



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 884

[Docket No. FDA-2014-N-0298]

Effective Date of Requirement for Premarket Approval for Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is issuing a proposed administrative order to require the filing of a premarket approval application (PMA) if the surgical mesh for transvaginal pelvic organ prolapse (POP) repair device is reclassified from class II to class III. The Agency is summarizing its proposed findings regarding the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to meet the statute's PMA requirements and the benefit to the public from the use of the device.

DATES: Submit either electronic or written comments on this proposed order by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. FDA intends that, if a final order based on this proposed order is issued, anyone who wishes to continue to market the device will need to submit a PMA within 90 days of the effective date of the final order or on the last day of the 30th calendar month beginning after the month in which the classification of the device in class III became effective, whichever occurs later. See section VI for more information about submitting a PMA. See section X for the effective date of any final order that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No. FDA-2014-N-0298, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- Mail/Hand delivery/Courier (for paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2014-N-0298 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Melissa Burns, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 1646, Silver Spring, MD 20993, 301-796-5616, melissa.burns@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background--Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94-295), the Safe Medical Devices Act of 1990 (Pub. L. 101-629), the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115), the Medical Device User Fee and Modernization Act of 2002 (Pub. L. 107-250), the Medical Devices Technical Corrections Act of 2004 (Pub. L. 108-214), the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85), and the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513(d) of the FD&C Act, devices that were in commercial distribution before the enactment of the 1976 amendments, May 28, 1976 (generally referred to as preamendments devices), are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

A preamendments device that has been classified into class III and devices found substantially equivalent by means of premarket notification procedures in section 510(k) of the

FD&C Act (21 U.S.C. 360(k)) to such a preamendments device or to a device within that type (both the preamendments and substantially equivalent devices are referred to as preamendments class III devices) may be marketed without submission of a PMA until FDA issues a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval. Section 515(b)(1) of the FD&C Act directs FDA to issue an order requiring premarket approval for a preamendments class III device.

Section 515(f) of the FD&C Act provides an alternative pathway for meeting the premarket approval requirement. Under section 515(f), manufacturers may meet the premarket approval requirement if they file a notice of completion of a product development protocol (PDP) approved under section 515(f)(4) of the FD&C Act and FDA declares the PDP completed under section 515(f)(6)(B) of the FD&C Act. Accordingly, the manufacturer of a preamendments class III device may comply with a call for PMAs by filing a PMA or a notice of completion of a PDP. In practice, however, the option of filing a notice of completion of a PDP has rarely been used. For simplicity, although the PDP option remains available to manufacturers in response to a final order under section 515(b) of the FD&C Act, this document will refer only to the requirement for filing and obtaining approval of a PMA.

On July 9, 2012, FDASIA was enacted. Section 608(b) of FDASIA amended section 515(b) of the FD&C Act, changing the process for requiring premarket approval for a preamendments class III device from rulemaking to an administrative order.

Section 515(b)(1) of the FD&C Act sets forth the process for issuing a final order. Specifically, prior to the issuance of a final order requiring premarket approval for a preamendments class III device, the following must occur: (1) Publication of a proposed order in the Federal Register; (2) a meeting of a device classification panel described in section 513(b) of

the FD&C Act; and (3) consideration of comments from all affected stakeholders, including patients, payors, and providers. In September 2011, FDA held a meeting of a device classification panel described in section 513(b) of the FD&C Act with respect to surgical mesh for transvaginal POP repair. As explained further in section V, this device classification panel meeting discussed whether surgical mesh for transvaginal POP repair should be reclassified or remain in class II, and the discussion included whether PMAs should be required for these devices. The panel recommended that the device be reclassified into class III because general controls and special controls together would not be sufficient to provide reasonable assurance of the safety and effectiveness of the device. The panel consensus was that premarket clinical data are needed for surgical mesh for transvaginal POP repair, and that each individual mesh device should be evaluated against a control arm of traditional "native tissue" (non-mesh) repair to demonstrate a reasonable assurance of safety and effectiveness. FDA is not aware of new information that would provide a basis for a different recommendation or findings. Indeed, the additional information received since the 2011 panel meeting and discussed further in section V highlights the need to review these devices under a PMA and reinforces the recommendation and findings of the panel.

Section 515(b)(2) of the FD&C Act provides that a proposed order to require premarket approval shall contain: (1) The proposed order, (2) proposed findings with respect to the degree of risk of illness or injury designed to be eliminated or reduced by requiring the device to have an approved PMA and the benefit to the public from the use of the device, (3) an opportunity for the submission of comments on the proposed order and the proposed findings, and (4) an opportunity to request a change in the classification of the device based on new information relevant to the classification of the device.

Section 515(b)(3) of the FD&C Act provides that FDA shall, after the close of the comment period on the proposed order, consideration of any comments received, and a meeting of a device classification panel described in section 513(b) of the FD&C Act, issue a final order to require premarket approval or publish a document terminating the proceeding together with the reasons for such termination. If FDA terminates the proceeding, FDA is required to initiate reclassification of the device under section 513(e) of the FD&C Act, unless the reason for termination is that the device is a banned device under section 516 of the FD&C Act (21 U.S.C. 360f).

A preamendments class III device may be commercially distributed without a PMA until 90 days after FDA issues a final order requiring premarket approval for the device, or 30 months after classification of the device in class III under section 513 of the FD&C Act becomes effective, whichever is later. Elsewhere in this issue of the Federal Register, FDA is proposing an order to reclassify surgical mesh for transvaginal POP repair from class II to class III. Therefore, assuming the reclassification order and the order to require PMAs are finalized, the date by which a PMA for surgical mesh for transvaginal POP repair must be filed will depend on the date the final reclassification order becomes effective and the date the final order to require PMAs is issued. If a PMA is not filed for such device by the later of the two dates specified in section 501(f)(2)(B) of the FD&C Act (21 U.S.C. 351(f)(2)(B)) (i.e., the 90th day after the date the order to require PMAs is issued and the last day of the 30th calendar month beginning after the month in which the classification in class III becomes effective), then the device would be deemed adulterated under section 501(f) of the FD&C Act unless the device is distributed for investigational use under an approved application for an investigational device exemption (IDE).

In accordance with section 515(b) of the FD&C Act, interested persons are being offered the opportunity to request reclassification of surgical mesh for transvaginal POP repair.

II. Regulatory History of the Device

Surgical mesh is a preamendments device classified into class II (§ 878.3300 (21 CFR 878.3300)). Beginning in 1992, FDA cleared premarket notification (510(k)) submissions for surgical mesh indicated for transvaginal POP repair under the general surgical mesh classification regulation § 878.3300. FDA has cleared over 100 510(k) submissions for surgical mesh with a POP indication. Elsewhere in this issue of the Federal Register, FDA is proposing to reclassify this device into class III under section 513(e) of the FD&C Act.

III. Dates New Requirements Apply

Assuming FDA finalizes the order proposing reclassification of surgical mesh for transvaginal POP repair this device will be classified into class III. In accordance with sections 501(f)(2)(B) and 515(b) of the FD&C Act, FDA is proposing to require that a PMA be filed with the Agency by the last day of the 30th calendar month beginning after the month in which the classification of the device in class III became effective, or on the 90th day after the date of the issuance of a final order under 515(b), whichever is later. An applicant whose surgical mesh for transvaginal POP repair was legally in commercial distribution before May 28, 1976, or whose surgical mesh for transvaginal POP repair has been found to be substantially equivalent prior to the issuance of a final order under section 515(b), will be permitted to continue marketing such class III device during FDA's review of the PMA, provided that a PMA is timely filed. FDA intends to review any PMA for the device within 180 days. FDA cautions that, under section 515(d)(1)(B)(i) of the FD&C Act, the Agency may not enter into an agreement to extend the review period for a PMA beyond 180 days unless the Agency finds that " * * * the continued

availability of the device is necessary for the public health."

FDA intends that, under § 812.2(d) (21 CFR 812.2(d)), the publication in the Federal Register of any final order based on this proposal will include a statement that, as of the date on which the filing of a PMA is required, the exemptions in § 812.2(c)(1) and (2) from the requirements of the IDE regulations for preamendments class III devices will cease to apply to any device that is subject to the final order and that is: (1) Not legally on the market on or before that date or (2) legally on the market on or before that date but for which a PMA is not filed by that date, or for which PMA approval has been denied or withdrawn.

If a PMA for a class III device is not filed with FDA within 90 days of the date of issuance of the final order requiring premarket approval for the device or 30 months after the classification of the device into class III, whichever is later, commercial distribution of the device must cease. The device may be distributed for investigational use only if the requirements of the IDE regulations in part 812 are met. The requirements for investigational use of significant risk devices include submitting an IDE application to FDA for review and approval. An approved IDE is required to be in effect before an investigation of the device may be initiated or continued under § 812.30. FDA, therefore, recommends that IDE applications be submitted to FDA at least 30 days before the date a PMA is required to be filed to avoid interrupting investigations.

IV. Device Subject to This Proposal

Surgical mesh for transvaginal POP repair can be placed abdominally or transvaginally to repair POP. When placed transvaginally, surgical 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). These devices are made of synthetic material, non-synthetic material, or a combination of both. They are marketed as either stand alone mesh products or mesh kits (i.e., the product includes mesh and instrumentation to aid insertion, placement, fixation, and/or anchoring).

Elsewhere in this issue of the Federal Register, FDA is proposing to identify surgical mesh for transvaginal POP repair in the new § 884.5980 (21 CFR 884.5980) in the following way: Surgical mesh for transvaginal POP repair is a prescription device intended to reinforce soft tissue in the pelvic floor. This device is a porous implant that is synthetic, non-synthetic, or both. This device does not include surgical mesh for other intended uses (see § 878.3300).

V. Proposed Findings With Respect to Risks and Benefits for Surgical Mesh for Transvaginal POP Repair

As required by section 515(b) of the FD&C Act, FDA is publishing its proposed findings regarding: (1) The degree of risk of illness or injury designed to be eliminated or reduced by requiring that these devices have an approved PMA and (2) the benefits to the public from the use of the devices.

These findings are based on the reports and recommendations of the Obstetrics and Gynecological Devices Panel from the meeting on September 8-9, 2011, and any additional information that FDA has obtained. Additional information regarding the risks as well as the classification of this device can be found in section V.3 as well as in the proposed order, published elsewhere in this issue of the Federal Register, proposing to reclassify these devices into class III. The device has the potential to benefit the public by aiding in the correction of cystocele (anterior repair), rectocele (posterior repair), uterine prolapse, or vaginal apical prolapse (apical repair). The risks associated with the device include perioperative risks (organ

perforation or injury and bleeding); mesh exposure; mesh extrusions; vaginal scarring, shrinkage, and tightening; pelvic pain; infection; de novo dyspareunia; de novo voiding dysfunction (e.g., incontinence); neuromuscular problems (including groin and leg pain); recurrent prolapse; and resurgery.

A. Summary of Data

In October 2008, as a result of over 1,000 adverse events received, FDA issued a Public Health Notification (PHN) informing clinicians and their patients of the adverse event findings related to use of urogynecologic surgical mesh (Ref. 1). The PHN also provided recommendations for clinicians on how to mitigate the risks associated with these devices and information for their patients. On July 13, 2011, based on an updated adverse event search, FDA issued a Safety Communication entitled "UPDATE on Serious Complications Associated With Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse" (Ref. 2).

The continued reports of adverse events also prompted FDA to consider other available information regarding the use of surgical mesh for transvaginal POP repair and to evaluate whether the classification of this device type should be reconsidered. FDA systematically evaluated the peer-reviewed scientific literature to revisit the fundamental question of the safety and effectiveness of surgical mesh for transvaginal POP repair. Based on its review, 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. FDA's detailed evaluation of the scientific literature is discussed in FDA's executive summary for the September 8-9, 2011, panel meeting which is discussed further in this document (Ref. 3).

On September 8-9, 2011, FDA convened a meeting of the Obstetrics and Gynecological Devices Panel (the Panel), a device classification panel described in section 513(b) of the FD&C Act, and referred the proposed reclassification of surgical mesh for transvaginal POP repair to the Panel for its recommendations on the proposed change in the device's classification from class II to class III (Ref. 4). The Panel consensus was that a favorable benefit-risk profile for surgical mesh used for transvaginal POP repair has not been well established. The Panel discussed the number of serious adverse events associated with the use of these devices and concluded that their safety is in question. In addition, the Panel consensus was that the effectiveness of surgical mesh for transvaginal POP repair has not been well established, and the device may not be more effective than traditional non-mesh surgery, especially for the apical and posterior vaginal compartments.

Additionally, the Panel consensus was that premarket clinical data are needed for surgical mesh for transvaginal POP repair, and the majority of panel members recommended that each individual mesh be evaluated against a control arm of traditional "native-tissue" (non-mesh) repair to demonstrate a reasonable assurance of safety and effectiveness for the device. Panel members emphasized that these studies should evaluate both anatomic outcomes and patient satisfaction and that the duration of followup should be at least 1 year, with additional followup in a postmarket setting.

The Panel's consensus was that each individual mesh device needed to undergo a comparison to native tissue repair in order to establish a reasonable assurance of safety and effectiveness. The Panel also emphasized that additional work should be focused on patient labeling and informed consent, including providing patients with benefit-risk information on available treatment options for POP--surgical and non-surgical options so patients understand

long-term safety and effectiveness outcomes. Panel members also recommended mandatory registration of implanted devices, as well as surgeon training and credentialing. They encouraged FDA to work with other stakeholders, such as clinical professional organizations and industry, to use existing databases and new data collection tools (e.g., registries) to develop a meaningful database on postmarket clinical outcomes.

B. Risks to Health

FDA has evaluated the risks to health associated with use of surgical mesh indicated for transvaginal POP repair. In doing so, FDA considered information from the reports and recommendations of the Panel meeting on September 8, 2011 (Ref. 4), the adverse event reports for these devices in FDA's Manufacturer and User Facility Device Experience Database, and the published scientific literature which is discussed in FDA's executive summary for the September 2011 Panel meeting (Ref. 3). Based on this information, FDA has identified the following risks:

1. Perioperative risks: Organ perforation or injury and bleeding (including hemorrhage/hematoma)
2. Vaginal mesh exposure: Clinical sequelae include pelvic pain, infection, de novo dyspareunia (painful sex for patient or partner), de novo vaginal bleeding, atypical vaginal discharge, and the need for additional corrective surgeries (possibly including mesh excision).
3. Mesh extrusion (e.g., into the bladder or rectum): Clinical sequelae include pelvic pain, infection, de novo dyspareunia, fistula formation, and the need for additional corrective surgeries (possibly including suprapubic catheter, diverting colostomy).
4. Other risks that can occur without mesh exposure or extrusion: Vaginal scarring, shrinkage, and tightening (possibly caused by mesh/tissue contraction); pelvic pain; infection

(including pelvic abscess); de novo dyspareunia; de novo voiding dysfunction (e.g., incontinence); recurrent prolapse; and neuromuscular problems (including groin and leg pain).

C. Benefits of the Device

Surgical mesh for transvaginal POP repair has the potential to benefit the public by aiding in the correction of cystocele (anterior repair), rectocele (posterior repair), uterine prolapse, or vaginal apical prolapse (apical repair). These findings are based on the reports and recommendations of the Panel meeting (Ref. 4), and the published scientific literature, which is discussed in FDA's executive summary for the Panel meeting (Ref. 3).

D. Summary of FDA Findings

FDA tentatively concludes that surgical mesh for transvaginal POP repair should be reclassified from class II to class III. FDA tentatively agrees with the Panel's consensus that the safety and effectiveness of this device type has not been established. FDA tentatively concludes that insufficient information exists regarding the risks and benefits of the device in order for FDA to determine that general and special controls together will provide reasonable assurance of the safety and effectiveness of surgical mesh intended for transvaginal POP repair. In addition, FDA tentatively determines that the risks to health identified previously in this document for the use of surgical mesh for transvaginal POP repair, in the absence of an established positive benefit-risk profile, present a potential unreasonable risk of illness or injury. Further, because FDA tentatively finds that there is insufficient valid scientific evidence, as defined in § 860.7 (21 CFR 860.7), for FDA to determine the probable risks and the effectiveness of the device type, FDA is proposing to require an individual demonstration that a reasonable assurance of safety and effectiveness exists for each device within this type. The manufacturer of each individual

device will have the opportunity to demonstrate the safety and effectiveness of the device for its intended use by submitting a premarket approval application.

VI. PMA Requirements

A PMA for surgical mesh for transvaginal POP repair would need to include the information required by section 515(c)(1) of the FD&C Act. Such a PMA should also include a detailed discussion of the risks identified previously, as well as a discussion of the effectiveness of the device for which premarket approval is sought. In addition, a PMA must include all data and information on the following: (1) Any risks known, or that should be reasonably known, to the applicant that have not been identified in this document; (2) the effectiveness of the device that is the subject of the application; and (3) full reports of all preclinical and clinical information from investigations on the safety and effectiveness of the device for which premarket approval is sought.

A PMA must include valid scientific evidence to demonstrate reasonable assurance of the safety and effectiveness of the device for its intended use (see § 860.7(c)(2)). Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. (See § 860.7(c)(2).)

To present reasonable assurance of safety and effectiveness of surgical mesh for

transvaginal POP repair, FDA tentatively concludes that manufacturers should provide the information summarized in this document. In addition, FDA strongly encourages manufacturers to meet with the Agency early through the presubmission program for any assistance in preparation of their PMA.

A. Indications for Use

Manufacturers should provide indications for use statements that include the route of placement for the mesh (i.e., transvaginal), the anatomical site of repair (e.g., anterior/apical, posterior/apical, or total), and specify any instrumentation required for implantation.

B. Device Description

A detailed description of the mesh design (e.g., material, material source, colorants) and use (i.e., mode of operation), as well as a brief description of the manufacturing processes, including a flowchart that describes how the mesh is assembled, should be provided.

If introducer instrumentation is packaged with the mesh, then a detailed description of the introducer instrumentation (e.g., material, material source, colorants) and the manufacturing processes for the instrumentation should be provided. Instrumentation that is packaged with the mesh will be reviewed in the PMA application. Introducer instrumentation that is provided separately and not packaged with the mesh will be reviewed separately in a 510(k) notification.

C. Sterilization and Shelf Life

Manufacturers should provide data that demonstrates that the mesh and the accessory introducer instrumentation retain their mechanical characteristics following sterilization and for the entire length of the intended shelf life. The mechanical characteristics for the mesh include at minimum: Compliance (i.e., elastic modulus), tensile strength, suture pullout strength, mesh arm(s) strength, burst strength, and tear resistance. If the introducer instrumentation includes a

mesh-deployment mechanism, this mechanism should function throughout the shelf life of the device.

D. Reprocessing

If the introducer instrumentation is intended for reuse, the manufacturer should provide data to validate the cleaning and disinfection/sterilization instructions.

E. Biocompatibility

Manufacturers should conduct biocompatibility testing on the device, including the mesh implant and introducer instrumentation, to fully characterize its safety profile prior to initiation of animal and clinical studies. This includes appropriate testing as outlined in Blue Book Memo #G-95-1 "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing'" (Ref. 5) (e.g., cytotoxicity, genotoxicity, hemolysis, sensitization, irritation or intracutaneous reactivity, acute systemic toxicity, subchronic toxicity, chronic toxicity, implantation and materials-mediated pyrogenicity).

F. Preclinical Bench Testing

Manufacturers should perform testing to obtain the following information on the mesh implant: Thickness, weave characteristics (i.e., woven or nonwoven), fiber type (i.e., monofilament or multifilament) exact pore size, density, compliance (i.e., elastic modulus), tensile strength, suture pullout strength, mesh arm(s) strength, burst strength, and tear resistance.

For devices composed of materials from animal sources, manufacturers should provide information on the species and tissue from which the animal material was derived, details on how the health of the herd is maintained, and how the health of each animal is maintained. Furthermore, manufacturers should test for residual cellular/DNA/protein matter on animal-derived mesh.

For devices containing degradable/absorbable components, manufacturers should provide in vitro and in vivo degradation rate data with supporting mechanical data (as described previously) to demonstrate adequate strength over time.

G. Preclinical Animal Studies

Manufacturers should conduct animal studies to evaluate in vivo performance of mesh in an appropriate animal model. If designed appropriately, these studies may also obviate the need for separate implantation studies to assess biocompatibility as indicated previously. The animal studies should be conducted for 6 months' duration to evaluate shrinking and/or calcification of the mesh, histology of the surrounding tissue, and extraction of the mesh. In addition, implantation of the mesh should occur in an appropriate anatomic location (i.e., not a subcutaneous pocket). Complete study reports for all the preclinical studies should include, but not be limited to: (1) A prospectively designed protocol and all protocol amendments; (2) a detailed description of the study design (e.g., description of animal species/animal models, control and test articles used, dose levels, detailed procedures for test article administration and collection of all study protocol parameters); (3) results for all parameters evaluated for each animal in the study; and (4) the analysis and interpretation of the study data.

H. Premarket Clinical Studies

FDA tentatively concludes that premarket clinical data is needed for all surgical mesh indicated for transvaginal POP repair to demonstrate a reasonable assurance of safety and effectiveness. FDA anticipates that these data may need to be collected in a patient- and evaluator-masked study that compares surgical mesh to a non-mesh control (i.e., traditional native tissue transvaginal repair) with respect to safety and effectiveness. This study should evaluate a clinically relevant measure(s) of effectiveness (e.g., prolapse at or above the hymenal

ring, subjective cure, and quality of life, no recurrent prolapse), key safety outcomes (e.g., serious adverse events, defined as hospital readmission or return to operating room), urinary and bowel function, sexual function, etc., as outcome measures. At least 1 year of outcome data should be provided in the PMA and an additional 2-4 years of followup should be conducted postmarket.

FDA intends to consider proposals for different study designs that meet the intent of the previously mentioned list and will decide on a case-by-case basis whether each proposed study design is likely to generate data adequate to support a PMA. FDA also intends to consider the use of study data collected by manufacturers in response to FDA issued postmarket surveillance study orders issued beginning on January 3, 2012, under section 522 of the FD&C Act (21 U.S.C. 360l) for transvaginal POP mesh products that are already legally marketed.

I. Professional Labeling

FDA would expect the professional (physician) labeling to include the following elements:

- Indications for Use statement;
- Contraindications;
- Device description (e.g., material type, introducer instrumentation included, and degradation rate when applicable);
- Images of the mesh and introducer instrumentation;
- Warnings;
- Precautions;
- Adverse event rates, including:
 - Perioperative risks:

- Organ perforation or injury;
- Bleeding (including hemorrhage and hematoma);
- Mesh exposure in the vagina;
- Mesh extrusion into another organ;
- Pelvic pain;
- Infection (by type);
- de novo dyspareunia;
- Vaginal scarring, shrinkage, and tightening;
- de novo vaginal bleeding;
- Atypical vaginal discharge;
- Fistula formation;
- de novo voiding dysfunction (e.g., incontinence);
- Neuromuscular problems (including groin and leg pain);
- Revision/resurgery;
- Recurrent prolapse;
- Summary of clinical data; and
- Step-by-step instructions, with images, on proper placement of the mesh.

J. Patient Labeling

FDA would also expect patient labeling to be provided for each device, and it should include, but not be limited to: (1) An explanation of POP, including anatomical issues, causes, and symptoms; a discussion regarding all available treatment options, including known risks and benefits of mesh placement based on the results of the clinical trial conducted; (2) a statement that surgical mesh is a permanent implant; instructions for postoperative care; and (3) a notice of

availability of an FDA Safety Communication. Patient labeling should also include a patient identification card that contains at a minimum the following information: Device name and lot number; patient name; date of implant; the type of repair performed (e.g., anterior or posterior); and the name and contact information for implanting physician and the device manufacturer.

VII. Opportunity to Request a Change in Classification

Before requiring the filing of a PMA for a device, FDA is required by section 515(b)(2)(D) of the FD&C Act to provide an opportunity for interested persons to request a change in the classification of the device based on new information relevant to the classification. Any proceeding to reclassify the device will be under the authority of section 513(e) of the FD&C Act.

A request for a change in the classification of surgical mesh for transvaginal POP repair devices is to be in the form of a reclassification petition containing the information required by § 860.123, including new information relevant to the classification of the device. Interested persons may also submit a reclassification petition related to the classification of the device to docket number for the proposed order reclassifying surgical mesh for transvaginal POP repair that is published elsewhere in this issue of the Federal Register.

VIII. Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

This proposed order refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of

Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The collections of information in 21 CFR part 807, subpart E, have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 814, subpart B, have been approved under OMB control number 0910-0231; the collections of information in part 812 have been approved under OMB control number 0910-0078; the collections of information under 21 CFR part 822 have been approved under OMB control number 0910-0449; and the collections of information under 21 CFR part 801 have been approved under OMB control number 0910-0485.

X. Proposed Effective Date

FDA is proposing that any final order based on this proposal become effective on the date of its publication in the Federal Register or at a later date if stated in the final order.

XI. Codification of Orders

Prior to the amendments by FDASIA, section 515(b) of the FD&C Act provided for FDA to issue regulations to require approval of an application for premarket approval for preamendments devices or devices found substantially equivalent to preamendments devices. Section 515(b) of the FD&C Act, as amended by FDASIA, provides for FDA to require approval of an application for premarket approval for such devices by issuing a final order, following the issuance of a proposed order in the Federal Register. FDA will continue to codify the requirement for an application for premarket approval, resulting from changes issued in a final order, in the Code of Federal Regulations (CFR). Therefore, under section 515(b)(1)(A) of the FD&C Act, as amended by FDASIA, in this proposed order, we are proposing to require approval of an application for premarket approval for surgical mesh for transvaginal POP repair

and, if this proposed order is finalized, we will make the language in § 884.5980 consistent with the final version of this proposed order.

XII. Comments

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

XIII. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at <http://www.regulations.gov>. (FDA has verified all the Web site addresses in this reference section, but we are not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

1. "FDA Public Health Notification: Serious Complications Associated With Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence", October 20, 2008, available at <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm>.
2. "FDA Safety Communication: UPDATE on Serious Complications Associated With Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse," July 13, 2011,

available at

<http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm>.

3. "FDA Executive Summary: Surgical Mesh for Treatment of Women With Pelvic Organ Prolapse and Stress Urinary Incontinence, Obstetrics & Gynecological Devices Advisory Committee Meeting", September 8-9, 2011, available at

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm262488.htm>.

4. FDA Meeting of the Obstetrics & Gynecological Devices Panel, September 8-9, 2011, available at

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm262488.htm>.

5. Blue Book Memo #G-95-1 "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing,'" May 1, 1995, available at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080735.htm>.

List of Subjects in 21 CFR Part 884

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 884 be amended as follows:

PART 884--OBSTETRICAL AND GYNECOLOGICAL DEVICES

1. The authority citation for 21 CFR part 884 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Add paragraph (c) to § 884.5980, Subpart F, to read as follows:

§ 884.5980 Surgical mesh for transvaginal pelvic organ prolapse repair.

* * * * *

(c) Date premarket application approval or notice of completion of a product development protocol is required. A premarket application approval or notice of completion of a product development protocol for a device is required to be filed with the Food and Drug Administration on or before [90 DAYS AFTER DATE OF PUBLICATION OF FINAL ORDER FOR PREMARKET APPLICATION OR 30 MONTHS AFTER DATE OF PUBLICATION OF FINAL ORDER RECLASSIFYING INTO CLASS III, WHICHEVER IS LATER], for any surgical mesh described in paragraph (a) of this section that was in commercial distribution before May 28, 1976, or that has, on or before [90 DAYS AFTER DATE OF PUBLICATION OF FINAL ORDER FOR PREMARKET APPROVAL APPLICATIONS OR 30 MONTHS AFTER DATE OF PUBLICATION OF FINAL ORDER RECLASSIFYING INTO CLASS III, WHICHEVER IS LATER] been found substantially equivalent to a surgical mesh described in paragraph (a) of this section that was in commercial distribution before May 28, 1976. Any other surgical mesh intended for transvaginal pelvic organ prolapse repair shall have an approved premarket application or declared completed product development protocol in effect before being placed in commercial distribution.

Dated: April 25, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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