Docket Submission to the September 8 and 9, 2011
Obstetrics and Gynecology Devices Panel
of the Medical Devices Advisory Committee:

SAFETY AND EFFECTIVENESS OF SURGICAL MESH FOR THE TREATMENT STRESS URINARY INCONTINENCE.

September 9, 2011

Prepared by
TRANSVAGINAL MESH INDUSTRY WORKING GROUP
AdvaMed, American Medical Systems, Bard Medical,
Boston Scientific, Ethicon Women's Health and Urology,
with assistance from Covidien, WL Gore, and Coloplast
August 30, 2011

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I. Executive Summary

Industry members have created a Transvaginal Mesh Industry Working Group (Working Group) through the trade association AdvaMed. This working group (comprised of Ethicon Inc, C.R. Bard, Boston Scientific, and American Medical Systems) submits this information to the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee to present data and information regarding the safety and effectiveness of surgical mesh devices used to treat stress urinary incontinence (SUI), and to present the Working Group's proposal on the premarket and postmarket regulatory pathway for these devices.

Section V of this submission provides an overview of the clinical success of surgical mesh products in the treatment of SUI. The data demonstrates that the benefits obtained with the use of surgical mesh for the treatment of SUI outweigh the risks.

Section VI, below, provides the Working Group's proposal on the premarket and postmarket regulatory pathway for transvaginal surgical mesh devices intended for the treatment of SUI (also referred to herein as, midurethral slings and tapes).

The Agency is considering changes to the regulation of these devices, such as reclassification from Class II to Class III, or additional premarket and postmarket regulatory requirements added to the Class II device requirements. The Working Group believes that the clinical data demonstrates that surgical mesh intended for the treatment of SUI is safe and effective, and that these products provide an important option to women in the treatment of this condition. We believe that the clinical success of these products for the treatment of SUI is well established and, therefore, the Working Group proposes that surgical mesh products intended for the treatment of SUI remain classified as Class II devices subject to the premarket notification (510(k)) requirements. However, in order to improve patient and physician information regarding these devices and support further advancement in the development of this technology, we propose that current guidance be substantially revised to ensure labeling consistency among marketed devices, and to standardize bench, in vitro, and in-vivo test requirements for SUI devices to support of 510(k) clearance.

II. Introduction: History of Vaginal Tape (Midurethral Slings)

Urinary incontinence is the unintentional loss of urine. SUI is prompted by a physical movement or activity – such as coughing, sneezing or heavy lifting – that puts pressure (stress) on the bladder (http://www.mayoclinic.com/health/stress-incontinence/DS00828).

The history of vaginal tape (today referred to as midurethral slings) for treatment of SUI first started in 1907 when Van Giordano described the use of a muscle structure (e.g., "sling") to serve as a support to the neck of the bladder for surgical treatment of incontinence. In the 1930s, muscle tissues were replaced with fascia. From that time onwards, multiple new materials were tested, some using muscle, some fascia and some transitioning to new products such as nylon or Marlex®[1].

In 1995, Ulmsten introduced the tension-free vaginal tape procedure, in which a woven prolene tape is positioned without fixation and in a tension-free manner at the level of the mid-urethra[2]. This novel, effective approach transformed the surgical treatment paradigm for SUI.

From 1995 onwards, slings have been continuously enhanced and many new innovations have surfaced to further improve the safety and effectiveness of the procedure to make it less invasive.

III. Sling Mesh Types – Features and Benefits

Mesh types used in slings have been classified into four different types, based on their pore size[3]. Meshes with pore sizes larger than 75µ are defined as Type I. Type II meshes have pore sizes less than 10µ whereas Type III and IV meshes have either microporous or submicronic pore sizes, respectively.

The advantages of type I prostheses are multiple. When interstices or pores are less than 10 microns, in each of their three dimensions, are present, bacteria averaging 1 micron cannot be eliminated by macrophages (16-20 micron) and neutrophilic granulocytes (9-15 micron), which are too large to enter a 10 micron 3-dimensional pore. Type I prostheses not only admit macrophages, they also allow rapid fibroplasia, ingrowth of collagen fibers and angiogenesis within their sufficiently wide pores, which prevents infiltration and growth of bacteria[3]. Peak ingrowth is reached at a pore size of around 400 - 500 microns. Larger pores limit the fibrosis process to the perifilament region and pores get filled with fat[7].

Type I meshes have been shown to be advantageous over other meshes as they present:

- Less foreign body reaction
- Lower risks of infections
- Rapid fibrinous fixation
- Greater tissue ingrowth

IV. Clinical Overview of Surgical Mesh for the Treatment of Stress Urinary Incontinence

A. Epidemiology and Definition

Approximately one in three women suffers from some degree of urinary incontinence. A Norwegian study reported the percentage of patients with SUI to be approximately half of all women with incontinence, the remainder characterized as urge (11%) and mixed-incontinence (36%)[8].

Additional studies have estimated that 30% of women older than 18 years of age may be negatively impacted by SUI. Both prevalence and severity of the conditions are associated with increasing age[9].

The variability in reported prevalence of SUI is mostly due to a lack of standard survey methodology. However, a definition for SUI was established by the International Continence Society Committee on Terminology in 2001[10]. The Table below summarizes the symptoms and observations associated with SUI.

Table 1: International Continence Society Standardization of Terminology of Lower Urinary Tract Dysfunction: Definition of stress urinary incontinence

Symptom: Subjective Indicator of Disease	Involuntary leakage on effort or exertion or on sneezing or coughing
Sign: Observed by Physician to Verify/Quantify Symptoms	Involuntary leakage from the urethra synchronous with exertion/effort or sneezing or coughing
Urodynamic Observations	Involuntary leakage during increased abdominal pressure without detrusor contractions

B. Anatomy of Stress Urinary Incontinence

Two physiological mechanisms contribute to the development of SUI[11]:

1) Hypermobility of a healthy urethra, due to a weakened support of the proximal urethra (or "Type 1 SUI"), and
2) Intrinsic sphincter deficiency, in which the sphincter fails to act as a tight outlet (or "Type 3 SUI").

"Type 2 SUI" is defined as an intermediate condition in which both physiological mechanisms may be involved.

Operative procedures for SUI are based on the physiological type of the disease[12], with Type 1 patients mostly treated by urethral/bladder neck stabilization, and Type 3 patients treated with urethral sphincter augmentation. Procedures described herein are designed to treat primarily Type 1 patients.

C. Patient Impact

SUI is not a life-threatening condition but has significant impact on a patient's quality of life. The Incontinence Quality of Life (I-QOL) questionnaire is one of the questionnaires that has been validated as an incontinence-specific outcome tool and has been utilized to determine the impact of SUI. Analyses with the I-QOL confirmed the role of SUI in creating avoidance behaviors and limiting opportunities for patients, impacting psychosocial functions and creating social embarrassment[13].

D. Traditional Surgical Treatment Options

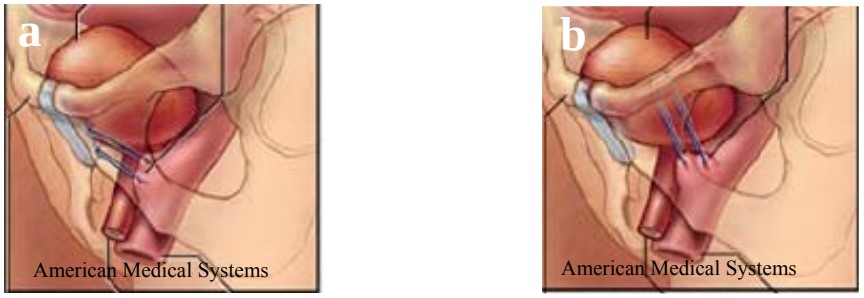
Prior to the introduction of slings, the treatment of Type 1 SUI was mostly achieved by lifting the tissues near the bladder neck and proximal urethra to a higher intrabdominal position, thus decreasing hypermobility. These procedures are called retropubic colposuspension and come in a number of variations, as described below and shown in Figure 1.

Marshall-Marchetti-Krantz Procedure: The Marshall-Marchetti-Krantz (MMK) procedure involves suspension of the bladder neck onto the periosteum of the pubis symphysis (the midline cartilaginous joint uniting the pubic bones).

Burch Procedure: This transabdominal technique involves suspending the paravaginal tissues towards ligaments on the pelvic sidewalls (ileopectineal "Coopers" ligament). Additional sutures are sometimes used to correct a significant vaginal wall prolapse.

A laparoscopic Burch procedure was also developed. Clinical outcomes for both Burch and laparoscopic Burch procedures were recently reviewed in a Cochrane review and found to be similar[14]. The Burch procedure was considered the "Gold Standard" for SUI for many years.

Figure 1: Graphical representation of the MMK (a) and Burch (b) Procedures for SUI



Success and Complication Rates of Traditional Treatment Options

While the success rate of the MMK procedure was high (85% at 5 years and 75% at 15 years), complication rates reached 21% of all cases, with an incidence of urethrovaginal fistulas in 0.3% and osteitis pubis in 2.5% of patients[15]. Long-term voiding disorders and *de novo* detrusor instability was observed in 11% of patients. The risks associated with the MMK procedure, including damaging the sphincter and developing osteitis pubis, prompted the development of the of Burch colposuspension procedure.

Following the Burch procedure, the objective continence rate post-surgery reached 84.3% in first-time patients, with 82% and 69% continuous success rates at 5 and 12 years. Beyond regular surgical risks associated with an open, abdominal procedure, long-term complications included voiding difficulties and urinary retention, which occurred in less than 4% patients, and development of rectocoele and, or enterocoele in 7% and 17% patients, respectively[16].

E. Medical Advances in Surgical Mesh Devices for SUI

Sling-augmented procedures underwent parallel development with open retropubic colposuspension procedures since the beginning of the 20th century. Autologous graft materials collected from the abdomen or the inner thigh were originally re-implanted as slings. The added morbidity of harvesting these autografts prompted development of other types of grafts, specifically allografts and xenographs. While these products were safe, their long-term efficacy was questionable[17]. Synthetic materials entered the SUI surgical market in the early 1960's with products such as the Marlex® graft. Early experience with these materials was suboptimal, with failure rates as high as 23% due to local complications[18].

1. Retropubic Tension-Free Vaginal Tape

In the mid 1990's, Ulmsten *et al* changed the SUI treatment therapy paradigm by suggesting that surgical correction focus on versus proximal urethra support. They designed a new surgical treatment, using synthetic grafts called "tension free vaginal tape", since the grafts were left without tension, restoring support to the urethra and reinforcing pubourethral ligaments.

Ulmsten's surgery was described as an "ambulatory procedure" – total surgery time amounted to 22 minutes conducted under local anesthesia and, more importantly, reached a clinical success equivalent to that reported with the Burch Procedure, with a cure rate of 84% at 2 years post-operatively[19].

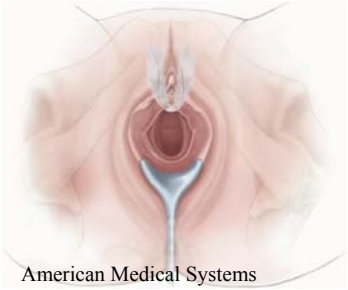
Building on Ulmen's work, today's sling procedures last approximately 30 minutes, allowing the majority of patients to void spontaneously soon after surgery and be discharged without a catheter.

2. Retropubic Midurethral Tapes: Top-to-Bottom and Bottom-to-Top Approaches

sling procedures can be defined as 'top-to-bottom' or 'bottom-to-top'. A 'bottom-to-top' approach indicates that the needles are passed from the vagina, inside the patient, up to the abdominal incisions. A 'top-to-bottom' approach is effectively the opposite, with needles being passed from the abdominal incision down to a sagittal incision in the vagina.

The final position of the sling is around the mid-urethra in what has been referred to as a "U-shape," as shown in Figure 2 below. Both approaches lead to the same configuration of the tape implant.

Figure 2: Graphical representation of a "U-shaped" positioning



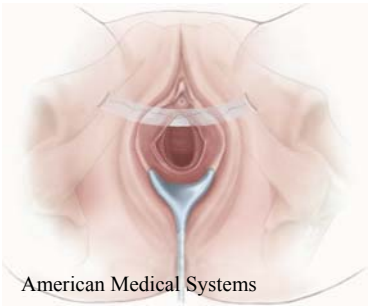
3. Transobturator System

While the sling procedures eliminated complications observed with the Burch procedure, they required blind passage of the needle holding the sling through the retropubic space, which occasionally resulted in perforation of the bladder. The transobturator approach was developed to avoid the bladder as well as rare but serious complications such as injury to major vessels or the bowel. The procedure was first described by Delorme in 2001[20]. It is an entirely perineal technique in which the route of the needle is parallel to

the perineal membrane and through the obturator membrane, remaining below the level of the pubocervical fascia and the levator plate.

The resulting position of the tape has been referred to as a "hammock" shape. This is due to the more lateral, horizontal placement of the mesh arms through the obturator foramen. The mesh sling is, however, still placed without tension at a midurethral position, as shown in Figure 3 below.

Figure 3: Graphical representation of a "Hammock shaped" positioning



The transobturator procedures were demonstrated to have similar efficacy to the retropubic procedures and reduced risk of bladder perforation. However, they did show a slight increase in adverse events, such as of groin/thigh pain.

4. Single Incision Transvaginal Slings

The transvaginal single incision sling is the latest development in devices addressing SUI, and involves only one vaginal incision, no abdominal incisions and can be performed in less than 10 minutes, under local anesthesia.

The single incision sling is placed using the same vaginal incision and position as in the transobturator approach. A small incision is made under the urethra and the sling is placed in a hammock type position, as shown in Figure 3 above. This procedure has also been described in a number of published reports and reached an overall cure rate at 12 months of 91.4%[21]. One meta-analysis concluded that single-incision slings are associated with a slightly lower objective cure rate on the short-term follow-up (RR: 0.85; 95% CI, 0.74-0.97) but also confirmed lower day 1 postoperative pain[22]. The meta-analysis has significant limitations as the more recently introduced single incision sling devices are not well evaluated.

F. Patient Selection

Patient selection for the procedures defined above follow general guidelines for surgical treatment of stress urinary incontinence. Specifically, stress urinary incontinence cannot be related to detrusor overactivity, fistulas or neurological disease. The clinical cough stress test is also recommended for patients undergoing surgery, to confirm the diagnosis[21]. The role of urodynamics in patient selection is less clear. The National Institute of Clinical Excellence (NICE) Guidelines on Urinary Incontinence mention that

"Urodynamics are of value if the clinical diagnosis is unclear prior to surgery or if initial surgical treatment has failed"[23].

As described above, the different placement approaches for slings also have risks and benefits that should be considered during patient selection. For instance, in an obese patient it may be easier to correctly place a retropubic sling, while a patient who is a riskier surgical candidate may be better treated with a single incision sling. The range of options allows determination of the optimal treatment for each patient's unique situation.

G. Physician Learning Curve

Patient selection and surgical technique are critical for the success of any surgical procedure. Transobturator and transvaginal sling procedures provide standardized technique and use well-recognized landmarks, which can facilitate the procedures and reduce risks. However, physicians performing these procedures must be knowledgeable in pelvic floor anatomy and surgery.

The learning curve is associated with complication rates in many medical procedures. Three studies in the English literature report the learning curve for the TVT procedure. Kuuva and Nielson found a decline in the number of complications per surgeon after 15 procedures[24]. Groutz et al found 5 bladder injuries in the first 20 patients, whereafter no further injuries occurred[25]. Schraffordt Koops et al, in their analysis of a large registry, also concluded that success was higher after surgeons had performed 20 TVT procedures[26].

In addition, product-specific training is required to ensure appropriate use of technologies. Thus, proper physician training and experience are a requirement for success. Members of the Working Group remain committed to providing state-of-the-art professional education programs to advance surgeon skill and knowledge in performing these procedures.

V. Safety and Effectiveness Data on Surgical Mesh for the Treatment of SUI

Below we provide an analysis of the clinical experience with surgical mesh products for the treatment of SUI. First, we discuss the results of our analysis of adverse event information. Second, we discuss the results from data obtained from published clinical literature. Finally, we provide a discussion regarding the risks and benefits of the use of surgical mesh for the treatment of SUI. In brief, we believe the data demonstrates that surgical mesh is safe and effective for use in the treatment of SUI. Moreover, the data support a recommendation that the device for SUI remain as a Class II device.

A. Adverse Event Data Analysis

The Working Group takes medical device reporting obligations seriously and members diligently monitor and report to the FDA complications associated with the use of our member's devices; however, there are inherent limitations with the adverse event reporting. As FDA noted in its White Paper, "[m]ultiple factors can affect MDR reporting, including increased use of urogynecologic surgical mesh in the clinical

community, increased awareness of the potential adverse events associated with mesh after the 2008 [FDA Public Health Notice], an increased number of new . . . meshes on the market, or an increase in the actual adverse events associated with mesh."[4] Wide variability in both the content of the reports and the circumstances prompting a person to report or not to report prevents reporting rates from being "used to reliably estimate incidence rates."[5] In fact, the FDA website states that "MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices". Therefore, while adverse event reports are useful, they must be considered in light of their inherent limitations.

However, to provide additional information and perspective to the MAUDE database number put forward by the FDA, internal MDR filing information from Working Group members was provided to AdvaMed for an analysis of MDR rates for the periods of January 1, 2005 – December 31, 2007 and January 1, 2008 – December 31, 2010. The combined data represents more than 90% of the units sold Each participating company evaluated their own MDR submissions and sales information to create summaries which were then sent to AdvaMed where the data was de-identified and aggregated. Each company maintains the actual evaluation report for each MDR.

Each MDR was evaluated for all instances of the five following outcomes: exposure, erosion, infection, pain, dyspareunia, and other. Erosion and exposure were specifically defined. Erosion refers to mesh visible inside hollow organ, e.g. inside bladder while exposure refers to event when the implanted mesh is not covered by epithelium, typically along suture lines. Each outcome was evaluated as serious, minor, or indeterminate defined as follows:

- Serious: major short-term effect, e.g. surgery, sepsis, severe pain requiring mesh removal or long term narcotics
- Minor: short term mild-moderate severity, minor long term effects
- Indeterminate: reported but severity was indeterminate

An additional outcome evaluation, "none" was possible under "other" if the report indicated a malfunction but no injury.

This review of the overall MDR rate, as well as rates associated with serious adverse events (SAE), indicated that while there was an increase in adverse events overall, the rate remains low with an average rate of 0.13% for the 2008 to 2010 period. When comparing the number of serious adverse events to the total adverse events for each time period, it was determined that the 2005 to 2007 period had a 33% rate of SAE/Total AE (0.02%SAE) and 2008 to 2010 had a rate of 31% (0.04% SAE). Therefore, the ratio between serious adverse events and total adverse events has remained constant between the two time periods. While the Working Group analysis is still saddled with many of the limitations of the MAUDE database itself, the usefulness of the denominator information allows a better analysis of the change in event rates.

B. Published Literature

The 2009 Cochrane Collaboration (Ogah et. al.) entitled "Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women" summarizes the results of published clinical trials on slings versus other available treatment options

available at the time of the review. The Cochrane review concluded that the current evidence base suggests that minimally invasive synthetic suburethral sling operations are as effective as traditional suburethral slings, open retropubic colposuspension and laparoscopic colposuspension in the short-term but with less postoperative complications. Objective cure rates are higher with retropubic tapes than with obturator tapes but retropubic tapes attract more complications. They also noted that most of the trials had short-term follow-up and the quality of the evidence was variable[27].

In a shortened version of this Cochrane analysis the authors stated that major complications such as nerve, bowel or major vascular injuries, pelvic hematoma, necrotizing fasciitis, ischiorectal abscess, and death are uncommon. The true incidence is more likely to be determined from large national registries and voluntary reporting registries or databases for reporting complications, such as the FDA's manufacturer and user facility device experience (MAUDE) than from small RCT's [6].

Several of these registries have reported on TVT. The number of procedures ranged from 809 to 2,795, and the rate of major complications was low: bladder perforation occurred in 2.7-3.9% of cases (significantly higher in those with previous pelvic organ prolapse or incontinence surgery). There was no record of the sequelae of the perforations. Reoperation rates relating to tape insertion or postoperative voiding dysfunction ranged from 1.6% to 2.4%; pelvichematoma occurred in 0.7% to 1.9% of women, the majority of which needed no intervention, and only one case of bowel injury was recorded. Registries of transobturator tapes reported much lower rates of complications (e.g., bladder perforation in 0.4%). Reoperation occurred in 0.8% to 2.2% of women and hematoma occurred in 1 out of 2,543 procedures. Urethral injury rates ranged from 0.08% to 0.1%. The above the meta-analysis concluded that minimally invasive synthetic suburethral sling operations are highly efficacious both in the short and medium term for treatment of women with SUI with low rates of complications[6].

In order to ensure that all relevant comparisons of midurethral sling studies to non-mesh methods were included in the scope, a literature review was conducted to identify randomized studies published since the cutoff date utilized by Ogah et. al. A total of five publications were identified and their results located in Appendix III, along with the literature search methodology utilized. These additional studies reinforce the findings from the Cochrane review.

The Working Group agrees that the literature appropriately identifies the adverse event profile associated with slings. Sling adverse events do occur; however, there are other adverse events in traditional surgery. The advancement of midurethral sling types has allowed surgeons and patients to determine the appropriate therapy options across a broader spectrum of patient population without having to compromise on risk as compared to benefit. As documented below, adverse events that do occur have been shown to be easily addressed.

Bladder perforation is the most common complication encountered in retropubic mid urethral slings. One large national registry in the Netherlands reported that all cases could be diagnosed during the procedure. This complication can be managed perioperativley by means of tape reinsertion and placement for an indwelling catheter for a short time. Schraffordt et al confirmed that at follow-up none of these patients had any problems[26]. Gold et al also stated that TVT-related urinary tract injury was not associated with

increased perioperative morbidity and that the cure rates were similar with and without injury[28].

The most common intraoperative problem with the transobturator midurethral slings is a 3.3% rate of increased intraoperative bleeding. This is slightly higher than the 1.9% reported for a series for the retropubic tension-free vaginal tapes. However, in a large Austrian registry on 2543 operations with 11 different transobturator tape systems, there were no intraoperative conversions for bleeding with the transobturator tapes, only 1 reoperation for a postoperative hematoma, and no reports of hematomas managed expectantly, while the retropubic TVT has an approximately 1% rate of bleeding problems requiring reintervention[29].

The extensive published literature demonstrates subjective and objective cure rates as measured to date to be similar to traditional therapy options. In addition, the sling option provides significant operative time savings as compared to other therapies, with the exception of the laparoscopic approach. There is also a clear health economic benefit to the midurethral slings in comparison with the open Burch colposuspension as a consequence of shorter operating times and hospital stays, in addition to the patience's full return to work in a shorter time frame[30].

C. Benefit/Risk Analysis

There are many factors that go into weighing the benefit of a device versus its risk. Factors the FDA considers in this determination include alternative treatment options and understanding of the device risk profile. Industry agrees with FDA that a given benefit/risk profile can alter over the market lifespan of the device. In the case of midurethral slings, significant learning and device design technological advances have allowed this treatment type to become common practice and further highlights the benefit being experienced by both patients and surgeons. Below is a summary of the Working Group's conclusion on midurethral sling benefit-risk determination based on the published literature and current field experience.

Type, Magnitude and Duration of the Benefit: The clinical benefit from midurethral sling procedures has been significant and long-lasting. The large patient population affected by SUI and successfully treated with midurethral slings further strengthens the overall benefit profile of these procedures.

Probability of the Patient Experiencing the Benefit: The appropriate patient population and the appropriate pre-surgical workup have been well established and shown to maximize success of the procedure and minimize risk. Patients return to daily activities sooner and experienced less pain as compared to traditional repairs.

Adverse Events and Serious Adverse Events: As demonstrated in published literature, the midurethral sling is associated with fewer peri-operative complications than traditional vaginal and abdominal surgeries. Post-operative complications due to the tapes are extremely rare and manageable.

In conclusion, there is strong evidence available to date that demonstrates that the midurethral sling has a favorable benefit/risk profile and that these procedures are

valuable treatment options for women suffering from SUI. The risk and benefit is well characterized and understood by the clinical community.

VI. Proposed Regulatory Pathway for Surgical Mesh for the Treatment of SUI:

The Working Group believes that the classification of surgical mesh devices intended for the treatment of SUI should remain Class II and subject to the 510(k) requirements. The adverse event data analyses, the review of scientific literature, and the risk/benefit information provided above all support a determination that the current regulatory scheme (i.e., Class II, 510(k) requirements) applicable to surgical mesh devices intended for SUI treatment provide reasonable assurance of the safety and effectiveness of the device. The mechanism of action and the benefit of midurethral slings in the treatment of SUI are well established and clinical studies have demonstrated at least equivalent results with lower associated morbidity rates for midurethral slings compared to traditional approaches. The risks associated with the use of midurethral slings are rare, manageable, and the rate of surgical risks is lower with the sling procedures than with traditional approaches. The data demonstrates that the current regulatory controls are adequate in ensuring the safety and effectiveness of surgical mesh devices intended for SUI treatment.

The Working Group also proposes that the current FDA guidance document, "Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh," issued March 2, 1999, be updated or replaced, to include specific information related to SUI for bench, *in-vitro* and *in-vivo* test requirements to support premarket clearance. In addition, the document should be revised to provide specific guidance allowing for clear, consistent, and uniform information for patients and physicians about the safety and effectiveness of these products. Continued use of the SUI clinical trial guidance document "Guidance for Industry and FDA Staff – Clinical Investigations of Devices Indicated for the Treatment of Urinary Incontinence" issued March 8, 2011, is appropriate. The Working Group believes that these changes will ensure that appropriate scientific evidence is provided for FDA review and assessment of SUI devices under the 510(k) process.

The use of surgical mesh has become widely accepted and often is the preferred treatment option within the medical community. The 510(k) process has facilitated the transformation of successful treatments for this condition. The application of the current regulatory scheme has supported innovation, facilitated improvement in surgical care, and timely access to treatment options for patients suffering from a difficult condition that is demonstrating a growing prevalence.

We note that FDA's July 2011 safety notice proposed the reclassification of the device from Class II into Class III, which would establish the more stringent premarket approval (PMA) regulatory requirements for these products. However, we do not believe that PMA requirements are necessary to provide reasonable assurance of the safety and effectiveness of the device. These devices do not pose an unreasonable risk of illness or injury to patients, and sufficient clinical information exists demonstrating that the devices have adequate safe and effective clinical performance. Therefore, we do not recommend that the device be reclassified into Class III.

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Appendix I – Transvaginal Mesh Industry Working Group Panel Presentation

Full Working Group slide presentation will be provided under separate cover

Appendix II – Cochrane Collaboration Publication

Appendix III – Literature Search Methodology and Summary

Appendix IV – Referenced Literature

Reference Literature will be provided electronically under separate cover

Post-Cochran Collaboration Publication Literature Review Methodology and Summary

Literature Search Methodology

The literature review was conducted on 18 August 2011 to assess clinical evidence from the date of the Cochrane Collaboration 2009 review, "Minimally invasive synthetic suburethral sling operations for stress injury incontinence in women (Review)" to describe the safety, efficacy and performance of those products when used as intended. The date range was selected to update information on synthetic suburethral sling versus non synthetic sling clinical studies.

The literature search was conducted using PubMed, which is a service of the U.S. National Library of Medicine that includes over 17 million citations from MEDLINE and other life science journals for biomedical articles. MEDLINE is a premier bibliographic database containing bibliographic citations and author abstracts from more than 5,000 biomedical journals published in the United States and 80 other countries. The medium used for this literature search of PubMed was online using Internet Explorer. The PubMed database was searched using the following search terms:

(urinary incontinence OR urodynamic stress incontinence OR urgency urinary incontinence OR urge incontinence urinary OR stress urinary incontinence OR SUI)
AND
(suburethral slings OR tension free vaginal tape OR tvt OR transvaginal tape OR transobturator tape OR tot OR tvt-o OR ivs OR sparc OR lynx OR monarc OR miniarc)

Limits: Humans, Female, Clinical Trial or Randomized Controlled Trial, English, Adult, date range 4/1/2008 – 8/16/2011

The literature search focused on randomized controlled human studies presented originally in English that referenced any synthetic suburethral sling versus non synthetic sling clinical studies. General review articles, editorials, letters, conference papers/posters and meeting abstracts, and non-human studies were excluded as the scientific rigor and data objectivity in these formats are not typically peer-reviewed and are not considered to be scientifically robust enough for clinical evidence determination.

Table 1: Updated Literature Post 2009 Cochrane Review – Synthetic versus Non-Synthetic Slings

Reference	Study Design	Outcomes	Comments
Guerrero et al. 2010	Prospective, Randomized study ***Geography*** UK ***Treatment*** Pelvicol graft vs. Autologous Fascial Sling (AFS) vs. tension free vaginal tape (TVT) ***Sample Size*** TVT = 72 Pelvicol = 50 AFS = 79 ***Follow-up*** 1 year	***Performance/efficacy*** AFS had longer operative times, p <0.001: • Pelvicol: 36 min • TVT: 35 min • AFS: 54 min AFS had higher Intermittent Self Catheterization rates, p <0.001: • Pelvicol: 0% • TVT: 1.5% • AFS: 9.9% ***Follow-up*** At 6 weeks: • All 3 arms subjectively equally effective At 6 months: • Pelvicol has reduced Improvement ,p < 0.003: o Pelvicol: 73% o TVT: 92% o AFS: 95% At 1 year: • Pelvicol has reduced Improvement ,p < 0.001: o Pelvicol: 61% o TVT: 93% o AFS: 90% • Pelvicol has poored Dry Rates, p 0.001: o Pelvicol: 22% o TVT: 55% o AFS: 48% No difference in the success rates between TVT and AFS.	During interim analysis, recruitment for Pelvicol arm stopped due to significantly poorer results. Due to poor recruitment rates, study was underpowered to demonstrate a difference between TVT and AFS.

Reference	Study Design	Outcomes	Comments
		Safety No statistical differences in bladder injury complications across all arms, p 0.6386. • Pelvicol: 1/50 • TVT: 4/72 • AFS: 2/79 One patient in the Pelvicol and one in the AFS arm required urethrolysis within 6 weeks of the initial procedure, p 0.444. AFS had a higher rate of self catheterization at 6 weeks (7/71 = 9.9%) than Pelvicol (0/47) or TVT (1/67), p 0.013. 9/46 (19.5%) women in the Pelvicol arm had further surgery for SUI by 1 year, while no patients required further surgery in TVT or AFS p < 0.0001.	
Téllez Martínez-Fornés et al. 2009	Open randomized study ***Geography*** Spain ***Treatment*** TVT vs. Colposuspension (CS) ***Sample Size*** TVT = 24 CS = 25 ***Follow-up*** 3 years	***Performance/efficacy*** TVT lower in the following categories, p < 0.0001: • Surgical time o TVT= 41.1 +/- 10.9 minutes o CS = 57.1 +/- 18.3 minutes • Consumption of Post-op analgesics o TVT = 6 [2.8-10.5] capsules o CS = 23.5 [18.0-31.5] capsules • Length of Post-op hospital stay o TVT = 1 [1-2] days o CS = 3 [3-3] days No statistically meaningful differences in Incontinence Severity Index (ISI) and Incontinence Impact Questionnaire (IIQ) scores between TVT and CS at 6 mo., 1 yr or 3 years(p = 0.02).	None

Reference	Study Design	Outcomes	Comments
		No statistically significant differences at any follow-up time point for post-op urinary urgency, post-op obstructive symptoms, one-hour pad test, uroculture or free flowmetry between the two treatments. ***Safety*** No statistically significant differences in the following intraoperative or postoperative complications: • Vesical lesion, p 0.19 o TVT = 4 (17.4%) o CS = 1 (4.2%) • Urinary infection, p 0.49 o TVT = 1 (4.3%) o CS = 0 • Urinary retention, p value = 1 o TVT = 5 (21.7%) o CS = 1 (4.3%) • Wound infection, p 0.35 o TVT = 3 (13%) o CS = 1 (4.2%) • Others, p 0.14 o TVT = 2 (8.7%) o CS = 7 (29.2%) • Readmission, p value = 1 o TVT = 0 o CS = 1 (4.2%) There was one instance of vaginal mucosa erosion caused by the urethral band requiring exeresis of the band, CS and closure of the vaginal mucosa.	
Tcherniakovsky et al. 2009	Randomized study ***Geography*** Brazil	***Performance/efficacy*** Procedure duration statistically different, p< 0.0001: • Safyre-T = 12.8 +/- 2.4 • Abdominal sling = 59.7 +/- 10.3	None

Reference	Study Design	Outcomes	Comments
	Treatment Safyre-t Transobturator Sling (TOT) vs.Abdominal Retropubic Sling (autologous aponeurosis of abdominal rectus muscles) ***Sample Size*** Safyre-T = 21 Abdominal sling = 20 ***Follow-up*** 12 months	No differences in efficacy (cure and failure rates) between Safyre-T and abdominal sling. The following were not statistically different: • Mean hospitalization time (hrs), p > 0.05: o Safyre: 24 o Abdominal sling: 48 • Mean post-op catheterization (hrs): o Safyre: 24 o Abdominal sling: 48 ***Safety*** One operative complication occurred: • Safyre-T: vesical perforation due to needle carrier No patient presented with excessive intraoperative bleeding, fever, post operative vaginal bleeding, or intense pelvic pain. Postoperative complications statistically different , p< 0.011: • Safyre-T = 3 o 1 vaginal mesh erosion, o 2 urinary retention • Abdominal sling = 12 o 1 suture dehiscence o 3 urinary retention o 2 urinary infection o 1 surgical wound infection o 5 seroma and/or hematoma	
Amaro et al. 2009	Randomized study ***Geography*** Brazil	***Performance/efficacy*** Operative time was significantly shorter in the TVT compared to AFS group, p < 0.05 • TVT = 33 (25-70) min	None

Reference	Study Design	Outcomes	Comments
	Treatment TVT vs. Autologous Fascial Sling (AFS) ***Sample Size*** TVT = 20 AFS = 21 ***Follow-up*** 36 months	• AFS = 70 (45-105) min No differences were observed in the following: • Mean dosage of analgesics (mg) (range), p > 0.05: o TVT: 142 (50-473) o AFS: 85 (15-269) • Mean hospitalization time (hrs) (range), p > 0.05: o TVT: 24 (24-48) o AFS: 24(24-48) • Mean post-op catheterization (hrs) (range), p > 0.05: o TVT: 24 (12-72) o AFS: 24 (12-48) • Mean days to normal activities (range), p > 0.05: o TVT: 30 (4-90) o AFS: 30 (3-90) • Satisfaction rate, p > 0.05: o TVT: unsatisfied 42%, satisfied 58% o AFS: unsatisfied 20%, satisfied 80% • Post-op condition-specifics, TVT and AFS, p > 0.05. • Cure rate, no significance in any group: o TVT: ▪ 1 month = 75% ▪ 12 months = 70% ▪ 36 months = 63% o AFS: ▪ 1 month =71% ▪ 12 months = 57% ▪ 36 months = 55%	

Reference	Study Design	Outcomes	Comments
		Safety No differences were observed in the following: • Bladder injuries, p 0.64 o TVT: 2 (10%) o AFS: 1 (4.8%) • De novo urgency symptoms o TVT: 42% o AFS: 40% Two patients (one from each group) died from other diseases within the 36 month follow-up period.	
Sharifiaghdas and Mortazavi 2008	Prospective, Randomized, Iran ***Treatment*** (TVT) vs. Autologous rectus Fascia Sling (AFS) ***Sample Size*** TVT = 52 AFS = 48, however 39 were lost-to-follow up after 1 year. TVT = 25 AFS = 36 used for analysis ***Follow-up*** Mean follow-up time in months: TVT = 38.5 AFS = 40	***Performance/efficacy*** The following were significantly shorter in the TVT compared to AFS group: • Mean operative time, p 0.01: o TVT = 45 (30-70) min o AFS = 80 (50-180) min • Mean post-op catheterization (days), p 0.001: o TVT: 1.3 (1–5) o AFS: 4.6 (3–6) • Mean hospitalization time (days), p 0.001: o TVT: 2 (1-5) o AFS: 5 (3-7) The following were not significantly different between TVT and AFS: • Objective cure rate (1 hr test pad), p 0.83 o TVT: 76% o AFS: 72% • Negative cough stress test , p 0.9 o TVT: 88% o AFS: 83% • Subjective cure (Incontinence Intensity Questionnaire), p 0.46 o TVT: 44.3 (range 35.2-61.5)	None

Reference	Study Design	Outcomes	Comments
		o AFS: 48.5 (range 38.5-69.7) • Satisfaction (VAS score), p 0.3 o TVT: 15 (72%) o AFS: 20 (55%) ***Safety*** The following differences were observed in TVT compared to AFS: • Bladder penetration, p 0.05: o TVT: 6 (24%) o AFS: 2 (8%) • Perioperative Bleeding (> or = to 100ml): o TVT: 6 (24%) o AFS: 11 (30%) • Perioperative Bleeding requiring blood transfusion (> or = to 250ml), p 1.00: o TVT: 1 (4%) o AFS: 1 (5%) The following operative complications were reported in the 6 to 12 month follow-up: • Residual urine >100ml, p 0.4: o TVT: 1 (4%) o AFS: 5 (14%) • Release of sling patient, p 1.00: o TVT: 1 (4%) o AFS: 2 (5%) The following operative complications were reported in the greater than 1 year follow-up: • Self reported de novo urge incontinence, p 0.1: o TVT: 1 (4%) o AFS: 8 (22%) • Changes in voiding pattern, p 0.5: o TVT: 5 (20%) o AFS: 11 (31%)	

Reference	Study Design	Outcomes	Comments
		The following post operative complications were reported: • AFS: 1 release of suprapubic knots at 1 mo. • AFS: 1 combined vaginoabdominal urethrolysis at 6 mo. • AFS: 1 suprapubic incisional repair at 8 mo. • TVT: 1 left sided suprapubic hernia in route of needle passage.	