formation of a fully functional tissue.

Both of these case study series provide evidence of active tissue replacement in the matrix and gradual resorption of the device. There were no histological signs of inflammatory response. MRI findings indicate integration of the device with host tissue and initial resorption of the device may occur between 6 and 12 months post-operatively. No adverse events were reported in the six patients. No damage to the joint or opposing articular surfaces was noted in relook arthroscopies. The findings are supportive of those from the animal studies.

Copies of the publications were included in [redacted] (Attachment B).

9.4.7 OUS Marketing Experience

The CMI, a product with similar shape but different indications and instructions for use from the CS, is currently approved and marketed in the [redacted]. In 2007 product distribution to [redacted]. As of September 200 [redacted] devices has been sold to ReGen's international distributor.

There have been [redacted] reported complaints involving a total of [redacted] devices [redacted]

9.4.8 Summary of Performance Testing

In summary, the data show that the CS demonstrates adequate strength for its intended use. Results of suture retention testing show the CS's strength is within the range of predicate surgical meshes, and similar to the Restore[®] and TissueMend[®] products, which are cleared for use in the shoulder and subjected to greater forces than those expected to be seen in the meniscus. Results of long-term animal testing (to 17 months) showed placement of the CS after resection of the dog meniscus resulted in tissue incorporation and subsequent tissue remodeling, and no failures occurred in this weight-bearing model. After 12 months post placement the remodeled tissue resembled the normal canine meniscus, and the junction between the CS and native meniscal rim generally could not be delineated.

Clinical data from 162 patients receiving the device, with a mean follow-up of 4.9 years, confirm the findings from ReGen's bench and animal studies that the CS has sufficient mechanical strength to remain in place and serve as an effective scaffold for growth of the patient's own tissue. Results from this clinical study included observations on 141 patients at re-look arthroscopy at approximately 12 months that showed patients had a mean gain of [redacted] in tissue surface area due to device placement, and in [redacted] of evaluable biopsies, extracellular matrix organization was seen. Clinical data from both published studies and a US Multicenter Clinical Trial indicate that neither the device itself nor the resultant new tissue causes any damage to the joint or the apposing articular surfaces. Therefore, the CS is as safe and effective as legally marketed surgical mesh predicates and raises no new types of safety or effectiveness questions when compared to those predicates with the same intended use, which is to reinforce soft tissue and provide a scaffold for replacement by the patient's own tissue.

The data presented shows that when used as a surgical mesh to reinforce and repair the meniscus in patients with chronic meniscus injury, the CS device provides patients with a statistically significant increase [redacted] in tissue within the meniscal defect. The patients also have statistically significant improvements from their pre-operative status in pain, function, self-assessment, satisfaction and activity level. In addition, the CS patients with chronic meniscus injuries experience statistically superior clinical outcomes to partial meniscectomy in regaining lost activity level and reducing the number of reoperations related to meniscus symptoms.

In summary, when used as a surgical mesh in patients with chronic meniscus injuries (one to three prior surgeries to the involved meniscus) the CS shows a positive safety profile.

10.0 SUBSTANTIAL EQUIVALENCE

A table summarizing the basis for the substantial equivalence of the CS to predicate devices is included as **Appendix C**.

10.1 Background

10.1.1 *Surgical Mesh Regulation*

Legally marketed surgical meshes are the predicate devices for the Collagen Scaffold (CS). The regulatory classification (21CFR§878.3300) describes a surgical mesh as “a metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists.” Initially surgical meshes were either metal or polymeric materials that were permanent implants; however, over the last decade many of the 510(k) cleared surgical meshes have been manufactured from absorbable materials.

The FDA has cleared the indications for use of the following two resorbable meshes:

- The Restore device (K031969, K001738 and K982330); and
- The TissueMend product (K031188 and K051766).

Labeling for these devices included the statement that they are: “...not intended to replace normal body structure or provide the full mechanical strength to repair (the defect)...the (implant) reinforces soft tissue and provides a resorbable (or remodelable) scaffold that is replaced by the patient’s own tissue.” This wording shows that these surgical meshes were intended to act as resorbable tissue scaffolds and not as permanent reinforcing meshes.

This description and intended use of these resorbable surgical meshes coincides with the description and intended use of the CS. Simply put, the CS is a similar surgical mesh to these other resorbable products that are for use in an articulating joint.

10.1.2 *Resorbable Surgical Mesh*

Initially soft tissue surgical mesh was constructed of non-absorbable polymeric materials. They were intended to be a permanent implant and add significant strength to weakened soft tissues. Clinically these materials were effective; however, they presented certain limitations, one of which was excessive stiffness either initially or after they were encapsulated by tissue. This stiffness resulted in surgical complications such as adhesions, erosion, restricted mobility and recurrence of the defects. Permanent synthetic implants also potentially act as a nidus for infection, and typically require removal to resolve the infection.

Resorbable materials were introduced to address these limitations. These materials did not have the inherent strength of the non-absorbable materials and they were not intended, "...to replace normal body structure or provide the full mechanical strength to repair..." the defect, as described in the Indications for Use for the DePuy and TEI Bioscience devices. These resorbable mesh devices are intended to, "...reinforce(s) soft tissue and provide a resorbable scaffold that is replaced by the patient's own soft tissue."

The clearance of resorbable meshes represented a clear shift from a non-absorbable, permanent device whose inherent properties were intended to provide permanent reinforcement to soft tissue defects. The resorbable soft tissue scaffolds had lower initial strengths but were designed to be replaced by the patient's own tissue during and after a period of restricted activity.

These resorbable scaffolds require sufficient strength to remain firmly attached to the host tissue and provide a stable environment for tissue growth and remodeling. They do not need the strength of the non-absorbable meshes because they are not intended to provide the full mechanical strength of the repair or to replace a normal body structure. While close tissue approximation is typically recommended as part of the surgical repair, it is not required and cannot be accomplished in many cases. These resorbable meshes are designed to bridge gaps in the tissue approximation and provide a scaffold for replacement by the patient's own tissue. It is that tissue which affects the repair and permanently reinforces the defect, not the mesh itself.

10.1.3. Soft Tissue Indications

From the initial indications of hernia repair and acetabular wall reconstruction, the Agency has cleared many products with specific indications for use under the general intended use of soft tissue reinforcement. The cleared indications for use of surgical mesh include:

- Achilles tendon;
- Anal fistulas;
- Biceps tendon;
- Bladder support;
- body wall defects;
- colon prolapse;
- enterocutaneous fistulas;
- facial defects;
- gastroenterological repair;
- lung resections;
- plastic & reconstructive procedures, including use in the face, head, neck;
- pubourethral support/urethral slings for treating urinary incontinence;
- treatment of Peyronie's disease;
- vertebral body of the spine.
- muscle flap reinforcement;
- patella tendon;
- pelvic floor reconstruction;
- quadriceps tendon;
- rectal fistulas;
- rotator cuff;
- sacrocolposuspension;
- soft tissue repair;
- suture line reinforcement;
- thoracic wall repair;

When focusing on each specific anatomic site or tissue there may be different questions that arise; however, when focusing on any one device's ability to fulfill the surgical mesh intended use to reinforce soft tissue, all of the pertinent safety and effectiveness questions are the same. In other words, a surgical mesh in the meniscus is no more distant from its predicate than a surgical mesh indicated for use in an anal fistula, the spine, a rotator cuff, or in lung repair. All of these uses are surgical mesh uses and that is what they have in common. FDA must compare the meniscus indication to its predicates in the same manner as the Agency managed comparisons between other new applications of surgical mesh and legally marketed devices. The company's bench testing, animal studies and human clinical trials support the safety and substantial equivalence of the device. They also support clinical outcomes benefits for the use of the device in patients with chronic meniscus injuries and a positive safety profile.

10.2 Predicate Devices

The following specific predicate devices are cited to establish the substantial equivalence of the CS based on intended use, technological characteristics and physical properties:

- Restore Orthobiologic Implant (K031969, K001738 and K982330);
- SIS Fistula Plug (K050337);
- TissueMend device (K031188 and K051766);
- Surgisis Mesh (K974540, K980431, K992159, K034039);
- BioBlanket Surgical Mesh (K043259 and K041923);
- ZCR Patch/Permacol (K992556, K013625, K021056, K043366, K050355);
- IMMIX Film (K024199 and K032673);
- SIS Plastic Surgery Matrix and SIS Facial Implant (K034039, K050246);
- Sportmesh (K052830)
- Optimesh (K014200)
- Marlex Mesh (pre-amendment).

A table summarizing the basis for the substantial of the CS to predicate devices is included as **Appendix C**.

10.3 The CS Has the Same Intended Use as FDA Cleared Surgical Meshes

The CS has the same intended use as the FDA cleared surgical meshes listed above. Like them, the CS is intended to reinforce soft tissue where weakness exists. Cleared surgical meshes perform this function in a number of ways. Some, like the Surgisis Mesh (K974540, K980431, K992159, K034039), the TissueMend device (K031188 and K051766) and the Restore implant (K031969, K001738 and K982330) reinforce the host tissue by being buttressed to the surface of tissue that is approximated. Some, reinforce by

bridging a gap or filling a void like the IMMIX device (K024199 and K032673), the SIS Fistula Plug (K050337), the SIS Plastic Surgery Matrix (K034039) and the Restore implant (K031969, K001738 and K982330). The CS device functions to reinforce soft tissue defects by both buttressing the remaining meniscus rim and horns, by bridging the gap between the meniscal rim and anterior and posterior horns and by filling the void left by the damaged meniscus tissue. All of this ultimately resulting in the CS providing a scaffold that is replaced by the patient's own tissue which serves to provide the long term reinforcement and repair of the meniscal defect.

The proposed instruction for use of the CS (**APPENDIX F**) includes the following Indications for Use statement:



The CS is not intended to replace a normal body structure or provide the full mechanical strength to repair the meniscus. The CS is sutured to the intact native meniscus which must be present for device use, and does not replace that structure or its function. The intact native meniscus rim, with or without the CS, continues to provide the biomechanical function of the meniscus in the knee by virtue of its mechanical integrity and anterior and posterior attachments. Once sutured to the meniscal rim, the CS functions to reinforce the remaining meniscal rim and anterior and posterior horns. In reinforcing the remaining meniscal rim, the CS allows the surgeon to preserve the anterior and posterior meniscal horns which are used as attachment points for the device. If the surgeon were to do a partial meniscectomy without the use of the CS device, he would have to remove the meniscal horns because without the reinforcement of the CS, the horns could get caught in the articulating joint and cause further damage to the native meniscus.

Use of the CS in the meniscus for filling a soft tissue defect is also similar to use of the Cook Biotech Fistula Plug (K050337) in treating anal, rectal and enterocutaneous fistulas by filling a soft tissue defect. The Fistula Plug is three dimensionally shaped to fit a fistula, just as the semi-lunar configuration of the CS is three dimensionally shaped to fit a defect in the meniscus. In the indication for fistula repair, the device is used to fill a defect or void in the natural body structure in the same way that the CS fills a defect or void in the meniscus created by partial meniscectomy performed to treat thinning, delamination or other damage to the meniscus. The Restore Device (K031969, K001738) is similarly used to fill a defect or void in the rotator cuff created by thinning or delamination of the tendon. In both cases, the devices are trimmed to size, sutured into the defect, and serve to reinforce the natural tissue structure. They also function as scaffolds to ultimately be replaced by the patient's own tissue which provides the long term reinforcement and repair of the defect by adding tissue volume to the thinned or deficient host tissue.

The CS bridges the gap between the meniscal rim and the anterior and posterior horns of the meniscus, like the IMMIX film which is indicated, "for the repair of hernia or other fascial defects that require the addition of a reinforcing, or bridging material to obtain the desired surgical result." Both devices function to reinforce the tissue defect by the addition of a scaffold that bridges the defect and is ultimately replaced by the patient's own tissue which functions to permanently reinforce the defect by replacing lost tissue volume.

In addition, the Agency has cleared surgical mesh for indications in plastic and reconstructive surgery of the face and head (ZCR Patch – K013625) and for soft tissue repair or reinforcement in plastic and reconstructive surgery (SIS Plastic Surgery Matrix – K034039 and SIS Facial Implant – K050246). This indication is for the filling of soft tissue defects (such as voids left due to trauma, scarring or tissue removal) and the devices provide minimal, if any, true biomechanical reinforcement other than to increase the tissue volume. The SIS Facial Implant is provided in a three dimensional strand configuration pre-attached to a trocar for ease of use. This is similar to the pre-configured three dimensional semi-lunar shape of the CS for ease of use in the meniscus.

Like the intended use of the DePuy Restore® Orthobiologic Soft Tissue Implant, the TEI Bioscience TissueMend, and the Artimplant Sportmesh, the CS is for reinforcement of soft tissue where weakness exists, and is not intended to replace normal body structure. All of these products are intended to provide a resorbable, or degradable, scaffold that is replaced by the patient's own tissue or is incorporated in the patient's own tissue. These predicates differ from the CS in that they are additionally indicated for use during rotator cuff surgery, as compared to the CS which is indicated for use during meniscus surgery.

Like the intended use of the Kensey Nash BioBlanket™, the CS is for the reinforcement and repair of soft tissue where weakness exists. While the CS is indicated for repair of meniscus defects, the Kensey Nash product also has indications of specific use for defects of the thoracic wall, muscle flap reinforcement, rectal and vaginal prolapse, reconstruction of the pelvic floor, suture line reinforcement, and for use during rotator cuff repair surgery.

While not a predicate, the Bionx Implant (K012334 and K955768), like the CS, is used for meniscus repair. The device is an absorbable polymeric material that is placed within the intra-articular space of the knee in the same manner as the CS device. These devices are regulated in Class II under 21 CFR 888.3030, *single/multiple component metallic bone fixation appliances and accessories*. These meniscus repair devices were found substantially equivalent to metal bone plates and screws, and are more distant from their predicates than any surgical mesh, including the CS, from its respective predicates. Both the Bionx Implant and the CS device function to repair damaged meniscus tissue with the goal of avoiding the permanent loss of meniscus tissue associated with the alternative surgical procedure which, in both cases, is partial meniscectomy. The Bionx Implant adds additional risks to the partial meniscectomy, including; infection, swelling, pain, effusions, numbness, and potential for damage to the adjacent articular surfaces. While the Bionx device had little, if any clinical data to support its safety at the time of clearance, the CS device has follow-up on approximately 170 patients in IDE clinical studies with mean follow-up of approximately 5 years.

In summary, with respect to intended use of the CS, no new issues of safety or effectiveness are raised in comparison to the predicate products when these devices are evaluated as surgical meshes. Specifically, when focusing on each different anatomic site or tissue there may be different questions that arise; however, when focusing on any one device's ability to fulfill the surgical mesh intended use to reinforce soft tissue, all of the pertinent types of safety and effectiveness questions are the same. In other words, a surgical mesh in the meniscus is no more distant from its predicate than a surgical mesh indicated for use in an anal fistula, a rotator cuff, or in lung repair. All of these uses are surgical mesh uses and that is what they have in common. FDA must compare the meniscus indication to its predicates in the same manner as the agency compared other new applications of surgical mesh to legally marketed devices. There are precedents for adding specific indications for surgical meshes based on availability of additional data, as evidenced by the new indications for the predicate products discussed. In addition, class II devices for meniscus repair have been cleared for use in the meniscus and pre-amendment use of surgical mesh in the intra-articular space of the knee has been documented.

10.4 Principles of Operation and Technological Characteristics

The CS is composed primarily of [redacted] similar to the porcine-derived collagen of the DePuy Restore® Implant, the cross-linked collagen of the Kensey Nash BioBlanket™, and the porcine-derived collagen of the Cook Biotech SIS Fistula Plug. Like the Cook Biotech product, the CS [redacted] [redacted] which are naturally occurring in the human body. Like the predicate devices, the CS is a biocompatible, sterile matrix that resorbs and is replaced by the patient's own tissue over time.

The CS product is [redacted]
[redacted]

Like the DePuy Restore product, the CS is [redacted] with a 3 dimensional micro-architecture. The DePuy product is available in a circular form with a nominal diameter of 63 mm, as compared to the semi-lunar shape of the CS product. The DePuy product is sterilized using electron beam irradiation as compared to gamma irradiated sterilization for the CS product. Both products are supplied in moisture resistant foil packaging and re-hydrated prior to use. Both can be trimmed to size for the target area, and are sutured into place.

Like the Kensey Nash BioBlanket, the CS is [redacted] available. The BioBlanket is supplied in sizes ranging to 5x10cm as compared to various sizes of the semi-lunar configuration for the CS. Both products are trimmed to the size needed and sutured into place and both are designed with a shape to accommodate the specific anatomic location.

Like the Cook Biotech SIS Fistula Plug, the CS is comprised of [redacted]. The SIS Fistula Plug is supplied in a three dimensional configuration for the specific application of filling a soft tissue defect (fistula), similar to the semi-lunar configuration in which the CS is available for meniscus use. The Cook product is EtO sterilized as compared to gamma irradiation of the CS product. Both products are rehydrated, trimmed as necessary to fill the defect, sutured into place, and remodeled by host tissue over time. Both the Cook product and the CS are manufactured in a pre-shaped configuration to fit the needs of the operating surgeon.

Like the Bionx Implants Meniscus Arrow™, the CS is comprised of material that is resorbed over time in the meniscus area. The Bionx product is comprised of a copolymer (poly-L/D-poly lactide) as compared to the collagen comprising the CS. Both devices provide temporary reinforcement of a defect in the meniscus while healing takes place and both devices are subjected to the same forces in the intra-articular space of the knee. Both devices have as their treatment goal to conserve tissue within the damaged or deficient meniscus.

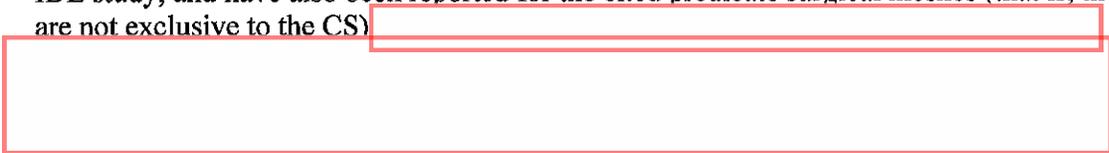
The CS for use in the meniscus and the DePuy, TEI Bioscience, and Artimplant devices for use in the repair of rotator cuff injuries are used in the same way to address the issues of surgical repair and tissue remodeling. All of these devices are used in articulating joints. In all cases the damaged tissue is thinned, delaminated or completely torn resulting in a gap and the frayed or damaged tissue is debrided or removed to prevent further damage to the remaining tissue. In the case of the rotator cuff, the standard surgical repair of the tear is undertaken, which involves suturing to secure the attachment of the tendon. In the case of the meniscus, the standard surgical technique is followed for treatment of an irreparable meniscus tear, which is a partial meniscectomy. The final step in both treatments is to trim the surgical mesh to fit the defect and suture it in place to allow integration and replacement by host tissue. Please refer to **Appendix P** for detailed diagrams showing this comparison.

In summary, based on the technological similarities of the CS to predicate devices, and supportive testing (please refer to **Section 9.0, Performance Testing**), the CS does not raise any new issues of safety or effectiveness which have not been addressed for its intended use. The extensive clinical performance data demonstrate that the CS maintains sufficient integrity as remodeling occurs, and provides reasonable assurance that the device is as safe and effective as legally marketed predicate devices for use for reinforcing or repairing soft tissue defects of the meniscus.

10.5 CS Device's Safety Profile is Comparable to its Predicate Surgical Meshes

The risks and potential complications of using the CS in the meniscus have been identified based on the clinical experience and monitoring of adverse events in a 313 patient IDE study with a mean follow-up of 4.9 years, with specific attention paid to those risks associated with use of the device in the study arm of this trial dealing with patients with chronic meniscus injuries. These risks were compared with those associated with use of predicate surgical meshes in other anatomical locations through an extensive review of predicate labeling, MDRs, and scientific publications (**Appendix Q**). The risks and complications associated with use of the CS include those associated with any surgical procedure and placement of surgical mesh for the various cleared indications; there were no reported adverse events that occurred during the IDE clinical study related to the device or device placement that were of a different type than those that have been reported for other surgical meshes.

The following complications listed include those associated with surgical procedures, in general, and those associated with placement of a surgical mesh in various anatomic locations. The complications marked with an asterisk were of the type reported during the IDE study, and have also been reported for the cited predicate surgical meshes (that is, they are not exclusive to the CS)



Complications associated with surgical mesh placement include [REDACTED]

[REDACTED] All of the complications identified above with an asterisk have been incorporated into device labeling, along with the other risks potentially associated with the CS for its intended use, based on clinical experience and risk analysis. See **Appendix F** - CS draft labeling designating these risks, and **Appendix Q** demonstrating that they are similar to the risks associated with a number of cleared surgical mesh devices. Furthermore, the [REDACTED] rate of serious device related adverse events for patients with chronic meniscus injuries is within the range of complications reported for predicate meshes in the hernia of 7% to 57% and for the reintervention rate in the Restore shoulder mesh of 16%.

Importantly, the level of risk associated with use of surgical mesh in the meniscus is lower than the risk seen in a number of other predicate mesh indications. This reflects the fact that initial implantation and failure of surgical mesh in many anatomic locations (e.g., abdominal wall, shoulder and hernia repair) requires intervention by an open surgical procedure which presents considerably greater risk to the patient than the arthroscopic procedure to implant or explant a CS in the meniscus.³⁹ Additionally, failure of surgical mesh in a number of other soft tissue indications (e.g., treatment of defects in the vertebral body of the spine or the lungs or body wall, hernia repair, or anal fistulas) presents greater health consequences than that associated with use in the meniscus. Should the CS fail in the meniscus, the patient is left with the standard-of-care treatment for irreparable meniscus injuries, partial meniscectomy.

This comparison shows that the complications associated with the use of the CS in the meniscus are the same as other soft tissue indications for surgical mesh. The comparison also shows that the CS in the meniscus raises no new types of safety and effectiveness questions compared to the legally marketed predicate devices.

The clinical data demonstrates that the serious adverse event rates associated with the use of the CS device in patients with meniscal injuries is not statistically different from that of partial meniscectomy. This is surprising because partial meniscectomy is a surgical procedure that simply removes the damaged meniscus tissue to alleviate the immediate mechanical and physical symptoms. It does not involve the use of an implant or suture and does not address the permanent loss of meniscus tissue which has been shown to cause long-term degenerative changes within the joint. Furthermore, in the population of

3 [REDACTED]

[REDACTED] was presented in the response to request for additional information dated [REDACTED] (section 6.3.2.3).

CONFIDENTIAL

patients with chronic meniscus injuries, at both 24 months post-operative and greater than 24 months, the rate of all adverse events is statistically higher for the partial meniscectomy patients than the CS patients which indicates that the CS device has a long-term safety profile that is at least comparable to, if not better than, partial meniscectomy.

Given the safety profile described above and taking into account the fact that the device reinforces the remaining meniscus allowing the surgeon to preserve the meniscal horns, the CS is as safe and effective as its predicates. This SE judgment itself supports a positive risk/benefit inherent in its conclusion.

The clinical data presented shows that when used as a surgical mesh to reinforce and repair the meniscus in patients with chronic meniscus injury, the CS device provides patients with a statistically significant increase in tissue within the meniscal defect. The patients also have statistically significant improvements from their pre-operative status in pain, function, self-assessment, satisfaction and activity level. In addition, the CS patients with chronic meniscus injuries experience statistically superior clinical outcomes to partial meniscectomy in regaining lost activity level and reducing the number of reoperations related to meniscus symptoms.

In summary, when used as a surgical mesh in patients with chronic meniscus injuries (one to three prior surgeries to the involved meniscus) the CS shows a positive safety profile and is substantially equivalent to the named predicate surgical meshes.