



REGEN
Biologics

Mark N. Melkerson
Division of General, Restorative, and Neurological Devices
Office of Device Evaluation - CDRH
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850



Re: Premarket Notification 
Trade Name: ReGen Collagen Scaffold (CS)
Response to Additional Information Request Dated; March 26, 2007

Dear Mr. Melkerson:

ReGen Biologics, Inc. (ReGen) is responding to the Division of General, Restorative and Neurological Devices' (DGRND's ) additional information (AI) request regarding the above referenced premarket notification (510(k)) submission. The contents of this response reflect the agreements reached during the  meeting with Donna-Bea Tillman, Ph.D., Director of the Office of Device Evaluation (ODE) and



□ □ □ □

From day one, ReGen has fully cooperated with DGRND. The current submission is one more expression of that cooperation. ReGen, however, remains concerned that the division requests for data exceed those necessary to demonstrate substantial equivalence of a surgical mesh and bear no resemblance whatsoever to the data and information relied upon by DGRND to classify other devices as class II surgical meshes. The application of this same review standard to the review of other 510(k) submissions will undoubtedly discourage and stifle the development of new medical technologies, as well as new uses for existing technology.

From ReGen's perspective, DGRND is summarily dismissing information comparing CS performance to predicate surgical mesh devices, and is instead imposing a PMA-like safety and effectiveness standard. In the context of a 510(k) for a surgical mesh indicated for use in the meniscus, data must demonstrate that the device is as safe in this indication as a predicate is in its respective indication, within the same broader use. This has been done in the 510(k) submission by a comparison of the intended use, labeling, and technological characteristics compared to a number of legally marketed predicates.

Indeed, rather than comparing the CS device to predicates, DGRND wants to compare it to a surgical technique, which by definition, cannot be a predicate for determining substantial equivalence. This is completely at odds with the division's substantial equivalence decisions for other surgical meshes with indications in new anatomic locations or structures. Certainly, this kind of approach is at odds with the Act, which requires that the agency only request additional information in the 510(k) context, "that is necessary to making substantial equivalence determinations." Sec. 513(i)(1)(D). Such requests were required to consider the least burdensome information necessary to demonstrate substantial equivalence. *Id.* These limitations appear lost in the current review.

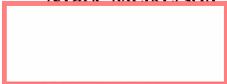
The information presented in this response demonstrates the following:

- The data from the prospective trial is applicable to this 510(k) submission because both involve the identical device with the same intended use and patient population;
- The analysis of adverse events collected from 313 patients with a mean follow-up of 4.9 years (maximum of 7 years) over a 10 year period under an FDA approved IDE protocol demonstrate that they are similar in nature and extent to complications associated with legally marketed surgical meshes intended for use in orthopedics and many other surgical specialties;
- The analysis of adverse events further demonstrates that the CS is as safe as traditional partial meniscectomy without use of a surgical mesh (independent of the long term negative consequences of the partial meniscectomy procedure due to irrecoverable tissue loss);

- Direct visual observation and assessment of the CS conducted by 25 surgeons in 141 relook surgeries and 136 biopsies, performed 1 year post-surgery, confirm that the device functions as a resorbable surgical mesh. It reinforces the remaining meniscal rim and horns and facilitates a significant increase in tissue within the meniscus defect which serves to further reinforce the remaining native meniscus. The clinical benefit of the CS is the same as other resorbable surgical meshes intended for use in reinforcing and repairing a soft tissue defect;
- Analyses of safety and effectiveness data demonstrate no difference in safety performance between the CS treatment group and partial meniscectomy control group in terms of serious adverse events, the primary clinical endpoints of pain, function and self-assessment, or in the secondary clinical endpoint of radiographic changes, and a positive risk/benefit profile is demonstrated by the increase of tissue in the meniscus;
- [redacted] the device is negligible in comparison to endogenous [redacted] levels and does not create a significant risk to patients; and
- The heavy metal limit for the device [redacted] consistent with the appropriate USP method, as determined through validation testing of the device. Animal and human testing of the device have not revealed any health problems associated with this limit.

[redacted] [redacted] it appear that there is anything we can do to achieve a substantial equivalence recommendation from the staff. But for Dr. Tillman's intervention in the context of our [redacted] ReGen's surgical mesh would be regulated unlike all other meshes. we hope this submission will result in a collegial review in which the staff communicates with ReGen to answer questions about the information and data in the 510(k) rather than make determinations based on misunderstandings or incomplete information. To that end, we stand ready to work with the staff and respond to any question the staff may have. We hope the same openness will exist within the agency.

A detailed response to each question posed in the AI letter follows in the attached document.



Please call to discuss any questions or comments. I can be reached at 201-651-3505, or via electronic mail at jdichiara@regenbio.com.

Sincerely,

Refer to hard copy for signature.

John Dichiara
Senior Vice President
Clinical, Quality and Regulatory

CC: Donna-Bea Tillman, Ph.D.

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 - H Line Listing of All Adverse Events**
 - I [Redacted] and Genotoxicity Testing**
 - J [Redacted]**
 - K Truthful and Accurate Statement**

[Redacted]

Additional Information Response

[Redacted]

1.

[Redacted]

RESPONSE:

[Redacted]

¹ Note the complications listed in the Instructions for Use from several of the predicate surgical meshes included in Appendix A.

[Redacted]

Additional Information Response

[Redacted]

2.

[Redacted]

RESPONSE:

[Redacted]

Regarding the safety data provided, we have the following concerns.

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[Redacted]

[redacted]
[redacted] tion Response

[redacted]

Response:

[redacted]

² Note the complications and adverse effects listed in the Instructions for Use for several legally marketed surgical meshes included in Appendix A

³ 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

[Redacted]

Additional Information Response

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Additional Information Response

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]
Additional Information Response
[Redacted]

[Redacted]

RESPONSE:

[Redacted]

⁵ Fairbank TJ. Knee joint changes after meniscectomy. J Bone and Joint Surg Br 1948;30:664-670

⁶ Lee SJ, Aadalen KJ, Malaviya P, Lorenz EP, Hayden JK, Farr J, Kang RW, Cole BJ. Tibiofemoral contact mechanics after serial medial meniscectomies in the human cadaveric knee. AM J Sports Med 2006; 34:1334-1344

⁷ Schimmer R, Brulhart K, Duff C, Glinz W. Arthroscopic partial meniscectomy: A 12-year follow-up and two-step evaluation of the long-term course. Arthroscopy 1998; 14:136-142

[Redacted]

Additional Information Response

[Redacted]

placement of the CS device and both techniques involve suturing of the meniscus and retraction

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Additional Information Response

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Additional Information Response

[Redacted]

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¹⁰ Fairbank TJ: Knee joint changes after meniscectomy. *J Bone Joint Surg* 1948; 30B:664-670.

¹¹ Barker SL, McNicholas MJ, Kader D, Abdon P, Adalberth T, McGurty D, Rowley DI, Walker CM. Meniscal regeneration in the long-term after total meniscectomy?. *J Royal Coll Surg Edinburgh* 1998;43:400-403.

[Redacted] tion Response

¹² Higuchi H, Kimura M, Shirakura K, Terauchi M, Takagishi K: Factors affecting long-term results after arthroscopic partial meniscectomy. Clin Orthop 2000; 377:161-168

¹³ The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry

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

¹⁵ Bolano LE, Grana WA. Isolated arthroscopic partial meniscectomy: Functional radiographic evaluation at five years. Am J Sports Med 1993; 21:432-437

[Redacted]
Additional Information Response
[Redacted]

¹⁶ 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

[Redacted]

Additional Information Response

[Redacted]

[Redacted]

RESPONSE:

[Redacted]

[Redacted]

Additional Information Response

[Redacted]

A. Patient Population

Subjects with irreparable meniscal tears were randomly assigned (1:1) to partial meniscectomy (control group) or partial meniscectomy plus CMI implantation (treatment group). Patient subjects included those having no prior meniscal surgery as well as those having up to three prior meniscal surgeries. Eligibility for enrollment was based on the predefined inclusion and exclusion criteria described below. Once eligibility was confirmed, the subject was enrolled in the study and surgery was scheduled.

Inclusion Criteria

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.
- 9.
- 10.
- 11.

[Redacted content for Inclusion Criteria]

Exclusion Criteria

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.

[Redacted content for Exclusion Criteria]

[Redacted]

Additional Information Response

[Redacted]

- 7.
- 8.
- 9.
- 10.
- 11.
- 12.

- 13.
- 14.
- 15.
- 16.
- 17.
- 18.

[Redacted]

All eligible subjects (treatment and control) underwent full thickness debridement of the involved meniscus extending at least into the red/white zone of the meniscus while assuring that the meniscal rim remained intact.

The protocol-recommended postoperative care for the CMI group included [Redacted]

[Redacted]

(partial meniscectomy only) were prescribed standard physical therapy which included full weightbearing as soon as tolerated, patellar mobilization, unrestricted range of motion, quadriceps and hamstring strengthening, and resumption of full activity as tolerated.

Assessments were performed preoperatively and through 24 months. Relook arthroscopies were performed in the treatment group at the 12 month follow-up, with biopsies collected to characterize the type of remodeled tissue present at the original meniscal defect site. Additional long-term follow up was conducted annually through 7 years by questionnaire mailed to the patient.

B. Patient Accounting Information

A total of 313 patients underwent treatment at 16 US clinical sites. Of the 313 patients, 52% (162/313) underwent partial meniscectomy followed by implantation of the CMI (CMI group),

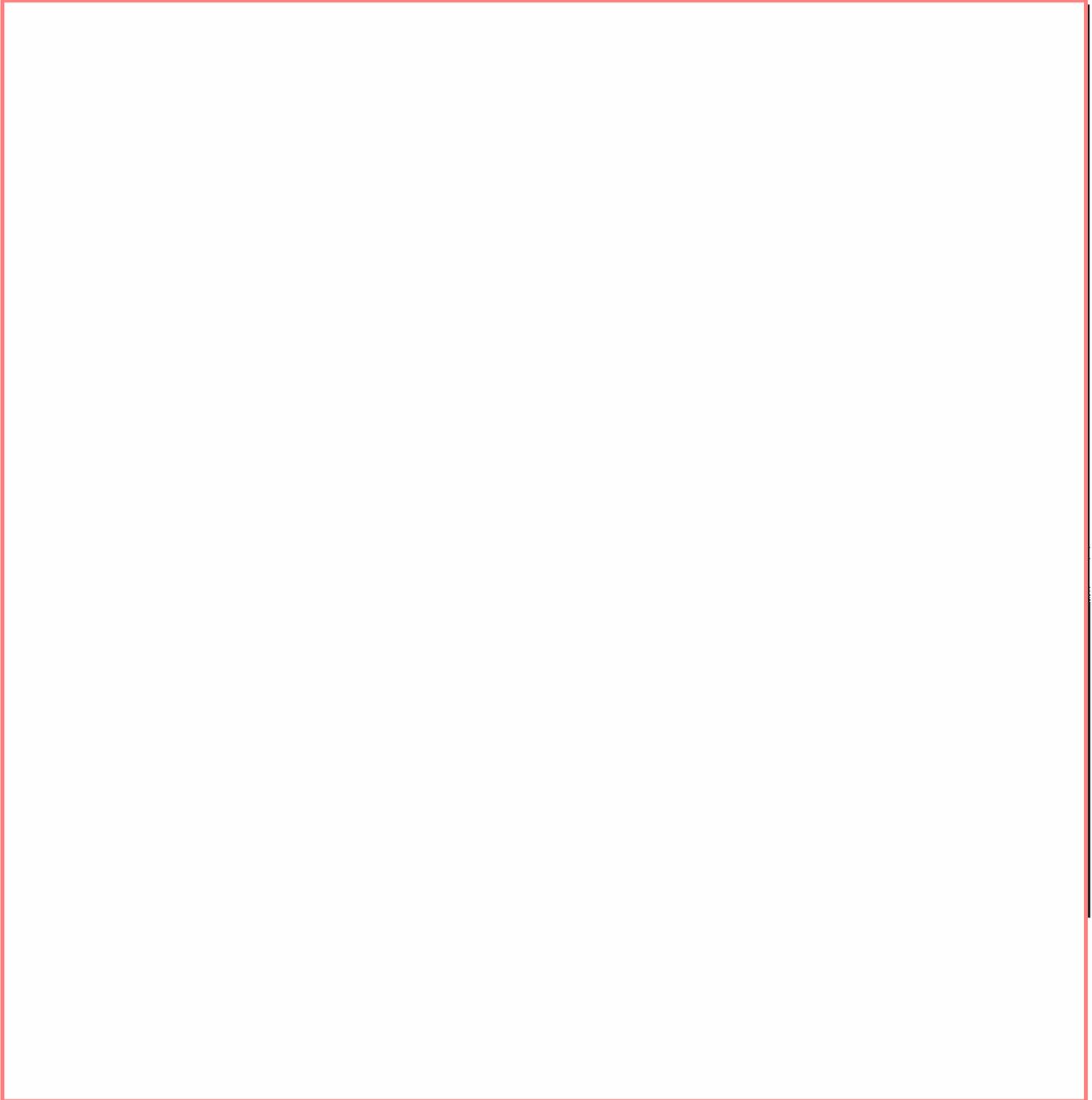
[Redacted]

Information Response

[Redacted]

while 48% (151/313) underwent partial meniscectomy alone (control group). **Table 3** below indicates patient disposition by site.

TABLE 3. SUBJECT ENROLLMENT BY INVESTIGATIONAL SITE



[Redacted]

Additional Information Response

[Redacted]

**TABLE 4: ACCOUNTABILITY OF TREATED SUBJECTS
VISITS AT EACH TIME POINT**

Patient Follow-Up	1-7 Days	6 Weeks	3 Months	6 Months	12 Months	24 Months	> 24 Months
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CMI (N = 162)

[Redacted]

C. Percentage of Meniscal Tissue Removed and Tissue Gain

[Redacted]

[Redacted]

[Redacted]

Additional Information Response

[Redacted]

FIGURE 3: TOTAL TISSUE DISTRIBUTION



Histological Evaluation of Tissue Biopsies

[Redacted]

Additional Information Response

[Redacted]

**Table 6. Histologic Evaluation at 12 Months
CMI Treated Subjects**

Parameter	Grade	CMI n (%)
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[Redacted]

[Redacted]

D.&E. Adverse Events and Complete Safety Information and Analyses

[Redacted]

Additional Information Response

[Redacted]

Analyses of safety information from the IDE study includes all adverse events and evaluation of serum to assess the formation of antibodies to the CMI product. The information on adverse events has been presented and thoroughly discussed in this document. Appendix C provides a complete analysis of these events by time course and stratified by patient and by event; by serious and non-serious AEs; and by device related AEs and presents summary statistics for all major analyses. Patient narratives exist only for patients undergoing explants (included as Appendix G). To assure the Division staff that all AE information has been disclosed and in lieu of submitting narratives, a line-by-line listing of adverse events is included in Appendix H.

[Redacted]

Serum Evaluation

In addition to the analyses of the AE data, a study was conducted to assess the development of antibodies against the CMI device through the examination of sera obtained from patients in both the CMI treatment group and control group for periods up to 12 months post-surgery. Serum samples were sent directly from the investigational sites to the laboratory at the University of Arizona for analysis. The laboratory was blinded to the treatment group for each serum sample.

[Redacted]

F. Complete Effectiveness Information and Analyses

[Redacted]

[Redacted]

Additional Information Response

[Redacted]

Primary Clinical Endpoints

[Redacted content]

[Redacted]

Additional Information Response

[Redacted]

Table 8. AVERAGE COMPOSITE SUBJECTIVE PAIN SCORE

Statistics	Pre-op	6 Weeks	3 Months	6 Months	12 Months	24 Months	>24 Months
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[Redacted]							
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Figure 4 – Average Subjective Pain Scores Over Time



Knee Function (Lysholm Knee Score)



[Redacted]

Additional Information Response

[Redacted]

[Redacted]

Table 9
LYSHOLM KNEE SCORE – CHANGE FROM BASELINE

	Post-operative Time Point		
	12 Months	24 Months	>24 Months

[Redacted]

Table 10
LYSHOLM KNEE SCORES

Statistics	Pre-op n (%)	6 Weeks n (%)	3 Months n (%)	6 Months n (%)	12 Months n (%)	24 Months n (%)	>24 Months n (%)
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[Redacted]

[Redacted]
Additional Information Response
[Redacted]

Figure 5 – Average Lysholm Scores Over Time



**Table 11: SELF-ASSESSMENT RATINGS
NUMBER OF GRADE CHANGES FROM BASELINE**

[Redacted]

[Redacted]

[Redacted]

Additional Information Response

[Redacted]

[Redacted]

Table 12: SELF ASSESSMENT OF INVOLVED KNEE

Statistics	Pre-op n (%)	6 Weeks n (%)	3 Months n (%)	6 Months n (%)	12 Months n (%)	24 Months n (%)	>24 Months n (%)
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[Redacted]

[Redacted]

Secondary Clinical Endpoint – Radiography

[Redacted]

[Redacted]
Additional Information Response
[Redacted]

Table 13. RADIOGRAPHIC EVALUATION - CHANGE FROM PRE-OP

Parameter Evaluated	12 Months			24 Months		
	CS	Control	n-value	CS	Control	n value

G. Justification for Pooling Patients in Protocols #9601 and #9602

[Redacted]

Additional Information Response

[Redacted]

[Redacted]

3.

[Redacted]

RESPONSE.

[Redacted]

[Redacted]

Additional Information Response

[Redacted]

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4.

[Redacted box for question 4]

¹⁷ Bissell MJ, Aggeler J. Dynamic reciprocity: how do extracellular matrix and hormones direct gene expression? *Prog Clin Biol Res.* 1987;249:251-262.

[Redacted]
Additional Information Response
[Redacted]

[Redacted]

RESPONSE:

[Redacted]

5.

[Redacted]

RESPONSE:

[Redacted]

[Redacted]

Additional Information Response

[Redacted]

[Redacted]

6. *Please provide a signed Truthful and Accurate Statement, the one provided on p.13 was not signed.*

RESPONSE:

A signed Truthful and Accurate Statement is provided with this response. (Appendix K)

7.

[Redacted]

RESPONSE:

[Redacted]

Please call to discuss any questions or comments. I can be reached at 201-651-3505, or via electronic mail at jdichiara@regenbio.com.

Sincerely,

[Redacted signature]

John Dichiara
Senior Vice President
Clinical, Quality and Regulatory

Appendix A

Instructions for Use from Predicate Surgical Meshes

**Instructions for Use
Restore Orthobiologic
Soft Tissue Implant**

FOR THE PERSONAL
ATTENTION OF THE SURGEON
RESTORE ORTHOBIOLOGIC
SOFT TISSUE IMPLANT

DEVICE DESCRIPTION

The Restore Orthobiologic Soft Tissue Implant is manufactured from layers of porcine small intestinal submucosa (SIS) that are pinned at angles to produce an isotropic, round implant, and dried. The implant is then packaged in a moisture barrier package. The device is intended to function as a resorbable scaffold that is gradually resorbed and replaced by the patient's own soft tissue.

STERILITY AND HANDLING

The Restore Orthobiologic Soft Tissue Implant is packaged dry in a double foil pouch and has been terminally sterilized by Electron Beam radiation with a dose of 20 kGy. The devices should be considered sterile unless the packaging has been opened or damaged. The devices should not be utilized if sterility or package integrity is questionable. Remove the device from the package using accepted aseptic technique. **THE RESTORE ORTHOBIOLOGIC SOFT TISSUE IMPLANT CANNOT BE REUSED OR RESTERILIZED.** The device must be soaked for 7-10 minutes in sterile saline/buffer or water prior to implanting. Warning - soaking for longer than 30 minutes may affect the integrity of the device.

CAUTION: The device must be kept refrigerated between 2 and 8°C (36 to 46°F). Confirm that the device has not passed the expiration date at the time of implantation. Protect the device from sharp objects and edges before and during implantation. Federal Law (USA) restricts this device to sale by or on the order of a physician.

INDICATIONS

The Restore Orthobiologic Soft Tissue Implant is intended for use in general surgical procedures for reinforcement of soft tissue where weakness exists. In addition, the implant is intended for use in the specific application of reinforcement of the soft tissues which are repaired by suture or suture anchors limited to the supraspinatus during rotator cuff surgery.

CONTRAINDICATIONS

This product should not be placed in individuals who are allergic to pork or pork products or who have a history of multiple severe allergies, allergies to animal derived products or an overly sensitized immune system.

This product is not indicated for or intended for use in massive chronic rotator cuff tears that cannot be mobilized or where the muscle tissue has undergone substantial fatty degeneration.

WARNINGS AND PRECAUTIONS

Preoperative

Before surgery, the surgeon should discuss with the patient all physical and mental limitations particular to the patient and all aspects of the surgery, the device, the rehabilitation program and follow-up. The discussion should include the limitations of any repair, the possible consequences that may result from these limitations and the necessity to follow the surgeon's instructions postoperatively.

Intraoperative

There is evidence that the potential for deep sepsis following implantation of devices may be reduced by the use of prophylactic antibiotics. It is important to discover and treat other pathologies in the affected soft tissue that may affect the patient's ability to return to activity.

Postoperative

For the postoperative management and gradual functional recovery of the repaired tissue, strict adherence by the patient to the surgeon's instructions and warnings is extremely important. The patient should be released with complete written instructions and warnings, regarding exercises and therapies and any limitations on their activities. Strict adherence to the surgeon's recommended postoperative management program is recommended.

POTENTIAL TISSUE RESPONSE IN EARLY POST-OPERATIVE PERIOD

When using the Restore Orthobiologic Implant for repair of soft tissue, the device is expected to significantly impact the wound healing response. Remodeling toward native tissue, as opposed to formation of scar tissue, is observed when Restore is used to facilitate and reinforce the repair of injured musculoskeletal tissues. As part of this remodeling sequence, the surgeon can and should expect to see signs of active proliferation of responding cells and of blood vessels at the repair site approximately two to four weeks post-operatively. Sometimes, this cellular response may be manifested in the following ways:

There may be localized redness and swelling that is moderately firm, and it may or may not be warm to the touch depending upon the degree of new blood vessel formation (angiogenesis) and blood vessel dilation. The amount of pain is patient dependent, as it is with most surgeries, and is in part related to the amount and location of the soft tissue swelling.

If the patient undergoes this angiogenic proliferative response, the surgeon can expect to see it in the second to fourth week post surgery. Within four to six weeks post-operatively, the response resolves and the subsequent clinical course is generally uneventful as tissue remodeling subsides and the patient returns to normal activity. These symptoms should not be mistaken for an infection.

POTENTIAL ADVERSE EFFECTS

The following are the most frequent adverse effects or complications encountered in soft tissue repair.

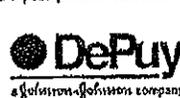
General

1. Infection
2. Adhesions
3. Sterile effusion
4. Instability
5. Increased stiffness postoperatively
6. General risks associated with surgery and anesthesia such as neurological, cardiac and respiratory deficit.

Potential Device related risks

1. Stretching or tearing of the device
2. Stiffness
3. Chronic synovitis or effusion
4. Prolonged postoperative rehabilitation
5. Delayed or failed incorporation of the device (failure of the device to be replaced by natural tissues)
6. Immunologic reaction

As with any surgical procedure and implant device, no assurances or guarantees can be made regarding the postoperative outcome or long term results.



DePuy Orthopaedics, Inc.
700 Orthopaedic Drive
Warsaw, IN 46580
USA
Tel: +1 (800) 366 6143

DePuy International Ltd
St. Anthony's Road
Leeds LS11 8DT
England
Tel: +44 (113) 270 0461
Fax: +44 (113) 272 4101

0502-00-736
Rev. B, 02/02

**Instructions for Use
Surgisis Gold
Hernia Repair Graft**

SURGISIS® GOLD™

H E R N I A R E P A I R G R A F T

FP0005-14



INTENDED USE: SURGISIS® GOLD™ Hernia Repair Graft is intended to be implanted to reinforce soft tissues where weakness exists. Indications for use include the repair of a hernia or body wall defect. SURGISIS GOLD is supplied sterile and is intended for one-time use.

CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

CONTRAINDICATIONS: This device is derived from a porcine source and should not be used in patients with known sensitivity to porcine material.

PRECAUTIONS:

- Do not resterilize. Discard all open and unused portions of the device.
- SURGISIS GOLD is sterile if the package is dry, unopened and undamaged. Do not use if the package seal is broken.
- Discard device if mishandling has caused possible damage or contamination, or if the device is past its expiration date.
- Ensure that device is rehydrated prior to cutting, suturing, stapling, or loading of the device laparoscopically.
- Ensure that all layers of SURGISIS GOLD are secured when suturing or stapling.
- Place device in maximum possible contact with healthy, well-vascularized tissue to encourage cell ingrowth and tissue remodeling.
- Suturing or stapling more than one device together may decrease device performance.
- No studies have been conducted to evaluate the reproductive impact of the clinical use of SURGISIS GOLD.

POTENTIAL COMPLICATIONS:

Possible adverse reactions with the use of any prosthesis may include, but are not limited to, infection, inflammation, adhesion, fistula formation, seroma formation, hematoma, and recurrence of tissue defect

STORAGE: This device should be stored in a clean, dry location at room temperature.

STERILIZATION: This device has been sterilized with ethylene oxide.

SUGGESTED INSTRUCTIONS FOR USING SURGISIS GOLD

These recommendations are designed to serve only as a general guideline. They are not intended to supersede institutional protocols or professional clinical judgment concerning patient care.

NOTE: Always handle SURGISIS GOLD using aseptic technique.

Required Materials

- Sterile forceps
 - Rehydration fluid: room temperature, sterile saline or sterile lactated Ringer's solution.
1. Using aseptic technique, remove the inner tray from its outer bag and place the tray in the sterile field.
 2. Open the tray carefully. Use the tray to rehydrate the device by adding room temperature, sterile saline or sterile lactated Ringer's solution.
 3. Allow SURGISIS GOLD to rehydrate for at least ten (10) minutes prior to cutting, suturing, stapling, or loading, the device laparoscopically.
 4. Prepare the hernia repair site using standard surgical techniques.
 5. Using aseptic technique, trim SURGISIS GOLD to fit the site, providing a small allowance for overlap.
 6. Using aseptic technique, transfer SURGISIS GOLD to the surgical site and suture or staple into place, avoiding excess tension.

NOTE: Surgical experience indicates that suturing or stapling SURGISIS GOLD with close tissue approximation produces better outcomes. Fundamental surgical principles suggest a suture spacing approximately equal to suture bite depth.

7. Complete the standard surgical procedure.
 8. Discard any unused portions.
- NOTE:** Interrupted sutures can provide additional security against recurrence of tissue defect in the event of suture failure.

If the device is cut too small for the defect, excess tension may be placed on the suture line. This can result in recurrence of the original tissue defect or development of a defect in the adjacent tissues.

MECHANICAL PROPERTIES

Nominal properties for Surgisis Gold are listed below:

Property	SURGISIS® GOLD™ Hernia Repair Graft
Suture Retention Strength*	3.08 ± 0.72 lb (1397 ± 325 g)
Burst Force **	99.0 ± 18.13 lb (44.9 ± 8.2 kg)

* 5-0 suture with 2 mm bite depth

** 25.4 mm diameter sphere

© COPYRIGHT COOK BIOTECH 2004

Manufactured for:

Cook Surgical

750 Daniels Way

P.O. Box 489

Bloomington, Indiana 47402 U.S.A.

Phone: 812-339-2235

Toll Free: 1-800-457-4500

Toll Free Fax: 800-554-8335

www.cooksurgical.com

**Instructions for Use
Surgisis IHM
Inguinal Hernia Matrix**

SURGISIS[®] IHM[™]
INGUINAL HERNIA MATRIX

FP0002-1E

COOK[®]
sis
Technology

INTENDED USE: SURGISIS[®] Inguinal Hernia Matrix is implanted to reinforce soft tissues in the inguinal floor to repair inguinal hernias.

SURGISIS[®] Inguinal Hernia Matrix is supplied sterile and is intended for one-time use.

CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

CONTRAINDICATIONS: This device is derived from a porcine source and should not be used in patients with known sensitivity to porcine material.

PRECAUTIONS:

- Do not resterilize. Discard all open and unused portions of the device.
- SURGISIS[®] Inguinal Hernia Matrix is sterile if the package is dry, unopened and undamaged. Do not use if the package seal is broken.
- Discard device if mishandling has caused possible damage or contamination, or if the device is past its expiration date.
- Ensure that device is rehydrated prior to cutting, suturing, stapling, or loading of the device laparoscopically.
- Care should be taken to avoid damaging the device when loading laparoscopically. It is recommended to load through a 10 mm or larger port.
- Ensure that all layers of SURGISIS[®] Inguinal Hernia Matrix are secured when suturing or stapling.
- Suturing or stapling more than one device together may decrease device performance.
- No studies have been conducted to evaluate the reproductive impact of the clinical use of SURGISIS[®] Inguinal Hernia Matrix

POTENTIAL COMPLICATIONS:

Possible adverse reactions with the use of any prosthesis may include, but are not limited to, infection, pain, inflammation, adhesion, fistula formation, seroma formation, hematoma, and recurrence of tissue defect.

STORAGE: This device should be stored in a clean, dry location at room temperature.

STERILIZATION: This device has been sterilized with ethylene oxide.

SUGGESTED INSTRUCTIONS FOR USING SURGISIS[®] Inguinal Hernia Matrix

These recommendations are designed to serve only as a general guideline. They are not intended to supersede institutional protocols or professional clinical judgment concerning patient care.

NOTE: Always handle SURGISIS[®] Inguinal Hernia Matrix using aseptic technique.

Required Materials

- Sterile scissors (if cutting required)
- Rehydration fluid; room temperature, sterile saline or sterile lactated Ringer's solution.
- Sterile tray

1. Using aseptic technique, remove the inner pouch from the outer pouch and place it in the sterile field.
2. Open the inner pouch carefully. Use a tray to rehydrate the device by adding room temperature, sterile saline or sterile lactated Ringer's solution.
3. Allow SURGISIS[®] Inguinal Hernia Matrix to rehydrate for at least ten (10) minutes prior to cutting, suturing, stapling, or loading the device laparoscopically.
4. Prepare the hernia repair site using standard surgical techniques.
5. Using aseptic technique, trim SURGISIS[®] Inguinal Hernia Matrix to fit the site, providing a small allowance for overlap.
6. Using aseptic technique, transfer SURGISIS[®] Inguinal Hernia Matrix to the surgical site and suture or staple into place, avoiding excess tension.
7. Complete the standard surgical procedure.
8. Discard any unused portions.

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Manufactured for:

Cook Surgical

750 Daniels Way

P.O. Box 489

Bloomington, Indiana 47402 U.S.A.

Phone: 812-339-2235

Toll Free: 1-800-457-4500

Toll Free Fax: 800-554-8335

**Instructions for Use
Surgisis AFP
Anal Fistula Plug**



COOK **sis**

Manufacturer:
Cook Biotech Incorporated
 1425 Innovation Place
 West Lafayette, IN 47906 U.S.A.
 Toll Free: 1-800-457-6300
 Toll Free Fax: 000-554-8335
 www.cookmedical.com

INTENDED USE:
 The SURGISIS Anal Fistula Plug is for replacement to reinforce soft tissue where a defect exists for repair of anorectal fistulas. This device is supplied sterile and is intended for one-time use.

CAUTION: Federal U.S.A. law restricts this device to sale by or on the order of a physician.

CONTRAINDICATIONS:

- This device is derived from a porous source and should not be used for patients sensitive to porous materials.
- Not for vascular use.

PRECAUTIONS:

- Do not sterilize, heat, or open and unused portions.
- Device is sterile if the package is dry, unopened and unincriminated. Do not use if the package seal is broken.
- Discard device if it is showing any signs of possible damage or contamination, or if the device is past its expiration date.
- Do not implant the device in a grossly infected or abscessed fistula tract.
- Ensure that the device is hydrated prior to placement cutting, or sewing.

GENERAL:

- Users should be familiar with surgical techniques for anorectal fistula repair.
- Users should exercise good surgical practice for the management of clean-contaminated, contaminated or infected fields.
- The potential for infection of the graft material following implantation may be reduced by the use of prophylactic antibiotics, and cleaning of the fistula tract (See Use of Antimicrobials).
- SURGISIS Anal Fistula Plug should be handled aseptically, minimizing contact with latex gloves.
- SURGISIS Anal Fistula Plug should be introduced through the internal (primary) fistula opening.
- SURGISIS Anal Fistula Plug should be drawn into the fistula tract only until the internal (primary) opening is satisfactorily closed/fasciated.
- The external (secondary) opening of the fistula tract should remain open.
- IMPORTANT:** Users should counsel patients on abstaining from heavy lifting or strenuous activity for a period of two weeks after anal fistula plug placement.

POTENTIAL COMPLICATIONS: Complications that can occur with the SURGISIS Anal Fistula Plug include, but are not limited to, inflammation, induration, migration, extrusion, stricture formation, infection, abscess, fistula recurrence, and delayed or failed incorporation of the device. If any of the following conditions occur, and cannot be resolved, device removal should be considered:

- Infection
- Fibrosis
- Acute or chronic inflammation (local application of surgical graft materials may be associated with transient, mild, local acute inflammation)
- Allergic reaction

STORAGE: This device should be stored in a clean, dry location at room temperature.

STERILIZATION: This device has been sterilized with ethylene oxide.

SUGGESTED INSTRUCTIONS FOR USE:
 These recommendations are designed to serve only as a general guideline. They are not intended to supersede the manufacturer's protocols or professional clinical judgment concerning patient care.

NOTE: Handle device using aseptic technique.

REQUIRED MATERIALS:

- A sterile gauze (padding) cloth or sterile drape
- 4% hydroxyethyl cellulose (HEC) 100 ml of room temperature sterile saline or sterile isotonic Ringer's solution
- Suitable resorbable suture, such as: D-shewms, 7-0 Vicryl, or D Vicryl

PREPARATORY:

- From the box, remove the outer package containing SURGISIS Anal Fistula Plug.
- Using aseptic technique, remove the outer pouch containing the SURGISIS Anal Fistula Plug from the outer package. Place the inner pouch in the sterile field.
- Using sterile gloved hands, open the inner pouch carefully, and aseptically remove the SURGISIS Anal Fistula Plug into a sterile instrument. Place the SURGISIS Anal Fistula Plug into the sterile dish in the sterile field.
- Use a suitable resorbable suture (approximately 12 inches in length) around the fat (narrow end) of the plug for pulling it into the fistula tract. (This step is not necessary if a suture suture will be placed which can be tied to the narrow end of the plug.)

- Add to the dish enough hydration fluid to fully submerge the SURGISIS Anal Fistula Plug. Allow the fistula plug to hydrate. Hydrate for a minimum of 5 minutes.
- Hydrate the patient and surgical site using standard surgical techniques appropriate for anal fistula repair.

NOTE: The recommended practice for preoperative bowel preparation in elective colorectal surgery includes mechanical bowel cleansing through the use of enemas and cathartic agents, and administration of prophylactic antimicrobial agents, oral or intravenous. Inadequate cleansing or inadequate antimicrobial prophylaxis can predispose the patient to infections. (1) (See Use of Antimicrobials)

PROCEDURAL:

- Perform under local, regional, or general anesthesia.
- Identify the internal (primary) fistula opening by inserting a sterile probe into the external (secondary) opening and navigating it through the fistula tract. Alternatively, insertion of appropriate sterile forceps (e.g. cup or hydrogen peroxide) into the external (secondary) opening of the fistula tract and identifying the site of emergence at the internal (primary) opening can also be used to assist in identifying the location of the internal opening.

NOTE: Failure to locate the internal (primary) opening may lead to persistence of the fistula. If the internal (primary) opening cannot be reliably identified, an alternative method of treatment should be considered.

- Gently clean the fistula tract as thoroughly as possible by flushing the tract with sterile saline, hydrogen peroxide, or comparable solution. Do not enlarge the tract.
- Insert a sterile hemostat, a fistula probe, suture or suitable instrument through the fistula tract, extending through the external (secondary) opening and extending to the internal (primary) opening. A suture suture may be placed and subsequently tied to the narrow end of the SURGISIS Anal Fistula Plug for pulling it into the tract.
- Clamp the suture suture to the bottom end of the fistula plug. Confirm that the plug is pulled to first into the internal (primary) opening, so the thicker end of the plug can be pulled snugly into the internal (primary) opening.
- Draw the free end of the SURGISIS Anal Fistula Plug into the internal (primary) opening and through the fistula tract until suture suture is taut and the plug securely blocks the internal (primary) opening.

IMPORTANT: The internal opening is the high-pressure zone of the fistula, as well as the site of ingress of fecal debris. The thicker end of the plug must therefore be securely engaged into the internal (primary) opening to prevent ingress of fecal debris. In addition, high pressures within the rectum and anal canal assist in maintaining the plug in the fistula tract by simple mechanical force.

- When the SURGISIS Anal Fistula Plug is properly positioned, trim away and discard any remaining portion of the plug that is not implanted in the fistula tract.

IMPORTANT: The anal fistula plug should be trimmed at the level of the bowel wall at the internal opening in order to minimize contact with bowel contents.

- Suture both ends of the SURGISIS Anal Fistula Plug in place with suitable resorbable suture. Refer to the instructions or suggested suture placement. Suture the internal end of the SURGISIS Anal Fistula Plug securely to the adjacent tissue, following adequate bites of bowel wall and fistula plug to prevent leakage of bowel contents into the fistula tract and to anchor the fistula plug to prevent migration through the tract. At the external (secondary) opening, suture the anal fistula plug, if exposed, with a suitable suture resorbable suture. If the anal fistula plug is not exposed, suture the end of the fistula plug to the skin at the rim of the opening using the surrounding suture line.

NOTE: Do not close the external (secondary) opening completely, so as to allow continued drainage of the fistula tract. Complete obstruction of the external (secondary) opening may result in accumulation of fluid, infection, or abscess.

- Place a sterile dressing over the implant site.

Use of Antimicrobials with SURGISIS Anal Fistula Plug
 Because the SURGISIS Anal Fistula Plug is used in surgical fields where infection cannot be avoided, the use of antimicrobials is common practice and may prevent infectious complications. (1-3) Both mechanical bowel cleansing and antibiotic prophylaxis of the patient have been used successfully, and the U.S. Centers for Disease Control recommends both cleansing and administration of prophylactic antibiotic and intravenous antimicrobial agents before elective colorectal operations. (3) (See reference for specific dose, timing, and drug choices.)

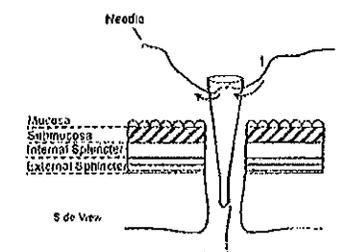
Typical gastrointestinal flora can be expected to include a variety of aerobic and anaerobic organisms. Therefore the following points should be considered:

- Antimicrobials, if used topically or systemically, should provide coverage against a wide spectrum of aerobic and anaerobic organisms. (4)
- Mechanically prepare the colon by appropriate use of enemas and cathartic agents.
- A dose of prophylactic antimicrobial agent should be given intravenously and timed such that a bactericidal concentration of the drug is established in the serum and tissues when the device is implanted.
- There are therapeutic levels of the anal fistula vacuum and issues throughout the operation. (2)

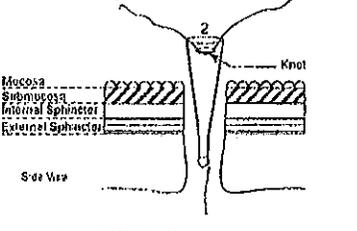
The presence of certain anaerobic organisms in the colon may predispose the patient to infection with the SURGISIS Anal Fistula Plug. (5-7) For example, organisms known to hinder neovascularization, epithelialization, and keloid fibrotic growth, (8) while penicillinase resistant (9) tetracycline (10) polymyxin D (9) and vancomycin (10) have all been reported to show antimicrobial activity. Careful consideration is required before using any antimicrobial or antibiotic (topical or systemic) that has not been proven compatible with surgical implantation and wound healing. However, no studies have been conducted to evaluate the combination of antimicrobials with SURGISIS Anal Fistula Plug placement.

SUGGESTED SUTURE PLACEMENT FOR ANCHORING THE SURGISIS ANAL FISTULA PLUG (To be performed after trimming the plug to fit the tract):

- Remove the unused plug slightly from the fistula tract to expose several millimeters of the larger diameter plug end. Pass the resorbable suture 2-3 mm deep through the plug, at approximately 3-4 mm from the large diameter end.

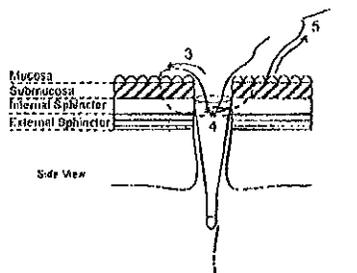


NOTE: Use an appropriate surgical knife to be suture down to the end of the plug, leaving the suture line uninfused.

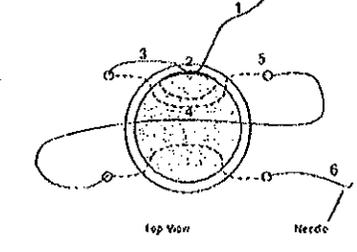


- Put the SURGISIS Anal Fistula Plug back into the tract to the final position. Pass the suture approximately 5 to 8 mm from the primary opening, through the mucosa, submucosa and underlying deep tissue layers. Ensure that adequate bite depths are taken to penetrate the deep tissue layers.

- Pass the suture through the head of the SURGISIS Anal Fistula Plug. Pass the suture into the underlying deep tissue and up through the submucosa and mucosa layers, as illustrated.



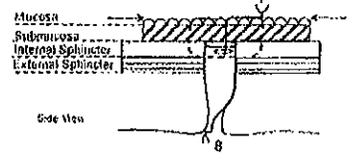
- Repeat the suture placement as indicated in steps 3 thru 5 on the opposite side of the primary opening.



- Insert the free loose ends of suture to draw the primary opening inward over the anal fistula plug, and tie the suture ends together. The head of the plug at the covered fistula tissue. There should be no part of the plug visible at the primary opening.

- If the narrow end of the anal fistula plug is exposed, it should be cut so that no material protrudes from the secondary opening. Secure the narrow end of the plug to skin at the rim of the opening, leaving the external opening of the tract unobstructed to allow continued drainage.

NOTE: No part of the SURGISIS Anal Fistula Plug should protrude from the fistula tract when the procedure is completed.



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Appendix B

Physician Letters of Support



June 12, 2007

To Whom It May Concern
Food and Drug Administration
Rockville, MD 20850

Re: Regen Collagen Scaffold (CS) Surgical Mesh FDA Submission

I am writing as one of the multi-center clinical trial investigators who has personal experience with 19 CMI patients and 18 controls with up to 7 years follow-up.

I can attest to the clinical need for availability of the CMI/CS device. The current options for treatment of significant meniscus injuries are meniscus repair, which is the treatment of choice (but is appropriate for only 20% or less of all significant meniscus tears), partial meniscectomy, and allograft meniscus transplantation. Partial meniscectomy remains the most frequent arthroscopic procedure in the United States, and has its limitations. While it usually is associated with short term success, there are frequently long term consequences of degenerative changes and clinical symptoms. Allograft meniscus transplantation has even more limitations, including concerns over disease transmission, availability, cost, and questionable long term efficacy.

The CMI/CS device is an alternative to partial meniscectomy in a high percentage of the patients undergoing partial meniscectomy. It provides the only possibility for these patients to regain tissue in the meniscus following this procedure, and provides the benefits of meniscus repair for non-repairable meniscus injuries. This is not dissimilar to the surgical meshes FDA has cleared for use in the shoulder and tendons of the leg and knee.

My personal experience with the CMI/CS in the IDE study is that the patients have done extremely well with the device. Re-look surgeries one year following implantation were part of the clinical protocol, and have documented that the device does indeed work to provide a significant increase in tissue in the meniscus, where there would be virtually none without the device. The reinforcement of the anterior and posterior meniscus horns allowed preservation of more of the native meniscus than would be possible if partial meniscectomy alone is carried out (where the resection has to be tapered to minimize the risk of re-tears).

In regard to safety, I encountered few, if any, real complications. I encountered none that would be considered major by any orthopaedic scientific journal. The complications I encountered were no different than my patients have experienced from the standard of care treatments for meniscus injuries (meniscus repair and partial meniscectomy). The IDE protocol required reporting of any event that was not of benefit to the patient as an adverse event, and this meant that we had to report many events that are considered part of the normal healing process for any

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June 12, 2007

treatment which I perform on the meniscus. It is impressive to me that no serious complications have been encountered in the overall clinical trial of approximately 150 devices which have been followed up to 7 years. There is no clinical downside to the procedure for the patient. If for some reason the device were to fail, the patient would be no worse off than if they had received a partial meniscectomy alone without utilization of the device. In addition, the failure patient would still have the option of having another CS procedure done if it is warranted.

In the 35 years that I have been a practicing orthopaedic surgeon, I have sub-specialized in sports medicine, particularly the knee. I have been particularly focused on meniscus lesions, and I am considered to be a pioneer in the field of meniscus repair. I have been in full time academic practice for my entire career, first at the [redacted] and for the last 32 years at the [redacted]. I have been active in the American Academy of Orthopaedic Surgeons, the American Orthopaedic Society for Sports Medicine, The Arthroscopy Association of North America, and the International Society of the Knee and ISAKOS (International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine), and am [redacted]

[redacted]. I am currently [redacted] [redacted]

Sincerely,

[redacted]



June 7, 2007

Food and Drug Administration
Rockville MD 20850

RE: ReGen Collagen Scaffold (CS) Surgical Mesh FDA Submission

To Whom It May Concern:

The following is a letter of support of the ReGen Collagen Scaffold (CMI/CS). I have been a primary investigator with the CMI/CS in the IDE study. I also have no financial interest in the ReGen Corporation.

I have extensive clinical experience in treating meniscus injuries of the knee. My initial orthopaedic training was at the [REDACTED] followed by a fellowship in sports medicine at the [REDACTED]. I have been in private practice for 15 years. I am currently a member of the American Academy of Orthopaedic Surgeons, American Orthopaedic Society for Sports Medicine, and Arthroscopy Association of North America, and [REDACTED].

The meniscus has been found through multiple basic science and clinical studies to be an important structure in cushioning the knee and preventing later arthritis of the knee. At this time, if the meniscus is not repairable, the standard of care is a partial to subtotal meniscectomy, essentially removing this damaged tissue. The unfortunate result is an increased risk of arthritis in these individuals. It appears that there is a direct correlation between the amount of remaining meniscal tissue and the risk of arthritis. Therefore, any treatment that can either preserve the meniscus, such as repair, or replace the meniscal tissue, such as the CMI/CS procedure, should help to decrease the future risk of arthritis of the knee. Since the U.S. population is continuing to increase its median age, the need for arthritis prevention procedures is also increasing. At this time, the CMI/CS is the only procedure available that actually provides a scaffold for meniscal tissue re-growth.

I have had extensive experience during the IDE study with the CMI/CS. My personal study population involved 45 patients, with 22 CMI/CS implants and 23 controls. I have an approximate seven-year follow-up. My general assessment of my personal results was that the CMI/CS patients have done better clinically than the controls. I had no significant complications in any of the patients where I implanted the CMI/CS. In general, the patients were quite pleased with the results following the CMI/CS surgery.

June 7, 2007

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In summary, I believe that there is an increasing demand in the U.S. for procedures that will replace damaged meniscal tissue in an attempt to prevent future arthritis. I believe that the present study with the CMI/CS implant has shown significant tissue re-growth and should be given FDA approval for its general use.

Sincerely





**U.S. Food and Drug Administration
Rockville, MD 20850**

June 8, 2007

Re: ReGen Collagen Scaffold Surgical Mesh FDA Submission

To Whom It May Concern:

I wish to convey my enthusiastic support of the Collagen Meniscal Implant (Collagen Scaffold).

I have been involved with the CMI research since 1995. I assisted [redacted] [redacted] during the Phase II trial. I was very impressed with the biologic concept of the device as well as the initial results obtained in the Phase II patients.

After beginning private practice and serving as a [redacted] [redacted] I was invited to participate in the Phase III randomized CMI trial. During the trial period, I implanted 15 Collagen Meniscal Implants as well as operating on 11 patients who served as controls. I have continued to follow these patients since the inception of the trial. I have been very impressed with the results to date as well as the extremely low complication rate in the CMI patients. Tissue regeneration observed at the one year post implant arthroscopic evaluation was very impressive.

As an orthopedic surgeon specializing in knee disorders, I am hopeful and excited to have the opportunity to be able to use the CMI in the near future. I currently have many patients who would benefit from the CMI if it were available for use in this country. Unfortunately, the current standard of care for patients with irreparable meniscus tears is excision. The CMI would enable these very same patients to regenerate new meniscal tissue, with the goal of restoring function and reducing to potential for early onset arthritis.

I humbly request FDA approval of the CMI. If you have any questions regarding my experience, observations or thoughts regarding the CMI, please feel free to contact me.



June 13, 2007

To Whom It May Concern:
Food and Drug Administration
Rockville, MD 20850

RE: ReGen Collagen Scaffold (DS) Surgical Mesh FDA Submission

I am writing this letter to express my support for the collagen scaffold/collagen meniscal implants made by ReGen. I have had a very favorable experience with the collagen scaffold and was involved in the original study enrolling 15 patients, 7 of whom received the collagen scaffold and 8 of whom were controls.

As background, I am presently the chief of The Division of Sports Medicine at the [REDACTED] and am an Associate Professor in the Department of Orthopaedics in the medical school. My practice is almost exclusively sports medicine. I have been in practice now for over nine years and I am writing to provide my clinical experience and insight with the collagen scaffold device.

The patients in my practice who received the collagen scaffold clearly demonstrated a greater symptomatic improvement as a result of this intervention. It is my opinion that their improved functional status directly correlates to the increased amount of meniscal tissue that was noted at their repeat arthroscopy one year from the implanted collagen scaffold. It is my clinical opinion that the tissue regrowth is providing a protective function for the cartilage surface of the knee joint. This would be in distinction to an arthroscopic partial meniscectomy where any torn or unstable tissue is debrided and there is no capacity to regrow any tissue.

Again, it is my feeling that the implanted collagen scaffold provides a framework for this tissue regrowth that typically is meniscal in gross and histologic appearance.

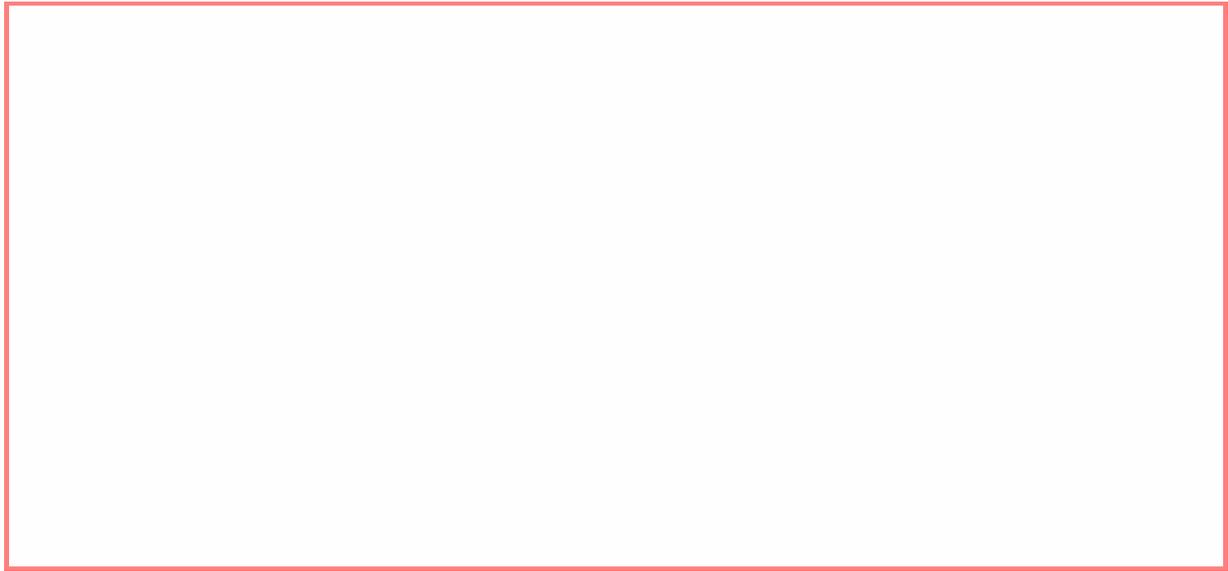
I feel there is a very strong and growing need for this type of medical device, as meniscal injuries resulting in significant cartilage loss and progressive joint deterioration are one of the most common conditions I treat in my practice. I also expect the number of patients treated with this condition to grow as the baby boomer demographic continues to expand and they demand being able to maintain an active lifestyle.

My personal research interests at the [redacted] focus on cartilage regeneration. I have recently published in the Journal of Bone and Joint Surgery, April of 2006, on my work regarding the need for cartilage regenerative technology. I see the collagen meniscal implant/collagen scaffold device as a significant improvement over what we have available clinically at this time. I am hopeful that continued support of the collagen meniscal implant/collagen scaffold device will improve both our treatment of cartilage and meniscal injuries and better understand the biologic components necessary to help create the future technology for meniscal cartilage regeneration.

I would be happy to discuss this letter of support with you at any time.

Sincerely,

[Redacted signature area]



[REDACTED]

Food and Drug Administration
Rockville, MD 20850

June 11, 2007

RE: ReGen Collagen Scaffold (CS) Surgical Mesh FDA Submission

To Whom It May Concern:

This letter is to provide background to the FDA on my clinical experience with the ReGen CMI/CS surgical mesh device. I have been an investigator in the IDE Multicenter Clinical study of this device for approximately 7 years.

I am an orthopaedic surgeon with a practice devoted solely to sports medicine. As such, I have extensive experience with treatment of meniscus injuries and have published on the biomechanics and clinical treatment of them. I have a particular interest in meniscus treatments that provide an alternative to partial or total meniscectomy which I view as a treatment of last resort for most meniscus injuries. I am a Full Professor in the Department of Orthopedics at [REDACTED]

[REDACTED] and am the Section Head of [REDACTED]

I have been in practice for 12 years and am a member of most every national society relevant to my field including but not limited to the American Academy of Orthopedic Surgeons, American Society of Sports Medicine and the International Cartilage Repair Society.

I strongly believe that meniscus preservation should be the major goal of any meniscus surgery, and preservation and replacement have been a major focus of my clinical and academic practice. In many cases, the only treatment option for patients with meniscus injuries deemed to be irreparable is partial meniscectomy. My own work on meniscus biomechanics and my clinical experience have shown that the short-term outcomes associated with partial meniscectomy are good; however, the long-term consequences in up to half of the patients treated are less than ideal. That is one of the reasons that I became an investigator in the clinical trial of the CMI. My experience in the trial included the implant of 3 of these devices with comparison to partial meniscectomy (control

Food and Drug Administration
Rockville, MD 20850
June 11, 2007
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patients). My personal experience and direct observations over approximately 6 years of follow-up on the device have been that the device can provide my patients with a significant increase in meniscus tissue. Second look arthroscopy has indicated that the resultant tissue is similar in physical appearance to that of native meniscus tissue. The complications associated with the use of the device are minimal and are similar to those of other meniscus treatments.

I feel that there is a definite need for devices like the CMI/CS that provide surgeons and patients with an alternative to permanent loss of meniscus tissue resulting from partial meniscectomy. In my personal experience, I feel that the device is safe and effective as a scaffold for replacement of tissue loss due to meniscus injury.

Sincerely,



Appendix C
Adverse Event Tables

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**I.a.1. All Serious AEs
By Time Period**





I.a.3. All Serious AEs – Day 1-7 (window 1-21 days) – By Event Category



I.a.4. All Serious AEs – 6 week (window 22-63 days) – By Event Category



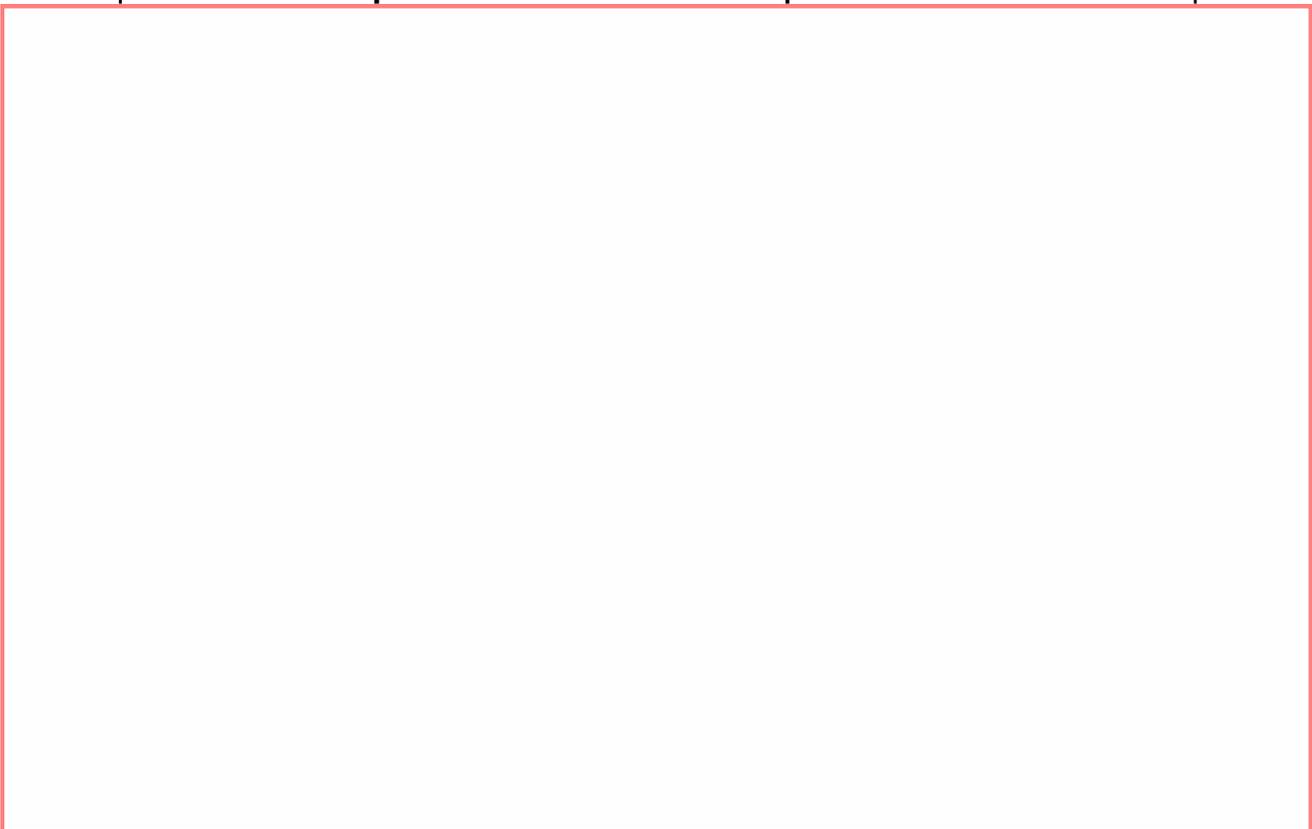
I.a.5. All Serious AEs – 3 Month (window 64-136 days) – By Event Category



I.a.6. All Serious AEs – 6 Months (window 137-273 days) – By Event Category



I.a.7. All Serious AEs – 12 Month (window 274-547 days) – By Event Category



I.a.8. All Serious AEs – 24 Month (window 548-912 days) – By Event Category



I.a.9. All Serious AEs – >24 Months (window >912 days) – By Event Category



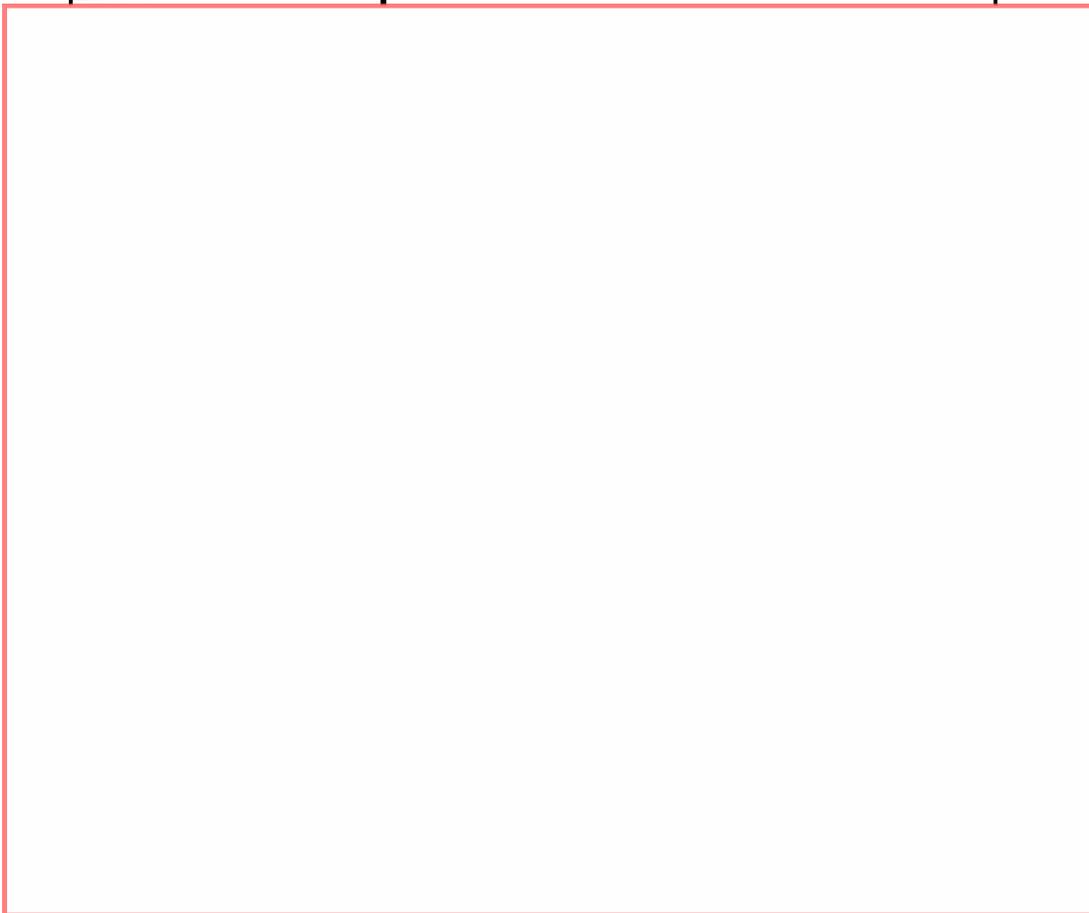
**II.a.1 Serious – Device Related AEs
By Time Period**



II.a.2. Serious - Operative Device Related AEs (day 0) – By Event Category



II.a.3. Serious – Day 1-7 Device Related AEs (window 1-21 days) – By Event Category



II.a.4. Serious – 6 Week Device Related AEs (window 22-63 days) – By Event Category



II.a.5. Serious - 3 Month Device Related AEs (window 64-136 days) – By Event Category



II.a.6. Serious – 6 Month Device Related AEs (window 137-273 days) – By Event Category



II.a.7. Serious – 24 Month Device Related AEs (window 548-912 days) – By Event Category



II.b.1. Serious – Definitely Device Related



II.b.2 Serious – 24 Month Definitely Device Related AEs (window 548-912 days) – By
Event Category



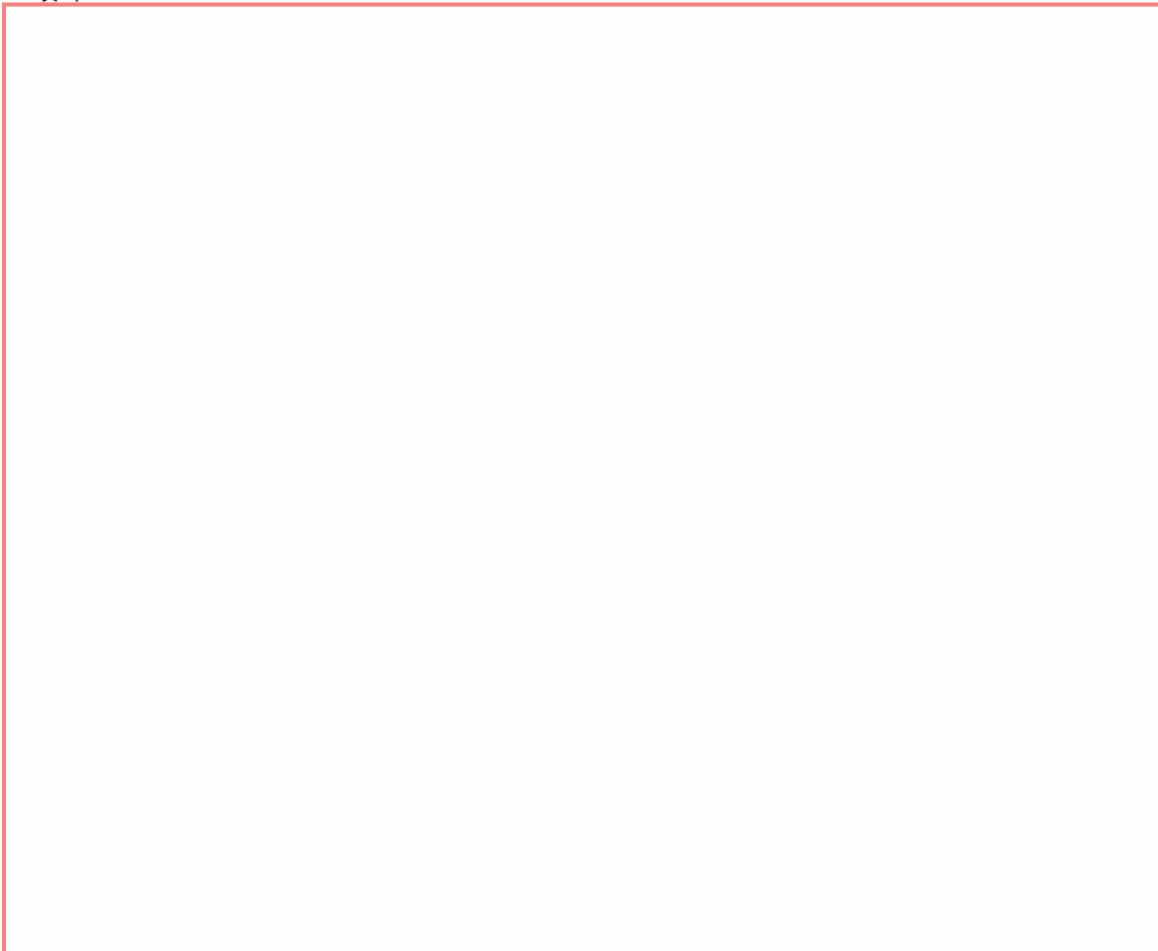
II.c.1. Serious – Probably Device Related AEs
By Time Period



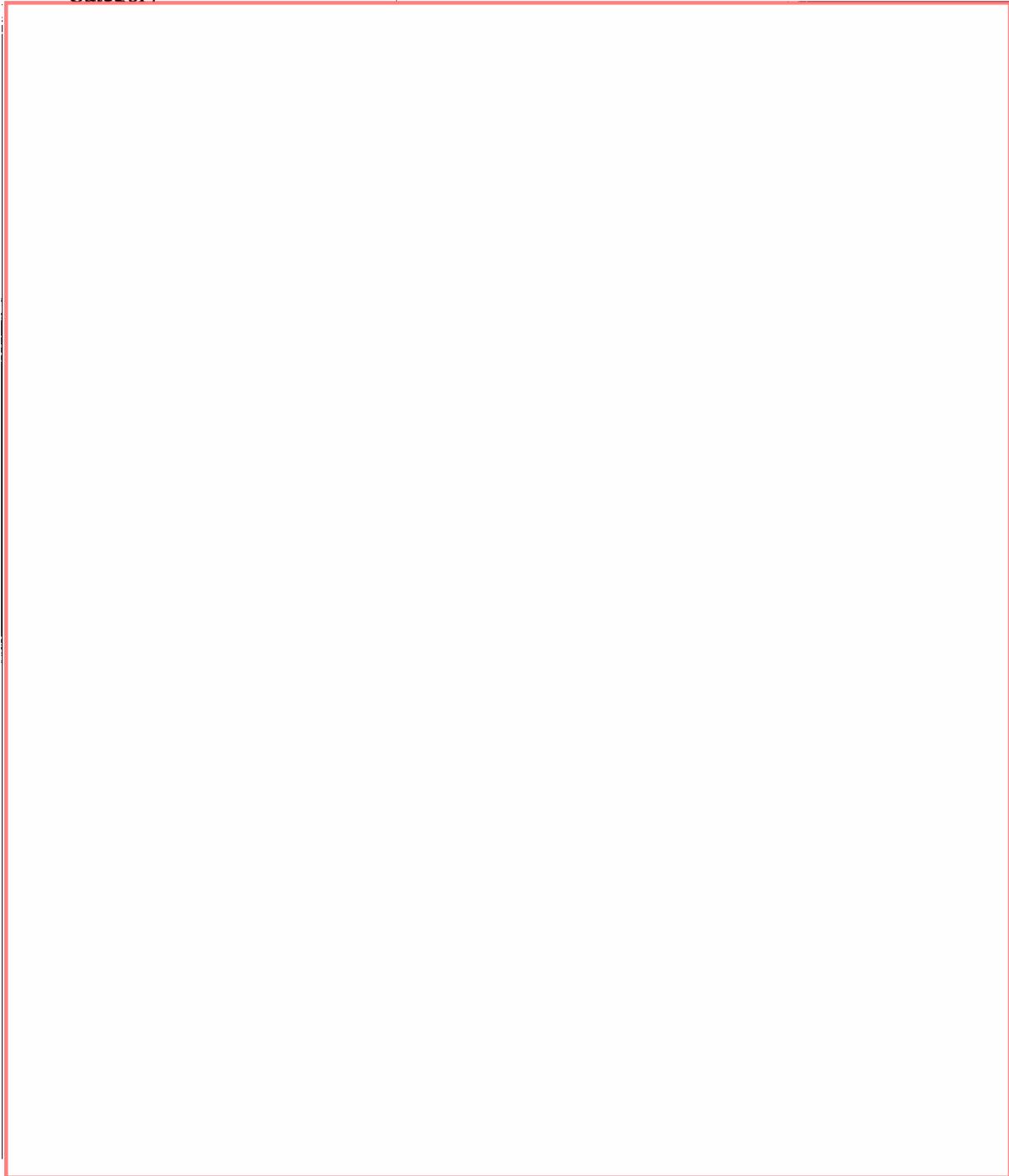
II.c.2. Serious -- Operative Probably Device Related AEs (day 0) -- By Event Category



II.c.3. Serious -- Day 1-7 Probably Device Related AEs (window 1-21 days) -- By Event



II.c.4 Serious – 6 Week Probably Device Related AEs (window 22-63 days) – By Event Category



II.c.5. Serious – 3 Month Probably Device Related AEs (window 64-136 days) – By



**II.c.6. Serious – 6 Month Probably Device Related AEs (window 137-273 days) – By
Event Category**



II.d.1. Serious -- Possibly Device Related AEs
By Time Period



II.d.2 Serious – 6 Week Possibly Device Related AEs (window 22-63 days) – By Event Category



II.d.3. Serious – 3 Month Possibly Device Related AEs (window 64-136 days) – By Event Category



II.d.4. Serious – 6 Month Possibly Device Related AEs (window 137-273 days) – By Event Category



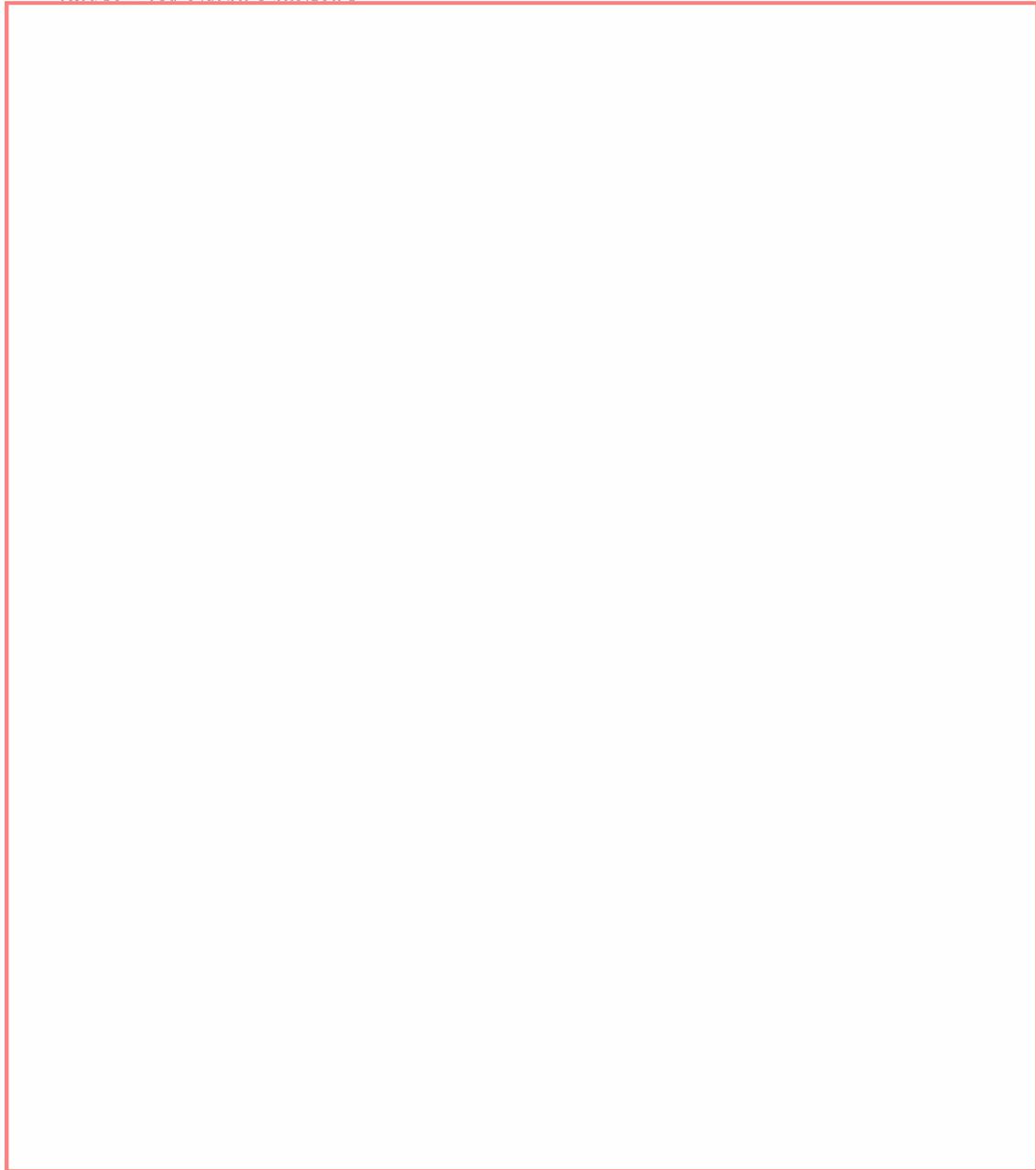
**II.e.1 Serious – Unknown Relationship to The Device AEs
By Time Period**



II.e.2. Serious – 6 Month Unknown Relationship to The Device AEs (window 137-273 days) – By Event Category



II.e.3. Serious – 12 Month Unknown Relationship to The Device AEs (window 274-547 days) – By Event Category



II.e.4. Serious – >24 Month Unknown Relationship to The Device AEs (window >912 days) – By Event Category



**II.f.1 Serious – Unrelated to The Device AEs
By Time Period**



II.f.2 Serious – Operative Unrelated to The Device AEs (day 0) – By Event Category

A large, empty rectangular box with a red border, intended for a table or chart related to the section header above.

II.f.3 Serious – Day 1-7 Unrelated to the Device AEs (window 1-21 days) – By Event Category

A large, empty rectangular box with a red border, intended for a table or chart related to the section header above.

II.f.4. Serious – 6 Week Unrelated to The Device AEs (window 22-63 days) – By Event Category



II.f.5. Serious – 3 Month Unrelated to The Device AEs (window 64-136 days) – By Event Category



II.f.6. Serious – 6 Month Unrelated to The Device AEs (window 137-273 days) – By Event Category

