

**SURGICAL MESH  
FOR TREATMENT OF WOMEN WITH  
PELVIC ORGAN PROLAPSE  
AND  
STRESS URINARY INCONTINENCE**

**FDA EXECUTIVE SUMMARY**

**OBSTETRICS & GYNECOLOGY DEVICES  
ADVISORY COMMITTEE MEETING**

**SEPTEMBER 8-9, 2011**

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## **1. INTRODUCTION**

On September 8-9, 2011, the Food and Drug Administration (FDA) will convene the Obstetrics & Gynecology Devices Advisory Committee to discuss the use of surgical mesh for treatment of pelvic organ prolapse (POP) and stress urinary incontinence (SUI).

The panel will be asked to provide input on the risks and benefits of surgical mesh used for POP repair based on the published literature and adverse event data from the FDA's Manufacturer and User Device Experience (MAUDE) database. The panel will also weigh in on the FDA's proposed premarket and postmarket regulatory strategies for surgical mesh indicated for POP repair, including reclassification into Class III (premarket approval) and postmarket surveillance studies.

The panel will also be asked to consider the risks and benefits of surgical mesh to treat SUI. The FDA is seeking the panel's input on the need for additional clinical studies (premarket and/or postmarket) on all or a subset of surgical mesh indicated to treat SUI based on data from the published literature and the MAUDE database.

This executive summary provides an analysis of the adverse event reports received by the FDA through the MAUDE database and an overview of the published literature for both the POP and SUI indications. This document also describes the regulatory options available to the FDA to address its concerns raised by the published literature and MAUDE reports. The clinical discussion is prefaced by an overview of several key regulatory considerations that must also factor into the panel's recommendations.

## **2. REGULATORY CONSIDERATIONS**

### ***2.1 Risk Based Classification & Regulation of Medical Devices***

The Medical Device Amendments to the Food, Drug, and Cosmetic Act (the Act) were enacted in 1976. These amendments classified device types into one of three classes (Class I, II, or III) based on the risks posed by the device and the regulatory controls needed to provide adequate assurance of its safety and effectiveness.

Per Section 513 of the Act [21 U.S.C. 360c] (a)(1), "There are established the following classes of devices intended for human use:

#### **(A) CLASS I, GENERAL CONTROLS**

- (i) A device for which the controls authorized by or under section 501, 502, 510, 516, 518, 519, or 520 or any combination of such sections are sufficient to provide reasonable assurance of the safety and effectiveness of the device.

- (ii) A device for which insufficient information exists to determine that the controls referred to in clause (i) are sufficient to provide reasonable assurance of the safety and effectiveness of the device or to establish special controls to provide such assurance, but because it—
  - (I) is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and
  - (II) does not present a potential unreasonable risk of illness or injury,is to be regulated by the controls referred to in clause (i).

(B) CLASS II, SPECIAL CONTROLS

A device which cannot be classified as a Class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance, including the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines (including guidelines for the submission of clinical data in premarket notification submissions in accordance with section 510(k)), recommendations, and other appropriate actions as the Secretary deems necessary to provide such assurance. For a device that is purported or represented to be for a use in supporting or sustaining human life, the Secretary shall examine and identify the special controls, if any, that are necessary to provide adequate assurance of safety and effectiveness and describe how such controls provide such assurance.

(C) CLASS III, PREMARKET APPROVAL

A device which because

- (i) it (I) cannot be classified as a Class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and (II) cannot be classified as a Class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and
- (ii) (I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or (II) presents a potential unreasonable risk of illness or injury,

is to be subject, in accordance with section 515, to Premarket approval to provide reasonable assurance of its safety and effectiveness.”

In summary, general controls apply to all three device classes and include establishment registration and device listing with the FDA, requirements for reporting and keeping records of adverse events, and compliance with the Quality System regulation.

Special Controls apply only to Class II devices. Special Controls may include one or more of the following:

- physician labeling
- patient labeling
- premarket studies, e.g., bench studies, animal studies, clinical studies to demonstrate substantial equivalence
- performance standard(s)
- guidance document
- enhanced postmarket surveillance
- patient registry

Class III devices are subject to an independent assessment of safety and effectiveness during premarket review. This includes the following premarket and postmarket controls:

- Premarket submission of valid scientific evidence to determine reasonable assurance of safety and effectiveness as described in 21 CFR 860.7 (b)(2)
- In depth premarket review of manufacturing information and pre-approval manufacturing inspection
- Post-approval studies to obtain long-term data (if needed)
- Annual reporting
- All postmarket device and labeling changes must be reported to FDA (significant changes require approval by the FDA prior to implementation)

## **2.2 *Premarket Review of Medical Devices***

Many Class II and most Class I devices are exempt from premarket review. The FDA reviews premarket notifications or 510(k) submissions for most Class II devices to determine whether the device is “substantially equivalent” to a legally marketed Class II device. In contrast to the determination the FDA makes in evaluating a premarket approval (PMA) application for Class III devices, the 510(k) review is comparative. 510(k) submissions may contain clinical data; however, these data are used to demonstrate substantial equivalence rather than to independently provide a reasonable assurance of safety and effectiveness for the device. Only Class III devices subject to PMA requirements allow for an independent assessment of safety and effectiveness premarket.

### **2.3 Section 522 Postmarket Surveillance Studies**

Although the FDA can order post-Approval studies for any device approved via a PMA submission, the FDA has more limited authority to order such studies for 510(k) devices. If a public health concern arises, postmarket surveillance under Section 522 of the Act is one means by which the FDA can obtain additional safety and/or effectiveness data for a device after it has been cleared through the 510(k) process or approved through a PMA, humanitarian device exemption (HDE), or product development plan (PDP) process. However, postmarket surveillance is not a substitute for obtaining the necessary premarket information to support 510(k) clearance or PMA, HDE, or PDP approval.

#### **2.3.1 Statutory Criteria**

Section 522 of the Act [21 U.S.C. 360l] authorizes the FDA to require postmarket surveillance in the following instances:

- a Class II or Class III device for which failure of the device would be reasonably likely to have a serious adverse health consequence (Section 522(a)(1)(A)(i) of the Act),
- a Class II or Class III device expected to have significant use in pediatric populations (Section 522(a)(1)(A)(ii) of the Act),
- a Class II or Class III device intended to be implanted in the human body for more than one year (Section 522(a)(1)(A)(iii)(I) of the Act), or
- a Class II or Class III device intended to be a life-sustaining or life-supporting device used outside of a user facility (Section 522(a)(1)(A)(iii)(II) of the Act).

One or more of the criteria above need to be met for Section 522 postmarket surveillance to be considered by the FDA.

#### **2.3.2 Postmarket Surveillance Study Process**

The Center for Devices and Radiological Health (CDRH) may identify device issues that are appropriate for evaluation in a postmarket surveillance study at any point during the life cycle of the device. Such issues may be identified through a variety of sources including analysis of adverse event reports, a recall or corrective action, post-approval study data, review of premarket data, reports from other governmental authorities, or review of scientific literature.

#### **2.3.3 Postmarket Surveillance Study Plans**

In general, Section 522(b)(1) of the Act authorizes the FDA to order prospective postmarket surveillance for a duration of up to 36 months unless the manufacturer and the FDA agree to extend that timeframe. Alternative study designs (*e.g.*, not prospective surveillance) may be recommended by the FDA or proposed by the sponsor. An interim and final reporting schedule is required as part of the study plan.

### 3. REGULATORY HISTORY OF SURGICAL MESH

#### 3.1 FDA Review of Surgical Mesh Indicated for POP and SUI

Surgical mesh was a pre-amendments device and was classified into Class II (21 CFR 878.3300). Since the 1950s, surgical mesh has been used to repair abdominal hernias. In the 1970s, gynecologists began using surgical mesh products indicated for hernia repair for abdominal repair of POP, and in the 1990s, gynecologists began using surgical mesh for surgical treatment of SUI and vaginal repair of POP. To do so, surgeons would cut the mesh to the desired shape for SUI repair or POP repair and then place the mesh through a corresponding incision. Over time, manufacturers responded to this clinical practice by developing mesh products specifically designed for SUI and POP repair.

In 1996, the Surgical Fabrics (ProteGen Sling) device manufactured by Boston Scientific Corporation became the first pre-configured surgical mesh product cleared via the 510(k) pathway for surgical treatment of SUI. (The ProteGen Sling was cleared with an indication for “pubourethral support,” a phrase which implies an indication for treatment of SUI.) However, use of mesh in SUI repair, referred to as slings or tape, did not become common until after the introduction of the Tension-Free Vaginal Tape (TVT™) System, manufactured by Ethicon/Gynecare, in 1998. This system was based on the work by Ulmsten and colleagues [1, 2] with the Ethicon Prolene hernia mesh. In 2002, Gynemesh® PS, also manufactured by Ethicon/Gynecare, became the first pre-configured surgical mesh product cleared for POP repair.

Over the next few years, surgical mesh products evolved into “kits” that included tools to aid in the delivery/insertion of the mesh. The first kit for SUI repair, the Island Biosurgical Bladder Neck Suspension Kit manufactured by Island Biosurgical, Inc., was cleared in 1997. The first kits for POP repair, the AMS Apogee™ System and the AMS Perigee™ System, both manufactured by American Medical Systems, Inc., were cleared in 2004. Surgical mesh kits continue to evolve in regards to introducer instrumentation, tissue fixation anchors, surgical technique, and incorporation of absorbable materials into the mesh intended to increase material compliance.

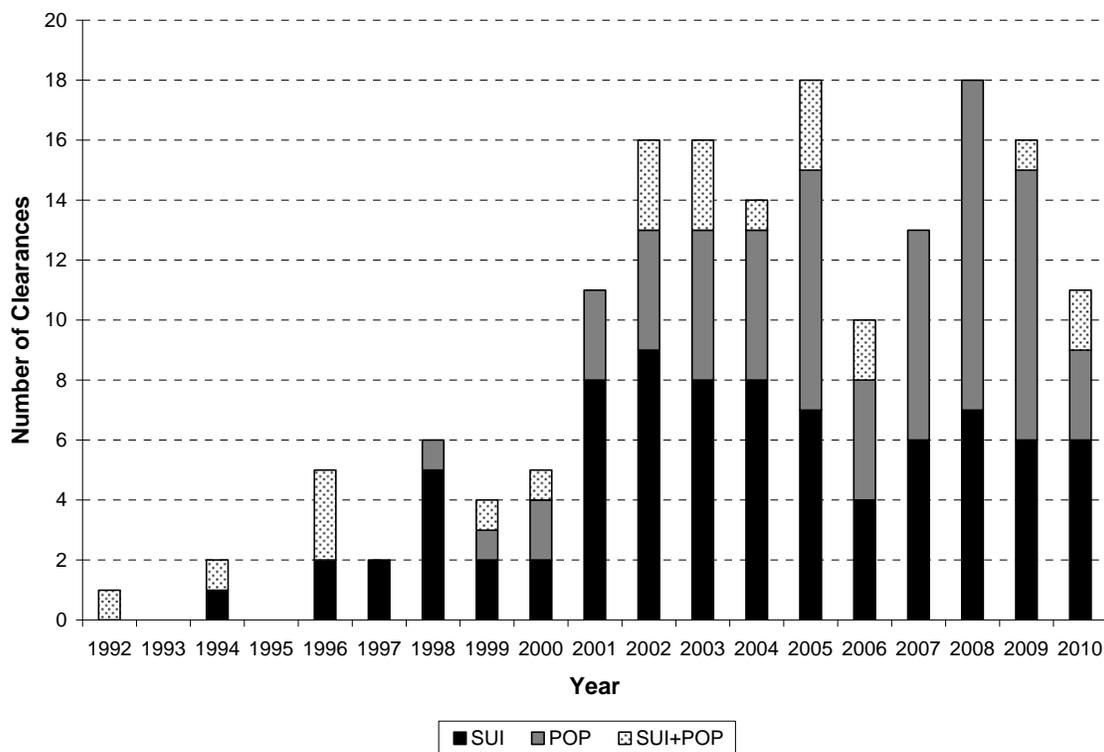
The FDA premarket notification review process did not request original clinical studies to support clearance of surgical mesh indicated for treatment of SUI or POP. Attempts to establish clinical effectiveness were undertaken later by the clinical community with clinical trials, published studies, and systematic reviews/meta-analyses. Some of this published literature was incorporated into later 510(k) submissions to support market clearance.

Premarket clearance of surgical mesh indicated for POP and SUI repair was typically based on pre-clinical bench and animal studies as described in the FDA Guidance Document “*Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh*” issued on March 2, 1999 (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073791.pdf>).

### 3.2 POP & SUI Surgical Mesh 510(k) Clearances

From 1992-2010, the FDA cleared 168 510(k)s for surgical mesh with urogynecologic indications. Examination of all cleared urogynecologic surgical mesh revealed a shift in Indications for Use statements from general soft tissue repair to inclusion of specific types of urogynecologic repair, *e.g.*, “reconstruction of the pelvic floor” and “pubourethral support.” Based on these broad statements, the FDA categorized these 510(k) submissions by repair type (SUI, POP, or both) to determine the number of cleared urogynecologic mesh devices. Using this criteria, the FDA found that it cleared 83 510(k)s for surgical mesh with an SUI indication, 63 with a POP indication, and 22 with both.

**Figure 1** shows the number of cleared urogynecologic surgical mesh submissions per year, broken down by indication. In 2001, the number of clearances per year doubled and increased another 50% the following year. When taking into account that some of these cleared submissions are for modifications to previously cleared devices, these 168 cleared submissions represent 127 devices: 62 for SUI, including 7 single-incision mini-slings; 49 for POP; and 16 for both (SUI+POP).



**Figure 1 – Urogynecologic Surgical Mesh 510(k) Clearances by Year (1992-2010).** This stacked column graph shows the number of cleared urogynecologic surgical mesh submissions each year from 1992-2010, broken down by indication—SUI, POP, or both (SUI+POP). As the graph indicates, after the year 2000, there was an increase in the number of clearances across all indications. (Please see Appendix I for a larger version of this graph.)

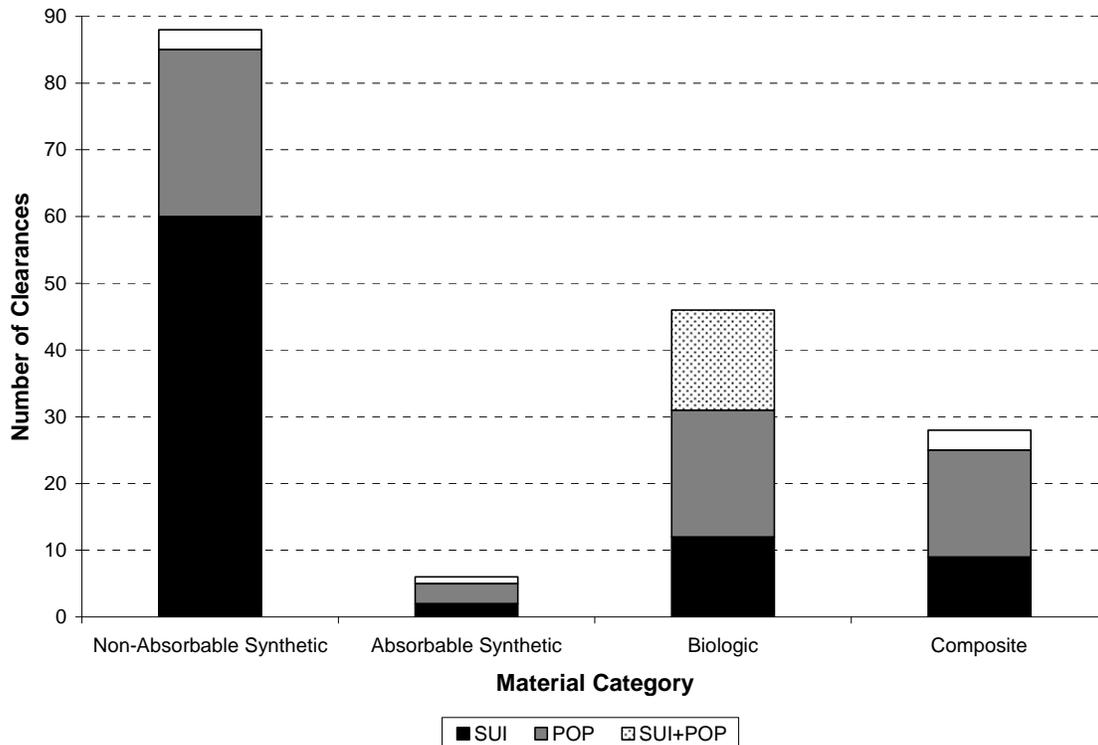
Surgical mesh materials can be divided into four general categories:

- non-absorbable synthetic (*e.g.*, polypropylene or polyester),
- absorbable synthetic (*e.g.*, poly(lactic-co-glycolic acid) or poly(caprolactone)),
- biologic (*e.g.*, acellular collagen derived from bovine or porcine sources), and
- composite (*i.e.*, a combination of any of the previous three categories).

The synthetic materials are supplied as either monofilament or multifilament fibers that are weaved into the mesh form. Typically, these fibers are weaved to create a porous architecture to reduce inflammatory tissue response to the mesh following implantation. In addition to the fiber type and weave, other factors such as the thickness of the fibers, the density and strength of the material, the implantation technique, and the biological and physical responses of the surrounding tissue influence the performance of the mesh [3].

Another means to reduce the inflammatory response and potentially enhance mesh performance is to manufacture lightweight, Type I (Amid classification [4]) mesh. Type I mesh products are composed of monofilament fibers that are weaved into a macroporous (>75 µm) architecture. The design of these types of mesh products promotes better integration into the host tissue through the formation of a scar net rather than a scar plate during the foreign body response [3].

The FDA's analysis of cleared urogynecologic surgical mesh submissions by material category revealed that more than half (52%, n=88) of the cleared submissions with a urogynecologic indication are composed of non-absorbable synthetic materials. The predominant material (91%) in this category is polypropylene (75% monofilament). Further review showed that almost one-third (27%, n=46) of the cleared submissions pertain to mesh products composed of biologic-based materials, with 41% of these indicated for POP repair. **Figure 2** shows the number of clearances for the four material categories described previously, broken down by indication.



**Figure 2 - Urogynecologic Surgical Mesh 510(k) Clearances by Material Category.** This stacked column graph shows the number of cleared submissions for urogynecologic surgical mesh per material category broken down by indication—SUI, POP, or both (SUI+POP). The majority of these submissions (52%,  $n=88$ ) pertain to mesh products composed of non-absorbable synthetic material, and most (91%) submissions in this material category are composed of polypropylene (75% monofilament). (Please see Appendix I for a larger version of this graph.)

Manufacturers continue to modify mesh properties such as density, porosity, and weave with the goal of minimizing the amount of permanent mesh implanted while providing sufficient tissue support.

## 4. POSTMARKET SIGNALS AND FDA RESPONSE

### 4.1 MAUDE Database Search 2005-2007

The FDA focused efforts on the safety of urogynecologic surgical mesh products following its review of concerning information received through multiple sources. These sources included (1) postmarket surveillance of medical device reports (MDRs), (2) concerns raised by the clinical community and citizens, and (3) the published literature. This included an article published in 2006 [5] that described new types of adverse events associated with mesh used for urogynecologic indications.

A 2008 search of the MAUDE database indicated that more than 1000 MDRs had been received for the 2005-2007 timeframe. The reported adverse events related to use of

surgical mesh for both POP and SUI repairs included mesh erosion, infection, pain, dyspareunia, vaginal scarring, urinary retention or urinary incontinence, and recurrence of POP and/or SUI.

#### **4.2 2008 Public Health Notification**

As a result of the large number of adverse events received, in October 2008, the FDA issued a *Public Health Notification (PHN)* informing clinicians and their patients of these findings, with recommendations on how to mitigate risks and how to counsel patients. The 2008 *PHN* can be found in **Appendix IV**.

#### **4.3 MAUDE Database Search 2008-2010**

In January 2011, the FDA completed another search of the MAUDE database for the 2008-2010 timeframe. This new search identified an additional 2874 MDRs for urogynecologic surgical mesh, with slightly more than half associated with POP repairs. A detailed analysis of the results of this search is provided for POP and SUI in **Section 5.2** and **Section 6.2**, respectively.

#### **4.4 FDA Epidemiologic Systematic Literature Review**

The FDA systematically evaluated the peer-reviewed scientific literature to revisit the fundamental question of the safety and effectiveness of surgical mesh for urogynecologic indications. The FDA's evaluation of the literature is provided for POP and SUI in **Section 5.3** and **Section 6.3**, respectively.

#### **4.5 2011 Safety Communication**

On July 13, 2011, based on the 2008-2010 MAUDE database search and the FDA epidemiologic systematic literature review, the FDA issued a *Safety Communication* titled "*UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse*" to inform the medical community and patients that:

- (1) serious complications associated with surgical mesh for vaginal repair of POP are not rare (contrary to what was stated in the 2008 *PHN*), and
- (2) it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair.

The *Safety Communication* also provided a list of recommendations for health care providers and patients to consider for before and after transvaginal POP repair with mesh.

The 2011 *Safety Communication* can be found in **Appendix V**.

#### 4.6 2011 White Paper

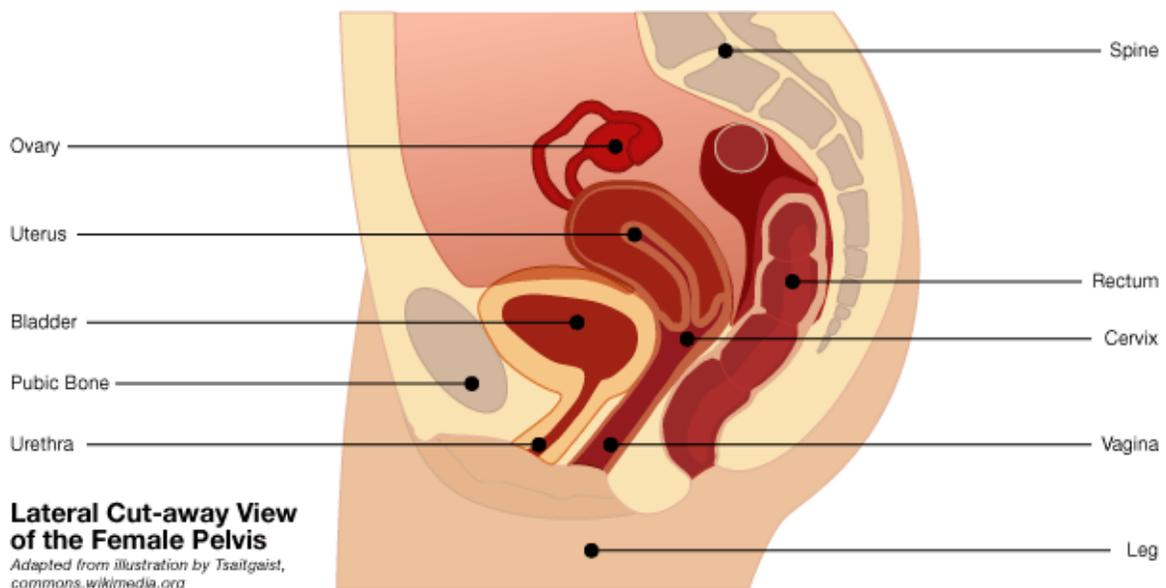
Also on July 13, 2011, the FDA issue a white paper titled “*Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse.*” The purpose of the white paper was to advise the public and the medical community of complications related to vaginal POP repair with mesh.

The 2011 White Paper can be found in **Appendix VI**.

### 5. SURGICAL MESH USED IN REPAIR OF PELVIC ORGAN PROLAPSE

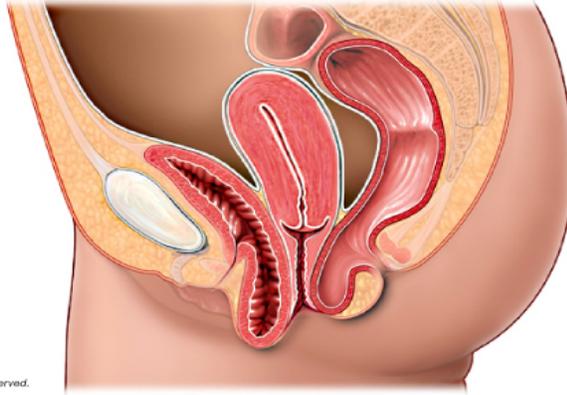
#### 5.1 Clinical Background of Mesh Used in Repair of Pelvic Organ Prolapse

**Figure 3** depicts normal pelvic anatomy. POP can occur in one or more compartments of the vagina, including the bladder (cystocele) (**Figure 4**), the uterus (procidentia) (**Figure 5**), the rectum (rectocele) (**Figure 6**), the top of the vagina (apical prolapse) or the bowel (enterocele).



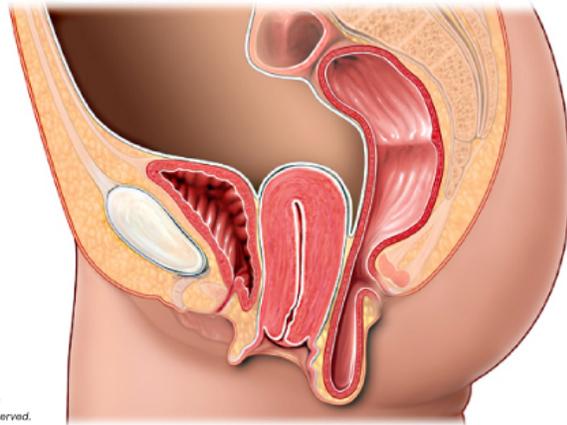
**Figure 3 – Normal Pelvic Anatomy.** This image is a lateral cut-away view of the female pelvis depicting normal anatomy. The vagina, cervix, uterus, ovary, urethra, bladder, rectum, pubic bone, spine, and leg are labelled.

**Cystocele**  
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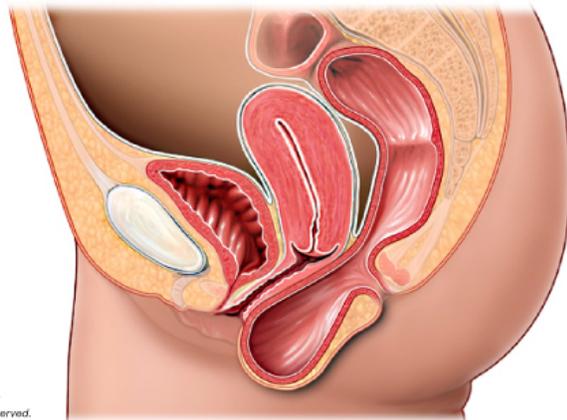
**Figure 4– Cystocele.** This image is a lateral cut-away view of the female pelvis depicting cystocele. In this image, the bladder has prolapsed past the vaginal introitus. The uterus and rectum have also prolapsed from their normal positions.

**Procidentia**  
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**Figure 5– Procidentia.** This image is a lateral cut-away view of the female pelvis depicting procidentia. In this image, the uterus has prolapsed to the vaginal introitus. The bladder and rectum have also prolapsed from their normal positions.

**Rectocele**  
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**Figure 6– Rectocele.** This image is a lateral cut-away view of the female pelvis depicting rectocele. In this image, the rectum has prolapsed past the vaginal introitus. The bladder and uterus have also prolapsed from their normal positions.

The Pelvic Organ Prolapse Quantification (POP-Q) system is commonly used to describe the degree of prolapse. The most distal portion of the prolapsing tissue is measured in the anterior vagina, vaginal apex, and posterior vagina relative to the vaginal opening. The degree of prolapse is described in stages from 0 to 4 based on distance from the vaginal opening. Higher stages indicate more severe prolapse and are more likely to be symptomatic [6].

Symptomatic POP can be managed conservatively with pelvic floor exercises or by using pessaries, or it can be repaired surgically. Surgical repair of prolapse can be performed transabdominally or transvaginally and may address one or more compartments in the vagina, depending on which areas are affected. The placement of surgical mesh is intended to increase the longevity of surgical POP repairs.

Use of mesh has become common practice for abdominal repair of prolapse (e.g., sacrocolpopexy) [7]. In general, sacrocolpopexy is used to support the vaginal apex and is not performed to repair prolapse that is primarily anterior or posterior. Vaginal repair of prolapse may be augmented with mesh or may be performed by tissue plication and suture only (i.e., native tissue or traditional repair).

In general, mesh products for vaginal POP repair are configured to match the anatomical defect they are designed to correct. Mesh can be placed in the anterior vaginal wall to aid in the correction of cystocele (anterior repair), in the posterior vaginal wall to aid in correction of rectocele (posterior repair), or attached to the vaginal wall and pelvic floor ligaments to correct uterine prolapse or vaginal apical prolapse (apical repair). **Table 1** indicates which surgical procedures can be used to correct the various vaginal compartments that may be contributing to prolapse. Mesh placed via an abdominal procedure to repair prolapse is typically done with stand alone mesh products, while prolapse repairs completed transvaginally can be completed with either stand alone mesh or mesh kits (includes mesh and instrumentation to aid insertion and/or placement).

	Type of Prolapse		
	Anterior	Posterior	Vaginal Apex
<b>Repair with Mesh (or Graft)</b>			
Mesh placed abdominally (open, endoscopic, robotic)			✓
Mesh placed vaginally	✓	✓	✓
<b>Repair Without Mesh</b>			
Vaginal Native Tissue/Traditional Repair	✓	✓	✓

**Table 1 – Surgical Procedures for Prolapse Repair.** This table indicates which surgical procedures can be used to correct prolapse of the anterior and posterior vaginal compartments and the vaginal apex.

## 5.2 MAUDE Data Analysis of Mesh Used in Repair of Pelvic Organ Prolapse

In January 2011, the FDA completed a search of the MAUDE database for the 2008-2010 timeframe. This new search identified an additional 2874 MDRs for urogynecologic surgical mesh, with slightly more than half associated with POP repairs. **Appendix I** describes the methodology for the MAUDE data analysis.

### 5.2.1 Demographic Data

The number of MDRs received by the FDA per year from 2008-2010 for surgical mesh used for POP repair is summarized in **Table 2**.

MDRs for POP Indication (2008-2010)	
Year	Number of MDRs
2008	303
2009	580
2010	620
<b>Total</b>	<b>1503</b>

**Table 2 – MDRs for POP Indication (2008-2010).** This table summarizes the number of MDRs received by the FDA per year from 2008-2010 for surgical mesh used for POP repair, as well as the total number of MDRs received over that timeframe.

- The types of adverse events were death (n=7), injury (n=1215), malfunction (n=279), and “other” (n=2).
- The reports were submitted by manufacturers (n=1419), voluntary reporters (*e.g.*, health professionals) (n=83), and user facilities (n=1).
- Patient gender was missing in some reports, although the assumption is that all patients were female based on the device indication.
- The age of the patient was missing in 940 reports. Among reports that specified the age of the patient (n=563), the following ages were reported: 20-30 years old (n=7, 1.2%), 30-40 years (n=28, 5.0%), 40-50 years (n= 113, 20.1%), 50-60 years (n=161, 28.6%), 60-70 years (n=137, 24.3%), 70-80 years (n=98, 17.4%), and 80-90 years old (n=19, 3.4%).

### 5.2.2 Death Reports

The seven deaths reported to the MAUDE database for patients for patients who underwent POP repair procedures with mesh are summarized in **Table 3**. Follow-up investigation of the death reports revealed that three of the deaths associated with POP repair were related to the mesh placement procedure (two bowel perforations, one hemorrhage). The deaths do not appear to be related to the mesh itself. Four deaths were

due to post-operative medical complications not directly related to the mesh placement procedure.

<b>Summary of Death Reports for POP Indication (n=7)</b>			
<b>Patient's Age</b>	<b>Summary of Report's Narrative</b>	<b>Brand name</b>	<b>Type of Procedure</b>
80	Mild heart attack after surgery – patient died later during cardiac catheterization with stroke & serious heart attack.	Apogee	Repair of vaginal wall prolapse
UNK	Postoperative cardiac arrest.	Prolift Pelvic Floor Repair	POP
61	Bowel perforation and infected hematoma were found 10 days after surgery – patient underwent colectomy & repair of rectal perforation. Patient died 2 days later due to multiple organ failure.	Gynecare Gynemesh PS	Sacrocolpopexy & sling procedure
62	Patient brought back to surgery for removal of retained surgical sponge on surgery day. Two days later patient died of pulmonary embolism.	Solyx	POP & sling procedure
64	Major vessel injury during procedure, unable to control bleeding – patient died after 12 units of blood transfusion in operating room.	Prolift Pelvic Floor Repair	POP
79	Hematoma and sigmoid perforation, patient underwent two laparotomies and died 5 weeks later of septic shock.	Prolift Pelvic Floor Repair	POP
65	Patient was discharged home on the third postoperative day, shortly after getting home, suffered massive pulmonary embolism and died.	Pinnacle	Anterior pelvic floor repair, hysterectomy, oophorectomy & sling procedure

**Table 3 – Death Reports for POP Indication (2008-2010).** This table summarizes the death reports received in the MAUDE database for the POP indication from 2008-2010.

### 5.2.3 Injury Reports

The adverse events reported for surgical mesh indicated for POP repair are presented in **Table 4**.

<b>Number and Percentile Rate of MDRs by Adverse Event for POP (2008-2010)</b>			
<b>Rank</b>	<b>Adverse Events</b>	<b># of MDRs</b>	<b>Percentile Rate</b>
1	Erosion	528	35.1%
2	Pain	472	31.4%
3	Infection	253	16.8%
4	Bleeding	124	8.2%
5	Dyspareunia	108	7.2%
6	Organ Perforation	88	5.8%
7	Urinary Problems	80	5.3%
8	Neuro-Muscular Problems	38	2.5%
9	Vaginal scarring (41)/Shrinkage (2)	43	2.8%
10	Recurrence, Prolapse	32	2.1%
*Total number of adverse events is larger than total number of MDRs because the majority of MDRs reported more than one adverse event.			

*Note: Twelve of the reports attributed the adverse events to shrinkage of the mesh, four reports to mesh migration, and three reports to folding/balling/crumpling of the mesh.*

**Table 4 – Number and Percentile Rate of MDRs by Adverse Event for POP (2008-2010).** This table lists each type of adverse event received in the MAUDE database for POP. The adverse events are ranked by the number received and percentile rate. The percentile rate was calculated by dividing the number of MDRs for each adverse event by the total number of MDRs received for POP (n=1503).

### 5.2.4 Required Interventions

Depending on the severity of the adverse events, required interventions ranged from application of topical estrogen cream, a course of antibiotics or trimming of the exposed mesh, to admission to the ER or hospital, bowel resection, and blood transfusion.

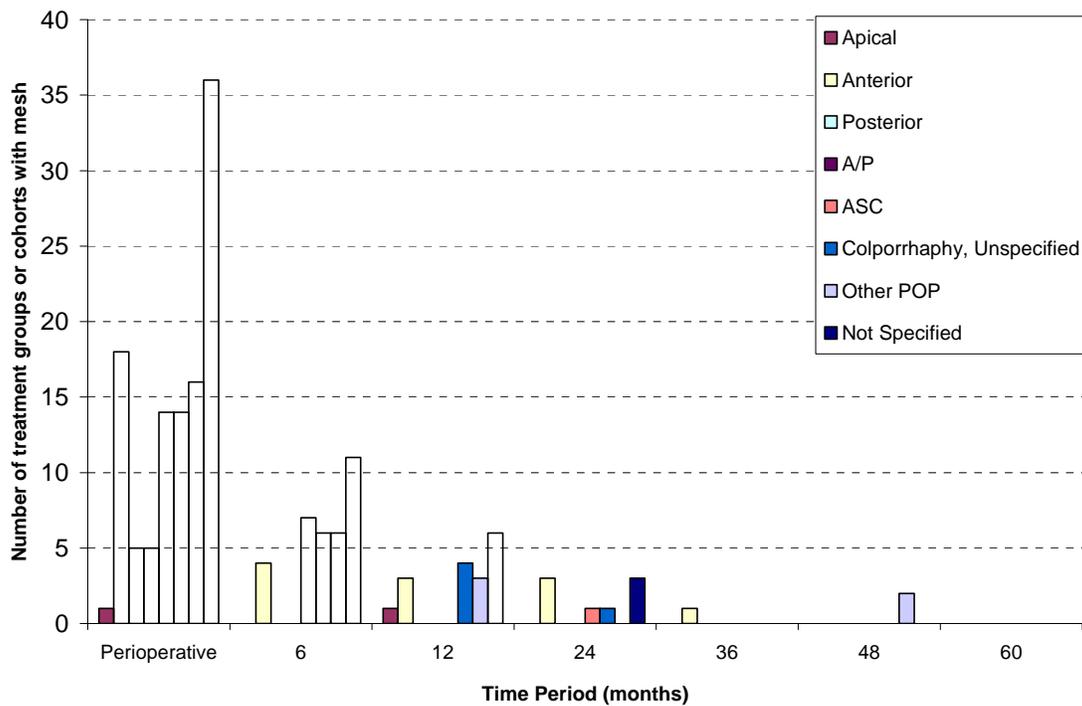
The most frequent required interventions were additional surgical procedure (n=416), partial or complete mesh removal (n=182), and hospitalization (n=71). Multiple required interventions were reported for some patients.

### 5.3 *Overview of Published Literature for Mesh Used in Repair of Pelvic Organ Prolapse*

The FDA systematically evaluated the peer-reviewed scientific literature to revisit the fundamental question of the safety and effectiveness of surgical mesh for urogynecologic indications. **Appendix III** describes the methodology for the systematic collection of data for abstraction and review from the published literature. The quantitative findings of the literature review are presented as weighted mean percentages. The percentage occurrence of an adverse event within a study treatment group or “cohort” was calculated by dividing the number of patients within the cohort who reported the adverse event within a specified timeframe of “follow-up” by the number of patients within the cohort who continued follow up through that specified timeframe. The percentages for each timeframe were then averaged across cohorts, weighting the percentage in each cohort according to the number of patients in the cohort.

Among the 60 articles reviewed on the treatment of POP using surgical mesh, 22 were randomized controlled trials (RCTs), and 38 were observational studies. Additionally, 15 systematic or meta-analysis were reviewed. For these 60 articles, the number of treatment groups or cohorts ranged from 1 to 3, and the number of patients per treatment group or cohort ranged from 13 to 577.

The majority of the studies evaluated anterior prolapse repair, followed by posterior and apical vaginal repair. The duration of follow-up ranged from perioperative (intraoperative to 48 hours post-operative) to 60 months. As shown in **Figure 7**, the majority of the studies reported adverse events and outcomes of perioperative period to 12 months post-operative. Only five studies reported a follow-up period beyond 12 months.



**Figure 7 – Number of treatment groups or cohorts of patients with surgical mesh for the treatment of POP by follow-up period.** This column graph displays the number of treatment groups or cohorts of patients broken down by time period (perioperative, 6, 12, 24, 36, 48, and 60 months post-operative) and stratified by the described POP repair (apical, anterior, posterior, anterior and posterior [A/P], abdominal sacrocolpopexy [ASC], colporrhaphy (i.e., vaginal repair) unspecified, other POP (more rare surgeries that did not fit into the previous categories), and not specified). (Please see Appendix I for a larger version of this graph.)

The FDA review identified a number of limitations with the existing literature: (1) results reflect both primary and repeat prolapse repairs, (2) most studies involve concomitant surgical procedures, (3) adverse event reporting is inconsistent, (4) inclusion/exclusion criteria are incompletely documented, (5) the majority of RCTs are not evaluator-blinded or adequately powered, and (6) few studies extend beyond two years.

In addition, the literature on POP repair largely represents studies in which the primary endpoint was ideal anatomic support, defined as prolapse Stage 0 or 1 (i.e., the lowest point of prolapse is more than 1 cm proximal to the vaginal opening). This outcome is not based on a correlation with symptomatology and is not necessary for most women to achieve symptomatic relief.

### ***5.3.1 Safety of Mesh Used in Repair of Pelvic Organ Prolapse Based on Published Literature***

#### ***Mesh-Specific Adverse Events***

In the published literature, mesh erosion into the vagina is the most common and consistently reported mesh-related complication following vaginal POP repair with mesh. Mesh erosion can result in serious complications unique to mesh procedures and is not experienced by patients who undergo traditional repair. Mesh erosion may require mesh removal to manage the sequelae (*e.g.*, pain, dyspareunia). This complication can be life-altering for some women as mesh removal may require multiple surgeries and sequelae may persist despite mesh removal [8].

A 2011 systematic review of the safety of vaginal POP repair with mesh by Abed *et al* cited a summary incidence of mesh erosion of 10.3% (95% CI, 9.7-10.9%; range 0-29.7%) within 12 months of surgery from 110 studies including 11,785 women in which mesh was used for vaginal POP repair [9]. The incidence of mesh erosion did not differ for non-absorbable synthetic mesh (10.3%) compared to biologic graft material (10.1%). For non-absorbable synthetic mesh erosions, 56% (448/795) required surgical excision in the operating room, with some women requiring two to three additional surgeries [9]. Less information is available about management of erosion from biologic grafts. For 35 women in which management of erosion from biologic grafts was discussed, half responded to local treatment with topical agents. The one RCT for anterior repair with non-absorbable synthetic mesh with 3 year follow-up found that 5% of patients had unresolved mesh erosion at 3 years [10].

Sacrocolpopexy appears to result in lower rates of mesh complications compared to vaginal POP surgery with mesh. A systematic review that included 54 studies and 7,054 women, reported the median mesh erosion rate to be 4% within 23 months following sacrocolpopexy [11].

Mesh contraction, causing vaginal shortening, tightening, and/or vaginal pain in association with vaginal POP repair with mesh, is another mesh-specific adverse event that has been reported in the literature [12, 13]. (Vaginal scarring and tightening can also occur following traditional repair.)

A systematic review of re-surgery rates found that vaginal surgery with mesh to correct vaginal apical prolapse is associated with a higher rate of complications requiring reoperation compared to sacrocolpopexy or traditional vaginal repair (7.2% vs. 4.8% vs. 1.9%, respectively) [14]. (For vaginal surgery with mesh, 24 studies including 3,425 women with mean follow-up 17 months were included in this systematic review. For sacrocolpopexy, 52 studies including 5,639 women with mean follow-up 26 months were included, and for traditional vaginal repair, 48 studies including 7,827 women with mean follow-up 32 months were included.)

Based on the FDA systematic epidemiologic literature review, the risk of mesh erosion for all POP repairs using mesh was reported throughout the follow-up period of 6 months to 3 years, and ranged from 7.7% to 19%. However, it is important to note the limited data beyond 12 months of follow-up, given that only 5 studies reported outcomes past one year. The FDA found that the weighted mean percentage for re-surgery for either mesh complications or recurrent prolapse in the literature was reported at 6 months, 12 months and 24 months as 8.2%, 8.5% and 5.5%, respectively.

The development of mesh complications might be affected by (1) the level of surgeon experience in pelvic floor reconstructive surgery and/or (2) training in POP mesh procedures. Unfortunately, we do not have evidence from clinical studies to ascertain whether, or quantify to what extent, inadequate training or skill might contribute to development of complications from mesh procedures. However, it must be acknowledged that in many of the RCTs with high reported rates of mesh erosion [15-17], the procedure was performed by surgeons with advanced training and experience with the mesh. Therefore, the FDA does not believe that the problems associated with mesh procedures can be attributed exclusively to surgical skill/training. Restricting use of mesh to surgeons with a specified level of experience and training would not eliminate mesh-related complications. The FDA believes that vaginal placement of surgical mesh for POP repair inherently introduces risks of complications that are unique to the mesh itself.

Other Reported Adverse Events

Other post-operative adverse events commonly reported in literature associated with POP repair with mesh were pain, infection, dyspareunia, urinary problems, and re-surgery. The weighted mean percentages for these outcomes as reported in the literature are presented in **Table 5**.

	Range of Weighted Mean Percentages (%)	Range of Follow-Up (months)
<b>Dyspareunia</b>	4.5 – 7.7	6 - 24
<b>Infection</b>	1.6 – 7.3	Perioperative - 24
<b>Pain</b>	1 – 9.8	Perioperative - 24
<b>Re-surgery</b>	5.5 - 8.5	6 - 24
<b>Urinary Problems</b>	4.7 – 10.2	6 - 24

**Table 5 – Other Post-Operative Adverse Events Associated with POP Repair.** The range of percentages of specific other adverse events reported in the literature by the range of follow-up. The percentages for each range of follow-up were averaged across cohorts, weighting the percentage in each cohort according to the number of patients in the cohort.

These adverse events listed in **Table 5** are not unique to POP procedures with mesh. Repeat surgery for complications appears to be highest for vaginal POP repair with mesh, followed by sacrocolpopexy and then traditional repair. Additionally, new onset SUI has been reported to occur more frequently following anterior repair with mesh compared to

traditional anterior repair [18]. Currently, there is no evidence in the literature that other post-operative adverse events occur more commonly following mesh repairs. Per the FDA literature review, based on calculations of weighted mean percentages, organ perforation (2.6%), hemorrhage (2.4%) and hematoma (1.4%) were the most commonly reported adverse events associated with POP procedures with mesh perioperatively. Organ perforation (including bladder, urethral, and vaginal perforations) appears to be a more commonly reported perioperative complication for anterior repair, than it is for anterior and posterior repair (A/P repair) and sacrocolpopexy. Hematoma was reported most commonly for posterior repair. The weighted mean percentage for hematoma reported in the literature for the treatment of POP was 2.9% for posterior repair, 2.1% for A/P repair, and 1.9% for unspecified POP repair.

The findings within the literature are consistent with what has been reported to the FDA through the MAUDE database.

**The panel will be asked to discuss the risks associated with vaginal mesh used for POP repair. The panel will be asked to discuss if given the incidence and severity of these adverse events, there is adequate assurance of the safety of vaginally placed mesh for POP repair.**

**The FDA has identified the following risks to be associated with vaginal mesh used for POP repair:**

**Peri-Operative Risks**

- **Organ perforation**
- **Bleeding (including hemorrhage/hematoma)**

**Long Term Risks**

- ***Mesh exposure into vagina.* Clinical sequelae include pelvic pain, infection, dyspareunia (painful sex for patient or partner), vaginal bleeding, vaginal discharge, and the need for additional corrective surgeries.**
- ***Mesh erosion into the bladder or rectum.* Clinical sequelae include pelvic pain, infection, dyspareunia, fistula formation and the need for additional corrective surgeries (possibly including suprapubic catheter, diverting colostomy).**
- ***Other risks that can occur without mesh erosion.* These risks include pelvic pain, infection, dyspareunia, urinary problems, vaginal scarring/shrinkage, recurrent prolapse, neuro-muscular problems.**

### 5.3.2 *Effectiveness of Mesh Used in Repair of Pelvic Organ Prolapse Based on Published Literature*

The published literature reveals that, while vaginal POP repair with mesh often restores anatomy, it has not been shown to improve clinical benefit over traditional non-mesh repair. This is particularly true for apical and posterior repair with mesh [15, 16, 19-23].

A systematic review of vaginal mesh kits for apical repair found that they appear effective in restoring apical prolapse in the short-term, but long-term outcomes are unknown [24]. Additionally, there is no evidence that vaginal apical repair with mesh is more effective than traditional vaginal apical repair. Specifically, only two RCTs have evaluated apical repair with mesh compared to traditional vaginal repair, and neither found a significant improvement in effectiveness with mesh augmentation [15, 16]. Both of these RCTs evaluated vaginal mesh kits for multi-compartment repair (*i.e.*, anterior, posterior, or total (anterior and posterior) mesh placement). Of these two trials, Withagen *et al* showed an anatomic benefit in the posterior compartment following posterior repair with mesh, but subjects in the trial who underwent posterior repair with mesh had less posterior prolapse at baseline than subjects who underwent traditional repair [16]. Iglesia *et al* did not show an anatomic benefit in the posterior compartment following posterior repair with mesh augmentation [15].

The only RCT to compare posterior repair with mesh to traditional posterior repair (without multiple compartment repair) showed that subjects who underwent mesh repair had worse anatomic outcomes than those who underwent traditional repair [21]. Two other RCTs that compared combined anterior and posterior repair with mesh to traditional anterior and posterior repair found no additional anatomic benefit to mesh augmentation in the posterior compartment [19, 20].

A 2010 review of management of posterior vaginal wall repair by Kudish and Iglesia states "*studies published to date do not support use of biologic or synthetic absorbable grafts in reconstructive surgical procedures of the posterior compartment as these repairs have not improved anatomic or functional outcomes over traditional posterior [repair]*" [25]. At the time, no studies comparing posterior repair with synthetic non-absorbable mesh to traditional posterior repair had been performed. The three trials in which synthetic non-absorbable mesh was used in the posterior compartment were published following this review [15, 16, 20]. The same authors note that when erosion of vaginal mesh occurs in the posterior compartment, it often requires excision of exposed mesh. Less common is mesh erosion partly or through the rectal mucosa. Kudish and Iglesia state that when this does occur "*a diverting colostomy may be needed to excise and repair the erosion site and lead to life-long morbidity for the patient.*"

The literature does suggest that there may be an anatomic benefit to anterior repair with mesh augmentation [10, 17-18, 22-23, 26-33]; however, there are significant limitations to that conclusion. Only two of eleven peer-reviewed publications on anterior prolapse repair were evaluator-blinded prospective RCTs. These two RCTs reached different conclusions. One showed no anatomical improvement for the mesh cohort compared to

the traditional non-mesh repair cohort [20]. The second evaluator-blinded RCT did show an anatomic benefit for mesh in the anterior compartment, but this RCT was a single-center, single-investigator study [28].

A recent reanalysis of one RCT comparing three techniques for anterior repair (two without mesh and one with mesh augmentation) showed no differences in effectiveness across all study groups when less stringent (and arguably more clinically meaningful) criterion for success, defined as prolapse at or above the vaginal opening, was applied [34]. The original trial defined recurrent prolapse as greater than Stage 1 at one year post implant and, using this definition, concluded that subjects who had anterior repair with mesh augmentation were less likely to have recurrent prolapse.

Additionally, patients who undergo traditional repair have equivalent improvement in quality of life [11, 20, 23, 28] when compared to patients who undergo vaginal POP repair with mesh. The FDA believes that use of a non-symptomatically relevant outcome measure (*i.e.*, ideal pelvic support) in these trials likely accounts for a larger differential in reported success rates between mesh and non-mesh repairs compared to a lack of difference in quality of life outcomes.

**The panel will be asked to discuss if there is adequate assurance of the effectiveness of vaginal mesh used for POP repair based on the available scientific evidence.**

**In answering this question, the panel will be asked to consider the following:**

- **pelvic compartment for repair, *i.e.*, anterior, posterior, apical, or multi-compartment**
- **clinical relevance of anatomic outcomes (*e.g.*, POP-Q score, or prolapse above and below the hymen) vis-à-vis patient satisfaction outcomes (*e.g.*, QoL instrument)**
- **whether use in certain sub-populations (*e.g.*, higher stage prolapse or recurrent prolapse) changes the profile for clinical benefit**
- **duration of patient follow-up**
- **synthetic mesh vis-à-vis biologically-derived grafts**

High rates of anatomic success have been reported following sacrocolpopexy [7]. Among 63 studies including 3,540 women with 6 month to 3 year follow-up, success rates ranged from 78 – 100% when defined as lack of apical prolapse and 58 -100% when defined as no prolapse at follow-up.

There are no clinical trials that directly compare outcomes following sacrocolpopexy, vaginal apical repair with mesh and traditional vaginal repair of apical prolapse. When comparing sacrocolpopexy and traditional vaginal repair for apical prolapse, it appears that sacrocolpopexy provides a better anatomic result than traditional repair. The three RCTs that have compared sacrocolpopexy to traditional vaginal repair found that anatomic outcomes were superior following sacrocolpopexy [7]. One of these studies

found superior symptomatic outcomes following sacrocolpopexy as well [35]. However, it is not clear that sacrocolpopexy results in significantly lower rates of repeat surgery for recurrent prolapse compared to traditional repair [22]. Specifically, one systematic review reported the rate of repeat surgery for recurrent prolapse at 2.3% for sacrocolpopexy (mean follow-up of 26 months) vs. 3.9% for traditional repair (mean follow-up of 32 months) [14].

### 5.3.3 Conclusion – Safety & Effectiveness of Mesh Used in Repair of Pelvic Organ Prolapse

The FDA believes that the rate and severity of mesh-specific adverse events following vaginal POP repair with mesh calls into question the safety of these devices. Additionally, the available scientific literature does not provide evidence that surgical mesh used for vaginal POP repair offers a clear improvement in effectiveness when compared to traditional repair. Based on these safety concerns in combination with the lack of demonstrated effectiveness over traditional POP repair, the FDA believes that rigorous scientific evidence is necessary for new vaginal POP mesh products prior to market entry in order to be able to adequately label these products in regards to their risks and benefits.

**Considering the safety and effectiveness concerns associated with these devices, the panel will be asked to discuss whether the risks associated with use of vaginal mesh for POP repair outweigh the benefit.**

The FDA believes that basic questions regarding the safety and effectiveness of mesh used for vaginal POP repair remain unanswered. The FDA believes that these questions can only be adequately addressed in randomized controlled trials (RCTs) comparing vaginal POP repair with mesh to traditional (non-mesh) repair are needed.

The FDA proposes the following study design to adequately assess the safety and effectiveness of a new mesh product for vaginal POP repair:

- Two co-primary endpoints: (1) clinically relevant measure of effectiveness, *e.g.*, the proportion of subjects with prolapse above the hymenal ring and (2) assessment of serious adverse events, *e.g.*, the number of adverse events requiring non-medical intervention at 12 months post-procedure.
- In order to claim study success, vaginal POP repair with the new mesh product should be superior to prolapse repair surgery without mesh in terms of effectiveness and non-inferior in terms of safety.
- The study subjects should be evaluated out to 12 months to support the safety and effectiveness prior to market entry. (The FDA would like to see continued follow-up for at least an additional two years post-market.)

**The panel will be asked to discuss whether clinical studies are necessary to provide a reasonable assurance of the safety and effectiveness of vaginal POP mesh. If yes, the panel will be asked to discuss the necessary study design, including patient selection criteria, controls, randomization, outcome measures, follow-up duration, etc.**

The FDA believes that surgical mesh used for abdominal POP repair has a more favorable risk/benefit profile, given its demonstrated anatomic benefit over traditional vaginal repair, low rates of repeat surgery for recurrent prolapse, and lower rates of mesh complications compared to vaginal POP repair with mesh. The FDA, therefore, does not believe that new mesh products designed for sacrocolpopexy should have these premarket clinical data requirements.

**The panel will be asked if they agree with the FDA's assessment that the safety and effectiveness of mesh used for abdominal POP repair has been demonstrated. If not, the panel will be asked to discuss the need for premarket and/or postmarket clinical data on these devices.**

#### ***5.4 Regulatory Options for Mesh Used in Repair of Pelvic Organ Prolapse***

##### ***5.4.1 Premarket Regulatory Options***

The following premarket options are currently available to the FDA to address its concerns regarding the use of mesh for POP repair.

1. Continue clearing vaginal mesh for POP repair without premarket performance data and require labeling changes to address known risks and lack of clinical benefit.
2. Continue clearing POP mesh as 510(k)s, but establish 513(a)(1)(B) "Special Controls" for these devices, which could include
  - physician labeling, *e.g.*, more narrow indication for use, restricting use to physicians with credentialed training, better instructions for use, etc.
  - patient labeling
  - more premarket studies, *e.g.*, bench studies, animal studies, clinical studies to demonstrate substantial equivalence (*e.g.*, RCT comparison to legally marketed predicate mesh product indicated for vaginal POP repair),
  - performance standard(s)
  - guidance document
  - enhanced postmarket surveillance
  - patient registry

3. Reclassify surgical mesh used for vaginal repair of POP from Class II to Class III.

- Section 513(e)(1) of the Act states “Based on new information respecting a device, the Secretary may, upon his own initiative or upon petition of an interested person, by regulation (A) change such device’s classification, and (B) revoke, because of the change in classification, any regulation or requirement in effect under section 514 or 515 with respect to such device.”
- Reclassification into Class III will mean that each manufacturer will need to independently demonstrate a reasonable assurance of safety and effectiveness for the manufacturer’s device relying upon valid scientific evidence as described in 21 CFR 860.7(b)(2).

*Note: It is important to recognize that this provision allows for a premarket RCT comparison to non-mesh surgical repair of POP.*

- Class III devices are subject to more rigorous requirements following approval compared to Class II devices. This includes post-approval studies, if needed, to obtain long-term data, annual reporting, and reporting of all device and labeling changes to the FDA (significant changes require approval by the FDA prior to implementation).
- The process of reclassification from Class II to Class III includes a number of specific steps and may take several years to complete. For POP mesh products currently on the market, the FDA may consider a grace period for manufacturers of those products to submit PMAs for FDA approval.
- While the reclassification process is proceeding, manufacturers could be required to conduct postmarket studies for devices already on the market via a 522 order, as discussed in **Section 5.4.2**. The 522 study could be designed to support a future PMA submission.

Because of the outstanding safety and effectiveness concerns for mesh products indicated for vaginal POP repair and an inability to adequately address these concerns via the 510(k) pathway, the FDA believes that 510(k) premarket notification is no longer an appropriate premarket pathway for devices indicated for vaginal POP repair. Therefore, the FDA believes that reclassification of these devices to Class III and evaluation via the PMA process is warranted.

**The panel will be asked to discuss the regulatory controls associated with Class II and Class III devices and discuss the usefulness of each set of controls, individually or taken together, to provide reasonable assurance of safety and effectiveness of vaginal POP mesh.**

#### 5.4.2 Postmarket Regulatory Options

In addition to the options of labeling, Special Controls, and reclassification, the FDA has the option to mandate postmarket surveillance studies under Section 522 of the Act for vaginal POP mesh products that are already legally marketed. Given the current risk/benefit evaluation of these devices and the concerns raised by the available scientific data, the FDA believes these “522 studies” are warranted and can help answer questions regarding the long term safety and effectiveness of vaginal mesh used for POP repair.

The FDA believes that the following additional considerations also support the need for 522 studies of currently marketed vaginal POP mesh products:

- Vaginal mesh for POP repair meets the statutory criteria for a 522 study because the device is intended to be implanted in the body for more than one year. In addition, failure of the device can result in mesh erosion, severe pain, fistula formation, and/or the need for surgical revision or mesh removal, which can be considered serious adverse health consequences.
- 522 studies could provide information regarding rates of adverse events and the anatomical effectiveness for each specific mesh product already legally marketed.
- Mandating 522 studies could begin in concert with the process of reclassification from Class II to Class III. The clinical data collected via 522 studies may be part of the data submitted for future PMA submissions, if both the 522 and the reclassification options are exercised.
- The FDA believes the concerns regarding vaginal mesh for POP repair warrant long term prospective follow-up for patients. This would mean that manufacturers of all current mesh products indicated for POP would enroll subjects and follow them a specified duration of time before analyzing data and submitting a final report. (As described in **Section 2.3**, the FDA can order prospective postmarket surveillance for up to 36 months.)

The postmarket setting influences the study design options available for 522 studies. To address the questions under consideration regarding vaginal POP mesh, the FDA may recommend a randomized clinical trial or prospective cohort study design that compares the device(s) to a control (*i.e.*, urogynecologic surgery without use of mesh) through a specified duration of follow-up (up to 36 months). Further, the FDA would recommend a study design including a population of women who are age 18 years or older with documented pelvic organ prolapse for whom surgery is scheduled. Inclusion and adjustment for the following risk factors would need to be considered: level of prolapse (above or below hymenal ring); primary versus recurrent prolapse; menopausal status; estrogen use; age; lifestyle factors; obesity; modification of mesh prior to placement; surgical technique or procedure used type of surgery.

Sponsors may also choose to develop a registry to address the questions, either as a single sponsor, in collaboration with multiple sponsors, or in conjunction with societies. The

FDA is amenable to facilitating creation of a multi-sponsor or society registry to address the public health concerns.

**The panel will be asked if they agree with the FDA that 522 studies are needed to evaluate vaginal POP mesh products currently on the market. If yes, the panel will be asked to discuss the type of clinical study that should be required for these devices. The panel will be asked to consider the following:**

- **What are the most important outcome measures to evaluate, primary and secondary?**
- **Should these studies have a control arm, and, if so, what are the optimal comparators (e.g., mesh-to-mesh, mesh-to-no mesh, vaginal-to-vaginal, vaginal-to-abdominal, etc.)? If a control arm is needed, should the study be randomized?**
- **How should the study address important co-factors such as whether this is a primary or recurrent prolapse, stage of prolapse, concomitant surgeries, anatomic compartment repaired, surgeon experience, other patient selection criteria?**
- **What is the appropriate duration for patient follow-up?**

## **6. SURGICAL MESH USED IN REPAIR OF STRESS URINARY INCONTINENCE**

### **6.1 *Clinical Background of Mesh Used in Repair of Stress Urinary Incontinence***

Stress urinary incontinence (SUI) is the involuntary leaking of urine associated with an increase in intraabdominal pressure, which may be caused by straining, physical activity, coughing or sneezing. Effective therapies for managing SUI include non-surgical intervention (e.g., behavioral and temporary mechanical support devices), as well as surgical procedures intended to provide long-lasting or permanent cure. Many operations to treat female SUI have been described in 20-21<sup>st</sup> century medical literature. These include the procedures listed below. As presented, the procedures are stratified by relative degree of invasiveness.

- **More Invasive Procedures for Treating SUI**
  - Anterior repair with Kelly plication
  - Open retropubic colposuspension
  - Pubovaginal sling
  - Bladder neck needle suspension
- **Minimally or Less Invasive SUI Procedures**
  - Tension-Free Vaginal Tape (TVT)
    - Retropubic
    - Transobturator
  - Single-incision mini-slings

Retropubic urethropexy (e.g., Burch colposuspension), which does not involve graft material, has a long history, but its popularity has declined over the past two decades with the introduction of less invasive procedures. Pubovaginal sling procedures using biologic graft material (often autologous fascia) similarly have declined in popularity. Anterior repair with Kelly plication to correct SUI in the presence of a cystocele and bladder neck needle suspension have a historical role in incontinence surgery but are rarely performed currently due to poor long term outcomes.

Since the late 1990s, surgical management of SUI has been increasingly dominated by “minimally invasive” synthetic and biologic suburethral slings placed retropubically or through the obturator foramen. In general, these devices require three small incisions—two skin incisions and a single incision in the vaginal mucosa. Originally placed in a tension free manner, suburethral slings are now often provided in kits with accessories for anchoring the ends of the sling in tissue. The most recent innovation in minimally invasive suburethral slings is the single-incision “mini-sling.”

The FDA did not request original clinical performance data for either the first generation minimally invasive suburethral slings or the single-incision mini-slings. A substantial number of quality clinical trials, as well as systematic reviews, have been published for the first generation minimally invasive slings that provide evidence of safety and effectiveness of these devices.

## 6.2 MAUDE Data Analysis for Mesh in Repair of Stress Urinary Incontinence

In January 2011, the FDA completed another search of the MAUDE database for the 2008-2010 timeframe. This new search identified an additional 2874 MDRs for urogynecologic surgical mesh, with slightly less than half associated with SUI repairs. **Appendix II** describes the methodology for the MAUDE data analysis.

### 6.2.1 Demographic Data

The number of MDRs received by the FDA per year from 2008-2010 for surgical mesh products used for SUI repair is summarized in **Table 6**.

MDRs for SUI Indication (2008-2010)	
Year	Number of MDRs
2008	368
2009	513
2010	490
<b>Total</b>	<b>1371</b>

**Table 6 – MDRs for SUI Indication (2008-2010).** This table summarizes the number of received by the FDA per year from 2008-2010 for surgical mesh used for SUI repair, as well as the total number of MDRs received over that timeframe.

- The types of adverse events received were death (n=3), injury (n=1131), malfunction (n=236), and “other” (n=1).
- The sources of reports were manufacturers (n=1276), voluntary reporters (e.g., healthcare professionals) (n=91), and user facilities (n=4).
- Patient gender was missing in some reports although the assumption is that all patients were female based on the device indication and exclusion of all the male urinary mesh device reports where gender was indicated.
- The age of the patient was missing in 1000 reports. Among reports that specified the age of the patient (n=371), the following ages were reported: 20-30 years old (n=3, 0.08%), 30-40 years (n=44, 11.9%), 40 to 50 years (n=108, 29.1%), 50-60 years (n=116, 31.3%), 60-70 (n=57, 15.4%), 70-80 years (n=39, 10.5%), and 80-90 years old (n=4, 1.1%).

### 6.2.2 Death Reports

The three deaths reported to the MAUDE database for patients who underwent SUI procedures with mesh are summarized in **Table 7**. Follow-up investigation of the death reports revealed that two deaths associated with SUI repair were related to the mesh placement procedure (two bowel perforations), but unrelated to the mesh itself. One death was related to complications from mesh removal.

Summary of Death Reports in SUI Indication (n=3)			
Patient's Age	Summary of Report's Narrative	Brand name	Type of Procedure
73 YR	Bowel perforation & adhesion – patient died next day; physician claims bowel perforation caused sepsis and necrotizing fasciitis, which resulted in patient death.	Advantage	Mid-urethral sling
UNK	Bowel perforation – patient died of toxic shock and cardiac arrest.	Advantage	Sling procedure
61 YR	Erosion & bleeding – patient on life support after mesh removal and died after life support was disconnected.	UNK (voluntary reporter)	Sling procedure

**Table 7 – Death Reports for SUI Indication (2008-2010).** This table summarizes the death reports received in the MAUDE database for the SUI indication from 2008-2010.

### 6.2.3 Injury Reports

The adverse events reported for adverse events indicated for SUI are presented in **Table 8**.

<b>Number and Percentile Rate of MDRs by Adverse Event for SUI (2008-2010)</b>			
<b>Rank</b>	<b>Adverse Events</b>	<b># of MDRs</b>	<b>Percentile Rate</b>
1	Pain	479	34.9%
2	Erosion	436	31.8%
3	Infection	260	18.9%
4	Urinary Problems	220	16.0%
5	Organ Perforation	110	8.3%
6	Recurrence, Incontinence	103	7.5%
6	Bleeding	103	7.5%
7	Dyspareunia	73	5.3%
8	Neuro-Muscular Problems	50	3.6%
9	Vaginal Scarring	22	1.6%
*Total number of adverse events is larger than the total number of MDRs because the majority of MDRs reported more than one adverse event			

*Note: Seven of the reports attributed the adverse events to shrinkage of the mesh, nine reports to mesh migration, and four reports to folding/balling/crumpling of the mesh.*

**Table 8– Number and Percentile Rate of MDRs by Adverse Event for SUI (2008-2010).** This table lists each type of adverse event received in the MAUDE database for SUI. The adverse events are ranked by the number received and percentile rate. The percentile rate was calculated by dividing the number of MDRs for each adverse event by the total number of MDRs received for SUI (n=1371).

### 6.2.4 Required Interventions

Depending on the severity of adverse events, required interventions ranged from application of topical estrogen cream, a course of antibiotics or trimming of the exposed mesh, to admission to the ER or hospital, bowel resection and blood transfusion. The most frequent required interventions were additional surgical procedure (n=394), partial or complete mesh removal (n=162), and hospitalization (n=58). Multiple required interventions were reported for some patients.

## 6.3 Overview of Published Literature for Mesh Used in Repair of Stress Urinary Incontinence

The FDA systematically evaluated the peer-reviewed scientific literature to revisit the fundamental question of the safety and effectiveness of surgical mesh used to repair stress urinary incontinence.

The FDA is seeking panel input on the conclusions that can be drawn from the published literature regarding the risk to benefit ratio of mesh used for treatment of SUI and whether premarket and/or postmarket data (e.g., 522 studies) should be required for these devices. In short, one FDA perspective is that mesh placed either retropubically or via the transobturator route to treat SUI are effective, and although the adverse event profile for these devices is not trivial, it does not rise to the level of questionable risk/benefit. In this case, additional premarket and/or postmarket studies may not be needed to evaluate the use of first generation minimally invasive slings, but subsets of devices with limited data (e.g. single-incision mini-slings) may need additional data.

Another FDA perspective is that while mesh for SUI repair in general appears to be effective, the literature, in conjunction with MAUDE reporting, indicates that serious complications can occur; and therefore, a case can be made for additional premarket and/or postmarket studies to better address the risk/benefit of all mesh products used for SUI.

The FDA does not believe that mesh used for SUI repair should be reclassified from Class II to Class III.

The FDA's discussion of the published literature is presented with effectiveness broken down by surgical procedures (invasive surgical procedures, retropubic and transobturator procedures, and single-incision mini-slings) and safety presented for all mesh products used for treatment of SUI. The evidence for effectiveness of SUI surgery without mesh compared to mesh procedures and comparative effectiveness of different mesh procedures are largely based on two recent Cochrane Reviews [36, 37] and a large RCT [38]. The FDA's review of the safety of mesh for SUI repair is presented based on the FDA's own systematic review of the literature. The FDA's methodology for this literature review is described in **Appendix III**.

### ***6.3.1 Effectiveness of Mesh Used in Repair of Stress Urinary Incontinence Based on Published Literature***

#### *Effectiveness of Invasive Surgery for SUI*

The Centers for Medicare & Medicaid Services (CMS) data indicate that open bladder neck suspension and pubovaginal sling procedures likely constitute a minority of SUI surgeries performed annually [39]. The Cochrane Collaboration systematic reviews of colposuspension evaluated the comparative surgical outcomes data for more invasive procedures [36]. The selection criteria were randomized or quasi-randomized controlled trials for which open retropubic colposuspension was one of the study arms. The Cochrane review reported that open colposuspension was more effective compared to anterior repair/Kelly plication and needle suspension procedures. Details of that review are not provided here as these procedures have fallen out of favor due to inferior long term outcomes compared to colposuspension and sling procedures [40]. A synopsis of the effectiveness findings for open retropubic colposuspension versus pubovaginal slings

and minimally invasive tension free vaginal tape procedures from the Cochrane review is provided in this section. Please note that results related to safety are presented in **Section 6.3.2.**

### *Open retropubic colposuspension vs. sling procedures (pubovaginal and TVT)*

Fourteen studies contributed to the analysis. Six studies compared colposuspension to pubovaginal slings. Eight studies compared colposuspension to tension free vaginal tape slings.

#### Subjective (Patient Reported) Failure

Regarding subjective (patient-reported) cure at one year, there was no statistical difference following colposuspension (8.7% failure) versus traditional sling (4.8% failure) (RR 1.92, 95% CI 0.57 to 6.50). Similarly, there was no statistical difference between colposuspension (26% failure) and TVT (31% failure) although the confidence interval was narrower (RR 0.85, 95% CI 0.63 to 1.17).

Subjective failure rates between one and five years were higher for colposuspension (46%) compared to traditional slings (35%) (RR 1.35, 95% CI 1.11 to 1.64). Failure rates at 1-5 years were not statistically different for colposuspension (29%) compared to TVT (32%) (RR 0.92, 95% CI 0.67 to 1.26).

Subjective failure rates between one and five years were higher for colposuspension (41%) compared with slings when traditional and TVT slings were combined (34%) (RR 1.21, 95% CI 1.02 to 1.42). In the two trials that reported data beyond five years, there was no significant difference in subjective failure rates between colposuspension and either traditional or self-fixating slings.

#### Objective (Clinician Reported) Failure

Objective failure at one year from three small trials found a 13% failure rate for open colposuspension versus 0% for traditional slings (RR 6.69, 95% CI 0.89 to 50.43). For open colposuspension versus TVT sling, the failure rates were 15% and 15% (RR 1.19, 95% CI 0.79 to 1.78).

Objective failure between one and five years for open colposuspension (14%) did not differ significantly from traditional sling (13%) (RR 1.11, 95% CI 0.75 to 1.66). Objective failure for open colposuspension (17%) also was not different compared to TVT (14%) (RR 1.22, 95% CI 0.72 to 2.06).

Objective assessment from five trials reporting one-year data found an 18% failure rate for colposuspension versus a 15% failure rate for tradition and self fixating sling procedures combined (RR 1.19, 95% CI 0.79 to 1.78). Between one and five years, the failure rate was 16% for colposuspension versus 14% for all slings combined (RR 1.15, 95% CI 0.84 to 1.58). Two trials with longer term (greater than 5 years) data showed

failure of colposuspension at 11% versus 17% for all slings (RR 0.70, 95% CI 0.30 to 1.64). (One of the latter two trials enrolled only 28 subjects.)

Heterogeneity across studies made it difficult to draw conclusions regarding duration of surgical procedure, hospital stay and duration of catheterization. In general, the traditional sling procedure using autologous fascia had longer operating time compared to colposuspension, whereas the TVT procedure had relatively shorter operating time compared to colposuspension.

### *Effectiveness of Minimally Invasive Surgical Procedures for SUI*

The Cochrane Collaboration systematic reviews evaluated synthetic suburethral sling procedures for SUI [37]. The selection criteria were randomized or quasi-randomized controlled trials for which a minimally invasive synthetic suburethral sling operation was one of the study arms. A synopsis of the Cochrane review findings comparing minimally invasive slings to pubovaginal slings and comparison of different styles of minimally invasive slings follows.

#### *Minimally invasive synthetic suburethral slings (MISS) vs. traditional pubovaginal slings (PVS)*

There were nine studies that evaluated MISS compared to traditional pubovaginal slings. Subjective cure within 12 months was evaluated in eight studies. Cure rate for MISS (75%) was not significantly higher compared to PVS (71%) (RR 1.03, 95% CI 0.94 to 1.13). A single study evaluated subjective cure between 6-24 months (median 12 months). This study found no significant difference between MISS (88%) and PVS (82%) (RR 1.07, 95% CI 0.93 to 1.24).

Objective cure (defined as absence of leaking during a stress test) was evaluated in one study (n=44). The cure rate for MISS was 70% versus 48% for PVS (RR 1.46, 95% CI 0.87 to 2.47).

Procedure duration and hospital stay were significantly shorter for MISS compared to PVS.

#### *MISS Retropubic TVT (Bottom-to-Top) vs. Retropubic SPARC (Top-to-Bottom) Approach*

Five studies enrolling 636 patients compared TVT (bottom-to-top MISS) versus SPARC (top-to-bottom MISS). Three studies evaluated subjective cure, *i.e.* self-reported absence of leaking with stress. At one year, TVT patients reported significantly higher cure (85%) versus SPARC (77%) (RR 1.10, 95% CI 1.01 to 1.20). One year objective cure using different criteria was evaluated in all five studies. Pooling all definitions of objective cure, both procedures performed well, although TVT had significantly higher cure rate (92%) versus SPARC (87%) (RR 1.06, 95% CI 1.01 to 1.11).

Data from two studies (combined n=124) evaluated duration of surgery and hospitalization. For the bottom-to-top approach, mean duration of surgery was 27.5 (standard deviation (SD) 2.7) minutes in one study and 32.74 (SD 8.43) minutes in the second study. For the top-to-bottom approach, mean duration was 28.1 (SD 7.5) minutes and 40.8 (SD 13.3) minutes for the first and second studies. The difference was not significant (mean difference -2.15 min (95% CI -4.68 to 0.38). Mean duration of hospitalization following bottom-to-top approach was 2.5 (SD 0.9) days and 3.14 (SD 1.43) days for the first and second studies. For top-to-bottom approach, mean length of hospitalization was 2.3 (SD 0.6) and 3.97 (SD 1.43) days. The mean difference was -0.03 days (-0.37 to 0.30). As indicated, none of these differences were statistically significant.

Mean Quality of Life (QOL) scores, based on the Incontinence Impact Questionnaire (IIQ), was evaluated in one study (n=84). Mean 12-month post-operative score for bottom-to-top was 45.3 (SD 18.4) versus 49.9 (SD 25.6) for top-to-bottom (mean difference -4.60, 95% CI -14.17 to 4.97). This difference was not statistically significant.

#### *MISS Trans Obturator medial-to-lateral (TOT) vs. Trans Obturator lateral-to-medial (TVT-O)*

Data from three small studies enrolling 260 patients were evaluated. One hundred and fifteen (115) underwent medial to lateral TOT procedure. In two studies evaluating subjective cure rates, there was no difference between TOT (81%) versus TVT-O (81%). Objective cure rates were evaluated in two studies. The cure rate for TOT (87%) was not statistically different from that for TVT-O (91%) (RR 0.95, 95% CI 0.86 to 1.04).

#### *MISS Monofilament vs. Multifilament Polymer Material*

Three studies reported outcomes on 472 patients randomized to monofilament mesh (TVT) versus multifilament (IVS). Two hundred and six were treated with monofilament. (It appears that 61 patients were treated with SPARC, also a monofilament mesh). Subjective cure rates with monofilament (83%) was not significantly greater compared with multifilament (77%) (RR 1.08, 95% CI 0.98 to 1.19). Objective cure rate from two studies was higher for monofilament (83%) versus multifilament (72%) (RR 1.15, 95% CI 1.02 to 1.30).

Duration of procedure and hospital stay did not differ between mono- and multifilament mesh.

#### *MISS Transobturator vs. Retropubic*

Twenty-four studies reported outcomes comparing transobturator versus retropubic mesh sling. Subjective cure at 12 months was evaluated in 10 studies enrolling 1281 patients. Subjective cure rate was 84%-85% for both routes. Objective cure rate at 12 months was

reported in 17 studies enrolling 2434 patients. The cure rate for transobturator (84%) was significantly lower compared to retropubic route (88%) (RR 0.96, 95% CI 0.93 to 0.99).

The mean duration of the procedure was shorter for the transobturator route (20 minutes) versus the retropubic route (27 minutes).

Quality of Life (QOL) data was available from 11 studies, however QOL instruments differed from study to study. In general, all but one study showed significant improvement for both surgical approaches without a significant difference between the two approaches. In a single study, the improvement in QOL score was significantly higher for retropubic approach compared to the transobturator approach [41].

NOTE: The Cochrane Review did not include a large RCT (n=597) by Richter *et al* comparing retropubic versus transobturator sling procedures [38]. Richter *et al* found a subjective cure rate for retropubic slings 62% versus 56% for transobturator slings (6.4 percentage point difference, 95% CI -1.6 to 14.3). They found an objective cure of 81% for retropubic versus 78% for transobturator (3.0 percentage point difference, 95% CI -3.6 to 9.6). Neither difference was significant. There were no significant differences in QOL outcomes between groups.

#### *Summary of Main Findings – Effectiveness of Minimally Invasive Synthetic Slings for SUI*

Overall, although there is a variety of minimally invasive synthetic slings that are placed differently, these slings appear to be as effective as open retropubic colposuspension. Outcomes data are predominantly relatively short term (1-2 years), however. The bottom-to-top retropubic approach appeared to be more effective in the short term compared to top-to-bottom retropubic approach. Monofilament tape appeared more effective than multifilament tapes. Objective and subjective cure rates were high for both transobturator and retropubic slings, with a slight advantage going to the retropubic approach.

#### *Effectiveness of Single Incision Mini Slings – A Subset of Minimally Invasive Synthetic Slings*

A recent innovation in the field of minimally invasive synthetic suburethral slings for SUI is the single incision “mini-sling.” This style of sling requires only one vaginal incision and requires less dissection compared to the standard minimally invasive slings. Compared to standard minimally invasive sling procedures for SUI, there is relatively little quality outcomes data on which to evaluate mini-slings.

Two RCTs [42, 43] and one review [44] are available to obtain preliminary assessment of mini-slings. Hinoul *et al* enrolled 194 subjects randomized to TVT-O versus TVT Secur [36]. One year follow-up outcomes were obtained for 85 TVT-O and for 75 TVT-Secur patients. Subjective reporting of SUI at one year was lower in the TVT-O group (8%) compared to TVT-Secur (24%) (p<0.05). Objective failure rate was 2.4% in the TVT-O group versus 16.4% in the TVT-Secur patients (p<0.05). The odds ratio (OR) for repeat

incontinence surgery at one year was significantly greater for TVT-Secur (OR 2.3, 95% CI 1.9 to 2.7). Incontinence QOL was significantly better in the TVT-O group.

Tommaselli et al reported on a smaller cohort (N=84) randomized to TVT-O versus TVT Secur [43]. Twelve month outcomes were available for 38 subjects in the TVT-O group and for 37 subjects in the TVT-Secur group. These authors reported one year objective cure rates were not significantly different for the two groups (81.6% versus 83.8% in the TVT-O versus TVT-Secur groups, respectively). Data on need for repeat incontinence surgery was not reported.

Walsh reviewed the literature for outcomes following TVT-Secur at one year [44]. Three studies provide comparative data for the “U-type” (akin to retropubic approach) compared to the “H-type” (akin to transobturator placement). Including non-randomized studies, the overall objective and subjective cure rates were approximately 76%. Objective cure rates were significantly higher for the U-type procedure. The rate of repeat incontinence surgery for within one year following a TVT-Secur procedure was 5%.

In summary, there exist limited quality comparative data (*i.e.*, two RCTs and one review) on which to draw conclusions regarding the effectiveness of single-incision mini-slings. The larger of the two RCTs found a significantly lower cure rates compared to first generation minimally invasive slings.

#### *Conclusion – Effectiveness of Mesh Used in Repair of Stress Urinary Incontinence Based on Selected Published Literature*

Open colposuspension results in objective SUI cure rates at one year ranging from 69% to 88%. The cure rate appears to decline by 15% - 20% at greater than five years. Data from studies comparing open colposuspension with sling procedures (pubovaginal and TVT) suggested similar efficacy. The risk of repeat incontinence surgery was not significantly different for colposuspension compared to the TVT sling.

There is a variety of minimally invasive synthetic slings for SUI and variations in the manner in which they are placed. Overall, these slings appear to be as effective compared to open retropubic colposuspension. However, outcome data are predominantly relatively short term (1-2 years). The bottom-to-top retropubic approach appeared to be more effective in the short term compared to top-to-bottom retropubic approach. Monofilament tape was more effective compared to multifilament tape. Objective and subjective cure rates were high for both transobturator and retropubic slings, with a slight advantage going to retropubic approach.

Compared to standard minimally invasive sling procedures for SUI, there is relatively little quality outcomes data on which to evaluate single incision mini-slings. What little quality comparative data are available (*i.e.*, two RCTs) suggest that mini slings may have lower cure rates compared to the first generation minimally invasive slings for SUI. In

the larger RCT, the rate of reoperation for incontinence was higher for mini-slings compared to transobturator slings.

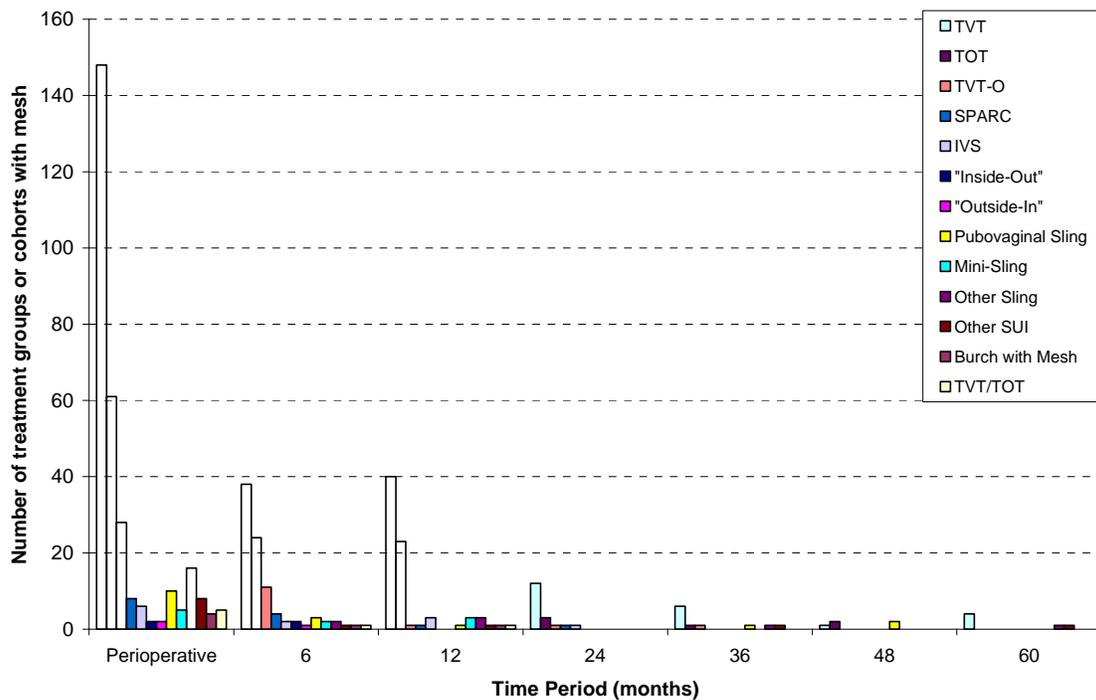
### ***6.3.2 Safety of Mesh Used in Repair of Stress Urinary Incontinence Based on Published Literature***

The FDA's review of the safety of mesh for SUI repair is presented based on the FDA's own systematic review of the literature. The FDA's methodology is presented in **Appendix III**. The findings of the literature review were presented as weighted mean percentages. The percentage occurrence of an adverse event within a study treatment group or "cohort" was calculated by dividing the number of patients within the cohort who reported the adverse event within a specified timeframe of "follow-up" by the number of patients within the cohort who continued follow up through the specified timeframe. The percentages for each timeframe were then averaged across cohorts, weighting the percentage in each cohort according to the number of patients in the cohort.

#### *Safety Evaluation Based on FDA Literature Review*

Among the 260 studies that were reviewed, there were 187 that evaluated the treatment of SUI using surgical mesh and 13 studies that used mesh for the treatment of both SUI and POP. The most commonly studied procedure using mesh for SUI repair was the TVT procedure, followed by the TOT procedure. **Figure 8** shows the number of treatment groups or cohorts of patients who had surgical mesh placed for the treatment of SUI as a function of the follow-up assessment times. (If a study included reports of adverse events for multiple time periods of follow-up, then the study is counted at each reported time period.)

There were 82 RCTs with at least one arm randomized to surgical mesh for the treatment of SUI, and there were 105 observational studies that included at least one group of patients using surgical mesh for treatment of SUI. As noted in **Figure 8**, there were very few studies that had follow-up assessments past 36 months. The vast majority of information that is available for SUI among all approaches is heavily weighted from the perioperative period (intraoperative to 48 hours post operative) to one year postoperative. The number of treatment groups or cohorts ranged from 1 to 3 and the number of patients per treatment group or cohort ranged from 10 patients to 2,795 patients.



**Figure 8 - Number of treatment groups or cohorts of patients with surgical mesh for the treatment of SUI by follow-up period.** This column graph displays the number of treatment groups or cohorts of patients broken down by time period (perioperative, 6, 12, 24, 36, 48, and 60 months post-operative) and stratified by the described SUI procedure. (Please see Appendix I for a larger version of this graph.)

The most commonly reported adverse events in the literature associated with surgical mesh for SUI repair included erosion, dyspareunia, infection, pain, urinary problems (including *de novo* SUI, urgency, frequency and overactive bladder), and re-surgery. This finding within the literature is consistent to what has been reported to the FDA through the MAUDE database.

It was found that between 9% and 17% of all women who had SUI treated with surgical mesh reported urinary problems from 6 months postoperatively to 60 months postoperatively. It also appears that with time there were increases in the proportion of women reporting urinary problems, re-surgery (range 2.5% at 6 months postoperatively to 6.2% at 12 months postoperatively), and any infection (5.1% perioperatively to 27.6% at 60 months postoperatively). The trend in urinary problems appeared to be largely driven by TVT procedures, compared to TOT procedures. The latter procedure demonstrated consistent rates (roughly 10%) of urinary problems across study follow-up periods.

The trend observed with urinary problems was similar with infection rates. Women who underwent TOT procedures had lower weighted rates of infection than women who had TVT procedures. Furthermore, it was observed that among TVT and TVT-O procedures, infection rates appeared to increase over time, while infection rates among TOT

procedures decreased from 10% during the perioperative period to 0.4% at 24 months postoperatively.

There was no apparent trend in erosion rates, which ranged from 0.25 % to 4% from at 6 months postoperatively to 60 months postoperatively. Weighted rates of reported pelvic or vaginal pain ranged from 22.2% at 60 months to 1.6% at 36 months but more consistently averaged at about 5%. Neuromuscular adverse events were reported at a rate of 1% or less over the follow-up measurement periods. Dyspareunia rates ranged from a high of 13.7% at 60 months to 0.64% at 12 months.

It should be noted that a limited number of studies followed patients past 36 months. Therefore, the weighted percentages are less stable for the longer follow-up periods, as they are weighted by only a few studies with smaller sample sizes. Additionally, there were very few studies that evaluated the TOT procedure after 24 months, and none that followed patients past 48 months.

The most common perioperative complications associated with sling procedures were organ perforation (including bladder, urethral, vaginal, and bowel perforation), hemorrhage, and hematomas. The weighted average of organ perforation across the literature was found to be 3.9%. The SPARC procedure, pubovaginal slings, and the TVT procedure have higher perforation rates of 10.1%, 8%, and 4.4%, respectively. Of women undergoing TOT procedures, 1.7% experienced perforation. The FDA's findings on the rates of organ perforations with surgical mesh are consistent to what has been reported in the available published systematic reviews and meta-analysis.

Hemorrhage was found to occur perioperatively among 31.7% of women. However, the definitions of hemorrhage were disparate across the literature; and therefore, clinically significant conclusions cannot be drawn from this rate. Hematomas were reported both during the perioperative period and up to 12 months post surgery. Perioperatively, 1.0% of women reported hematomas, while at 12 months, 1.5% of women had either a reported or clinically observed pelvic hematoma. Much like hemorrhage, there was no clear definition of a hematoma across the literature, and as such, clinically significant conclusions cannot be drawn from the hematoma rate.

#### *Safety Evaluation Based on Cochrane Reviews*

While there have been no Cochrane reviews or meta-analyses conducted with the primary objective of evaluating complications of surgical mesh among SUI patients, a Cochrane review by Lapitan *et al* [36] evaluated open retropubic colposuspension to other techniques including sling procedures. Another Cochrane review by Ogah *et al* [37] compared minimally invasive slings to pubovaginal slings with comparisons of different styles of minimally invasive slings for SUI. Both reviews present results of comparisons of AEs between groups and the findings are summarized below.

### *Open retropubic colposuspension vs. sling procedures (pubovaginal and TVT)*

Data from six trials on perioperative complications showed significantly lower rates of perioperative complications during colposuspension (37%) versus sling procedures (48%) (RR 0.76, 95% CI 0.66 to 0.88). Data from six trials showed a lower risk of voiding dysfunction following colposuspension (2.2%) versus any sling procedure (6.3%) (RR 0.37, 95% CI 0.22 to 0.63). This outcome may have been skewed by one large study [45]. Compared to TVT sling procedures, there was no significant difference in urodynamic voiding dysfunction compared to colposuspension (5.4% for open colposuspension versus 5.7% for TVT (RR 0.92, 95% CI 0.46 to 1.85). The comparative risk of bladder perforation differed for traditional sling and TVT. Based on a single study, the rate of bladder perforation was higher during open colposuspension (3.0%) versus traditional pubovaginal sling (0.6%) (RR 4.95, 95% CI 1.09 to 22.44). Based on data from five studies, the risk was lower during open colposuspension (1%) versus TVT (7%) (RR 0.19, 95% CI 0.07 to 0.52).

The only study that reported the need for repeat incontinence surgery did not show a significant difference between open colposuspension (3.4%) and TVT sling (1.2%) (RR 1.94, 95% CI 0.47 to 7.98).

### *Minimally invasive synthetic suburethral slings (MISS) vs. traditional pubovaginal (PVS) sub-urethral slings*

There were nine studies that evaluated MISS compared to traditional pubovaginal slings. Post-operative voiding dysfunction for MISS (10.2%) was not significantly different from PVS (13.4%) (RR 0.75, 95% CI 0.38 to 1.48). Data from three studies that evaluated *de novo* urgency showed less (5.7%) following MISS versus 17% after PVS surgery (RR 0.36, 95% CI 0.16 to 0.79).

### *MISS Retropubic TVT Bottom-to-Top vs. Retropubic SPARC Top-to-Bottom Approach*

Five studies enrolling 636 patients compared TVT (bottom-to-top MISS) versus SPARC (top-to-bottom MISS). There was no difference between procedures regarding perioperative complications. The rate of bladder perforation was lower with TVT (4.7%) compared to SPARC (8.5%) (RR 0.55, 95% CI 0.31 to 0.98). Vaginal mesh erosion was reported in four studies. The rate of erosion was significantly lower following TVT (0.7%) versus SPARC (3.4%) (RR 0.27, 95% CI 0.08 to 0.95). Regarding detrusor overactivity, in one study the rate for bottom-to-top was 3.4% versus 1.7% for top-to-bottom (RR 2.0, 95% CI 0.19 to 21.45). For *de novo* urgency or urge incontinence, the rate for bottom-to-top was 10% versus 12.3% for top-to-bottom (RR 0.84, 95% CI 0.52 to 1.34). The rate of voiding dysfunction was 2.2% among TVT patients which was significantly lower compared to SPARC patients (6.0%) (RR 0.40, 95% CI 0.18 to 0.90).

*MISS Trans Obturator medial-to-lateral (TOT) vs. Trans Obturator lateral-to-medial (TVT-O)*

Data from three small studies enrolling 289 patients were evaluated. There were no differences between the groups for operative blood loss, perioperative complications (2.7% versus 2.0% for TOT and TVT-O, respectively), or bladder perforation (0% versus 2.2% for TOT and TVT-O).

*MISS Monofilament vs. Multifilament Polymer Material*

Three studies reported outcomes on 472 patients randomized to monofilament mesh (TVT) versus multifilament (IVS). The only statistically significant difference found in this comparison between these mesh materials was from two trials that reported the rate of mesh erosion as 1.3% for monofilament and 6% for multifilament (RR 0.25, 95% CI 0.06 to 1.00).

*MISS Transobturator vs. Retropubic*

Twenty-four studies reported outcomes comparing transobturator versus retropubic mesh sling. From 18 studies, the rate of bladder perforation was significantly lower with the transobturator route (0.3%) versus the retropubic route (5.5%) (RR 0.14, 95% CI 0.07 to 0.26).

From 14 studies, the rate of mesh erosion (1.3% for transobturator and 1.9% for retropubic) did not differ significantly between the two approaches (RR 1.58, 95% CI 0.83 to 3.00). Groin pain was significantly higher for transobturator (12%) versus retropubic (1.7%) (RR 6.0, 95% CI 3 to 11). There was no difference between groups for *de novo* urgency and detrusor overactivity. There was a significantly lower rate of voiding dysfunction in the transobturator group (4%) versus retropubic group (7%) (RR 0.63, 95% CI 0.44 to 0.89).

NOTE: The Cochrane Review did not include a large RCT (n=597) by Richter *et al* comparing retropubic versus transobturator sling procedures [38]. Richter *et al* found that the rate of voiding dysfunction requiring surgical intervention was 2.7% in the retropubic group and 0% in the transobturator group (p=0.004). Mesh erosion or exposure classified as serious occurred in 3.0% of retropubic cases and 0.6% among transobturator cases (p=0.067). (Serious mesh exposure was defined as “when surgical, endoscopic, or radiologic intervention was required or a life-threatening complication requiring intensive care developed.”)

*Single Incision Mini Slings – A Subset of Minimally Invasive Synthetic Slings*

As discussed previously, there is a relatively new field of minimally invasive synthetic slings for SUI, known as the single-incision “mini-sling.” There are two RCTs [42, 43] and one review article [44] available to obtain preliminary assessment of mini-slings. Hinoul *et al* enrolled 194 subjects randomized to TVT-O versus TVT Secur and 12-

month follow-up outcomes were obtained [42]. There was higher perioperative blood loss, higher mesh exposure and greater need for surgical re-intervention in the TVT-Secur group. The authors of this study noted that it is possible that some study results reflect a learning curve for TVT-Secur procedure. Similarly, Tommaselli et al randomized 84 subjects to TVT-O and TVT-Secur [43]. They observed a trend towards higher rate of moderate blood loss (and a single case of transient severe blood loss) among TVT-Secur subjects. At one year, there were no cases of mesh erosion in the TVT-O group, and a single case in the TVT-Secur group.

Walsh reviewed the literature for outcomes following TVT-Secur at one year [44]. Three studies provide comparative data for the “U-type” (akin to retropubic approach) compared to the “H-type” (akin to transobturator placement). The rate of mesh exposure at 12 months was 2.4%. The incidence of *de novo* overactive bladder symptoms was 10%.

### Conclusion – Safety of Mesh Used in Repair of Stress Urinary Incontinence Based on Published Literature

The Cochrane reviews are limited in the ability to fully evaluate the safety of profile of surgical mesh used in SUI patients. The main objective of these reviews is to evaluate effectiveness of SUI procedures using RCTs that have compared a mesh procedure to another approach. Single or multiple arm observational studies that evaluated mesh are therefore excluded from these reviews. In order to capture adverse event information from these studies, the FDA conducted its own systematic literature review including any study with at least one treatment group who underwent a mesh procedure for SUI.

The FDA’s systematic literature review found that the weighted average rates of urinary problems, re-surgery rates, and perioperative organ perforations were similar to overall rates presented in published meta-analyses and systematic reviews. However, there were many complications not reported or rarely reported in the Cochrane reviews that were identified or observed at a greater rate in the FDA systematic literature review, *e.g.*, pain, infection, dyspareunia, hematoma, and neuromuscular issues. Furthermore, the RCTs included in the Cochrane reviews typically had limited follow-up times, and other non-RCTs presented longer term data on complications, *e.g.*, erosion or resurgeries related to mesh.

The Cochrane reviews did however identify noteworthy differences between mesh procedures and open colposuspension. The risk of perioperative complications favored colposuspension compared to all sling procedures combined, and the risk of voiding dysfunction was similar between colposuspension and the TVT sling. The risk of bladder perforation was higher for colposuspension compared to all sling procedures combined, but lower for colposuspension when compared to the TVT sling.

The Cochrane reviews and the review conducted by the FDA found that complication rates between mesh approaches may differ considerably. The Cochrane review found that the retropubic approach had a higher rate of bladder perforation, whereas the

transobturator approach was more likely to result in groin pain. Finally, one of the two RCTs [42] comparing single-incision mini-slings with TVT-O found that reoperation for incontinence was higher for mini-slings compared to transobturator slings. The Cochrane review and the review conducted by the FDA are limited in that many women in the identified studies had a history of previous incontinence surgery or underwent concomitant surgeries, including surgeries for POP.

**The panel will be asked to discuss the risks associated with vaginal mesh used for SUI repair. The panel will be asked to discuss if given the incidence and incidence and severity of these adverse events, if is there adequate assurance of the safety of suburethral mesh slings for surgical management of female SUI.**

**The FDA has identified the following risks to be associated with vaginal mesh used for SUI repair:**

**Peri-Operative Risks**

- **Organ perforation**
- **Bleeding (including hemorrhage/hematoma)**

**Long Term Risks**

- ***Vaginal Exposure of Mesh (Mesh “Erosion”).* Clinical sequelae include pelvic pain, infection, dyspareunia (painful sex for patient or partner), vaginal bleeding, vaginal discharge, urinary problems, and the need for additional corrective surgeries.**
- ***Other Risks.* These risks include pelvic pain, infection, dyspareunia, urinary problems, recurrent incontinence, mesh erosion into bladder, and neuro-muscular problems.**

**6.3.3 Conclusion – Safety and Effectiveness of Mesh Used in Repair of Stress Urinary Incontinence**

The safety and effectiveness of the first generation of minimally invasive synthetic slings for SUI have been evaluated in several randomized controlled clinical trials. The vast majority of slings evaluated are monofilament polypropylene mesh slings. Outcome data from peer reviewed literature have established the effectiveness of minimally invasive synthetic slings at achieving objective cure of SUI that is no different than invasive methods. The risk of vaginal mesh erosion from any minimally invasive synthetic sling is less than 5%. Other risks of minimally invasive synthetic slings include perioperative complications such as bladder perforation and groin pain. In the systematic review of literature conducted by the FDA and based on adverse event reports in the MAUDE database, there is potential for serious complications with mesh products indicated for SUI repair. The FDA is concerned that safety outcomes may not have been

comprehensively evaluated by RCTs to date and that the safety of SUI repair with mesh needs to be further considered in evaluating the overall risk to benefit profile of these products.

After considering all available data on both safety and effectiveness, and considering the risk/benefit profile, it appears that new premarket clinical trials are not warranted for minimally invasive slings for SUI unless the device has new features (*e.g.* new polymer or coating) that could affect device performance. The FDA recognizes, however, that the strength of this conclusion is limited by what is largely short duration (2 years) follow-up in the literature with limited data available past 3 years of follow-up.

**The panel will be asked if they agree with the FDA’s assessment that the effectiveness of first generation minimally invasive suburethral slings for SUI repair has been demonstrated. If not, the panel will be asked to discuss the need for premarket and/or postmarket clinical data on these devices.**

The FDA believes that new clinical performance data are needed in the premarket setting to ensure the safety and effectiveness of the second generation synthetic slings or “single incision mini slings.” The FDA’s position is based on the small number of non-randomized studies and two randomized controlled studies which suggest that mini slings may be less effective compared to the first generation minimally invasive synthetic slings. Preliminary safety outcomes suggest that the mini-sling may be associated with greater intraoperative blood loss and lead to higher rates of vaginal mesh erosion compared to first generation slings. Although future randomized controlled trials may lead to different conclusions, the FDA believes that premarket performance data are needed at this time to support market clearance of the second generation synthetic slings.

The regulatory threshold for the FDA to request clinical outcomes data is different for the premarket setting compared to the postmarket setting. The FDA believes that whereas the published literature provides sufficient clinical performance data to support new premarket notifications for the first generation SUI sling, it may be appropriate to require special postmarket surveillance studies to improve the FDA’s understanding of the safety profile of all types of minimally invasive slings (including mini-slings).

Finally, the FDA recognizes that all minimally invasive synthetic slings (including mini-slings) are associated with risk of failure as well as patient injury. The FDA believes, however, that the peer reviewed literature affords sufficient understanding of the nature and severity of risks from minimally invasive synthetic slings to enable FDA to review these devices under the Special Controls provisions of 510(k) premarket notification as Class II medical devices. The FDA is not proposing to reclassify these devices from Class II to Class III (Premarket Approval).

## 6.4 Regulatory Options for Mesh Used in Repair of Stress Urinary Incontinence

### 6.4.1 Premarket Options

The FDA is seeking panel input on the risk/benefit profile for retropubic and transobturator slings, which do not typically require premarket clinical data to support clearance of these devices. The FDA may request clinical performance data for retropubic and transobturator slings if the proposed mesh product is significantly different from currently marketed devices (*e.g.* new polymer or coating).

However, due to the lack of safety and effectiveness data available regarding mini-slings, the FDA believes that premarket performance data may be needed to support clearance of this subset of mesh used for SUI repair. The FDA anticipates that the type of study needed to support clearance of mini-slings would be similar to that described in the FDA Guidance Document “*Clinical Investigations of Devices Indicated for the Treatment of Urinary Incontinence*” issued on March 8, 2011

(<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070854.pdf>).

In accordance with the Guidance Document, the recommended study design for mini-slings may include the following:

- evaluation of a randomized, controlled trial comparing the mini-sling to a cleared standard minimally invasive suburethral sling
- primary effectiveness endpoint(s) evaluating difference in pad weight and/or incontinence episodes pre-surgery and 6-12 months postoperatively
- evaluation of safety endpoints, including mesh erosion and urinary retention

**The panel will be asked to discuss if they believe that premarket clinical studies are needed for mini-slings. If yes, the panel will be asked to discuss the necessary study design, including patient selection criteria, controls, randomization, outcome measures, follow-up duration, etc.**

Because comparison of mini-slings to cleared slings can be conducted via the 510(k) pathway, the FDA does not feel that reclassification to Class III is necessary for SUI mesh products.

However, the FDA is considering whether or not additional Special Controls are needed to ensure the safety and effectiveness of SUI mesh products. As described in **Section 2.1.2**, Special Controls may include any of the following:

- improvements in physician labeling, *e.g.*, more narrow indication for use, restricting use to physicians with credentialed training, better instructions for use, etc.
- patient labeling

- more premarket studies, *e.g.*, bench studies, animal studies, clinical studies to demonstrate substantial equivalence (*e.g.*, RCT comparison to legally marketed predicate mesh product indicated for SUI repair),
- performance standard(s)
- guidance document
- enhanced postmarket surveillance
- patient registry

**The panel will be asked to discuss each Special Control and whether it, alone or in combination with other Special Controls, would adequately mitigate the risks of these devices (either for all mesh products for SUI or a subset).**

#### **6.4.2 Postmarket Options**

The FDA is seeking panel input regarding the need for postmarket surveillance (*i.e.*, 522 studies) for surgical mesh indicated for treatment of SUI. The FDA would like the panel to consider whether 522 studies may only be needed for cleared mini-slings, all cleared surgical mesh indicated for SUI, or not needed for these devices.

The FDA has an option to mandate postmarket surveillance studies under Section 522 of the Act for those mesh products indicated for SUI that are already legally marketed. Given the current risk/benefit evaluation of these devices, the FDA believes that 522 studies may be warranted. Specifically, the FDA is considering ordering postmarket surveillance studies to confirm the nature, severity, or frequency of suspected problems reported in adverse event reports or in the published literature and to address the long term or infrequently reported safety and effectiveness issues of these devices. (As described in **Section 2.3**, the FDA can order prospective postmarket surveillance for up to 36 months.)

The FDA believes that the following additional considerations may also support the need for 522 studies of currently marketed mesh products indicated for SUI repair:

- Urogynecologic use of surgical mesh for SUI repair meets the statutory criteria for a 522 study because the device is intended to be implanted in the body for more than one year. In addition, failure of the device can result in mesh erosion, severe pain, fistula formation, and/or the need for surgical revision or mesh removal, which may be considered serious adverse health consequences.
- 522 studies could provide information regarding rates of adverse events for each specific mesh product already legally marketed.
- Clinical data collected via 522 studies may be included in labeling changes to the cleared 510(k) labeling.

The postmarket setting influences the study design options available for 522 studies. To address the questions under consideration, the FDA may recommend a randomized clinical trial or prospective cohort study design that compares the device(s) to a control (*i.e.*, urogynecologic surgery without use of mesh) through a pre-specified duration of follow-up (up to 36 months). Further, the FDA would recommend a study design including a population of women who are age 18 years or older with documented stress urinary incontinence diagnosis for whom surgery is scheduled. Inclusion and adjustment for the following risk factors would need to be considered: validated severity score for stress urinary incontinence; menopausal status; estrogen use; age; lifestyle factors; obesity; modification of mesh prior to placement; surgical technique or procedure used type of surgery.

Sponsors may also choose to develop a registry to address the questions, either as a single sponsor, in collaboration with multiple sponsors, or in conjunction with societies. The FDA is amenable to facilitating creation of a multi-sponsor or society registry to address the public health concerns.

**The panel will be asked consider whether 522 studies are needed for cleared mini-slings, all cleared surgical mesh indicated for SUI, or not needed for these devices. If the panel believes 522 studies are needed for all or just a subset of these products, the panel will be asked to discuss the type of clinical study that should be required, with consideration to patient selection, controls, randomization, outcome measures, concomitant surgeries, follow up duration, etc.**

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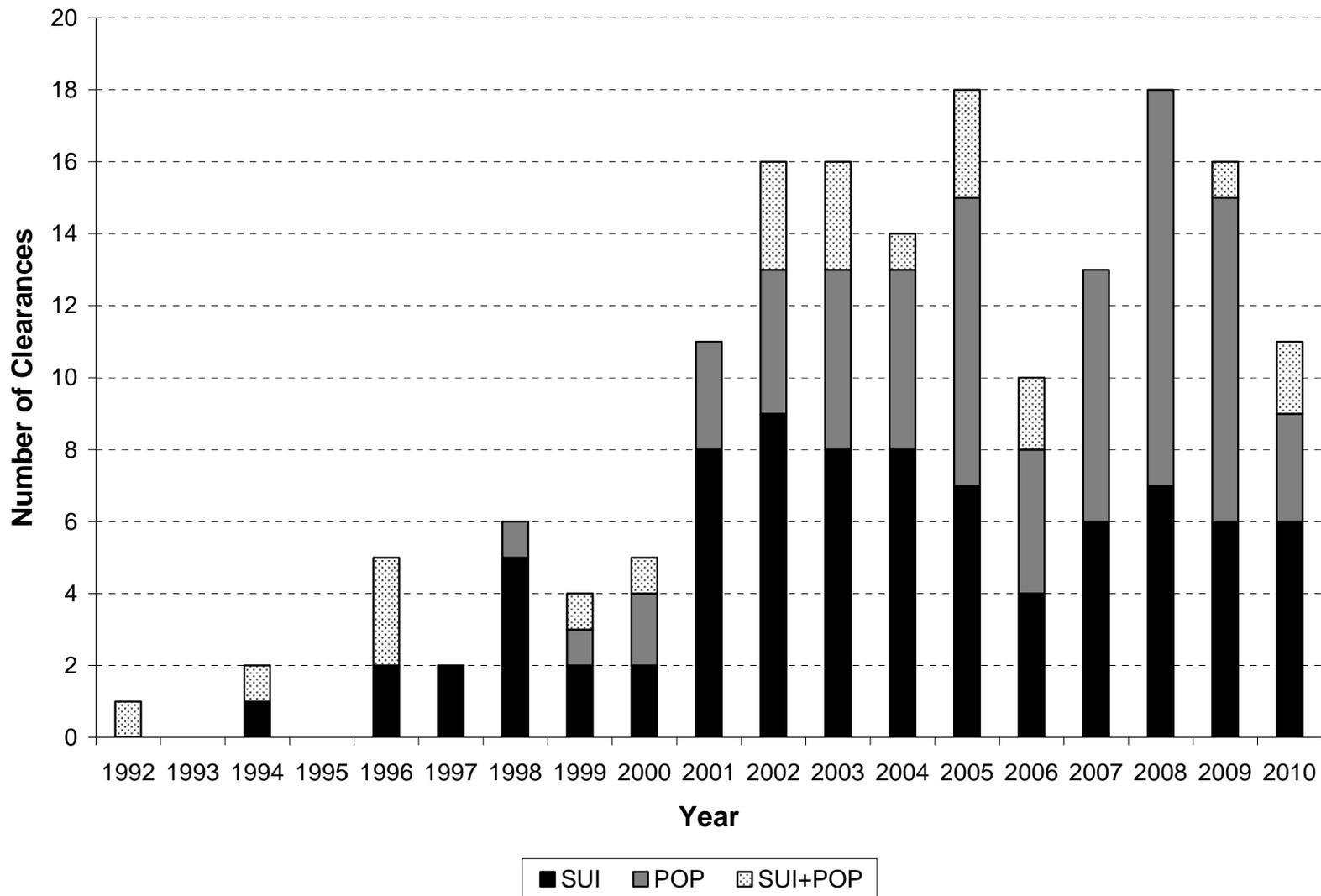
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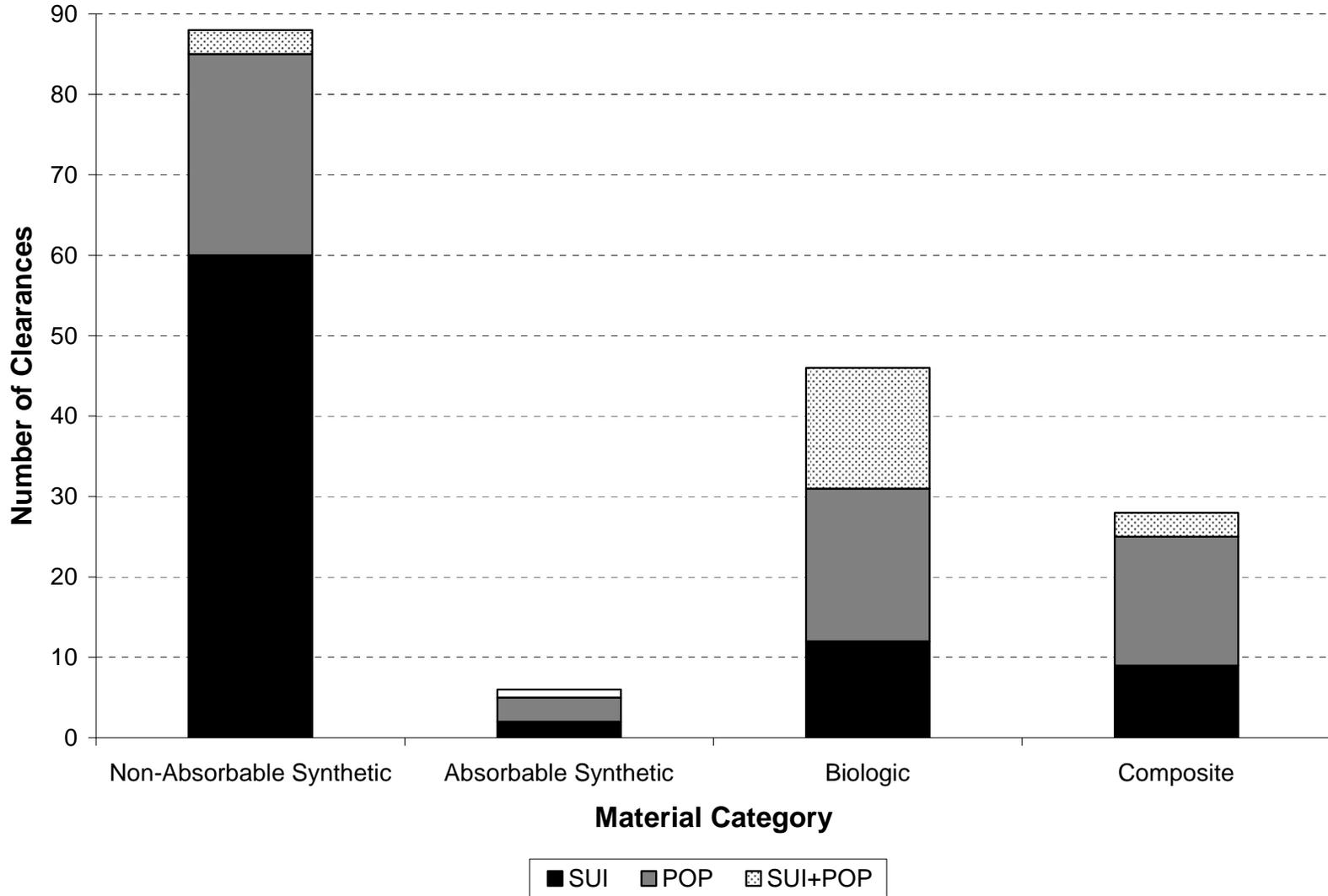
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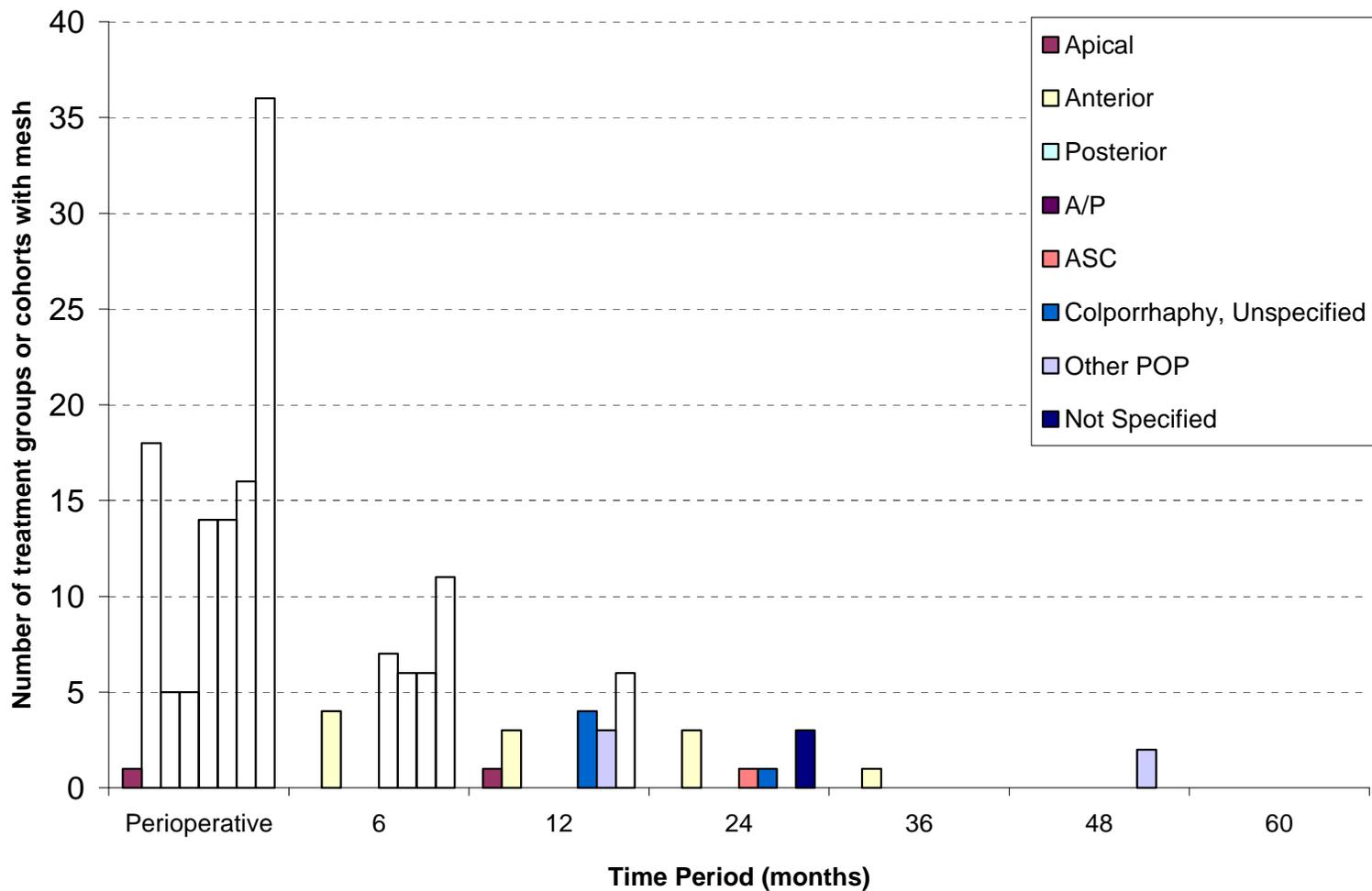
APPENDIX I - GRAPHS



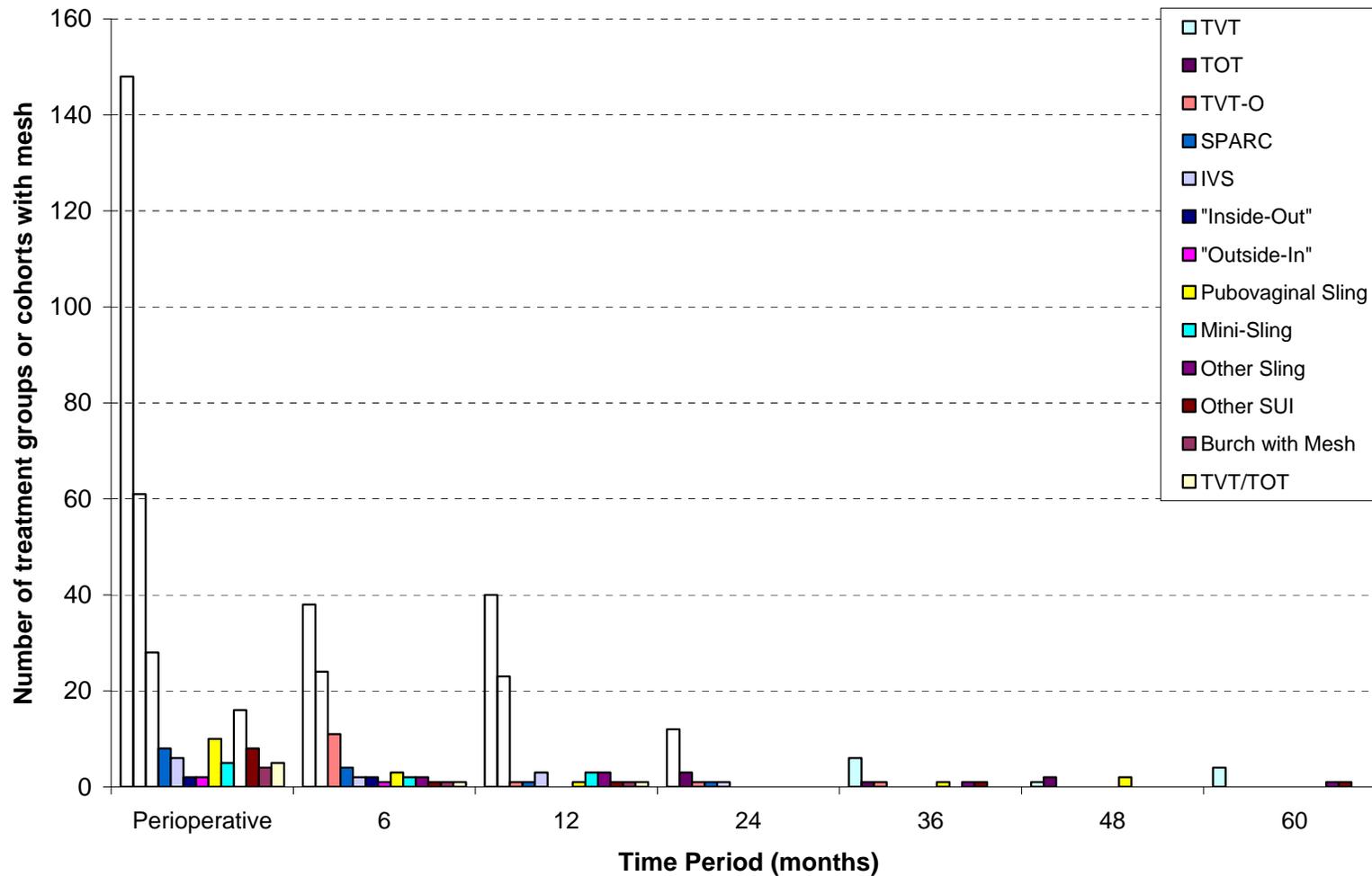
**Figure 1 – Urogynecologic Surgical Mesh 510(k) Clearances by Year (1992-2010).** This stacked column graph shows the number of cleared submissions each year from 1992-2010, broken down by indication—SUI, POP, or both (SUI+POP). As the graph indicates, after the year 2000, there was an increase in the number of clearances across all indications.



**Figure 2 - Urogynecologic Surgical Mesh 510(k) Clearances by Material Category.** This stacked column graph shows the number of cleared submissions for urogynecologic surgical mesh per material category broken down by indication—SUI, POP, or both (SUI+POP). The majority of these submissions (52%, n=88) pertain to mesh products composed of non-absorbable synthetic material, and most (91%) submissions in this material category are composed of polypropylene (75% monofilament).



**Figure 7 – Number of treatment groups or cohorts of patients with surgical mesh for the treatment of POP by follow-up period.** This column graph displays the number of treatment groups or cohorts of patients broken down by time period (perioperative, 6, 12, 24, 36, 48, and 60 months post-operative) and stratified by the described POP repair (apical, anterior, posterior, anterior and posterior [A/P], abdominal sacrocolpopexy [ASC], colporrhaphy (i.e., vaginal repair) unspecified, other POP (more rare surgeries that did not fit into the previous categories), and not specified).



**Figure 8 - Number of treatment groups or cohorts of patients with surgical mesh for the treatment of SUI by follow-up period.** This column graph displays the number of treatment groups or cohorts of patients broken down by time period (perioperative, 6, 12, 24, 36, 48, and 60 months post-operative) and stratified by the described SUI procedure.

## APPENDIX II – METHODS AND LIMITATIONS OF MAUDE DATA ANALYSIS

### I. Method for MAUDE Analysis

The Manufacturer and User Facility Device Experience (MAUDE) database was searched using two search criteria:

- Product codes: FTL and FTM
- Date report received from Jan 1, 2008 through Dec 31, 2010

This search generated 6,290 reports of all types of mesh products, including those with urogynecology, hernia, male urology, neurosurgery, and orthopedic indications.

The following MDRs were deleted from the 6290 MDRs:

- Duplicate reports,
- Reports with unknown device specifications,
- Reports related to mesh products for orthopedic and spine surgery,
- Reports related to mesh products indicated for male incontinence
- Hernia meshes, and
- Wrong entries: Reports with wrong product code, or entered as mesh by error

The number of remaining MDRs that included urogynecology meshes came to 2874. The reports were separated into two groups based on indication, SUI and POP. The final number of reports in the two indications came to 1,503 reports in POP group, and 1,371 reports in SUI group. The details of the analyses are presented in **Section 5.2** and **Section 6.2** for POP and SU respectively.

### II. Limitations of MAUDE Data Analysis

- The reports were unduplicated using Excel's auto-unduplication function, not by reviewing the individual reports. A few unduplicated reports might still exist in the data. This auto-function does not identify reports that have different numbers but are related to the same events. Additionally, if one event has two reports – *i.e.*, one from manufacturer and one from a voluntary reporter – but they are not linked in the MAUDE database as one event, they will not be picked by the auto-function as one event. The number of these reports is not large enough to affect the overall results.
- Many voluntary reporters used layman terminology to describe their adverse events, reported incorrect procedure(s), or the incorrect manufacturer name or brand names. As a result, a few reports might be misclassified. The number of these reports is not large enough to affect the overall results.
- A large number of reports in each indication specified two or three procedures in one surgical operation. These reports were categorized according to the device brand name indication.

- A number of reports indicated the use of more than one mesh of the same brand or of different brand names, but the adverse event reported in the narrative is not linked to one specific brand.
- Even though the results of data mining were refined multiple times, it is still possible that a few reports are placed in the wrong group or in the wrong adverse event groups.

### **APPENDIX III – METHODOLOGY FOR SYSTEMATIC EPIDEMIOLOGIC REVIEW OF PUBLISHED LITERATURE**

The FDA evaluated the peer-reviewed scientific literature to revisit the fundamental questions of safety and effectiveness of surgical mesh for POP and SUI. A systematic literature review was conducted by searching the PubMed database from January 1996 to April 2011. The initial search yielded 925 articles that included randomized controlled trials, observational studies and systematic reviews and meta-analysis. Observational studies that had less than 50 participants per treatment arm, non-clinical studies, studies on cost-analysis, case reports, practice guidelines, and reviews (non-systematic and non-meta-analysis) were excluded. All randomized controlled trials were included, regardless of sample sizes in arms. A total of 260 articles that compared a mesh surgery to a non-mesh surgery, a mesh surgery to another mesh surgery, or procedures involving surgical mesh were fully reviewed to evaluate the safety and effectiveness of surgical mesh for POP and SUI.

The quantitative findings of the review of literature are presented as weighted mean percentages. The percentage occurrence of an adverse event within a study treatment group or “cohort” was calculated by dividing the number of patients within the cohort who reported the adverse event within a specified timeframe of “follow-up” by the number of patients within the cohort who continued follow up through the specified timeframe. The percentages for each timeframe were then averaged across cohorts, weighting the percentage in each cohort according to the number of patients in the cohort.

**APPENDIX IV – 2008 PUBLIC HEALTH NOTIFICATION**

## Medical Devices

### FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence

For updated information about Surgical Mesh for Pelvic Organ Prolapse, see: [UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse](#)<sup>1</sup>, released July 13, 2011.

Issued: October 20, 2008

Dear Healthcare Practitioner:

This is to alert you to complications associated with transvaginal placement of surgical mesh to treat Pelvic Organ Prolapse (POP) and Stress Urinary Incontinence (SUI). Although rare, these complications can have serious consequences. Following is information regarding the adverse events that have been reported to the FDA and recommendations to reduce the risks.

#### Nature of the Problem

Over the past three years, FDA has received over 1,000 reports from nine surgical mesh manufacturers of complications that were associated with surgical mesh devices used to repair POP and SUI. These mesh devices are usually placed transvaginally utilizing tools for minimally invasive placement.

The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia.

Treatment of the various types of complications included additional surgical procedures (some of them to remove the mesh), IV therapy, blood transfusions, and drainage of hematomas or abscesses.

Specific characteristics of patients at increased risk for complications have not been determined. Contributing factors may include the overall health of the patient, the mesh material, the size and shape of the mesh, the surgical technique used, concomitant procedures undertaken (e.g. hysterectomy), and possibly estrogen status.

#### Recommendations

Physicians should:

- Obtain specialized training for each mesh placement technique, and be aware of its risks.
- Be vigilant for potential adverse events from the mesh, especially erosion and infection.
- Watch for complications associated with the tools used in transvaginal placement, especially bowel, bladder and blood vessel perforations.
- Inform patients that implantation of surgical mesh is permanent, and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication.
- Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall (in POP repair).
- Provide patients with a written copy of the patient labeling from the surgical mesh manufacturer, if available.

[Additional patient information](#)<sup>2</sup> can be found on the following FDA Consumer website.

#### Reporting Adverse Events to FDA

FDA requires hospitals and other user facilities to report deaths and serious injuries associated with the use of medical devices. If you suspect that a reportable adverse event was related to the use of surgical mesh, you should follow the reporting procedure established by your facility.

We also encourage you to report adverse events related to surgical mesh that do not meet the requirements for mandatory reporting. You can report directly to MedWatch, the FDA Safety Information and [Adverse Event Reporting program online](#)<sup>3</sup>, by phone at 1-800-FDA-1088, or obtain [the fillable form online](#)<sup>4</sup>, print it out and fax to 1-800-FDA-0178 or mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787.

#### Getting More Information

If you have questions about this Notification, please contact FDA's Office of Surveillance and Biometrics by e-mail at [phann@fda.hhs.gov](mailto:phann@fda.hhs.gov) or by phone at 301-796-6640.

[FDA Medical Device Public Health Notifications](#)<sup>5</sup> are available on the Internet. You can also be notified through email each time a new Public Health Notification is added to our web page. To subscribe, visit: [http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_39](http://service.govdelivery.com/service/subscribe.html?code=USFDA_39)<sup>6</sup>.

Sincerely,

Daniel G. Schultz, MD  
Director  
Center for Devices and Radiological Health  
Food and Drug Administration

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#### Links on this page:

1. <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm>
2. <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm142636.htm>
3. <http://www.fda.gov/Safety/MedWatch/default.htm>
4. <http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm>
5. <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/default.htm>
6. [http://service.govdelivery.com/service/subscribe.html?code=USFDA\\_39](http://service.govdelivery.com/service/subscribe.html?code=USFDA_39)

**APPENDIX V – 2011 SAFETY COMMUNICATION**

## Medical Devices

### FDA Safety Communication: UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse

Date Issued: July 13, 2011

#### Audience:

- Health care providers who implant surgical mesh to repair pelvic organ prolapse and/or stress urinary incontinence
- Health care providers involved in the care of patients with surgical mesh implanted to repair pelvic organ prolapse and/or stress urinary incontinence
- Patients who are considering or have received a surgical mesh implant to repair pelvic organ prolapse and/or stress urinary incontinence

**Medical Specialties:** gynecology, urogynecology, urology, general surgery, internal medicine, family practice, emergency medicine

#### Device:

Surgical mesh is a medical device that is generally used to repair weakened or damaged tissue. It is made from porous absorbable or non-absorbable synthetic material or absorbable biologic material. In urogynecologic procedures, surgical mesh is permanently implanted to reinforce the weakened vaginal wall to repair pelvic organ prolapse or to support the urethra to treat urinary incontinence.

#### Background:

##### Pelvic Organ Prolapse

Pelvic organ prolapse (POP) occurs when the tissues that hold the pelvic organs in place become weak or stretched. Thirty to fifty percent of women may experience POP in their lifetime with 2 percent developing symptoms. When POP happens, the organs bulge (prolapse) into the vagina and sometimes prolapse past the vaginal opening. More than one pelvic organ can prolapse at the same time. Organs that can be involved in POP include the bladder, the uterus, the rectum, the top of the vagina (vaginal apex) after a hysterectomy, and the bowel.

##### Stress Urinary Incontinence

Stress urinary incontinence (SUI) is a leakage of urine during moments of physical activity, such as coughing, sneezing, laughing, or exercise.

#### Purpose:

On Oct. 20, 2008, the FDA issued a Public Health Notification and Additional Patient Information on serious complications associated with surgical mesh placed through the vagina (transvaginal placement) to treat POP and SUI.

Based on an updated analysis of adverse events reported to the FDA and complications described in the scientific literature, the FDA identified surgical mesh for transvaginal repair of POP as an area of continuing serious concern.

The FDA is issuing this update to inform you that serious complications associated with surgical mesh for transvaginal repair of POP are **not rare**. This is a change from what the FDA previously reported on Oct. 20, 2008. Furthermore, it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair in all patients with POP and it may expose patients to greater risk. This Safety Communication provides updated recommendations for health care providers and patients and updates the FDA's activities involving surgical mesh for the transvaginal repair of POP.

*The FDA continues to evaluate the effects of using surgical mesh to repair SUI and will communicate these findings at a later date.*

For detailed information, please see: [Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse](#).<sup>1</sup>

#### Summary of Problem and Scope:

In the Oct. 20, 2008 FDA Public Health Notification, the number of adverse events reported to the FDA for surgical mesh devices used to repair POP and SUI for the previous 3-year period (2005 – 2007) was "over 1,000." Since then, from Jan. 01, 2008 through Dec. 31, 2010, the FDA received 2,874 additional reports of complications associated with surgical mesh devices used to repair POP and SUI, with 1,503 reports associated with POP repairs and 1,371 associated with SUI repairs. Although it is common for adverse event reporting to increase following an FDA safety communication, we are concerned that the number of adverse event reports remains high.

From 2008 – 2010, the most frequent complications reported to the FDA for surgical mesh devices for POP repair include mesh erosion through the vagina (also called exposure, extrusion or protrusion), pain, infection, bleeding, pain during sexual intercourse (dyspareunia), organ perforation, and urinary problems. There were also reports of recurrent prolapse, neuro-muscular problems, vaginal scarring/shrinkage, and emotional problems. Many of these complications require additional intervention, including medical or surgical treatment and hospitalization.

In order to better understand the use of surgical mesh for POP and SUI, the FDA conducted a systematic review of the published scientific literature from 1996 – 2011 to evaluate its safety and effectiveness. The review showed that transvaginal POP repair with mesh does not improve symptomatic results or quality of life over traditional non-mesh repair. The FDA continues to evaluate the literature for SUI surgeries using surgical mesh and will report about that usage at a later date.

In particular, the literature review revealed that:

- Mesh used in transvaginal POP repair introduces risks not present in traditional non-mesh surgery for POP repair.
- Mesh placed abdominally for POP repair appears to result in lower rates of mesh complications compared to transvaginal POP surgery with mesh.
- There is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh.
- While transvaginal surgical repair to correct weakened tissue between the bladder and vagina (anterior repair) with mesh augmentation may provide an anatomic benefit compared to traditional POP repair without mesh, this anatomic benefit may not result in better symptomatic results.

The FDA's literature review found that *erosion* of mesh through the vagina is the *most common and consistently reported mesh-related complication* from transvaginal POP surgeries using mesh. Mesh erosion can require multiple surgeries to repair and can be debilitating for some women. In some cases, even multiple surgeries will not resolve the complication.

*Mesh contraction* (shrinkage) is a *previously unidentified risk* of transvaginal POP repair with mesh that has been reported in the published scientific literature and in adverse event reports to the FDA since the Oct. 20, 2008 *FDA Public Health Notification*. Reports in the literature associate mesh contraction with vaginal shortening, vaginal tightening and vaginal pain.

Both mesh erosion and mesh contraction may lead to severe pelvic pain, painful sexual intercourse or an inability to engage in sexual intercourse. Also, men may experience irritation and pain to the penis during sexual intercourse when the mesh is exposed in mesh erosion.

The complications associated with the use of surgical mesh for POP repair have not been linked to a single brand of mesh.

#### Recommendations for Health Care Providers:

As stated in the Oct. 20, 2008 Public Health Notification, the FDA continues to recommend that health care providers should:

- Obtain specialized training for each mesh placement technique, and be aware of the risks of surgical mesh.
- Be vigilant for potential adverse events from the mesh, especially erosion and infection.
- Watch for complications associated with the tools used in transvaginal placement, especially bowel, bladder and blood vessel perforations.
- Inform patients that implantation of surgical mesh is permanent, and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication.
- Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall in POP repair using surgical mesh.
- Provide patients with a copy of the patient labeling from the surgical mesh manufacturer if available.

In addition, the FDA also recommends that health care providers:

- Recognize that in most cases, POP can be treated successfully without mesh thus avoiding the risk of mesh-related complications.
- Choose mesh surgery only after weighing the risks and benefits of surgery with mesh versus all surgical and non-surgical alternatives.
- Consider these factors before placing surgical mesh:
  - Surgical mesh is a permanent implant that may make future surgical repair more challenging.
  - A mesh procedure may put the patient at risk for requiring additional surgery or for the development of new complications.
  - Removal of mesh due to mesh complications may involve multiple surgeries and significantly impair the patient's quality of life. Complete removal of mesh may not be possible and may not result in complete resolution of complications, including pain.
  - Mesh placed abdominally for POP repair may result in lower rates of mesh complications compared to transvaginal POP surgery with mesh.
- Inform the patient about the benefits and risks of non-surgical options, non-mesh surgery, surgical mesh placed abdominally and the likely success of these alternatives compared to transvaginal surgery with mesh.
- Notify the patient if mesh will be used in her POP surgery and provide the patient with information about the specific product used.
- Ensure that the patient understands the postoperative risks and complications of mesh surgery as well as limited long-term outcomes data.

#### Recommendations for Patients:

##### Before Surgery

Be aware of the risks associated with surgical mesh for transvaginal repair of POP. Know that having a mesh surgery may put you at risk for needing additional surgery due to mesh-related complications. In a small number of patients, repeat surgery may not resolve complications.

Ask your surgeon about all POP treatment options, including surgical repair with or without mesh and non-surgical options, and understand why your surgeon may be recommending treatment of POP with mesh.

In addition, ask your surgeon these questions before you agree to have surgery in which surgical mesh will be used:

- Are you planning to use mesh in my surgery?
- Why do you think I am a good candidate for surgical mesh?
- Why is surgical mesh being chosen for my repair?
- What are the alternatives to transvaginal surgical mesh repair for POP, including non-surgical options?
- What are the pros and cons of using surgical mesh in my particular case? How likely is it that my repair could be successfully performed without using surgical mesh?
- Will my partner be able to feel the surgical mesh during sexual intercourse? What if the surgical mesh erodes through my vaginal wall?
- If surgical mesh is to be used, how often have you implanted this particular product? What results have your other patients had with this product?
- What can I expect to feel after surgery and for how long?
- Which specific side effects should I report to you after the surgery?
- What if the mesh surgery doesn't correct my problem?
- If I develop a complication, will you treat it or will I be referred to a specialist experienced with surgical mesh complications?
- If I have a complication related to the surgical mesh, how likely is it that the surgical mesh could be removed and what could be the consequences?
- If a surgical mesh is to be used, is there patient information that comes with the product, and can I have a copy?

##### After Surgery

- Continue with your annual and other routine check-ups and follow-up care. There is no need to take additional action if you are satisfied with your surgery and are not having complications or symptoms.
- Notify your health care provider if you have complications or symptoms, including persistent vaginal bleeding or discharge, pelvic or groin pain or pain with sex, that last after your follow-up appointment.
- Let your health care provider know you have surgical mesh, especially if you plan to have another surgery or other medical procedures.
- Talk to your health care provider about any questions you may have.

If you had POP surgery, but do not know whether your surgeon used mesh, ask your health care provider at your next scheduled visit.

##### FDA Activities:

The FDA is working in several areas to assess and improve the safety and effectiveness of urogynecologic mesh products. The FDA will:

- Convene the Obstetrics-Gynecology Devices Panel of the Medical Device Advisory Committee, on September 8-9, 2011. The panel will discuss and make recommendations regarding the safety and effectiveness of transvaginal surgical mesh for POP and SUI.
- Explore regulatory solutions to answer questions about the safety and effectiveness of urogynecologic mesh products that are now being marketed and those that will be reviewed for marketing in the future.
- Continue to monitor adverse events reported to FDA associated with surgical mesh used to repair POP and SUI, as well as assessing any and all data as it becomes available.

##### Reporting Problems to the FDA:

Prompt reporting of adverse events can help the FDA identify and better understand the risks associated with medical devices. If you suspect a problem with

surgical mesh, we encourage you to file a voluntary report through [MedWatch, the FDA Safety Information and Adverse Event Reporting program](#)<sup>2</sup>. Health care personnel employed by facilities that are subject to the [FDA's user facility reporting requirements](#)<sup>3</sup> should follow the reporting procedures established by their facilities. Device manufacturers must comply with the [Medical Device Reporting \(MDR\) regulations](#)<sup>4</sup>.

To help us learn as much as possible about the adverse events associated with surgical mesh to repair POP and SUI, please include the following information in your reports, if available:

- Manufacturer's name
- Product name (brand name)
- Catalog number
- Lot number
- Size
- Date of implant
- Date of explant (if mesh was removed)
- Details of the adverse event and medical and/or surgical interventions (if required)
- Type of procedure (e.g., anterior or posterior repair, sacral colpopexy, sling procedure for SUI)
- Surgical approach: (e.g., vaginal, abdominal, laparoscopic)
- Reason for mesh implantation: (e.g., POP of the uterus, bladder, rectum, vaginal apex or bowel, SUI)
- Specific postoperative symptoms experienced by the patient with time of onset and follow-up treatment

**Contact Information:**

If you have questions about this communication, please contact the Division of Small Manufacturers, International and Consumer Assistance (DSMICA) at [DSMICA@FDA.HHS.GOV](mailto:DSMICA@FDA.HHS.GOV), 800-638-2041 or 301-796-7100.

*This document reflects the FDA's current analysis of available information, in keeping with our commitment to inform the public about ongoing safety reviews of medical devices.*

**Additional Information**

- [Urogynecologic Surgical Mesh Implants](#)<sup>5</sup>
- [Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse \(July 2011\) \(PDF - 243KB\)](#)<sup>6</sup>
- [Press Release: Surgical placement of mesh to repair pelvic organ prolapse poses risks](#)<sup>7</sup>
- [Federal Register Notice: Urogynecologic Surgical Mesh](#)<sup>8</sup>

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**Links on this page:**

1. [/downloads/MedicalDevices/Safety/AlertsandNotices/UCM262760.pdf](#)
2. <http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>
3. [/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm2005737.htm](#)
4. [/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/ucm2005737.htm](#)
5. [/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/default.htm](#)
6. [/downloads/MedicalDevices/Safety/AlertsandNotices/UCM262760.pdf](#)
7. [/NewsEvents/Newsroom/PressAnnouncements/ucm262752.htm](#)
8. [http://www.ofr.gov/OFRUpload/OFRData/2011-17695\\_PI.pdf](http://www.ofr.gov/OFRUpload/OFRData/2011-17695_PI.pdf)

**APPENDIX VI – 2011 WHITE PAPER**

# Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse

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**July 2011**



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## I. EXECUTIVE SUMMARY

In October 2008, the FDA issued a [Public Health Notification \(PHN\)](#) to inform clinicians and patients of adverse events related to urogynecologic use of surgical mesh, and to provide recommendations on how to mitigate risks and how to counsel patients. Following the *PHN*, the FDA continued to monitor the outcomes of urogynecologic use of surgical mesh. A search of the FDA's Manufacturer and User Device Experience (MAUDE) database from the last 3 years (January 1, 2008 - December 31, 2010), identified 2,874 Medical Device Reports (MDRs) for urogynecologic surgical meshes, including reports of injury, death, and malfunctions. Among the 2,874 reports, 1,503 were associated with pelvic organ prolapse (POP) repairs, and 1,371 were associated with stress urinary incontinence (SUI) repairs.

The FDA also conducted a systematic review of the scientific literature to learn more about the safety and effectiveness of POP and SUI using surgical mesh. The FDA determined that (1) serious adverse events are NOT rare, contrary to what was stated in the 2008 *PHN*, and (2) transvaginally placed mesh in POP repair does NOT conclusively improve clinical outcomes over traditional non-mesh repair.

The FDA is providing this update to advise the public and the medical community of complications related to transvaginal POP repair with mesh. The FDA plans to convene an advisory panel meeting of outside experts in September 2011 to discuss these findings and the types of clinical studies necessary to better assess the risks and benefits of using mesh to treat POP and SUI. In addition FDA is considering regulatory changes that may improve our understanding of the safety and effectiveness of this device.

The FDA continues to evaluate the effects of using surgical mesh for the treatment of SUI and will report about that usage at a later date.

## II. OVERVIEW

Surgical mesh is a metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists [1].

Surgical mesh has been used since the 1950s to repair abdominal hernias. In the 1970s, gynecologists began using surgical mesh products indicated for hernia repair for abdominal repair of pelvic organ prolapse (POP), and in the 1990s, gynecologists began using surgical mesh for surgical treatment of stress urinary incontinence (SUI) and transvaginal repair of pelvic organ prolapse (POP). To do so, surgeons cut the mesh to the desired shape and placed it through a corresponding incision. Over time, in response to a perceived demand in the surgical community, manufacturers developed mesh products specifically designed for SUI and POP. In 1996, the FDA cleared the first surgical mesh product specifically for use in SUI, and in 2002, the FDA cleared the first surgical mesh product specifically for use in POP. Over the next few years, surgical mesh products for transvaginal POP repair became incorporated into "kits" that included tools to aid in the delivery and insertion of the mesh. Surgical mesh kits continue to evolve, adding new insertion tools, tissue fixation anchors, surgical techniques, and absorbable and biologic materials.

Surgical mesh products are currently regulated as Class II devices and are reviewed under the 510(k) Premarket Notification Program. The FDA’s premarket review of these devices has primarily focused on data supporting the adequacy of mechanical performance and material safety. Bench and/or animal testing have been used to confirm that engineering specifications are met and that the mesh material is biocompatible. Clinical performance data typically has not been used to support clearance for POP or SUI urogynecologic mesh products.

Surgical mesh materials can be divided into four general categories:

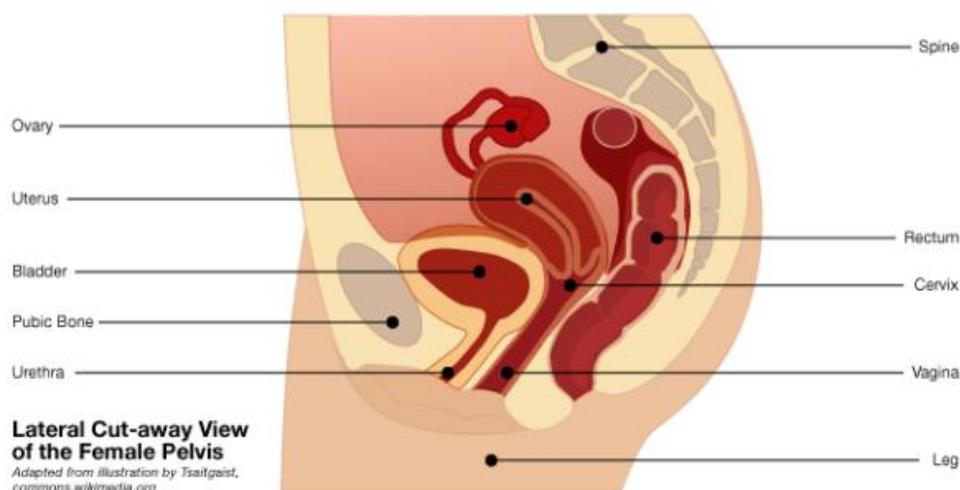
- non-absorbable synthetic (e.g., polypropylene or polyester)
- absorbable synthetic (e.g., poly(lactic-co-glycolic acid) or poly(caprolactone))
- biologic (e.g., acellular collagen derived from bovine or porcine sources)
- composite (i.e., a combination of any of the previous three categories)

Most surgical mesh devices cleared for urogynecologic procedures are composed of non-absorbable synthetic polypropylene.

### **Surgical Mesh for Urogynecologic Procedures**

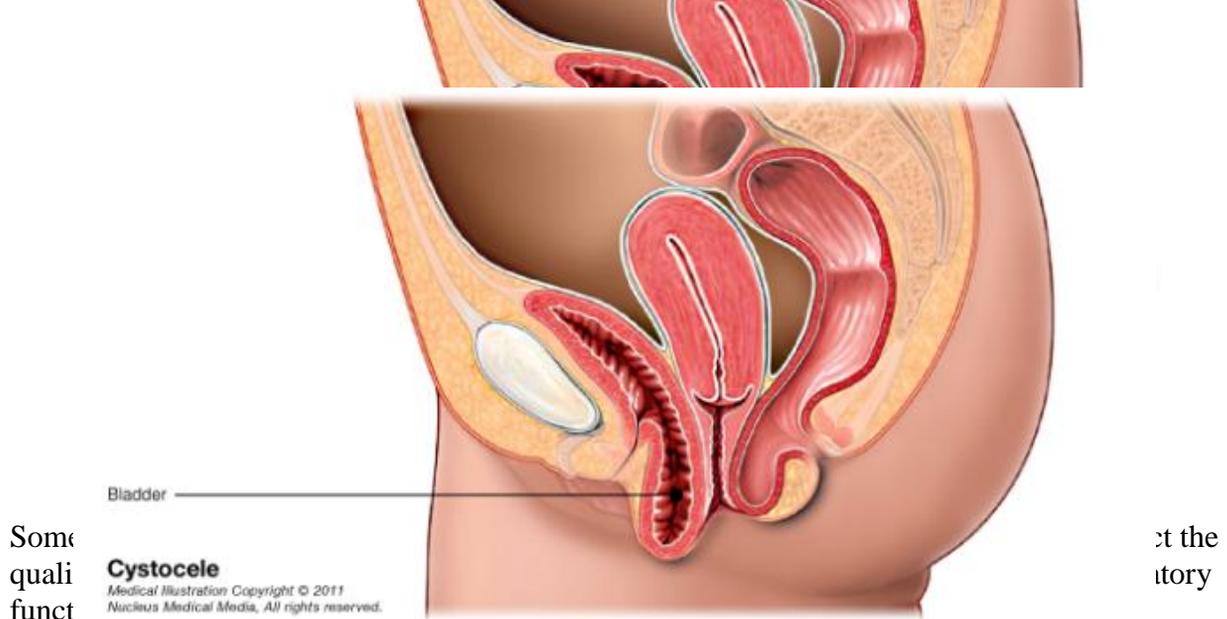
Surgical mesh can be used for surgical repair of SUI and POP. SUI affects an estimated 20-40 percent of women [2]. Treatment may be conservative (such as exercise to strengthen the pelvic floor muscles) or surgical. Surgical repair of SUI can be performed through an abdominal incision, using sutures (Burch urethropexy), or through a vaginal incision, by placing a biologic or synthetic “sling” (e.g., surgical mesh) under the urethra to help prevent urinary loss during physical activity.

Following promising continence outcomes using surgical mesh slings for SUI repair, surgeons began using surgical mesh to augment transvaginal POP repairs. POP occurs when the pelvic floor tissues that hold the pelvic organs in place become weakened or stretched, often from childbirth (see **Figure 1** for normal anatomy). This causes the pelvic organs to bulge (or



**Figure 1.**

prolapse) into the vagina. The pelvic organs sometimes prolapse past the vaginal opening, and more than one pelvic organ can prolapse at the same time. The organs involved in POP may include the bladder (cystocele) (Figure 2), the uterus (procidentia) (Figure 3), the rectum (rectocele) (Figure 4), the top of the vagina (apical prolapse) or the bowel (enterocele).



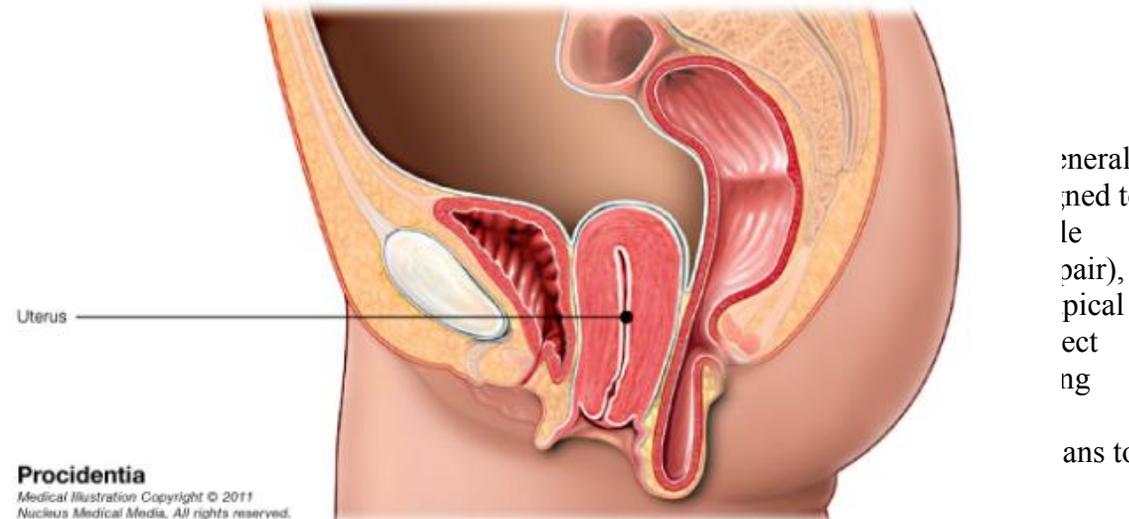
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**Figure 2.**

A woman's estimated lifetime risk of POP is 30-50 percent, with 2 percent of women becoming symptomatic [3]. Symptomatic POP can be managed conservatively with either pelvic floor muscle exercises or vaginal inserts to support the prolapsing tissue (pessaries). Surgical correction of symptomatic POP can be performed with or without mesh.

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**Figure 3.**

Market data from manufacturers indicate that in 2010 approximately 300,000 women underwent surgical procedures in the United States to repair POP and approximately 260,000 underwent surgical procedures to repair SUI. According to industry estimates, approximately one out of three POP surgeries used mesh, and three out of four of the mesh POP procedures were done transvaginally. For SUI surgeries, over 80 percent were done transvaginally with mesh.



### **III. SUMMARY OF ADVERSE EVENT REPORTS**

The FDA conducted a search of the Manufacturer and User Device Experience (MAUDE) database for medical device reports (MDRs) of adverse events associated with all urogynecologic surgical mesh products received from January 1, 2005 - December 31, 2010. The search identified 3,979 reports of injury, death, and malfunction. Among the 3,979 reports, 2,874 reports were received in the last 3 years (January 1, 2008 - December 31, 2010), and included 1,503 reports associated with POP repairs and 1,371 associated with SUI repairs. The number of MDRs associated with POP repairs increased by more than 5-fold compared to the number of reports received in the previous 3 years (January 1, 2005 - December 31, 2007).

Multiple factors can affect MDR reporting, including increased use of urogynecologic surgical mesh in the clinical community, increased awareness on the potential adverse events associated with mesh after the 2008 *PHN*, an increased number of new POP meshes on the market, or an increase in the number of actual adverse events associated with mesh. Determining the exact cause or causes of the increase is difficult. Regardless, the FDA believes the overall increase in the number of serious adverse event reports is cause for concern.

From 2008 to 2010, the most frequent complications reported to the FDA from the use of surgical mesh devices for POP repair included vaginal mesh erosion (also called exposure, extrusion or protrusion), pain (including painful sexual intercourse known as dyspareunia), infection, urinary problems, bleeding, and organ perforation. There were also reports of recurrent prolapse, neuro-muscular problems, vaginal scarring/shrinkage and emotional problems. Many of the MDRs cited the need for additional intervention, including medical or surgical treatment and hospitalization. Vaginal shrinkage was not reported in the previous three year period corresponding to the 2008 *PHN*.

Between 2008 and 2010, there were seven reported deaths associated with POP repairs. Follow-up investigation on the death reports revealed that three of the deaths associated with POP repair were related to the mesh placement procedure (two bowel perforations, one hemorrhage). Four deaths were due to post-operative medical complications not directly related to the mesh placement procedure.

### **IV. REVIEW OF THE LITERATURE**

Due to ongoing concerns in the clinical community and the safety signals identified from adverse event reports, the FDA evaluated the peer-reviewed scientific literature to revisit the fundamental questions of safety and effectiveness of surgical mesh for POP and SUI. The literature presented in this document includes all relevant randomized controlled trials (RCTs), all relevant systematic reviews, and a subset of observational studies that presented data on adverse events associated with transvaginal repair of POP using mesh from January 1996 through April 2011. The FDA continues to evaluate the literature for SUI surgeries using surgical mesh and will report on that usage at a later date.

## Safety

The literature review identified the following safety concerns with transvaginally placed surgical mesh for POP repair:

- Patients who undergo POP repair with mesh are subject to mesh-related complications that are not experienced by patients who undergo traditional surgery without mesh [7-9, 15, 16, 19-24].
- Adverse events associated with transvaginally placed mesh can be life-altering for some women [13, 14, 17]. Sequelae (e.g., pain) may continue despite mesh removal.
- Mesh-associated complications are not rare. The most common mesh-related complication experienced by patients undergoing transvaginal POP repair with mesh is vaginal mesh erosion [7-9, 15, 16, 19-24]. Based on data from 110 studies including 11,785 women, approximately 10 percent of women undergoing transvaginal POP repair with mesh experienced mesh erosion within 12 months of surgery [23].
- More than half of the women who experienced erosion from non-absorbable synthetic mesh required surgical excision in the operating room. Some women required two to three additional surgeries [23].
- Mesh contraction, causing vaginal shortening, tightening, and/or vaginal pain in association with transvaginal POP repair with mesh, is increasingly reported in the literature [13, 17].
- New onset SUI has been reported to occur more frequently following mesh augmented anterior repair compared to traditional anterior repair without mesh [12].
- Transvaginal surgery with mesh to correct vaginal apical prolapse is associated with a higher rate of complication requiring reoperation and reoperation for any reason compared to traditional vaginal surgery or sacral colpopexy [20].
- Abdominal POP surgery using mesh (sacral colpopexy) appears to result in lower rates of mesh complications compared to transvaginal POP surgery with mesh, with the median vaginal mesh erosion rate reported at 4 percent within 23 months of surgery [22].

## Effectiveness

The literature review found that while transvaginal POP repair with mesh often restores anatomy, it has not been shown to improve clinical benefit over traditional non-mesh repair, as evidenced by the following key findings:

- Transvaginal apical or posterior repair with mesh does not appear to provide any added benefit compared to traditional surgery without mesh [5-8, 18, 22, 24].
- Only two RCTs compared multi-compartment repair (including apical repair) with mesh to traditional repair, and neither found a significant improvement in effectiveness with

mesh augmentation [7, 8]. A systematic review of vaginal mesh kits for apical repair found they appear effective in restoring apical prolapse in the short-term, but long-term outcomes are unknown [21].

- Although one RCT showed anatomic benefit for posterior repair with mesh, mesh subjects in the trial had less posterior prolapse at baseline than subjects who underwent traditional repair [8]. Three other RCTs that have evaluated mesh augmentation in the posterior compartment did not show an anatomic benefit from using mesh [5, 6, 7].
- There does appear to be an anatomic benefit to anterior repair with mesh augmentation [5, 8, 9-12, 18, 19, 22, 24]. This anatomic benefit may not result in superior symptomatic outcomes or lower rates of repeat surgery for recurrent prolapse compared to traditional POP repair without mesh [26].
- Patients who undergo traditional POP repair without mesh have equivalent improvement in quality of life when compared to patients who undergo transvaginal POP repair with mesh [5, 8, 9, 11].
- Compared to traditional vaginal surgery without mesh, abdominal apical prolapse repair with mesh (sacral colpopexy) results in less recurrent prolapse, although it has not been shown to reduce the rate of repeat surgery for recurrent prolapse [22].

### **Limitations of Existing Literature**

The existing literature has several important methodologic limitations that impact the interpretation of the available data, including:

- The majority of studies use an effectiveness outcome that pertains to ideal pelvic support, which is not necessary for most women to achieve symptomatic relief [26];
- Results reflect both primary and repeat prolapse repairs;
- In most studies subjects undergo various additional POP procedures and/or combined POP-SUI procedures;
- Adverse events are inconsistently defined and reported;
- Many studies are poorly designed and/or conducted, are underpowered, use incompletely documented inclusion/exclusion criteria, have inadequate evaluator masking, and fail to account for variable lengths of patient follow-up; and
- Very few studies extend past 2 years.

## **V. SUMMARY OF KEY FINDINGS**

Based on evaluation of adverse event reports and assessment of the scientific literature, the FDA has NOT seen conclusive evidence that using transvaginally placed mesh in POP repair improves

clinical outcomes any more than traditional POP repair that does not use mesh, and it may expose patients to greater risk.

In particular, these products are associated with serious adverse events, including vaginal mesh erosion (also called exposure, extrusion or protrusion), a complication which can require multiple surgeries to repair and may result in continued sequelae (e.g., pain) even after mesh removal. Compounding the concerns regarding adverse events are performance data that fail to demonstrate improved clinical benefit over traditional non-mesh repair, particularly for transvaginal apical and posterior repair. While the literature suggests an anatomic benefit to anterior repair with mesh augmentation, this anatomic benefit may not result in superior clinical outcomes, and the associated risk of adverse events should be considered.

Based on these findings, the FDA is considering regulatory changes that may improve our understanding of the safety and effectiveness of these devices and has specific recommendations for patients and healthcare providers below.

## **VI. RECOMMENDATIONS FOR PATIENTS**

The FDA recommends that women considering surgery for pelvic organ prolapse:

Before surgery:

- Be aware of the risks associated with transvaginal POP repair.
- Know that having a mesh surgery may increase the risk for needing additional surgery due to mesh-related complications. In a small number of patients, repeat surgery may not resolve complications.
- Ask their surgeons about all POP treatment options, including surgical repair with or without mesh and non-surgical options, and understand why their surgeons may be recommending treatment of POP with mesh.

After surgery:

- Continue with annual and other routine check-ups and follow-up care. Patients do not need to take action if they are satisfied with their surgery and are not having complications or symptoms.
- Notify their health care providers if they develop complications or symptoms, including persistent vaginal bleeding or discharge, pelvic or groin pain or pain with sex, that last after the last follow-up appointment.
- Let their health care providers know if they have surgical mesh, especially if planning to have another related surgery or other medical procedures.
- Talk to their health care providers about any questions or concerns.
- Ask their surgeons at their next routine check-up if they received mesh for their POP surgery if they do not know if mesh was used.

## **VII. RECOMMENDATIONS FOR HEALTH CARE PROVIDERS**

The FDA encourages health care providers to:

- Recognize that in most cases, POP can be treated successfully without mesh thus avoiding the risk of mesh-related complications.
- Choose mesh surgery only after weighing the risks and benefits of surgery with mesh versus all surgical and non-surgical alternatives.
- Consider these factors before placing surgical mesh:
  - Surgical mesh is a permanent implant that may make future surgical repair more challenging.
  - A mesh procedure may put the patient at risk for requiring additional surgery or for the development of new complications.
  - Removal of mesh due to mesh complications may involve multiple surgeries and significantly impair the patient’s quality of life. Complete removal of mesh may not be possible and may not result in complete resolution of complications, including pain.
  - Mesh placed abdominally for POP repair may result in lower rates of mesh complications compared to transvaginal POP surgery with mesh.
- Inform the patient about the benefits and risks of non-surgical options, non-mesh surgery, surgical mesh placed abdominally and the likely success of these alternatives compared to transvaginal surgery with mesh.
- Notify the patient if mesh will be used in her POP surgery and provide the patient with information about the specific product used.
- Ensure that the patient understands the postoperative risks and complications of mesh surgery as well as limited long-term outcomes data.
- Continue to follow the recommendations provided in the [2008 PHN](#).

## VIII. FDA ACTIVITIES

### Safety Communication

The FDA is issuing a new [FDA Safety Communication](#) that provides an update to the 2008 FDA *PHN*. The *Safety Communication* focuses on transvaginal POP repair with mesh. The objective of the *Safety Communication* is to inform health care providers and patients that the risks of serious complications associated with transvaginal POP repair with mesh are NOT rare, contrary to what was stated in the 2008 *PHN*. This updated communication identifies vaginal shortening, tightening, and/or pain due to mesh contraction as a previously unidentified risk of transvaginal POP repair with mesh, and it provides recommendations for patients and health care providers.

### Consideration of Regulatory Changes

The FDA is considering regulatory changes that may improve our understanding of the safety and effectiveness of this device. Considerations include:

- A change in risk classification of mesh used for transvaginal POP repair from Class II to Class III, which would require manufacturers to submit premarket approval applications, including relevant clinical data for these devices.

- Clinical studies to address the risks and benefits of mesh used to treat POP and SUI.
- Expanded post-market monitoring of device performance.

### **Advisory Meeting**

On September 8-9, 2011, the FDA will convene a meeting of the Obstetrics-Gynecology Devices Panel of the Medical Devices Advisory Committee to discuss the safety and effectiveness of transvaginal placement of mesh for POP and SUI procedures. A notice of this meeting was published in the [Federal Register](#).

## **IX. HOW TO REPORT INFORMATION TO THE FDA**

Prompt reporting of adverse events can help the FDA identify and better understand the risks associated with medical devices. The FDA encourages health care professionals and consumers to report suspected problems with surgical mesh to the FDA by filing a voluntary report through [MedWatch](#), the FDA Safety Information and Adverse Event Reporting program. Health care personnel employed by facilities that are subject to the [FDA's user facility reporting requirements](#) should follow the reporting procedures established by their facilities. Device manufacturers must comply with the [Medical Device Reporting \(MDR\) regulations](#).

## **X. CONCLUSION**

The FDA has identified serious safety and effectiveness concerns over the use of surgical mesh for the transvaginal repair of pelvic organ prolapse (POP) based on a review of adverse events reported to the FDA and an assessment of the scientific literature.

In addition to providing an updated [FDA Safety Communication](#) to promote understanding of the risks associated with transvaginal POP repair using surgical mesh and to encourage informed decision-making by patients and health care providers about the use of mesh, the FDA will convene an Advisory Panel of outside experts to consider clinical studies that may improve our understanding of the safety and effectiveness of urogynecologic mesh.

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## **XII. GLOSSARY OF TERMS USED IN THIS DOCUMENT**

<b>Anterior repair</b>	surgical repair to correct weakened tissue between the bladder and vagina
<b>Apical repair</b>	surgical repair to correct prolapse of the top of the vagina
<b>Colostomy</b>	surgical procedure in which the healthy end of the large intestine or colon is brought through the anterior abdominal wall to provide an opening for feces to leave the body instead of the rectum
<b>Colporrhaphy</b>	surgical correction of the vagina
<b>Cystocele</b>	prolapse of the bladder into the vagina
<b>Dyspareunia</b>	painful sexual intercourse
<b>Federal Register</b>	the official daily publication for rules, proposed rules, and notices of federal agencies and organizations, as well as executive orders and other presidential documents.
<b>Mesh erosion</b>	mesh that wears through (“erodes”) tissue and becomes exposed, also called exposure, extrusion or protrusion
<b>Morbidity</b>	diseased state, disability, or poor health
<b>Pelvic organ prolapse (POP)</b>	bulge of organs/structures surrounding the vagina into the vagina or extending beyond the vaginal opening, caused by laxity of supporting tissue of the vagina
<b>Posterior repair</b>	surgical repair to correct prolapse of the tissue between the vagina and rectum
<b>Procidentia</b>	prolapse of the uterus
<b>Rectocele</b>	prolapse of the rectum
<b>Sacral Colpopexy</b>	surgical correction of vaginal apical prolapse (via abdominal or laparoscopic route) in which mesh is attached to the vaginal apex on one end and the sacrum on the other
<b>Stress Urinary Incontinence (SUI)</b>	leakage of urine during moments of physical activity
<b>Vaginal apex</b>	top of the vagina