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

SAFETY AND EFFECTIVENESS OF
TRANSVAGINAL SURGICAL MESH USED FOR REPAIR OF
PELVIC ORGAN PROLAPSE

September 8, 2011

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Table of Contents

I. EXECUTIVE SUMMARY ............................................................................................................... 3

II. INTRODUCTION: ...................................................................................................................... 6

III. SAFETY AND EFFECTIVENESS DATA ON SURGICAL MESH FOR THE TREATMENT
OF POP ......................................................................................................................................................... 6
    A. ADVERSE EVENT DATA ANALYSIS ............................................................................................. 7
    B. PUBLISHED LITERATURE .............................................................................................................. 8

IV. REGULATORY OVERSIGHT OF TRANSVAGINALLY PLACED MESH PRODUCTS
FOR POP: CLASS II DEVICE WITH SPECIAL CONTROLS ........................................................... 15
    A. CLINICAL DATA FOR NEW PRODUCTS: ....................................................................................... 15
        1. Pre-Market Data: ......................................................................................................................... 15
        2. Post Market Clinical Data ......................................................................................................... 16
        3. Product Labeling ....................................................................................................................... 16
        4. Patient Labeling ........................................................................................................................ 16
    B. CLINICAL DATA FOR EXISTING PRODUCTS ............................................................................ 17
        1. Post Market Data: ......................................................................................................................... 17
        2. Product Labeling ....................................................................................................................... 17
    C. TRAINING: ..................................................................................................................................... 17

V. RATIONALE FOR DEVICE CLASS II DESIGNATION .................................................................. 18

VI. REFERENCES ................................................................................................................................. 19
I. EXECUTIVE SUMMARY

The Transvaginal Mesh Working Group (Working Group), comprised of Ethicon, Inc., C.R. Bard, Boston Scientific, and American Medical System, in collaboration with the Advanced Medical Technology Association (AdvaMed), makes this submission to the Obstetrics and Gynecology Device Panel of the Medical Devices Advisory Committee to present data and information regarding the safety and effectiveness of transvaginal surgical mesh devices to treat Pelvic Organ Prolapse (POP).

This Working Group believes that the use of surgical mesh in transvaginal procedures for the treatment of POP is safe and effective, that serious adverse events remain rare and it is a valuable treatment option for women.

This Working Group also believes that:

- The class II, 510(k) requirements are appropriate for surgical mesh devices intended for POP treatment.

- Special controls can be implemented to ensure the adequacy and reliability of labeling information provided to both patients and physicians, and also to ensure consistency in the evaluation of the safety and effectiveness of new products through standardized requirements, including performance of pre- and post-market clinical trials.

- Industry will work with Societies to develop and support training programs to ensure physicians have appropriate knowledge of the use of these products.

POP is the condition that results when the normal supporting structures of the vagina deteriorate. The resultant support loss can cause any or all of the following structures to prolapse (drop out of position): urethra, bladder, bowel, and/or cervix/uterus/vaginal vault. This prolapse can produce such symptoms as a sensation of bulge, difficulty with bowel or bladder function, pain and/or dyspareunia (painful intercourse). Traditional treatment options for POP include hysterectomy, colporrhaphy (plication of pubocervical or rectovaginal fascia), sacro-colpopexy (suturing of vaginal apex to the sacral promontory using either mesh or fascial bridge) performed either abdominally or laparoscopically and sacrospinous fixation (securing the vaginal apex to the sacrospinous ligament). Mesh products were introduced as supporting materials in the surgical treatment of POP to address the high levels of recurrence rates associated with traditional repairs using the patient’s own tissue.1,2,3,4 As a result of ongoing innovation with mesh products for POP, surgeons can now treat women suffering from POP with pre-shaped mesh kits that allow for placement of a light-weight mesh implant via a transvaginal procedure. Key to the successful treatment of POP with surgical mesh is appropriate patient selection and surgeon experience.
In July 2011, the Food and Drug Administration (FDA) issued an updated safety notification concerning the safety and effectiveness of transvaginal surgical mesh devices for POP repair and a White Paper titled, *Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse*. While the 2011 notification references similar kinds of complications as had been reported in FDA’s 2008 notification, FDA changed its prior assessment of the frequency of adverse events (AEs) associated with these devices, and identified surgical mesh for transvaginal repair of POP as an area of continuing serious concern. Based on its updated assessment, FDA is considering changes to the regulation of transvaginal mesh products, such as reclassification from Class II to Class III or additional pre-market and post-market regulatory requirements.

Section III of this submission provides an overview of the Working Group’s assessment of the safety and effectiveness of transvaginal mesh devices for POP. Based on our analysis of adverse event information and our review of published scientific literature, the Working Group has concluded that the benefits obtained with the use of transvaginally placed surgical mesh for the treatment of POP provide an important treatment option for patients.

Section IV provides the Working Group’s proposal on the pre-market and post-market regulatory paradigm for transvaginally placed surgical mesh devices intended for the treatment of POP. The Working Group proposes that these devices remain as Class II devices subject to the premarket notification (510(k)) requirements. However, in order to enhance patient and physician information regarding these devices and support further innovation of this technology based on the continued collection of clinical evidence, we are proposing additional regulatory requirements be implemented via Class II Special Controls for transvaginal surgical mesh devices for POP. Our recommendations include the following:

- Twelve month pre-market clinical study, powered appropriately, to support clearance of new transvaginal mesh kits
- Follow up post-market studies to continue monitoring of patients from pre-market clinical study (3-5 years)
- Uniform product labeling that includes a summary of clinical data as well as identification of patient subpopulations that are at risk for adverse events (AEs) associated with use of transvaginal mesh kits
- Patient labeling that informs patient of product risks and benefits and alternate treatment options in average lay person terms
- Standardized bench, in vitro and in vivo test requirements
- Training Programs: The development and support of training programs to ensure physicians have appropriate knowledge of the use of these products.
The data contained in this submission demonstrates that transvaginally placed surgical mesh devices for POP, in certain populations, provide adequate assurance of safety and effectiveness. The Working Group looks forward to working with FDA to develop and implement additional regulatory requirements that will ensure continued access to and advancement of this important patient option.
II. INTRODUCTION:

The use of mesh materials was initially described for abdominal wall repair. Implantable meshes have played a significant role in the treatment of complex hernias and other abdominal wall reconstruction procedures for decades. In 1996, the use of a transvaginal mesh (the Marlex® mesh) was first reported for urogynecological procedures. Mesh products were introduced as supporting materials in the surgical treatment of POP to address the high levels of recurrence rates associated with traditional repairs using the patient’s own tissue. The practice of using mesh thus developed, with physicians cutting materials in appropriate geometric shapes to perform the procedures. In 2002, the idea of creating kits similar to transvaginal tape (TVT) kits used to treat stress urinary incontinence emerged, and the first transvaginal mesh “kit” to treat POP became commercially available. Mesh kits contain the pre-shaped mesh implant(s) as well as the accessory tools needed for transvaginal placement of the device.

Surgical meshes available to date are the result of continuous research and development efforts. The evolution of the devices has leveraged the clinical experience of pelvic floor surgeons with the material science and R&D knowledge of scientists and engineers working in industry. For example, the density and design of the early mesh products was believed to have contributed to complications and was thus replaced with macroporous meshes. Knitted meshes, softer and more pliable than the woven ones, followed suit, along with meshes that had optimal pore size for tissue ingrowth and vascularization. These examples highlight the innovation that has taken place in this field and which plays a critical role in the ongoing objective to improve patient outcomes. Along with improvements to mesh design, physician expertise has grown resulting in an increase in the clinical research occurring in the field. Women most likely to benefit from transvaginal mesh augmented procedures are those with a higher chance of recurrence. Literature suggest that the following subpopulations of women have a higher risk of prolapse recurrence: reoccurring prolapse after traditional repair, severe POP (stage III/IV), anterior vaginal wall prolapse, and or women with poor tissue quality.

III. SAFETY AND EFFECTIVENESS DATA ON SURGICAL MESH FOR THE TREATMENT OF POP

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

The Working Group takes medical device reporting obligations seriously and diligently monitor and report to the FDA complications associated with the use of our devices; however, there are inherent limitations with the adverse event reporting. As FDA noted in its White Paper, [m]ultiple factors can affect MDR reporting, including increased use of urogynecologic surgical mesh in the clinical community, increased awareness of the potential adverse events associated with mesh after the 2008 [FDA Public Health Notice], an increased number of new . . . meshes on the market, or an increase in the actual adverse events associated with mesh. Wide variability in both the content of the reports and the circumstances prompting a person to report or not to report prevents reporting rates from being “used to reliably estimate incidence rates.” In fact, the FDA website states that “MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices”. Therefore, while adverse event reports are useful, they must be considered in light of their inherent limitations.

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

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

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

An additional outcome evaluation, “none” was possible under “other” if the report indicated a malfunction but no injury.
This review of the overall MDR rate, as well as rates associated with serious adverse events (SAE), indicated that while there was an increase in serious adverse events, the rate of SAEs remains low with an average rate of 0.16% for the 2008 to 2010 period compared to a rate of 0.05% for the 2005 to 2007 period. When comparing the number of serious adverse events to the total adverse events for each time period, it was determined that the percentage of SAEs to total AEs remained constant (within 2%) between the two time periods. While the Working Group analysis is still saddled with many of the limitations of the MAUDE database itself; the use of the denominator information allows a better analysis of the change in event rates.

B. Published Literature

The Working Group reviewed the literature that FDA referenced in its July 2011 White Paper. The Working Group agrees with FDA that these literature articles identify the adverse events associated with the treatment of POP using transvaginally placed mesh kits. However, these adverse events must be considered relative to the benefits these procedures provide and in consideration of the adverse events associated with the other treatment options for women suffering from POP (e.g., traditional vaginal surgery, sacral colpopexy).

Pelvic organ prolapse impacts a significant number of women and a variety of options exist to address this condition: surgical intervention, non surgical intervention (e.g., pelvic floor muscle exercises or pessary-use), or no treatment at all. Figure 5-1 schematically depicts the incidence (by approximation) of POP diagnosis and treatment of women in the United States (2010)\textsuperscript{13}. The figure shows that less than 20% of the diagnosed population is treated surgically and of this population, only 13% undergo repair with a pelvic floor repair kit.
Effectiveness of Transvaginal Mesh:

Prolapse repair using transvaginal mesh kits has been shown to be an effective treatment option in multiple randomized controlled trials when assessing objective anatomical outcome measures for the treatment of POP. Table 5-1 summarizes seven randomized controlled trials that compared anatomic success of transvaginal placement of permanent synthetic mesh or transvaginal mesh kits to traditional vaginal native tissue repairs. These studies were referenced in FDA’s July 2011 White Paper.
Table 5-1: Randomized Controlled Trials Comparing Mesh Repair to Native Vaginal Tissue Repair

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th># Patients</th>
<th>Follow Up</th>
<th>Anatomic Cure</th>
<th>Anatomic Cure</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sivaslioglu</td>
<td>2008</td>
<td>90</td>
<td>12</td>
<td>91%</td>
<td>72%</td>
<td>p&lt;.05</td>
</tr>
<tr>
<td>Nguyen</td>
<td>2008</td>
<td>75</td>
<td>12</td>
<td>87%</td>
<td>55%</td>
<td>p&lt;.05</td>
</tr>
<tr>
<td>Carey</td>
<td>2009</td>
<td>139</td>
<td>12</td>
<td>81%</td>
<td>65.6%</td>
<td>p=.07</td>
</tr>
<tr>
<td>Nieminen</td>
<td>2010</td>
<td>202</td>
<td>36</td>
<td>87%</td>
<td>59%</td>
<td>p&lt;.0001</td>
</tr>
<tr>
<td>Iglesia</td>
<td>2010</td>
<td>65</td>
<td>9.7</td>
<td>40.6</td>
<td>29.6</td>
<td>NS</td>
</tr>
<tr>
<td>Withagen</td>
<td>2011</td>
<td>194</td>
<td>12</td>
<td>90.4</td>
<td>54.8</td>
<td>p&lt;.001</td>
</tr>
<tr>
<td>Altman</td>
<td>2011</td>
<td>389</td>
<td>12</td>
<td>82.3</td>
<td>47.5</td>
<td>p=0.008</td>
</tr>
</tbody>
</table>

All studies cited above demonstrated anatomical effectiveness of transvaginal mesh repair. Even though the difference did not reach statistical significance in two of the aforementioned studies (Carey and Iglesia), it must be noted that overall, mesh repairs showed greater anatomical success. It should also be noted, that Quality of Life (QoL) outcomes were measured using different tools in each of the studies cited above. Results reported for both mesh procedures and traditional procedures reflect statistically significant improvements in QoL scores.
The higher anatomical success rate has been a topic of debate in light of other findings that show there is no difference in symptomatic relief between non-mesh and transvaginal mesh kit procedures. One must keep in mind, however, that these studies were not designed to detect differences in subjective (symptomatic) outcomes as they were addressing the primary objective outcome measure as prescribed by the International Continence Society\(^{19}\). Barber et al. has shown that the patient’s assessment of overall improvement following POP repair correlates most significantly with the absence of vaginal bulge symptoms\(^{20}\). In the largest randomized controlled trial to date (389 patients randomized), the primary outcome was a composite of the objective anatomical outcome and the subjective absence of the symptom of vaginal bulging, 12 months after the surgery\(^{11}\). This primary composite outcome was significantly more common in the women treated with transvaginal mesh repair (60.8%) than in those who underwent colporrhaphy (34.5%). The study also noted a significant functional difference for the feeling of bulge alone: 75% (transvaginal mesh repair) vs. 62% (traditional repair) after 1 year (p= 0.008). It must be pointed out that this large RCT only addressed anterior vaginal wall prolapse.

There is one randomized controlled trial and three observational cohort series with data greater than 36 months that support the durability of transvaginal mesh\(^{17,21,22,23}\).

**Safety of Transvaginal Mesh for POP Repair**

Both mesh and non-mesh procedures to treat POP carry risks for complications, as well as for prolapse recurrence. Diwadkar et al. compared the post operative complications and reoperation rates for surgical procedures correcting apical vaginal prolapse in a meta-analysis.\(^{24}\). Table 5-2 summarizes the results and demonstrates that overall, each treatment option has similar total complications rates.
### TABLE 5-2: Weighted Averages of Complications:
Prolapse Reoperation Rates and Total Reoperations Rates\(^{24}\)
(Abbreviated table - For complete table see reference #24, Appendix III)

<table>
<thead>
<tr>
<th></th>
<th>Traditional repair</th>
<th>Sacral colpopexy</th>
<th>Mesh kits</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of studies</td>
<td>48</td>
<td>52</td>
<td>24</td>
</tr>
<tr>
<td>Number of patients</td>
<td>7,827</td>
<td>5,639</td>
<td>3,425</td>
</tr>
<tr>
<td>Mean Follow Up Time</td>
<td>32.6</td>
<td>26.5</td>
<td>17.1</td>
</tr>
<tr>
<td>(mths)</td>
<td>% (CI)</td>
<td>% (CI)</td>
<td>% (CI)</td>
</tr>
<tr>
<td>Total Complication rate</td>
<td>15.3 (14.7-16.3)</td>
<td>17.1 (16.1-18.1)</td>
<td>14.5 (13.3-15.7)</td>
</tr>
<tr>
<td>Reoperation for prolapse recurrence</td>
<td>3.9 (3.5-4.4)</td>
<td>2.3 (1.9-2.7)</td>
<td>1.3 (1.0-1.7)</td>
</tr>
<tr>
<td>Total reoperation rate</td>
<td>5.8 (5.3-6.3)</td>
<td>7.1 (6.4-7.8)</td>
<td>8.5 (7.6-9.4)</td>
</tr>
<tr>
<td>Mesh exposure/ infection</td>
<td>0.5</td>
<td>2.2</td>
<td>5.8</td>
</tr>
<tr>
<td>Cystotomy</td>
<td>0.4</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Ureteral injury</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Bowel injury</td>
<td>0.4</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Bleeding complication</td>
<td>2.8</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Wound complications</td>
<td>0.5</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>PE / DVT</td>
<td>0.1</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>1.5</td>
<td>1.5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

The authors do point out that the data must be interpreted in light of the fact that the mesh kit studies included in the analysis had a shorter follow up and a smaller sample size. While we acknowledge these limitations in interpreting the rates of AEs, the data show that each surgical option has its own inherent risks that differ in number and severity. The risks associated with each procedure must be taken into account along with the most appropriate treatment option for the patient’s specific prolapse, general physical condition and previous surgical history, as well as the surgeon’s specific surgical expertise.

Appendix I contains an overview of the standardized training programs the Working Group supports on the appropriate use of transvaginal mesh devices for POP, which we will discuss in more detail below. We are committed to optimizing this surgeon training through collaboration with FDA and professional societies in light of the importance of surgical technique in patient outcomes.
As noted in the table above, as well as in the FDA’s 2011 Safety Notification, mesh exposure is the most commonly reported AE for mesh kits. Mesh exposure through the vaginal epithelium is a well characterized adverse event that can be successfully managed in the majority of cases. Proper surgical technique, such as use of proper mesh, and minimally-sized incisions significantly impact outcomes. Abed et al. performed a meta-analysis on 110 studies including 11,785 women who had a vaginal prolapse repair with mesh, of whom 10.3% had mesh exposure. These exposures were mostly identified within one year of surgery. 5.8% required surgical intervention to correct this complication. This is consistent with more recent literature on surgical reintervention for exposure: 3% (Altman) and 3.6% (de Landsheere et al). Rates of mesh erosion into visceral organs is rare and have been reported in the literature as case reports, not as AEs in published clinical trials. Similarly, long term experience with these identical mesh materials in abdominal sacrocolpopexy procedures has confirmed that erosion into the hollow viscera remains a rare complication.

Predisposing conditions that may lead to mesh exposures are becoming more apparent. These include:

- Concomitant hysterectomy
- Patient age
- Surgeon experience
- Smoking
- Diabetes mellitus

Another adverse event associated with all pelvic floor surgery (as opposed to mesh-specific complications) is dyspareunia and pelvic pain. Dyspareunia and pelvic pain following POP repair, with or without mesh, are often due to a number of causes such as pre-existent pelvic pain, estrogen deficiency and vaginal foreshortening. Both are highly complex to evaluate and currently there is limited robust data. Pelvic organ prolapse repair, whether abdominal or vaginal, whether using native tissue or mesh, appears to have a high rate of associated dyspareunia. Transvaginal mesh repairs have de novo dyspareunia rates comparable to traditional repairs.

While the FDA 2011 Safety Notification identified mesh contraction (shrinkage) as a previously unidentified risk of transvaginal POP repair, mesh shrinkage is a well recognized complication, as previously studied in abdominal hernia surgery. In 2008, Caquant et al reported on 684 patients who had undergone a flat mesh graft placement for POP. He reported a shrinkage rate of 11.7%.
Based on the Working Group’s review of adverse events (MAUDE database) and our assessment of the published literature, transvaginally placed surgical mesh for POP is effective (with proven anatomic and functional improvements) and has an acceptable safety profile. There are many factors that go into weighing the benefit of a device versus its risk. Factors the FDA considers in this determination include alternative treatment options and understanding of the device risk profile. The Working Group agrees with FDA that a given benefit/risk profile can alter over the market lifespan of the device. In the case of transvaginal mesh, significant learning and device design technological advances have allowed this treatment type to become a viable treatment option for women. Below is a summary of the Working Group’s conclusion on transvaginal mesh benefit-risk determination based on the published literature and current field experience.

Type, Magnitude and Duration of the Benefit: Transvaginal mesh procedures appear to provide clinical benefit. Initial long term data indicate durability of repair, however, continued collection of long term robust evidence is critical to continue to evaluate the risk/benefit ratio.

Probability of the Patient Experiencing the Benefit: In view of the aging population as well as the obesity epidemic, a durable transvaginal mesh repair will become an increasingly important treatment option. In certain sub-populations, the benefit will be more pronounced as already demonstrated in the repair of anterior vaginal wall prolapse and patients undergoing secondary prolapse repairs.

Adverse Events and Serious Adverse Events: As demonstrated in published literature, the transvaginal mesh is associated with mesh-specific adverse events, predominantly mesh exposures into the vagina. These mesh-specific AEs are well characterized and in the majority of cases are manageable.

In conclusion, the Working Group believes that mesh kits provide a valuable treatment option for women suffering from this challenging condition.
IV. REGULATORY OVERSIGHT OF TRANSVAGINALLY PLACED MESH PRODUCTS FOR POP: CLASS II DEVICE WITH SPECIAL CONTROLS

The Working Group proposes that the classification of transvaginally placed surgical mesh devices intended for the treatment of POP remain as Class II subject to the 510(k) requirements. The safety and effectiveness of mesh products for POP has been established through bench testing, cadaveric modeling and animal testing and has been corroborated in the medical literature by both RCTs and observational trials. This conclusion supports the determination that the current regulatory scheme (Class II, 510(k) requirements) is appropriate for surgical mesh devices intended for POP treatment.

Currently, mesh products used for the treatment of POP are regulated by general controls as well as FDA’s Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance - Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh (March 2, 1999)\textsuperscript{32}. This guidance is applicable to all surgical mesh regardless of its intended use and was issued prior to the use of mesh in the treatment of POP. We, therefore, recommend that a new special controls document be developed that clearly defines the appropriate data for continuing to assess the safety and effectiveness of transvaginally placed mesh products used to treat POP. Sufficient clinical information exists about currently marketed mesh products to develop appropriate special controls for these devices. Special controls can be implemented to ensure the adequacy and reliability of labeling information provided to both patients and physicians, and also to ensure consistency in the evaluation of the safety and effectiveness of new products through standardized requirements, including performance of pre-and post-market clinical trials. FDA may require any firm currently marketing or intending to market, surgical mesh for the treatment of POP, to comply with the specific requirements detailed in the special controls guidance document.

The Working Group proposes an outline for the new Special Controls Guidance document for transvaginal surgical mesh intended for the treatment of POP located in Appendix II. Below are critical new elements of the proposed guidance document. The Special Controls Guidance would require the generation of clinical evidence to support pre and post market requirements, including products currently on the market as well as enhanced surgeon training programs.

A. Clinical Data for NEW PRODUCTS:

1. Pre-Market Data:

The Working Group proposes that a statistically powered, 12 month pre-market clinical study be required for clearance of a new transvaginal mesh kit associated with the types of changes listed below. Typically, powering these studies will require enrollment of 200-300 patients.
• indications for use dissimilar from a legally marketed device of the same type;
• designs dissimilar from designs previously cleared under a premarket notification; or
• new technology, i.e., technology different from that used in legally marketed devices of the same type.

For some new devices that represent a transformational change (e.g., addition of a drug or specific indication) change from currently marketed devices it may be appropriate to conduct a randomized control clinical study. Such a study will use an appropriate control, be statically powered, control bias, with a duration of 12 months follow-up.

2. **Post Market Clinical Data**
Post market clinical data may be required for new products via the continuation of the follow-up of patients from the pre-market studies described above. It may be appropriate that the design of the post-market study be a Post Market Surveillance design to address specific concerns from the premarket study. Typically, the duration of these post-market studies will be 3-5 years, including the duration of the premarket study. The Working Group recommends that longer term data be collected through these prospective studies, which we believe will be more effective than registries.

The Working Group recognizes that pre-market and post clinical data requirement will vary depending on the type of device, or change to a device, and that clinical requirements should be discussed with FDA prior to trial initiation.

3. **Product Labeling**
Labeling of new products will contain a summary of the product-specific pre-market clinical data collected in support of product clearance. A detailed summary of risks associated with the use of mesh kits will also be included. Patient subpopulations that are at risk for adverse events associated with transvaginal mesh procedures will be identified. Lastly, adequate information will be provided to ensure proper use of the device.

4. **Patient Labeling**
Patient labeling will also be created to assist the patient in understanding the benefit from the treatment with the device, what those benefits are, relevant contraindications, warnings, precautions, adverse events and alternative treatments. The patient labeling should use terminology that is well know and understood by the average lay person.
B. Clinical Data for EXISTING PRODUCTS

1. Post Market Data:
The Working Group believes previously-cleared mesh products are safe and effective for the
treatment of POP. In light of the questions raised by FDA’s safety notice, we propose to conduct
“active surveillance” studies on 200-500 patients for 3 years on our currently marketed products.
This surveillance would monitor AE rates and reoperation rates. The results of this data collection
would be incorporated into the device labeling.

2. Product Labeling
Product labeling for currently marketed products will include a summary of published clinical
data for transvaginal mesh product. Labeling will be updated as post-marketing studies are
completed. A summary of risk/ benefits associated with transvaginally placed mesh kits as well
as adequate information to ensure proper use will be included in product labeling.

C. Training:
The Working Group is committed to working with certifying boards and specialty societies in
developing practice guidelines and training programs to assist surgeons on the appropriate use of
transvaginal mesh devices for POP. We recommend that the following requirement be added to
the special controls guidance document. Manufacturers should develop a clinician training
program on the device that includes

1. methods for training on the use of the device and appropriate
   methods to describe the safety and risks of the device in the
treatment of patients with pelvic organ prolapse;
2. guidelines on the characteristics of the intended patient population
   and information on patients who may be have a higher incident of
   AE’s (e.g. diabetics, smokers)

The Working Group will work with FDA on the details of the special control to define what
standards should be covered in training, pre and post market clinical data collection.
V. RATIONALE FOR DEVICE CLASS II DESIGNATION

The Working Group believes that the implementation of the special controls described above will ensure that appropriate scientific evidence is provided for FDA’s continued review and assessment of POP devices under the 510(k) process. The application of the current Class II (510(k)) regulatory scheme has supported innovation, continued improvements in standards of care, and patient access to fast-paced treatment advancements for this very difficult condition.

The Working Group notes that FDA’s July 2011 safety notice had proposed the reclassification of the device from Class II into Class III, which would establish the more stringent premarket approval (PMA) regulatory requirements for these products. However, as described above, Special Controls can be used to gather clinical data, and the other more stringent PMA requirements relate to areas such as pre-market inspections and the submission of manufacturing data, which are not pertinent to the concerns raised by the FDA. The mechanism of action for mesh devices in the treatment of POP is well-established. The complications associated with the use of the transvaginal mesh devices are well-documented. Clinical studies have demonstrated comparable effectiveness relative to traditional surgeries. Overall, these devices have adequate safe and effective clinical performance. Therefore, we do not recommend that the device be reclassified into Class III. The Class II special controls regulatory scheme provides FDA sufficient controls to ensure the safety and effectiveness of these important products and will foster the timely development of more advanced, next generation mesh devices for POP repair.
VI. REFERENCES


5. Urogynecologic Surgical mesh, Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ prolapsed, July 2011, FDA, CDRH


13. Sources: UpToDate, Trinity/EWHU SP market models (NHANES, Solucient, IMS, Millennium Reports) 2010


23 Dennis Miller, Vincent Lucente, Elizabeth Babin, Patricia Beach, Prospective Clinical Assessment of the Transvaginal Mesh Technique for Treatment of Pelvic Organ ProlapseV5-Year Results Female Pelvic Med Reconstr Surg 2011;17: 139-143

25 Abed H, Rahn DD, Lowenstein L, Balk EM, Clemons JL, Rogers RG. Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials: A systematic review. *Int Urogynecol J Pelvic Floor Dysfunct.* 22:789-798


32 Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance - Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh (March 2, 1999), FDA, CDRH
Appendix I

This appendix contains overviews of surgeon training programs from three of the Working Group companies: Ethicon Inc, American Medical Systems, Boston Scientific.
ETHICON Women’s Health & Urology Professional Education

ETHICON Women’s Health & Urology Professional Education utilizes a variety of programs to help train surgeons on the safe and effective use of our products. Product trainings are facilitated by qualified surgeon faculty utilizing content approved by our copy review process. Surgeon trainees are selected based on their experience and skills in relevant procedures. Training modalities include preceptorship, proctorship and hands-on courses with lab. We constantly measure our Professional Education programs and make improvements.

**Faculty:**

Surgeon faculty are carefully selected for their skills and experience in relevant procedures. Many are leaders of professional societies and involved in residency and fellowship training. They are trained to the specific product indications, contraindications, clinical data as well specific technical and patient care tips for maximizing successful outcomes and managing complications. Additionally, they are privileged, licensed and board certified in the procedures that they teach.

**Surgeon Trainee:**

Surgeon trainees must have privileges to perform the relevant procedure. They must have experience and a surgical practice focused on the disease state that they seek training. Additionally, they often must complete pre-requisite training including patient selection, anatomy and procedural steps.

**Training Modalities:**

**Online:**

<table>
<thead>
<tr>
<th>Webcast</th>
<th>Web-delivered didactic; may include Q&amp;A with faculty and/or telesurgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-Modules</td>
<td>Interactive, web-delivered content to include learner assessment</td>
</tr>
<tr>
<td>Podcasts</td>
<td>Web delivered audio content; may include Q&amp;A with faculty</td>
</tr>
</tbody>
</table>

**Live:**

<table>
<thead>
<tr>
<th>Preceptorship</th>
<th>Surgeon trainee travels to faculty’s OR to observe 3-4 procedures. Includes live surgery, didactic, Q&amp;A; may also include hands-on with the patient or models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proctorship</td>
<td>Faculty travels to surgeon trainee’s OR for 3-4 procedures. Includes live surgery, didactic, Q&amp;A; may also include faculty scrub privileges.</td>
</tr>
<tr>
<td>Course</td>
<td>Faculty leads didactic, lab, breakouts and Q&amp;A. May include surgical simulators, animal</td>
</tr>
</tbody>
</table>
models or cadavers.

**Constant Improvement:**

Surveys of surgeon trainees, faculty and our Professional Education and company personnel are utilized to measure our performance and make constant improvement. Subjective and objective feedback is used to adjust the curricula, content and faculty delivery of the training.
American Medical Systems Overview of Training Program

From the introduction of the first POP transvaginal mesh kit, AMS has offered surgeons multiple levels of training. These consist of the following:

- Workshops that include anatomy and product information, didactic and cadaver work.
- Proctoring and Preceptoring – allowing surgeons to both see trained surgeons doing the procedure and to perform their first procedures with expert guidance
- Advanced user workshops that allow experienced user to learn from each other. Discussions may center around techniques used in specific patient groups, how to handle specific adverse events, latest thinking on technique etc

All physicians who desire training have it available, and AMS encourages all physicians to be trained prior to using our products.
Boston Scientific’s Physician Training Programs

Boston Scientific provides robust training to Urogynecologists, Surgical Gynecologists and Urologists who would like to enhance their surgical technique to advance the quality of patient care. Our training programs especially focus on our Pelvic Floor Reconstruction (PFR) and Stress Urinary Incontinence (SUI) product portfolio.

Faculty Preparation:

Physician faculty who teach on our behalf have gone through a rigorous selection process to qualify. Criteria to select faculty include:

- Clinical expertise and experience performing cases relevant to the particular program
- Capacity and ability to conduct programs
- Hospital privileges, licensing, certification and restrictions, if applicable

The annual contracting process helps ensure that each faculty member’s performance is carefully scrutinized so that only the most qualified, talented surgeons teach on Boston Scientific’s behalf.

Attendee Qualification:

Physician attendees must also qualify to be eligible for training programs. These criteria include:

- An expressed or demonstrated need for a particular training program, including the physician having current privileges to perform a particular procedure
- The program relates to the therapeutic area in which the physician practices
- The physician has not received or undertaken a similar training program unless there is a demonstrated need for the physician to attend a recurrent training session

These criteria help ensure that the appropriate physicians attend our training programs.

Training Options:

Boston Scientific offers three (3) distinct training options. They include:

1. Proctorships/Preceptorships: Surgical observation in the O.R.
2. Cadaver Labs: Didactic and device implantation in a hands-on lab setting
3. Speaking Programs: Didactic presentation onsite or via Web-Ex technology

Physicians can elect a training option which addresses their educational need.

Metrics:

In an effort to protect the integrity of our training programs, surveys are administered. These quantitative and qualitative assessments help ensure that the training programs are robust and that the most appropriate faculty members continue to teach on our behalf.
APPENDIX II

SPECIAL CONTROLS FOR TRANSVAGINAL
SURGICAL MESH FOR THE TREATMENT OF POP

Product Description

Packaging: A description of the packaging to be used to maintain the sterility of the device.

Expiration Date: Data supporting the expiration date for a product should be submitted. The appropriateness of accelerated stability data is determined by device composition.

Biocompatibility: In accordance with the Blue Book Guidance G95-1, (“Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing"), acceptable test results should be supplied for the biological tests listed below. Standard protocols such as those identified by the USP or ASTM should be used in conducting the biocompatibility testing, if possible. Such tests should be performed on devices ready for surgical use (i.e., after manufacture, sterilization and packaging for commercial distribution). NOTE: The above tests may not be relevant or necessary in all cases, such as when a manufacturer submits a marketing application for a device which has the exact same material specifications as a previously marketed product, and/or for which the tradename and device claims are the only changes being made.

Product Characterization: Information about the product structure is required. Testing of the following characteristics of surgical mesh should include:

- Tissue Ingrowth: should be assessed in an appropriate model
- Mesh thickness
- Mesh weave characteristics
- Pore size
- Filament size, shape, and length
- Mesh density
- Tensile strength
- Stiffness
- Suture pullout strength
- Burst strength
- Elasticity
- Tear resistance

Human Factors: When appropriate Human Factors testing should be considered computer modeling and cadaver studies should be consider as ways to assess ability of surgeons to utilize the delivery tool/surgical pathway, location of mesh placement with respect to anatomical features.
For Biodegradable Devices: Required information should document the rate of product resorption and how specific device properties (e.g., suture pullout strength, burst strength and/or tear resistance) change as a function of time. Such studies should be performed in vivo or in a manner expected to accurately predict product decomposition (e.g., in comparable cellular and proteolytic environments at 37°C).

Clinical Data for NEW PRODUCTS:

1. **Pre-Market Data:**
The Working Group proposes that a statistically powered, 12 month pre-market clinical study be required for clearance of a new transvaginal mesh kit associated with the types of changes listed below. Typically, powering these studies will require enrollment of 200-300 patients.

   - indications for use dissimilar from a legally marketed device of the same type;
   - designs dissimilar from designs previously cleared under a premarket notification; or
   - new technology, i.e., technology different from that used in legally marketed devices of the same type.

For some new devices that represent a transformational change (e.g., addition of a drug or specific indication) change from currently marketed devices it may be appropriate to conduct a randomized control clinical study. Such a study will use an appropriate control, be statically powered, control bias, with a duration of 12 months follow-up.

2. **Post Market clinical data**
Post market clinical data may be required for new products via the continuation of the follow-up of patients from the pre-market studies described above. It may be appropriate that the design of the post-market study be a Post Market Surveillance design to address specific concerns from the premarket study. Typically, the duration of these post-market studies will be 3-5 years, including the duration of the premarket study. The Working Groups recommends that longer term data be collected via these prospective studies rather than registries.

The Working Group recognizes that pre-market and post clinical data requirement will vary depending on the type of device, or change to a device, and that clinical requirements should be discussed with FDA prior to trial initiation.

3. **Product Labeling**
Labeling of new products will contain a summary of the product-specific pre-market clinical data collected in support of product clearance. A detailed summary of risks associated with the use of mesh kits will also be included. Patient subpopulations that are at risk for adverse events associated with transvaginal mesh procedures will be identified. Lastly, adequate information will be provided to ensure proper use of the device.
4. **Patient Labeling**
Patient labeling will also be created to assist the patient in understanding who may benefit from the treatment with the device, what those benefits are, relevant contraindications, warnings, precautions, adverse events and alternative treatments. The patient labeling should use terminology that is well known and understood by the average lay person.

**Clinical Data for EXISTING PRODUCTS**

5. **Post Market Data:**
The Working Group believes previously-cleared mesh products are safe and effective for the treatment of POP. In light of the questions raised by FDA’s safety notice, we propose to conduct active surveillance studies on 200-500 patients for 3 years on our currently marketed products. This surveillance would monitor AE rates and reoperation rates. The results of this data collection would be incorporated into the device labeling.

6. **Labeling**
Product labeling will include a summary of published clinical data for transvaginal mesh product. Labeling will be updated as post-marketing studies are completed. A summary of risk/benefits associated with transvaginally placed mesh kits as well as adequate information to ensure proper use will be included in product labeling.

**Training:**

1. The Working Group is committed to working with certifying boards and specialty societies in developing practice guidelines and training programs to assist surgeons on the appropriate use of transvaginal mesh devices for POP.
2. The Working Group recommends that the following requirement be added to the special controls guidance document. Manufacturers should develop a clinician training program on the device that includes
   a) methods for training on the use of the device and appropriate methods to describe the safety and risks of the device in the treatment of patients with pelvic organ prolapse;
   b) guidelines on the characteristics of the intended patient population and information on patients who may be have a higher incident of AE’s (e.g. diabetics, smokers)
APPENDIX III

Reference articles will be provided under separate cover and are not meant for posting to the public docket due to copyright issues.