

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: Final order.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is issuing a final order to require the filing of a premarket approval application (PMA) or notice of completion of a product development protocol (PDP) for surgical mesh for transvaginal pelvic organ prolapse (POP) repair.

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

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background—Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended, 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 (section 510(k) of the FD&C Act (21 U.S.C. 360(k)) procedures 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.

Under section 515(f) of the FD&C Act, the manufacturer of a preamendments class III device may comply with a call for PMAs by filing a PMA or 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 the filing and obtaining approval of a PMA.

On July 9, 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144) 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 requiring premarket approval. 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. FDA published a proposed order to require PMAs for surgical mesh for transvaginal POP repair in the **Federal Register** of May 1, 2014 (79 FR 24642), and convened a meeting of a device classification panel (the "Panel") as discussed in the proposed order preamble and in this document. FDA received and has considered approximately 25 comments on this proposed order, as discussed in section III.

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.

A preamendments class III device may be commercially distributed without a PMA until 90 days after FDA issues a final order (a final rule issued under section 515(b) of the FD&C Act prior to the enactment of FDASIA is considered to be a final order for purposes of section 501(f) of the FD&C Act (21 U.S.C. 351(f))) requiring premarket approval for the device, or 30 months after final classification of the device under section 513 of the FD&C Act, whichever is later. For surgical mesh for transvaginal POP repair, the later of these two time periods is 30 months after final classification of the device.

Therefore, section 501(f)(2)(B) of the FD&C Act requires that a PMA for such devices be filed by the last day of the 30th calendar month following the effective date of the final order to reclassify these devices into class III. If a PMA is not filed by this date, then the device would be deemed adulterated under section 501(f) of the FD&C Act.

Also, a preamendments device subject to the order process under section 515(b) of the FD&C Act is not required to have an approved investigational device exemption (IDE) (see part 812 (21 CFR part 812)) contemporaneous with its interstate distribution until the date identified by FDA in the final order requiring the filing of a PMA for the device. At that time, an IDE is required only if a PMA has not been filed. If the manufacturer, importer, or other sponsor of the device submits an IDE application and FDA approves it, the device may be distributed for investigational use. If a PMA is not filed by the later of the two dates, and the device is not distributed for investigational use under an IDE, the device is deemed to be adulterated within the meaning of section 501(f)(1)(A) of the FD&C Act, and subject to seizure and condemnation under section 304 of the FD&C Act (21 U.S.C. 334) if its distribution continues. Other enforcement actions include, but are not limited to, the following: Shipment of devices in interstate commerce may be subject to injunction under section 302 of the FD&C Act (21 U.S.C. 332), and the individuals responsible for such shipment may be subject to prosecution under section 303 of the FD&C Act (21 U.S.C. 333). FDA requests that manufacturers take action

to prevent the further use of devices for which no PMA has been filed.

II. Regulatory History of the Device

Surgical mesh is a preamendments device, which was classified into class II (§ 878.3300 (21 CFR 878.3300)) in 1988. Beginning in 1992, FDA cleared premarket notification (510(k)) submissions for surgical mesh indicated for 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 repair indication.

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 (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, vaginal placement of surgical mesh for 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 indicated 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. FDA published proposed orders to reclassify surgical mesh for transvaginal POP repair from class II to class III (the 513(e) proposed order) and to require the filing of a PMA if the reclassification is finalized (the 515(b) proposed order) in the **Federal Register** of May 1, 2014 (79 FR 24634; 79 FR 24642). Elsewhere in this issue of the **Federal Register**, FDA is issuing a final order to reclassify these devices from class II to class III.

III. Public Comments in Response to the Proposed Order

In response to the 515(b) proposed order, FDA received 26 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) Nine comments were received from individuals or family members of individuals who underwent mesh repair for POP and/or stress urinary incontinence (SUI) and reported complications or adverse events experienced during or after their procedures. The complications and adverse events reported including organ perforation, mesh exposure, or extrusion into the vagina and/or visceral organs (in some cases requiring additional surgery), chronic pain, infection, lack of mobility, painful sexual intercourse, self-catheterization, recurrent prolapse and/or incontinence, blood loss during surgery (in some cases requiring transfusion), nerve damage, need for mesh removal and/or 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 and SUI. The complications and adverse events reported by these commenters are consistent with those addressed in the 513(e) and 515(b) proposed order preambles, and discussed at the 2011 meeting of the Panel. The comments did not identify any adverse event information that was not already considered by FDA and the Panel.

(Comment 2) Thirteen commenters 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 are outside the scope of the proposed order and this final order. As stated in the 513(e) proposed order preamble, “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) Eight 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 indicated 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.

As stated earlier in this document, FDA issued a proposed order (79 FR 24642) under section 515(b) of the FD&C Act to require the filing of PMAs for these devices following reclassification, which would require an individual demonstration of a reasonable assurance of safety and effectiveness for surgical mesh for transvaginal POP repair. In the 515(b) proposed order preamble, FDA recognized the recommendations from the Panel that additional work should be focused on patient labeling and providing patients with benefit-risk information on available treatment options for POP, including surgical and nonsurgical options, so patients understand potential long-term safety and effectiveness outcomes. In the 515(b) proposed order, FDA tentatively asserted that it expects PMAs for these devices to include professional and patient labeling, and that the patient labeling include, among other things, the risks and benefits of the device and all available treatment options. These findings are adopted, in part, in the final order (see section IV, “The Final Order”).

Therefore, FDA does not believe that 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 that there is sufficient evidence at this time to support a mandatory recall of this device. Under section 518(e)(1) of the FD&C Act (21 U.S.C. 360h(e)(1)) 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 safety and effectiveness of surgical mesh for transvaginal POP repair based on valid scientific evidence.

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 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.

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

(Comment 4) Two comments were related to the need for testing prior to marketing, including an evaluation of the polypropylene material used to fabricate surgical mesh. One commenter stated that polypropylene material is inappropriate for implantation.

(Response) FDA believes that a thorough evaluation of the material used to fabricate the surgical mesh is needed to provide a reasonable assurance of safety and effectiveness of the device. FDA discussed in the 515(b) proposed order preamble information that should be submitted in a PMA to address these issues. FDA is adopting these findings, in part, in the final order (see section IV, “The Final Order”).

Specifically, in the proposed order, FDA stated that manufacturers should provide biocompatibility, preclinical bench testing and preclinical animal studies, among other 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 proposed order preamble also states 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. FDA is adopting these findings in the final order (see section IV, “The Final Order”).

(Comment 5) Two comments were related to the timeline for requiring PMAs and requested that the requirement for premarket approval be immediately implemented. One commenter requested that the PMA requirement be retroactively applied to devices currently on the market.

(Response) Section 501(f)(2)(B) of the FD&C Act outlines the timeframe in which a PMA must be filed by manufacturers of currently marketed devices that are subject to a 515(b) order for the manufacturers to continue legally marketing their device. For devices subject to a 515(b) order, the provision states that a PMA must be submitted by the 90th day after the date the order to require PMAs is issued or the last day of the 30th calendar month beginning after the month in which the classification in class III becomes effective, whichever occurs later. For surgical mesh for transvaginal POP repair, the later of these two time periods is 30 months after final classification of the device. FDA must abide by the timeframe outlined in the FD&C Act, and therefore may not require manufacturers of devices subject to the final order to submit a PMA immediately.

(Comment 6) One comment suggested that the timeframe for filing a PMA (within 30 months of the final reclassification) may not allow for adequate patient followup of ongoing clinical studies and requested that FDA consider the current status of clinical studies that may be used to support PMA submission.

(Response) FDA has carefully considered the current status of ongoing clinical studies of currently marketed surgical mesh for transvaginal POP repair, including studies being conducted in response to FDA postmarket surveillance study orders issued starting on January 3, 2012, under section 522 of the FD&C Act (21 U.S.C. 360l), and has concluded that the statutory timeframe for filing a PMA (the last day of the 30th calendar month beginning after the month in which the classification in class III becomes effective) is appropriate to allow adequate patient followup of ongoing clinical studies. In the 515(b) proposed order preamble, FDA stated the expectation that “[a]t 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 believes it is reasonable to expect that a manufacturer of surgical mesh who is subject to a section 522 postmarket surveillance study order issued in 2012 or 2013 will be able to collect 1 year of outcome data within 30 months of the final reclassification.

(Comment 7) One comment addressed FDA’s ability to review a PMA submitted for surgical mesh for transvaginal POP repair within 180 days. The comment stated that a 180-day PMA review commitment may not

be attainable and the timeline does not allow for panel review. The commenter requested clarification regarding what actions will be taken should the PMA not be approved within the 180-day review period.

(Response) Under section 515(d)(1)(A) of the FD&C Act, unless an exception applies, FDA must either issue an order approving or deny approval of a PMA within 180 days after receipt of a PMA. FDA can provide an extension for review when a major amendment is submitted by the applicant or requested by FDA (21 CFR 814.37(c)(1)). The extended time period for submitting an amendment allows for, among other things, additional time for panel review of specific device data. Generally, a major amendment includes a previously unreported study, significant updated data from a previously reported study, detailed new analyses of previously submitted data, or required information previously omitted.

FDA intends to review any submitted PMA for this device type within the required timeframe. As soon as it completes its review of a PMA, FDA will issue an approval order (§ 814.45(d) (21 CFR 814.45(d))), an approvable letter (§ 814.45(e)), a not approvable letter (§ 814.45(e)), or an order denying approval (§ 814.45(a)). FDA strongly encourages manufacturers to meet with the Agency early through the presubmission program for any assistance in preparation of their PMA to help to expedite the PMA review process.

(Comment 8) One comment questioned FDA's reviewing urogynecologic surgical mesh instrumentation in a PMA if the instrumentation is packaged with the surgical mesh versus reviewing instrumentation in a 510(k) notification if the instrumentation is packaged separately from the surgical mesh. The commenter stated that the regulatory requirements for instrumentation should be based on indication and not its packaging configuration.

(Response) FDA agrees that the regulatory requirements for urogynecological surgical mesh instrumentation should be based upon the indications for use of the instruments and the risk of the instrumentation when used as intended. Based on the indications for use and the risks posed by these devices, in the 515(e) proposed order, FDA proposed to reclassify these devices from class I to class II and establish special controls. FDA is not finalizing this proposed reclassification and special controls at this time. On February 26, 2016, FDA will convene a panel to discuss these

devices prior to finalizing their reclassification. These devices are currently classified as class I under (21 CFR 876.4730) (*Manual gastroenterology-urology surgical instrument and accessories*) and may be legally marketed without premarket review, but would require 510(k) notification if the proposed reclassification of the devices is finalized.

When these devices and surgical mesh for transvaginal POP repair are packaged together, after 510(k) notification is required for the instrumentation, manufacturers may wish to include both products in a PMA for convenience. Manufacturers are permitted but not required to do so. If such instrumentation is included in a PMA, FDA is clarifying that information regarding the manufacturing process of the instrumentation does not need to be submitted in a premarket submission, as previously stated in the 515(b) proposed order preamble (see section IV, "The Final Order").

(Comment 9) One comment related to the types of bench testing FDA outlined in the 515(b) proposed order that should be included in a PMA and whether the various type of tests apply to all mesh types. For example, the commenter noted that many currently marketed surgical meshes indicated for transvaginal POP repair use integrated anchors or are self-fixating and do not utilize sutures; therefore suture pullout strength, which was identified in the 515(b) proposed order as a mesh characteristic that should be evaluated, would not be a relevant performance specification for these types of meshes. The commenter requested that FDA allow manufacturers to include a justification as to why certain testing is not relevant to performance specifications of a particular device design.

(Response) FDA recognizes that the data required to support premarket approval may vary by device. In the 515(b) proposed order preamble, FDA identified the information that should be included in a PMA to provide a reasonable assurance of safety and effectiveness of surgical mesh for transvaginal POP repair, including evaluation of specific mechanical characteristics. FDA agrees that manufacturers should be allowed to justify why specific tests are not relevant to their specific mesh design in lieu of testing. As noted in the 515(b) proposed order preamble, FDA strongly encourages manufacturers to meet with the Agency early through the presubmission program for any assistance in preparation of their PMA.

(Comment 10) One comment related to FDA's expectations regarding biocompatibility and preclinical animal study evaluation. The commenter requested clarification regarding why FDA recommended conducting biocompatibility testing prior to initiation of animal studies. The commenter also noted that in the 515(b) proposed order, FDA identified a biocompatibility test (haemocompatibility), which is not outlined in the Center for Devices and Radiological Health (CDRH) Blue Book Memo #G-95-1—"Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing,'" as a test for consideration for a permanent implant with tissue/bone contact. The commenter seeks clarity regarding the specific biocompatibility testing FDA believes should be conducted and a rationale for any testing not outlined in the Blue Book Memo.

(Response) The biocompatibility testing outlined in the 515(b) proposed order preamble is consistent with that recommended in the FDA guidance document "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" issued on March 2, 1999 (Ref. 2). There are two biocompatibility studies recommended in the guidance document (and the 515(b) proposed order) that are not included in CDRH's Blue Book Memorandum #G95-1—"Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing,'" dated May 1, 1995 (Ref. 3)—pyrogenicity and hemolysis. FDA recommended pyrogenicity testing to help protect patients from the risk of febrile reaction (Ref. 4). FDA recommended hemolysis testing on surgical mesh for transvaginal POP repair because red blood lysis in the surgical field may adversely affect the healing process.

FDA generally recommends that biocompatibility testing be completed prior to preclinical animal study evaluation to ensure that the preclinical animal study evaluation results are valid and can be used to support the final device design. If biocompatibility testing and the preclinical animal study evaluation are conducted simultaneously and biocompatibility testing results are problematic or identify a safety concern resulting in changes to the device design or materials, the preclinical animal study evaluation may need to be repeated. In addition, the results of biocompatibility

testing may prompt the need for additional preclinical evaluation. As noted in the 515(b) proposed order preamble, FDA strongly encourages manufacturers to meet with the Agency early through the presubmission program for any assistance in preparation of their PMA.

(Comment 11) One comment stated that the preclinical animal study requirements outlined in the 515(b) proposed order are not clearly defined and requested that FDA provide additional information on study design and animal model selection as well as the risks that are intended to be mitigated by the proposed animal study.

(Response) Preclinical animal studies are intended to evaluate the safety of the device, specifically the local and systemic effects of the device. Preclinical animal studies may not be needed to evaluate all surgical mesh for transvaginal POP repair; however, preclinical animal studies may be appropriate in some situations, for example, to evaluate a new mesh material or characterize the resorption rate of a resorbable surgical mesh product. FDA strongly encourages manufacturers to meet with the Agency early through the presubmission program to receive feedback regarding the need for preclinical animal studies, study design, and animal model selection to evaluate a specific surgical mesh for transvaginal POP repair.

(Comment 12) One comment stated that the use of postmarket surveillance studies to fulfill clinical requirements for the PMA creates confusion regarding how such a study can have two purposes (postmarket surveillance and PMA approval) without compromising the study design and statistical rigor of the study. The comment also stated that the 5-year followup implied in the 515(b) proposed order is not in line with 3-year followup requested in the postmarket surveillance orders.

(Response) In the 515(b) proposed order preamble, FDA outlined expectations for data collection, safety and effectiveness outcomes, and study followup. FDA noted that we intend to consider proposals for different study designs and will decide on a case-by-case basis whether each proposed study design is likely to generate data adequate to support a PMA (79 FR 24642 at 24647). In addition, we noted that FDA intends to consider the use of study data collected by manufacturers in response to FDA issued postmarket surveillance study orders (79 FR 24642 at 24647). FDA believes that data from the section 522 postmarket surveillance studies may be able to fulfill the clinical requirements to support PMA

approval—in addition to fulfilling the regulatory requirements of the orders issued under section 522 of the FD&C Act—if appropriately designed. However, as noted in the 515(b) proposed order preamble, FDA strongly encourages manufacturers to meet with the Agency to discuss specific proposals utilizing the presubmission program.

In addition, FDA noted the following in the postmarket surveillance orders issued under section 522 of the FD&C Act: “Although FDA has not come to a final decision on reclassification, you may wish to consider the data requirements for a PMA in deciding the design of your 522 study. If you are interested in utilizing data collected to fulfill this 522 order to also fulfill a possible future PMA, we suggest you indicate your interest on the cover letter of your 522 study plan and discuss with FDA possible 522 study designs that may be sufficient to support a PMA application.” For those manufacturers who indicated interest in using a 522 study to support a future PMA, FDA’s review of their 522 protocol assessed both the requirements of the 522 order and the ability to generate sufficient data to support premarket approval.

FDA also notes that the 522 orders requested collection of safety and effectiveness outcomes for surgical mesh for transvaginal POP repair at 6 months, 12 months, 18 months, 24 months, and 36 months following surgery. Therefore, FDA expects that the 522 studies should be designed to collect the 1-year outcomes requested to support premarket approval. FDA acknowledges that the 522 orders requested 3-year followup. However, FDA notes that based on its detailed review of the information provided in a PMA, we may request additional postmarket followup.

(Comment 13) One comment stated that FDA’s expectation, set forth in the 515(b) proposed order, that patient labeling include a notice of availability of an FDA Safety Communication could be “conflicting” and lead to confusion because it is unclear how a reference to this communication would be appropriate for a device with an approved PMA establishing its safety and effectiveness. The commenter stated that the patient labeling should be focused on the benefit-risk profile of each product as established in the related PMA and requested that FDA consider alternative methods for providing the information found in the FDA communication to patients.

(Response) FDA agrees that patient labeling should be reflective of the risks and benefits of individual devices. FDA also believes that there is important,

relevant information in FDA’s Safety Communication that may be helpful to patients even after PMAs are approved for this device type (Ref. 5). For example, the Safety Communication included information regarding the potential risks of surgical mesh for transvaginal POP repair, nonsurgical options, and recommended questions that patients should ask their surgeon, which may be relevant even after PMAs are approved for this device type. However, FDA acknowledges that including the notice of availability of the Safety Communication may not be the best way to provide patients with the relevant information. As a result, FDA is revising this expectation and is now recommending that patient labeling include relevant information from FDA’s Safety Communication and/or FDA’s Urogynecologic Surgical Mesh Implants Web page (Ref. 6), including but not limited to, recommended patient questions for their surgeon, FDA activities related to surgical mesh for transvaginal POP repair, and FDA contact information.

To help ensure that patients are adequately informed, FDA also recommends that a link to FDA’s Urogynecologic Surgical Mesh Implants Web page be included in the patient labeling because it provides timely and transparent information to the public, including appropriate stakeholders and patients.

(Comment 14) One comment regarding the patient identification card discussed in the 515(b) proposed order noted that the card can be easily provided by the manufacturer, compliance with use of the card is dependent on the implanting physician, and should not lead to followup activities for the manufacturer.

(Response) FDA recognizes that a successful identification system requires support from parties other than the manufacturer, such as the implanting physician and patient. FDA’s expectation, as set forth in the 515(b) proposed order preamble, was that patient labeling include a patient identification card, which would be initially provided by the manufacturer. FDA does not anticipate further followup actions by the manufacturer. These findings are adopted, in part, in the final order (see section IV, “The Final Order”).

IV. The Final Order

Under section 515(b)(3) of the FD&C Act, FDA is adopting its findings, in part, as published in the preamble of the 515(b) proposed order (79 FR 24642) and issuing this final order to require the filing of a PMA for surgical mesh for

transvaginal POP repair. As discussed in this document, FDA is amending certain previous findings. The Agency now finds that: (1) Manufacturing process information of the specialized instrumentation should not be included in a premarket submission and (2) patient labeling should include relevant information from FDA's Safety Communication and/or FDA's Urogynecologic Surgical Mesh Implants Web page rather than the notice of availability of FDA's Safety Communication. The patient labeling should also include a link to the FDA's Urogynecologic Surgical Mesh Implants Web page. This final order will revise 21 CFR part 884.

Under the final order, a PMA for surgical mesh for transvaginal POP repair is required to be filed on or before July 5, 2018, for any preamendments class III devices that were in commercial distribution before May 28, 1976, or that has been found by FDA to be substantially equivalent to such a device on or before July 5, 2018. Any other device subject to this order is required to have an approved PMA in effect before it may be marketed.

If a PMA for any of the preamendments class III devices subject to this order is not filed by this date, that device will be deemed adulterated under section 501(f)(1)(A) of the FD&C Act, and commercial distribution of the device must cease immediately.

The device may, however, be distributed for investigational use, if the applicable requirements of the IDE regulations (part 812), including obtaining IDE approval, are met on or before 30 months after the effective date of this order. There will be no extended period for filing an IDE, nor exemption from the IDE requirements (see § 812.2(d)), and studies may not be initiated without appropriate IDE approvals, as required.

V. 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.

VI. 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 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 822 have been approved under OMB control number 0910–0449; and the collections of information under 21 CFR 801 have been approved under OMB control number 0910–0485.

VII. 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 PMA 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 PMA 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 a PMA approval in the Code of Federal Regulations. Therefore, under section 515(b)(1)(A) of the FD&C Act, as amended by FDASIA, in this final order, we are requiring PMA approval for surgical mesh for transvaginal POP repair and we are making the language in 21 CFR 884.5980 consistent with this final order.

VIII. 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.

1. 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>.
2. “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” issued on March 2, 1999. Available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073791.pdf>.

3. Blue Book Memorandum #G95–1—“Use of International Standard ISO–10993, ‘Biological Evaluation of Medical Devices Part 1: Evaluation and Testing’” issued on May 1, 1995. Available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm080735.htm>.
4. “Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers,” June 2012. Available at <http://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm310098.pdf>.
5. “Update on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse: FDA Safety Communication” issued on July 13, 2011. Available at <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm>.
6. FDA's Urogynecologic Surgical Mesh Implants Web page. Available at <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/default.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, 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 paragraph (c) to § 884.5980 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 July 5, 2018, 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 July 5, 2018, 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 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: December 30, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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