



Obstetrics and Gynecology Devices Panel

Surgical Mesh for Transvaginal Repair of Pelvic Organ Prolapse in the Anterior Vaginal Compartment

Hilton Washington, DC/North 620 Perry Pkwy., Gaithersburg, MD 20877
Salons A, B, C and D

24 HOUR SUMMARY

Open Public Hearing (OPH)

The Panel heard seventeen presentations from patients, advocacy groups, clinicians, an attorney, a professional society, research groups, manufacturers, and an MDR data analyst. Patients and patient advocacy groups shared a variety of experiences, many with debilitating adverse events and some with positive experiences following a mesh repair. Other speakers advocated for collection of long term data, the need for robust premarket studies, the importance of appropriate training, and further delineation of risks during the informed consent process. Some speakers requested removal of transvaginal mesh from the market, while others noted the need for mesh for transvaginal repair to remain an option for women.

FDA Presentation

The FDA review team presented an overview of the regulatory history and safety and effectiveness data on surgical mesh used for transvaginal POP repair in the anterior and anterior/apical compartment. The safety and effectiveness information presented included a review of the FDA's medical device report (MDR) database and a review of the published literature. The FDA also provided its perspective on the benefit/risk profile of mesh for transvaginal POP repair in the anterior and anterior/apical compartment. The FDA stated that transvaginal mesh for POP in anterior and anterior/apical compartment repair poses risks that are unique to mesh (e.g., erosion/exposure) and that these risks are greater than those of native tissue repair. The FDA also noted that while anatomic/objective outcomes of effectiveness generally favor mesh, subjective outcomes demonstrate similar effectiveness when compared to native tissue repair. The FDA determined that to demonstrate a reasonable assurance of safety and effectiveness, transvaginal mesh for repair of anterior and anterior/apical compartment POP should be superior to native tissue repair. In addition, the FDA concluded that longer-term outcomes are needed to establish a favorable benefit/risk profile for this device type, as it is a permanent implant. The FDA also presented information on concomitant procedures, patient characteristics, including surgical and medical history, and surgeon experience and training. FDA concluded that these may impact the safety and effectiveness outcomes of transvaginal mesh for POP repair in the anterior and anterior/apical compartment. In closing, the FDA asked the panel for recommendations on how to evaluate the safety and effectiveness of surgical mesh placed in the anterior and anterior/apical compartment for prolapse repair.

Manufacturer Presentations

The FDA presentation was followed by presentations by manufacturers of currently marketed surgical mesh for anterior/apical repair, Boston Scientific Corporation (BSC) and Coloplast.

Boston Scientific Corporation

BSC provided an overview of their currently marketed transvaginal mesh devices, Uphold LITE and Xenform. BSC stated that Uphold LITE has a lower density compared to historical POP mesh devices, resulting in reduced complications and improved outcomes. BSC provided results of the NICHD SUPeR study that uses Uphold LITE and concluded that the device provides three-year success with uterine-sparing hysteropexy. BSC cited published literature that evaluated Uphold LITE and Xenform to support lower mesh exposure rates and long-term durability for these devices. Additionally, BSC provided data from the 522 postmarket surveillance studies for Uphold LITE and Xenform. BSC stated that Uphold LITE data was comparable to native tissue repair (NTR) across all analyses for the primary composite efficacy endpoint, which included anatomic success, subjective success, and no retreatment for POP. BSC also stated that serious adverse events for Uphold LITE were comparable to NTR at 12 months. Next, BSC provided the results of the Xenform 522 study. BSC stated that Xenform was non-inferior to NTR for the composite primary efficacy endpoint. They also stated that serious adverse events were comparable to NTR at 12 months with low mesh exposure rates. BSC stated that their 522 data showed clinical benefit at 12 months and proposed that the superiority of mesh compared to NTR should not be required. BSC also discussed the importance of training and experience, detailing the BSC-led physician education and training programs. BSC concluded that mesh may be appropriate for certain populations and should remain an option for women in consultation with their physicians.

Coloplast

Coloplast presented information on the Restorelle DirectFix Anterior Mesh, including MDR data and the published literature on the current generation of transvaginal mesh devices for anterior POP treatment (e.g., devices with characteristics similar to Restorelle mesh). They concluded that all studies showed an improvement in objective outcomes, an improvement in subjective outcomes (when measured), and low rates of exposure/extrusion. They noted that some of these results were observed beyond 12 months. Coloplast also described the design of their 522 study and stated that it had dual purpose, to provide real world post-market surveillance out to 36 months and to provide 12-month effectiveness and safety outcome data to support a PMA. Coloplast did not provide data from this 522 study, stating the information was under review with the Agency. Coloplast concluded that the published literature is dominated by mesh that is no longer marketed and that current mesh characteristics are associated with lower incidences of exposure/extrusion. Coloplast stated that patients and physicians need options such as transvaginal mesh and that real-world evidence suggests that patients/physicians are making benefit/risk determinations.

Professional Society Presentations

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (ACOG) provided an overview of ACOG's guidance on the use of transvaginal mesh for repair of anterior POP. ACOG stated that

transvaginal mesh should be limited to high risk patients, including those with recurrent prolapse or medical comorbidities. ACOG stated that patients should provide informed consent after review and discussion of benefits and risks of the procedure. ACOG emphasized the importance of training for surgeons who perform POP and patient selection. ACOG also discussed recommendations for the evaluation of mesh for transvaginal prolapse repair including the importance of assessing subjective and objective outcomes, using validated questionnaires, and collecting long term data (noting that the longest studies report data at 5 and 7 years). Regarding the currently marketed devices, ACOG stated that better quality data should be collected.

American Urogynecologic Society

The American Urogynecologic Society (AUGS) provided considerations for the evaluation of transvaginal POP mesh repairs in the anterior compartment. AUGS stated that women are better served by having more treatment options available and transvaginal mesh for procedures for anterior prolapse are a reasonable choice for some patients. AUGS emphasized the importance of balancing safety risks with benefits. While AUGS does not support the routine use of transvaginal mesh for POP, they outlined certain patient characteristics that increase the potential benefit of the transvaginal mesh. AUGS also recommended assessing benefit through use of subjective and objective outcomes, conducting long term safety and effectiveness assessments of these devices (e.g., 5-10 years), and completing subpopulation analyses.

Society of Gynecologic Surgeons

The Society of Gynecologic Surgeons (SGS) provided results of their systematic review of graft and mesh used in transvaginal repair of prolapse compared to native tissue repair. They found that mesh resulted in favorable anatomic outcomes compared to native tissue repair. There were no differences in subjective outcomes such as quality of life, urinary function, and sexual function. Erosion rates ranged from 1.4 – 19%. SGS raised a concern about the comparison of mesh used in the apical compartment to native tissue repair and reiterated their published recommendations from the systematic review. SGS also emphasized the importance of surgeon training and experience and consideration of patient characteristics.

Panel Deliberations and FDA Questions

Panel Deliberations

The Panel discussed the information provided in the stakeholder presentations in preparation for discussion of FDA's specific questions to the Panel.

Panel Questions

The Panel considered eight discussion questions prepared by the FDA. The Panel's recommendations are summarized below:

Effectiveness

- 1. In light of its increased risks compared to native tissue repair, to demonstrate reasonable assurance of effectiveness, FDA believes that surgical mesh used in the anterior or anterior/apical vaginal compartment for transvaginal prolapse repair should be superior to native tissue repair. Does the Panel agree?**

- a. If yes, at what timepoint should superiority be demonstrated, e.g., 12, 24, 36 months, or longer?
- b. If no, how should the effectiveness of mesh compare to native tissue repair and at what timepoint should the effectiveness be assessed?
- c. Does the Panel have additional comments related to the mesh material (e.g., polypropylene or non-crosslinked biologic) or other mesh characteristics?

In response to this question, the Panel recommended the following:

- The Panel consensus was that in the general population of women who are candidates for transvaginal repair of prolapse, mesh should be superior to native tissue repair for effectiveness at 12, 24, and 36 months.
- The Panel noted that for specific sub-populations of women who may not be candidates for a native tissue repair (e.g., women who previously failed a native tissue repair), non-inferiority to native tissue repair may be acceptable. In those specific sub-populations, non-inferiority should be demonstrated at 12, 24, and 36 months.
- The Panel also encouraged collection of longer term data beyond 36 months for effectiveness.

2. The FDA literature review identified that while anatomic/objective outcomes generally favor mesh, subjective outcomes demonstrate similar effectiveness for mesh and native tissue repair. FDA believes that both anatomic/objective and subjective outcomes should be used to assess the effectiveness of transvaginal anterior or anterior/apical mesh repair compared to native tissue repair.

- a. Does the Panel agree that both objective and subject outcomes should be used to assess the effectiveness of mesh compared to native tissue repair?
- b. If the Panel agrees that both anatomic/objective and subjective outcomes should be used to assess effectiveness, should improvement in both outcomes be required to consider a patient to be a success? Why or why not?
- c. Should the assessment of anatomic/objective outcomes be completed by a blinded evaluator?
- d. FDA believes improvement or resolution of patient symptoms are an important component in demonstrating effectiveness of a mesh versus native tissue repair. Please address the following:
 - i. How should symptoms be measured (e.g., validated questionnaire)?
 - ii. How should we assess if a patient has a meaningful/significant improvement (e.g., what if a patient has symptoms but is not bothered by the symptoms)?
 - iii. How is a patient's assessment of her symptoms affected by sexual activity (or other patient factors) (e.g., would a patient who is not sexually active find her prolapse less bothersome compared to a sexually active patient)?
 - iv. When patients are not blinded to their treatment (mesh or native tissue repair), how might that affect their assessment of symptoms?
- e. Does the Panel have additional comments related to the mesh material or other mesh characteristics?

In response to the question, the Panel recommended the following:

- The Panel agreed that both objective and subjective outcomes should be used to assess effectiveness of transvaginal mesh for anterior/apical repair of POP as compared to NTR.

- The Panel recommended that both objective and subjective measures should be required for success; however, the Panel emphasized that subjective measures were more important than objective measures to assess effectiveness.
- The Panel recommended the utilization of validated questionnaires to measure symptoms. The Panel stated that patients should complete these questionnaires at baseline to provide for an appropriate comparison at later timepoints in the study.
- The Panel noted that patient assessment of symptoms may be affected by sexual activity, but that reported symptoms are very patient-specific. The Panel recommended that trials include patients that are sexually active.
- The Panel recommended that patients and providers be blinded when possible.

Safety

3. The following adverse events have been associated with mesh and/or native tissue repair and are being collected in the 522 studies:

- a. Pelvic pain**
- b. Erosion/exposure**
- c. Dyspareunia**
- d. De novo voiding dysfunction (e.g., incontinence)**
- e. Infection**
- f. Vaginal shortening**
- g. Atypical vaginal discharge**
- h. Neuromuscular problems**
- i. Vaginal scarring**
- j. De novo vaginal bleeding**
- k. Fistula formation**

Please discuss these adverse events and consider their importance, potential to be debilitating, how they should be assessed, when they should be assessed, and key considerations related to the mesh material or other mesh characteristics. Please also comment on any important adverse events that may be missing.

In response to the question, the Panel recommended the following:

- The Panel discussed adverse events associated with the use of transvaginal mesh for POP repair and concluded that those listed in the question were appropriate
- The Panel also recommended that FDA consider assessing intraoperative complications, repeat operations, and recurrent urinary tract infections.
- The Panel noted the importance of thorough baseline/pre-operative objective and subjective assessments.
- The Panel also recommended asking subjects to provide feedback on quality of life and whether they would have the procedure again based on their experience.

4. To demonstrate reasonable assurance of safety, FDA believes the adverse event profile for mesh placed in the anterior or anterior/apical vaginal compartment should be comparable to native tissue repair, or any increase in risk should be offset by a corresponding improvement in effectiveness. FDA also believes that all adverse events (not just those adjudicated as device or procedure related adverse events or serious adverse events) should be considered, along with their severity/seriousness, timing, resolution, and

relatedness to the device and/or procedure should be used to evaluate the safety of mesh compared to native tissue repair.

- a. Does the Panel agree with this approach?**
- b. What are the effectiveness scenarios where an increased safety risk may be acceptable (e.g., patient with recurrent prolapse)?**
- c. At what timepoint should comparable safety (or increase in risk offset by a corresponding improvement in effectiveness) be demonstrated, e.g., 12, 24, 36 months, or longer?**
- d. Does the Panel have additional comments related to the mesh material or other mesh characteristics?**

In response to the question, the Panel recommended the following:

- The Panel agreed that all adverse events should be considered, along with their severity/seriousness, timing, resolution, and relatedness to the device and/or procedure.
- The Panel agreed that there are some scenarios in which an increased safety risk may be acceptable (e.g., patients with recurrent prolapse, patients with specific medical conditions that increase the risk of additional complications or patients with prior abdominal surgery).
- The Panel noted that 12-month safety data are not adequate, and that adverse events can be observed beyond 12 months.

Patient Population

- 5. The FDA literature review identified concomitant procedures (hysterectomy and sling placement) and surgical/medical history (age, obesity, current level of sexual activity, parity, premenopausal estrogen therapy, diabetes, and smoking) that may affect the safety or effectiveness outcomes of an anterior or anterior/apical mesh or native tissue repair.**
 - a. Does the Panel agree that the identified concomitant procedures and surgical/medical history may affect the safety or effectiveness of a mesh or native tissue repair?**
 - b. Which additional concomitant procedures or surgical/medical history could affect the safety or effectiveness outcomes of mesh or native tissue repair in the target compartment?**
 - c. How should FDA factor concomitant procedures and surgical/medical history in its interpretation/evaluation of study results (e.g., balance of these characteristics between study arms, assessment of adverse events associated with concomitant procedure versus primary procedure)?**

In response to the question, the Panel recommended the following:

- The Panel agreed that the identified concomitant procedures and surgical/medical history may affect the safety and effectiveness of a mesh or native tissue repair.
- The Panel identified apical and posterior compartment repair as additional procedures that could affect the safety or effectiveness outcomes for mesh or native tissue repair in the target compartment.
- The Panel identified connective tissue disorders, chronic lung disease, and obesity as medical history that could affect the safety or effectiveness outcomes for mesh or native tissue repair in the target compartment.
- The Panel consensus was that the concomitant procedures performed during the study should be identified and stratified when evaluating the data.

6. In non-randomized studies, selection bias can influence safety and effectiveness outcomes. FDA believes the following factors may determine whether a patient undergoes a mesh versus native tissue repair.

- **Patient (e.g., recurrent prolapse, severity of prolapse, age, obesity, sexual activity, parity, other surgical/medical history)**
- **Procedure (e.g., need for a concomitant procedure)**
- **Clinical Site (e.g., whether site offers only mesh versus native tissue repair, whether the site is a specialty center for one type of repair)**
- **Surgeon (e.g., experience with mesh versus native tissue repair, surgeon preference based on individual patient characteristics)**

Please discuss how these factors or any additional factors may bias the safety and effectiveness outcomes of a native tissue or mesh repair.

In response to this question, the Panel recommended the following:

- The Panel consensus was that of the above four factors listed, patient, concomitant procedures, and surgeon experience would be more likely to bias safety and effectiveness outcomes.
- The Panel noted that clinical site factors were least likely to bias safety and effectiveness outcomes.
- The Panel stated that many of the factors identified are encountered during real world use and that any factors that put a patient at higher risk would likely bias that patient toward a mesh repair (e.g., recurrent prolapse or degree of prolapse).
- The Panel also noted that a surgeon's experience in performing a particular type of repair could bias them toward one type of repair.
- The Panel stated that a randomized controlled trial would be ideal but acknowledged the difficulty of performing this type of study.

7. The FDA literature review indicated that surgeon experience may affect safety and effectiveness outcomes of a mesh or native tissue repair.

- a. Please comment on how a physician's level of training and experience affects safety and effectiveness outcomes for mesh versus native tissue repair.**
- b. How should FDA incorporate the level of training and experience of investigators in a clinical study in its interpretation/evaluation of study results (e.g., need for comparable experience between study arms, clinical study results may not reflect real world results)?**

In response to the question, the Panel recommended the following:

- The Panel noted that surgical experience is expected to affect outcomes, with higher volume surgeons being less likely to have adverse outcomes.
- The Panel recommended that for studies of transvaginal mesh devices, the level of experience in both surgical volume and fellowship training status be provided.

8. Surgical mesh for transvaginal repair of pelvic organ prolapse in the anterior or anterior/apical compartment is an implant, and its benefit/risk profile may change over time.

- a. What is the appropriate expectation for the durability of a mesh repair and native tissue repair (e.g., remainder of the patient's lifetime)?**

- b. How quickly should the data demonstrate the benefit of a mesh repair versus a native tissue repair?**
- c. In broad terms, a device subject to PMA is approved for marketing when the benefit/risk profile is favorable for its proposed indications for use, with a reasonable assurance of safety and effectiveness. In light of this regulatory framework, what is the most appropriate time point to assess benefit/risk to support a marketing application, e.g., 12, 24, 36 months, or longer?**
- d. What is the appropriate duration of follow up needed to support marketing approval versus the follow up needed postmarket? What data should be collected postmarket? Please consider rare adverse events, long-term durability, and use of real world evidence to collect safety and effectiveness outcomes.**
- e. Does the Panel have additional comments related to the mesh material or other mesh characteristics?**

In response to the question, the Panel recommended the following:

- The Panel noted that a reasonable expectation of the durability of repair would be 10 years.
- The Panel recommended that 36 months was the most appropriate timepoint to assess benefit/ risk for transvaginal mesh for anterior/apical repair of POP.
- The Panel recommended 18-24 months of data for marketing approval and 5 years of postmarket follow up to assess longer-term safety and effectiveness.