DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 884

[Docket No. FDA–2014–N–0297]

Obstetrical and Gynecological Devices; Reclassification of Surgical Mesh for Transvaginal Pelvic Organ Prolapse Repair

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is issuing a final order to reclassify surgical mesh for transvaginal pelvic organ prolapse (POP) repair from class II to class III. FDA is reclassifying these devices based on the determination that general controls and special controls together are not sufficient to provide reasonable assurance of safety and effectiveness for this device, and these devices present a potential unreasonable risk of illness or injury. The Agency is reclassifying surgical mesh for transvaginal POP repair on its own initiative based on new information.

DATES: This order is effective on January 5, 2016.

FOR FURTHER INFORMATION CONTACT: Sharon Andrews, Center for Devices and Radiological Health, 10903 New Hampshire Ave., Bldg. 66, Rm. G110, Silver Spring, MD 20993, 301–796–6529, *Sharon.Andrews@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background—Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended, established 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.

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices), are automatically classified by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and 21 CFR part 807.

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112–144) was enacted. Section 608(a) of FDASIA amended section 513(e) of the FD&C Act, changing the mechanism for reclassifying a device from rulemaking to an administrative order. Section 513(e) of the FD&C Act provides that FDA may, by administrative order, reclassify a device based upon ''new information.'' FDA can initiate a reclassification under section 513(e) of the FD&C Act or an interested person may petition FDA to reclassify a device. The term ''new information,'' as used in section 513(e) of the FD&C Act, includes information developed as a result of a reevaluation of the data before the Agency when the device was originally classified, as well as information not presented, not available, or not developed at that time. (See, *e.g., Holland-Rantos Co.* v. *United States Department of Health, Education, and Welfare,* 587 F.2d 1173, 1174 n.1 (D.C. Cir. 1978); *Upjohn* v. *Finch,* 422 F.2d 944 (6th Cir. 1970); *Bell* v. *Goddard,* 366 F.2d 177 (7th Cir. 1966).)

Reevaluation of the data previously before the Agency is an appropriate basis for subsequent action where the reevaluation is made in light of newly available authority (see *Bell,* 366 F.2d at 181; *Ethicon, Inc.* v. *FDA,* 762 F.Supp. 382, 388–391 (D.D.C. 1991)), or in light of changes in ''medical science'' (*Upjohn,* 422 F.2d at 951). Whether data before the Agency are old or new data, the ''new information'' to support reclassification under section 513(e) must be ''valid scientific evidence,'' as defined in section 513(a)(3) of the FD&C Act and 21 CFR 860.7(c)(2). (See, *e.g., Gen. Medical Co.* v. *FDA,* 770 F.2d 214 (D.C. Cir. 1985); *Contact Lens Mfrs. Assoc.* v. *FDA,* 766 F.2d 592 (D.C. Cir. 1985), cert. denied, 474 U.S. 1062 (1986).)

To be considered in the reclassification process, the ''valid scientific evidence'' upon which the Agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, *e.g.,* the contents of a pending premarket approval application (PMA). (See section 520(c) of the FD&C Act (21 U.S.C. 360j(c)).)

Section 513(e)(1) of the FD&C Act sets forth the process for issuing a final reclassification order. Specifically, prior to the issuance of a final order reclassifying a 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 to a public docket.

FDA published a proposed order (the 513(e) proposed order) to reclassify this device in the **Federal Register** of May 1, 2014 (79 FR 24634). FDA received and has considered approximately 200 comments on this 513(e) proposed order, as discussed in section II.

FDA held a meeting on September 8 and 9, 2011 (76 FR 41507, July 14, 2011) of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee (''the Panel''), a device classification panel described in section 513(b) of the FD&C Act, to discuss whether surgical mesh for transvaginal POP repair should be reclassified into class III or remain in class II (Ref. 1). The Panel discussed a number of serious adverse events associated with use of surgical mesh for transvaginal POP repair. The Panel consensus was that the safety of surgical mesh for transvaginal POP repair is not well established and that, depending on the compartment, placement of surgical mesh for transvaginal POP repair may not be more effective than traditional ''native-tissue'' repair without mesh. As such, the Panel concluded that the risk-benefit profile of surgical mesh for transvaginal POP repair is not well established. The Panel consensus was that general controls and special controls together would not be sufficient to provide reasonable assurance of the safety and effectiveness of surgical mesh for transvaginal POP repair, and that these devices should be reclassified from class II to class III (Ref. 1). FDA is not aware of new information since the

Panel meeting that would provide a basis for a different recommendation or findings.

In the 513(e) proposed order, FDA also proposed to reclassify surgical instrumentation for urogynecologic surgical mesh procedures from class I to class II and establish special controls. FDA is not finalizing the proposed reclassification and special controls for surgical instrumentation for use with urogynecologic surgical mesh at this time. As stated in the 513(e) proposed order preamble, FDA will convene a panel to discuss specialized surgical instrumentation for use with urogynecologic surgical mesh prior to finalizing reclassification of instrumentation for this use. On February 26, 2016, the Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee will have a panel meeting to discuss and make recommendations for reclassification of these specialized surgical instrumentation devices.

II. Public Comments in Response to the 513(e) Proposed Order

In response to the 513(e) proposed order to reclassify surgical mesh for transvaginal POP repair, FDA received approximately 200 comments. The comments and FDA's responses to the comments are summarized in this section. Certain comments are grouped together under a single number because the subject matter of the comments is similar. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which it was submitted.

(Comment 1) Approximately 70 comments were received from individuals or family members of individuals who underwent mesh repair for POP, stress urinary incontinence (SUI), and/or hernias and reported complications or adverse events experienced during or after their procedures. The complications and adverse events reported included organ perforation, bleeding, chronic pain, mesh exposure or extrusion into the vagina and/or visceral organs (in some cases requiring additional surgery), infection, atypical vaginal discharge, painful sexual intercourse, self-catheterization, recurrent prolapse and/or incontinence, additional corrective surgery, and other permanent and/or life-altering adverse events.

(Response) FDA appreciates the comments received from individuals sharing their experiences following surgical mesh repair for POP, SUI, and/or hernias. The complications and adverse events reported by these commenters are consistent with those addressed in the 513(e) proposed order preamble and discussed at the 2011 Panel meeting. The comments did not identify any adverse event information that was not already considered by FDA and the Panel.

(Comment 2) Approximately 50 comments requested reclassification of surgical mesh for indications other than transvaginal POP repair, including for SUI and hernia.

(Response) Surgical mesh for indications other than transvaginal POP repair is outside the scope of the 513(e) proposed order and this document. In the 513(e) proposed order (79 FR 24634 at 24636), FDA stated that this proposed order does not include surgical mesh indicated for surgical treatment of stress urinary incontinence, sacrocolpopexy (transabdominal POP repair), hernia repair, and other non-urogynecologic indications.

(Comment 3) Approximately 50 comments requested a ban, recall, or ''suspension of use'' of all surgical mesh devices.

(Response) As stated previously, surgical mesh for indications other than transvaginal POP repair is outside the scope of this final order. For the reasons discussed in this document, FDA does not believe that a ban, recall or suspension of use of surgical mesh for transvaginal POP repair is warranted at this time.

Section 516 of the FD&C Act (21 U.S.C. 360f) authorizes FDA to ban a device when, on the basis of all available data and information, FDA finds that the device presents substantial deception or an unreasonable and substantial risk of illness or injury and, where such deception or risk could be corrected or eliminated by labeling or change in labeling and with respect to which the Secretary of the Department of Health and Human Services (Secretary) provided written notice to the manufacturer specifying the deception or risk of illness or injury, the labeling or change in labeling to correct the deception or eliminate or reduce such risk, and the period within which such labeling or change in labeling was to be done, such labeling or change in labeling was not done within such period.

FDA does not believe there is sufficient evidence at this time to support the banning of this device. Based on a review of the published literature, as described in the 513(e) proposed order preamble and this document, input from clinical organizations, and the Panel's recommendations, FDA has determined that the safety and effectiveness of surgical mesh for transvaginal POP repair has not been established and that the collection of additional clinical evidence on these devices is needed. Such additional evidence may provide information to allow FDA to impose controls to mitigate the risks and more clearly characterize the benefits of these devices. In addition, FDA believes there are potential benefits from surgical mesh used for transvaginal POP repair including treatment of POP in appropriately selected women with severe or recurrent prolapse. As such, FDA has not determined that this device presents an unreasonable and substantial risk of illness or injury.

FDA also does not believe there is sufficient evidence at this time to support a mandatory recall of this device. Under section 518(e) of the FD&C Act (21 U.S.C. 360h(e)), if the Secretary finds that there is a reasonable probability that a device intended for human use would cause serious, adverse health consequences or death, the Secretary shall issue an order requiring the appropriate person (including the manufacturers, importers, distributors, or retailers of the device) to immediately cease distribution of such device, and to immediately notify health professionals and device user facilities of the order and to instruct such professionals and facilities to cease use of such device.

FDA does not believe a mandatory recall of all currently marketed surgical mesh for transvaginal POP repair is warranted. Based on a review of the published literature as described in the 513(e) proposed order preamble and this document, input from clinical organizations, and the Panel's recommendations, FDA believes that there is not sufficient evidence at this time to support a finding that there is a reasonable probability that surgical mesh for transvaginal repair of POP would cause serious adverse health consequences or death. As described in the 513(e) proposed order preamble and discussed at the 2011 Panel meeting, the safety and effectiveness of surgical mesh for transvaginal repair of POP has not been established and these devices should be evaluated in clinical studies that compare the device to native tissue repair in order to establish a reasonable assurance of safety and effectiveness.

It is unclear what commenters were referencing when they asked FDA to ''suspend the use'' of these devices. As stated previously, FDA does not believe a ban or recall is warranted at this time, and as stated in this document, there are other actions FDA has taken and may take in the future to ensure that there is

a reasonable assurance of the safety and effectiveness of surgical mesh for transvaginal POP repair.

FDA believes other regulatory actions it has taken will help the Agency to better understand the risk-benefit profile of these devices. FDA issued postmarket surveillance orders under section 522 of the FD&C Act (21 U.S.C. 360l) to manufacturers of surgical mesh for transvaginal POP repair starting on January 3, 2012. The postmarket surveillance orders allow FDA to continue to evaluate the benefit-risk profile of the device. Further, by reclassifying these devices to class III and requiring PMA approval, FDA can require an independent demonstration that a reasonable assurance of safety and effectiveness exists for each device within this type. Elsewhere in this issue of the **Federal Register**, FDA is issuing a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) (the 515(b) final order) to require the filing of a PMA or notice of completion of a product development protocol for surgical mesh for transvaginal POP repair. The preamble of the 515(b) final order provides further information regarding the data and scientific evidence needed for a PMA.

FDA will consider other regulatory actions relating to this device as appropriate in the future.

(Comment 4) Approximately 20 comments stated that the polypropylene material used to fabricate surgical mesh is inappropriate for implantation. These comments contend that the degradation of the polypropylene mesh in vivo may lead to systemic effects that can cause serious complications.

(Response) FDA believes that a thorough evaluation of the material used to fabricate surgical mesh for transvaginal POP repair is needed to provide a reasonable assurance of safety and effectiveness of the device. The findings set forth in the 515(b) proposed order preamble, as discussed in this document, address this issue (these findings are adopted, as amended, in the 515(b) final order that is published elsewhere in this issue of the **Federal Register**).

In the 515(b) proposed order preamble, FDA stated that manufacturers should provide information in their PMAs regarding biocompatibility, preclinical bench testing and preclinical animal studies, among other proposed information, to demonstrate reasonable assurance of safety and effectiveness of surgical mesh for transvaginal POP repair. Such performance data, which may generally include assessment of the mesh chemical and physical characteristics, in vitro chemical characterization studies, and in vivo preclinical implantation studies, will be reviewed by FDA to determine whether the risks associated with implantation of the polypropylene material are appropriately mitigated. The 515(b) proposed order preamble also stated that a PMA would need to include the information required by section 515(c)(1) of the FD&C Act, which includes manufacturing information. FDA's review of such manufacturing information will allow the Agency to evaluate whether the polypropylene material is safe and effective for transvaginal POP repair.

(Comment 5) One comment stated that FDA should not include non-crosslinked biologic grafts in this reclassification and that such grafts should not be subject to postmarket surveillance studies. The comment stated that the 513(e) proposed order cited relatively few studies that examine the use of biologically derived grafts for POP repair. The comment also noted that FDA's analysis did not distinguish crosslinked versus non-crosslinked biologic grafts. The comment requested that FDA review additional data, including a summary of 18 publications regarding non-crosslinked biologic grafts submitted by the commenter, and consider the different risk profiles of biologic grafts and specifically whether non-crosslinked biologic grafts should be reclassified.

(Response) As discussed in the response to comment 9, FDA performed an updated review of the literature to consider new clinical information available since publication of the 513(e) and 515(b) proposed orders and additional publications cited by the commenter, and whether non-crosslinked biologic grafts should be reclassified. Based on this review, FDA believes that there is currently insufficient evidence to support a finding that the benefit-risk profile of non-crosslinked biologic grafts differs from that of synthetic meshes. There is little evidence overall on biologic grafts (as compared to synthetic meshes), and the majority of studies evaluating non-crosslinked biologic grafts are on small populations and are not prospective. Moreover, the limited clinical evidence that is available indicates that like synthetic surgical mesh for transvaginal POP repair, non-crosslinked biologic mesh is associated with adverse events and does not demonstrate effectiveness compared to traditional (*i.e.,* native tissue) repair of POP.

The commenter cited 18 publications reporting outcomes for non-crosslinked biologic graft for use in transvaginal or transabdominal POP repair (Refs. 2 through 19). As described in this document, these publications in totality do not provide sufficient evidence of the reasonable safety and effectiveness of non-crosslinked biologic grafts.

Of these publications, 6 of the 18 report outcomes on fewer than 15 study subjects (Refs. 2 through 7). Due to the small sample size, the outcomes from these publications are difficult to interpret and FDA could not conclude that the risk profiles of non-crosslinked biologic grafts were different than synthetic meshes.

Of the remaining 12 publications, 1 describes outcomes after sacrocolpopexy (Ref. 2), 1 describes use of a non-crosslinked biologic graft to cover a vaginal wall defect following explantation of a synthetic mesh to treat prolapse (Ref. 3), and 1 describes transperineal repair of rectocele (Ref. 4). These uses are outside the scope of the reclassification.

One publication reported a retrospective review of non-contemporaneous mesh-augmented (non-crosslinked biologic and synthetic) versus native tissue anterior compartment repair (Ref. 5). One author in that report switched to the mesh-augmented technique part way through the period covered by the study due to dissatisfaction with native tissue repair. This may affect the objectivity of the study results and may lead to a conclusion that inappropriately favors mesh-augmented repair. Anatomic success was greater in mesh-augmented patients; however, objective anatomic success was defined as Stage 0 or 1 using the Baden-Walder system (Stage 0—normal position, Stage 1—descent halfway to the hymen). This may represent an ideal outcome, but does not necessarily represent a clinically relevant outcome. As discussed in the 513(e) proposed order preamble, prolapse staging systems like the Pelvic Organ Prolapse Quantification (POP–Q) are ''not correlated with POP symptoms or patient assessment of improvement [(Barber et al., 2009)].''

Another publication reported long-term followup in a retrospective patient cohort (N = 41) who had undergone graft repair of anterior or posterior vaginal prolapse compared to a contemporaneous cohort of ''matched'' native tissue repair controls (Ref. 6). Subjective outcomes were significantly better in the graft cohort; however, recurrence tended to be greater in the graft cohort when defined strictly as ≥POP–Q Stage 2. This means that the graft cohort experienced greater anatomic failure when using POP–Q

Stage 1 as the cutoff for anatomic success.

One publication described a retrospective case review without native tissue control (Ref. 7). This review (N = 65) found a subjective success (no symptoms and no bulge beyond the hymen) rate of 92 percent. Reoperation rate for de novo and recurrent prolapse was 7.7 percent, and three women had repeat surgery at the same anatomic site (anterior compartment). Because this study did not include a control group, we are unable to compare safety and effectiveness outcomes between patients who received mesh and patients who underwent native tissue repair.

Two publications described prospective cohorts. In one small series (N = 21), women with recurrent prolapse underwent anterior, posterior, or combined anterior/posterior repair with non-crosslinked biologic mesh (Ref. 8). Mean POP–Q scores preoperatively were Ba = 0.63 versus Ba = 1.75 postoperatively. Preoperative Bp score was −0.2 versus Bp −2.2 postoperatively. The authors reported a mean followup of 29 months. Six patients reported persistent bulge, and eight patients reported vaginal discomfort. This study has a small sample size and does not allow for comparison to native tissue repair.

The other prospective cohort study (N = 50) evaluated patient-reported outcomes at 6 months following posterior compartment repair augmented with non-crosslinked mesh (Ref. 9). Although significant improvements were noted for vaginal symptoms, sexual matters score and quality of life on the International Consultation on Incontinence Questionnaire vaginal symptoms questionnaire, anatomic outcomes were not collected. Therefore, effectiveness outcomes cannot be evaluated from this study.

Only three of the remaining publications described prospective randomized controlled trials (RCTs) comparing anterior or posterior vaginal repair using non-crosslinked biologic graft versus native tissue repair (Refs. 10 through 12). None of the three RCTs defined anatomic success as the leading edge of prolapse at or above the hymenal ring, which is considered a more clinically relevant outcome compared to POP–Q score. The criterion for anatomic success of prolapse repair in the American Urogynecologic Society (AUGS) Pelvic Floor Disorders Registry is leading edge at or above the hymen (Ref. 13).

The final publication identified by the commenter described prospective followup of a cohort assembled from a retrospective chart review (N = 59) (Ref. 14). This report does define anatomic success at the hymenal ring. Objective recurrence of prolapse in this study was approximately 31 percent.

Regarding mesh exposure/erosion, the publications cited by the commenter suggests that the risk of vaginal exposure/erosion for the non-crosslinked mesh is low. In the 513(e) proposed order preamble, FDA noted that the incidence of mesh exposure did not differ between nonabsorbable synthetic mesh (10.3 percent) and biologic graft material (10.1 percent) (Ref. 15).

For other types of surgical complications, one RCT (N = 56) found that the number of complications in the mesh group was greater compared to the native tissue repair group (Ref. 10). Blood loss was greater for mesh versus native tissue rectocele repair in another RCT (N = 160) (Ref. 12). In the same RCT, there was a trend towards increased risk of wound separation following non-crosslinked graft repair versus native tissue repair; however, the outcome did not reach statistical significance.

In addition, serious adverse events are reported in association with non-crosslinked biologic graft, including pain necessitating resurgery (Ref. 14). In this study, surgical complications included cystotomy (6.8 percent) and enterotomy (1.7 percent). Twenty-four percent of subjects had postoperative voiding dysfunction, and there was a 5.1 percent rate of hemorrhage requiring transfusion. (It is unclear whether these complications were device-related). The rate of dyspareunia at followup was 8.3 percent. The study did not include a control group, so it is unknown how the benefits and risks of graft-augmented repair with the non-crosslinked biologic graft would have compared with a native tissue repair.

In summary, there is insufficient available evidence from prospective studies using an appropriate primary endpoint for anatomic success on which to evaluate the effectiveness of transvaginal POP repair using non-crosslinked biologic mesh versus native tissue repair. The available clinical outcomes provide evidence that non-crosslinked biologic mesh is associated with adverse events. There are no data from RCTs with long-term followup that demonstrate clinical effectiveness of this material for transvaginal POP repair compared to native tissue repair.

As a result of these findings, FDA is not differentiating between non-crosslinked biologic grafts and synthetic mesh for transvaginal POP repair in this reclassification order and is reclassifying *all* of these devices from class II to class III. FDA's decision is in line with the 2011 Panel, which did not recommend stratification of surgical mesh for transvaginal POP repair by material characteristics.

(Comment 6) Approximately 20 comments stated that patients were not adequately informed of the possible complications following mesh implantation or that patients were not informed prior to surgery that mesh would be implanted.

(Response) FDA believes that patients should be adequately informed regarding the possible complications associated with surgical mesh. As stated in the FDA Safety Communication published in July 2011 (Ref. 16), health care providers should: (1) Inform patients that implantation of surgical mesh is permanent and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication; (2) inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall in POP repair using surgical mesh; and (3) provide patients with a copy of the patient labeling from the surgical mesh manufacturer, if available. The 2011 Safety Communication also includes recommendations for patients to help them obtain the appropriate information prior to a surgical mesh repair.

The Panel recommended that FDA focus on development of patient labeling and provide patients with benefit-risk information on available treatment options for POP, including surgical and nonsurgical options, to help patients understand long-term safety and effectiveness outcomes (Ref. 1, p. 150).

For these reasons, in the findings of the 515(b) proposed order, which are adopted as amended in the 515(b) final order that is being published elsewhere in this issue of the **Federal Register**, FDA asserted that manufacturers should include in their PMAs for these devices professional and patient labeling, and that the patient labeling would be expected to include, among other things, the risks and benefits of the device and available treatment options. Therefore, it is expected that PMAs for these devices include professional and patient labeling, and that the patient labeling include, among other things, the risks and benefits of the device and available treatment options.

(Comment 7) Approximately 30 comments stated that surgical mesh should be adequately tested, including

rigorous clinical evaluation prior to marketing. Comments also emphasized the need to understand the long-term effects of surgical mesh.

(Response) FDA agrees that surgical mesh for transvaginal POP repair should be adequately tested prior to marketing to provide a reasonable assurance of safety and effectiveness. FDA believes that surgical mesh for transvaginal POP repair should undergo mechanical and chemical characterization and performance evaluation, biocompatibility, sterilization validation, shelf life, and preclinical in vivo testing to provide a reasonable assurance of safety and effectiveness of the device prior to marketing. In addition, surgical mesh for transvaginal POP repair should be evaluated clinically, specifically to evaluate the safety and effectiveness of the device compared to native tissue repair. In the 515(b) final order that is being published elsewhere in this issue of the **Federal Register**, FDA is requesting that manufacturers provide this information to support premarket approval of surgical mesh for transvaginal POP repair.

With respect to long-term effects of surgical mesh, FDA believes that the clinical evaluation of surgical mesh for transvaginal POP repair should include long-term followup. FDA issued postmarket surveillance orders under section 522 of the FD&C Act for these devices that will collect long-term followup out to 3 years post implantation.

The comments also referenced surgical mesh for SUI and sacrocolpopexy. As stated previously, surgical mesh for indications other than transvaginal repair of POP is outside the scope of this final order.

(Comment 8) Approximately five comments stated the mesh for treatment of female SUI and sacrocolpopexy should not be reclassified to class III.

(Response) As stated previously, surgical mesh for indications other than transvaginal POP repair are outside the scope of this final order.

(Comment 9) One comment stated that FDA should evaluate recent data on POP mesh repair as the recent literature is more representative of current technologies, instructions for use, and physician training of currently marketed devices and that erosion rates and complication rates are lower in current literature than compared to rates cited in the 513(e) proposed order.

(Response) FDA conducted an updated review of the literature published since the 513(e) and 515(b) proposed orders were issued and reviewed additional publications cited by the commenter, summarized in further detail in this document, and determined that the weight of the evidence indicates that use of surgical mesh for transvaginal POP repair is not strongly or consistently associated with increased benefits over native tissue repair in the treatment of stage 2 or higher POP. Overall, the evidence indicates that mesh surgeries take longer to perform, result in greater blood loss, and have a considerable risk of postoperative mesh erosion in comparison to native tissue repair. In addition, there is suggestive evidence that use of surgical mesh for transvaginal POP repair may pose a higher risk of de novo POP relative to native tissue repair.

The majority of studies identified by the commenter, and considered in the updated literature review conducted by FDA, assessed the anterior compartment; therefore, it is difficult to draw conclusions on the differential effects of mesh by compartment, relative to native tissue repair. Furthermore, data from prospective, randomized studies comparing surgical mesh and native tissue repair using a clinically relevant definition of success are limited at this time. The benefit-risk profile comparison favors native tissue repair over use of surgical mesh for transvaginal POP repair. FDA concludes that the updated literature review further supports the reclassification of surgical mesh for transvaginal POP repair from class II to class III as reasonable assurance of safety and effectiveness for the device has not been demonstrated.

The comment stated that four recent systematic reviews on surgical options for POP continue to support use of transvaginal mesh to treat anterior wall prolapse (Refs. 17 through 20). One of these systematic reviews was cited in the 513(e) proposed order preamble (Ref. 19) and therefore is not discussed in detail here. This systematic review evaluated surgical management of POP in women and concluded that ''The use of grafts (biological or synthetic) reduces the risk of prolapse symptoms and recurrent anterior vaginal prolapse on examination when compared to native tissue repairs (colporrhaphy). However, the advantages of a permanent polypropylene mesh must be weighed against disadvantages including longer operating time, greater blood loss, prolapse in other areas of the vagina, new onset urinary stress incontinence, and the mesh becoming exposed in the vagina in 11 percent of women. In general, there is a lack of evidence to support transvaginal mesh operations used in apical or posterior compartment surgery.'' The second of these two reviews reported on anterior vaginal compartment repair specifically (Ref. 18). The review specific to anterior vaginal compartment repair noted that improved anatomic outcomes conferred by surgical mesh used for anterior POP repair are not always accompanied by improvement in subjective outcomes. Whereas polypropylene mesh appears to lead to improvement in both anatomic and subjective outcomes, these results did not lead to improved functional outcomes using validated questionnaires or to a lower reoperation rate for POP. This review concluded that surgical mesh is significantly associated with longer operating time, greater blood loss, and development of POP in another vaginal compartment. The author also noted a nonsignificant tendency towards higher cystotomy, de novo dyspareunia, and de novo SUI rate compared to native tissue anterior repair.

The third systematic review cited by the commenter was to address nonsurgical treatments for POP, effects of POP surgery by vaginal compartment, and how different mesh materials affect surgical repair of POP (Ref. 17). Regarding anterior prolapse repair with mesh, the author did not reach a conclusion regarding the need for reoperation for POP or SUI following index POP surgery; however, anterior repair using surgical mesh was found to increase risk for revision of the vaginal wound due to mesh exposure.

The focus of the fourth systematic review cited by the commenter described complications following POP repair using surgical mesh (Ref. 20). The review found that the mean total complication rate in the anterior compartment was 27 percent and that there was an 8 percent rate of complications ≥ grade III on the Clavien-Dindo classification system (*i.e.,* requiring surgical, endoscopic, or radiological intervention).

The comment also stated that these recent systematic reviews report complication rates that required surgical intervention ranging from 6.3 to 9 percent in the anterior compartment versus the ''upper bound of 22 percent cited in the proposed order.'' In the 513(e) proposed order preamble, FDA stated the following: ''From the one RCT that directly compared sacrocolpopexy to transvaginal POP repair with mesh (both using synthetic nonabsorbable mesh), overall re-surgery within 2 years postoperative was significantly more common following transvaginal POP repair with mesh than laparoscopic sacrocolpopexy, with rates of 22 percent (12/55) and 5 percent (3/53),

respectively (p = 0.006) (79 FR 24637).'' The 22 percent cited by FDA in the 513(e) proposed order preamble was not specific for anterior repair, but rather included all vaginal compartments.

In addition to the four recent systematic reviews discussed previously, the commenter cited 43 published reports, of which 31 are abstracts or poster presentations. Based on the limited scientific evidence in these abstracts and poster presentations, they are difficult to evaluate, and therefore, FDA was unable to draw any conclusions from these publications. The comment stated that collectively, the studies report mesh exposure rates of 0 to 8 percent and of the mesh exposures, only approximately 38 percent required surgical intervention. The comment stated this outcome represents a reduction compared to the 7.2 percent rate cited in the 513(e) proposed order. However, the 7.2 percent rate cited by FDA in the 513(e) proposed order preamble was the rate of reoperation due to any complication, and not specifically for mesh exposure-related complications.

The comment also stated that the more recent literature defines success as improved anatomic and subjective outcomes compared to native tissue repair. Of the publications that were not abstracts or posters, there is only one in which surgical mesh repair was compared to native tissue (Ref. 21). In that study, the primary outcome was ideal anatomic support based on POP–Q stage, and not subjective outcomes. Anatomic success, defined as POP–Q stage 0 or 1 was greater for the surgical mesh repair in the anterior compartment; however, improvement in quality of life was not statistically significant between groups. In addition, subjects in the surgical mesh group had statistically significant longer hospital stays, operative time, and estimated blood loss.

With one exception, of the publications cited by the commenter to represent success rates for one line of mesh products, the definition of a success was ideal anatomic support (Refs. 22 through 27). As noted in the 513(e) proposed order preamble, ideal anatomic support is not a prerequisite for improvement in patient symptoms. As stated previously in this document, the anatomic criterion for success following surgical repair of prolapse in the AUGS Pelvic Floor Disorders Registry is absence of leading edge of prolapse beyond the hymen, not POP–Q Stage ≤ 1. In addition, because these studies did not compare outcomes between mesh repair and native tissue repair, it is unknown whether the success among mesh subjects would have exceeded that of native tissue repair.

One publication that evaluated more clinical and/or subjective outcomes compared two mesh products (Ref. 26). The failure of the mesh repair ranged from 24 percent to 46 percent, depending on the outcome measure. Mesh exposure occurred at a rate of 8 percent. Pelvic pain was reported at 7.4 percent, and of study subjects who were sexually active, 12.7 percent reported painful intercourse. In one prospective study (N = 30), no anatomic outcomes were reported; however, the report stated that no patients had symptoms of recurrent prolapse at 12 months of followup. Two patients in this cohort had mesh erosion which required partial mesh excision (Ref. 28).

The remaining publications cited in the comment address mesh exposure, mesh repair as an ambulatory procedure, and stability of an anchor device used to attach the mesh to an anatomic target (Refs. 29 through 31). The rate of mesh exposure in the first study was 8.1 percent (Ref. 28). None of these publications compared mesh repair to native tissue repair, nor does any reflect a study designed to evaluate surgical success.

In summary, FDA concludes that the literature published since the 513(e) and 515(b) proposed orders were issued and the additional literature cited by the commenter further supports the reclassification of surgical mesh for transvaginal POP repair from class II to class III.

(Comment 10) One comment noted that direct comparison of safety results between sacrocolpopexy, transvaginal repair, and native tissue repair can be misleading if the vaginal repair does not have a vaginal vault component.

(Response) Based on the evidence cited in the 513(e) proposed order preamble, FDA concluded that the types of risks associated with transvaginal mesh for POP repair are similar across different vaginal compartments. FDA is unaware of any new evidence that supports the conclusion that the types of risk associated with transvaginal mesh for POP are different across different vaginal compartments. However, FDA acknowledges that the frequency of different types of adverse events may vary across different vaginal compartments. FDA's conclusion is in line with the Panel, which did not recommend that reclassification be stratified by compartment. For the reasons discussed in the 513(e) proposed order preamble and in this document, the reclassification applies to all transvaginal mesh for POP repair regardless of location of repair.

(Comment 11) One comment stated that the 513(e) proposed order makes definitive statements regarding benefit/risk, when in fact additional studies are needed to establish benefit/risk.

(Response) FDA disagrees that the 513(e) proposed order makes definitive statements regarding benefit/risk. Throughout the 513(e) proposed order preamble, FDA described its conclusions as ''tentative.''

III. The Final Order

Under section 513(e) of the FD&C Act, FDA is adopting its findings as published in the preamble to the 513(e) proposed order (79 FR 24634). FDA is issuing this final order to reclassify surgical mesh for transvaginal POP repair from class II to class III. FDA is reclassifying these devices based on the determination that general controls and special controls together are not sufficient to provide reasonable assurance of safety and effectiveness for this device. In addition, in the absence of an established positive benefit-risk profile, FDA has determined that the risks to health associated with the use of surgical mesh for transvaginal POP repair identified previously present a potential unreasonable risk of illness or injury.

FDA has modified the proposed identification in § 884.5980(a) for surgical mesh for transvaginal pelvic organ prolapse repair to clarify that the materials of construction may include synthetic material, non-synthetic material, or a combination of synthetic and non-synthetic materials.

IV. Analysis of 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.

V. Paperwork Reduction Act of 1995

This final 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 814, subpart B, have been approved under OMB control number 0910–0231; and the collections of information under 21 CFR part 801 have been approved under OMB control number 0910–0485.

VI. Codification of Orders

Prior to the amendments by FDASIA, section 513(e) of the FD&C Act provided for FDA to issue regulations to reclassify devices. Although section 513(e) of the FD&C Act, as amended, requires FDA to issue final orders rather than regulations, FDASIA also provides for FDA to revoke previously issued regulations by order. FDA will continue to codify classifications and reclassifications in the Code of Federal Regulations (CFR). Changes resulting from final orders will appear in the CFR as changes to codified classification determinations or as newly codified orders. Therefore, under section 513(e)(1)(A)(i) of the FD&C Act, as amended by FDASIA, in this final order, we are codifying the reclassification of surgical mesh for transvaginal POP repair into class III in 21 CFR 884.5980.

VII. References

The following references are on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *http://www.regulations.gov*. FDA has verified the Web site addresses, as of the date this document publishes in the **Federal Register**, but Web sites are subject to change over time.

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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, 21 CFR part 884 is 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 § 884.5980 to subpart F to read as follows:

§ 884.5980 Surgical mesh for transvaginal pelvic organ prolapse repair.

(a) *Identification.* Surgical mesh for transvaginal pelvic organ prolapse repair is a prescription device intended to reinforce soft tissue in the pelvic floor. This device is a porous implant that is made of synthetic material, non-synthetic material, or a combination of synthetic and non-synthetic materials. This device does not include surgical mesh for other intended uses (§ 878.3300 of this chapter).

(b) *Classification.* Class III (premarket approval).

Dated: December 30, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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