



MAY 01 2014

Food and Drug Administration  
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Michael Carome, M.D.  
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Re: Citizen Petition- Docket Number FDA-2011-P-0641

Dear Dr. Carome:

This letter is in response to the above referenced citizen petition dated August 25, 2011, and filed by the Food and Drug Administration (FDA or agency) on August 26, 2011. FDA provided an interim response to your petition on February 10, 2012. In your citizen petition you requested that the FDA: (1) ban the marketing of all non-absorbable surgical mesh products for transvaginal repair of pelvic organ prolapse (POP); (2) order all manufacturers of non-absorbable surgical mesh specifically designed for transvaginal repair of POP to recall these devices; and (3) classify all new non-absorbable surgical mesh product for transvaginal repair of POP as class III devices and approve them for marketing only under a premarket approval application (PMA).

FDA has reviewed your petition and, as we discuss below, we share some of the concerns outlined there. However, the agency does not believe that a ban or recall of non-absorbable surgical mesh for transvaginal repair of POP is warranted at this time. Further, a citizen petition is not the appropriate mechanism for requesting a reclassification of a device. See 21 C.F.R. 10.30(a) and 21 C.F.R. 860.130. Reclassification petitions must be filed in accordance with 21 C.F.R. 860.123. Your request does not meet the content and form requirements of that regulation.

Although we are denying your requests for a ban and a recall, we are taking actions, described later in this response, to address many of the concerns you discuss in your citizen petition.

## **I. Background**

Beginning in 1992, the FDA cleared premarket notification (510(k)) submissions for surgical mesh indicated for POP repair under the general surgical mesh regulation 21 C.F.R. 878.3300. Surgical mesh is a medical device that is generally used to repair weakened or damaged tissue. This mesh is made of synthetic material, non-synthetic material, or a combination of both. It can be used for urogynecologic procedures, including abdominal or transvaginal repair of POP and treatment of stress urinary incontinence (SUI).

On October 20, 2008, as a result of over 1,000 adverse events received, the FDA issued a *Public Health Notification (PHN)* informing clinicians and their patients of the adverse event findings related to use of urogynecologic surgical mesh.<sup>1</sup> The PHN also provided recommendations on how to mitigate the risks associated with these devices and how to counsel patients. On July 13, 2011, based on an updated adverse event search and a review of the published literature, the FDA issued a Safety Communication titled “UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse.”<sup>2</sup> The FDA’s Safety Communication informed the public that serious complications associated with surgical mesh for transvaginal repair of POP are not rare. This was a change from what the FDA previously reported on October 20, 2008. Furthermore, the safety communication stated that “it was not clear whether transvaginal POP repair with mesh is more effective than traditional non-mesh repair in all patients with POP and it may expose patients to greater risk.” The continued reports of adverse events and the published literature also prompted the FDA to consider the information available regarding the use of surgical mesh for transvaginal POP repair and to evaluate whether the classification of this device type should be reconsidered.

On September 8-9, 2011, the FDA referred the proposed change in classification from class II to class III of surgical mesh for POP to the Obstetrics and Gynecological Devices Panel (the Panel) for its recommendations, in accordance with §513(e)(1) of the Federal Food, Drug and Cosmetic Act (FD&C Act) and 21 CFR §860 subpart C.<sup>3</sup> The Panel’s consensus was that a favorable benefit-risk profile for surgical mesh for transvaginal POP repair had 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 was in question. In addition, Panel members agreed that surgical mesh for transvaginal POP repair may not be more effective for this use than traditional non-mesh surgery, especially for the apical and posterior vaginal compartments. As a result, 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. Lastly, the majority of the Panel concluded 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.

Panel members also recommended that manufacturers of surgical mesh for transvaginal POP repair conduct postmarket studies of currently marketed devices, and that such studies would help define the risk/benefits of the mesh versus non-mesh POP repair. On January 3, 2012, FDA issued postmarket surveillance study orders (“522 orders”) to manufacturers of surgical mesh for transvaginal POP repair under its authority in section 522 of the FD&C Act since the devices

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<sup>1</sup> FDA Public Health Notification: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence, October, 28, 2008, available at <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm061976.htm>.

<sup>2</sup> FDA Safety Communication entitled “UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse,” July 2011, available at <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm262435.htm>.

<sup>3</sup> 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>.

meet these criteria: (1) its failure would be reasonably likely to cause mesh erosion/exposure, severe pain, and fistula formation, which would meet the definition of "serious adverse health consequences" at 21 CFR § 822.3(j); and (2) the device is intended to be implanted in the body for more than one year. In January 2012, the FDA issued 88 postmarket surveillance orders under section 522 of the FD&C Act to 33 manufacturers for transvaginal POP mesh products that are already legally marketed. As of May 1, 2014, the FDA has issued a total of 126 postmarket surveillance orders to 33 manufacturers of transvaginal POP mesh products. As a result of these 522 orders, many manufacturers have elected to cease marketing devices indicated for transvaginal POP repair.

In your petition you request that the FDA, pursuant to sections 516 and 518 FD&C Act, 21 U.S.C. §§ 360f and 360h, and 21 C.F.R. §§ 10.30, 810, and 895, immediately:

- (1) Ban the marketing of all currently available non-absorbable surgical mesh products specifically designed and labeled for transvaginal repair of POP- which were used in an estimated 67,500 surgical procedures in the U.S. in 2010- because these devices (a) offer no clinically significant benefits in comparison to surgical repairs for POP performed without placement of surgical mesh; and (b) have high rates of serious complications, many of which require additional surgical intervention and some of which are not amendable to surgical correction and result in permanent life-altering harm, therefore presenting "an unreasonable and substantial risk of illness or injury," the standard for the FDA to institute proceedings to ban a device under the device law, 21 U.S.C. §360f and 21 C.F.R. §895.21(a);
- (2) Order all manufacturers of non-absorbable surgical mesh products specifically designed and labeled for transvaginal repair of POP to recall these products; and
- (3) Require that any non-absorbable surgical mesh product specifically designed and labeled for transvaginal repair of POP that is proposed for marketing in the future be classified as a class III device and be approved for marketing only under a premarket approval application (PMA) that includes data from well-designed, prospective clinical trials that provide a reasonable assurance that the surgical mesh is safe and effective.

## **II. Request that FDA Ban Marketing of Non-Absorbable Surgical Mesh Products labeled for Transvaginal Repair of POP**

The FD&C Act authorizes FDA to ban a device only where, 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 eliminated or corrected by labeling or change in labeling and with respect to which the 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." See 21 U.S.C. §360f. You request that FDA ban non-absorbable surgical mesh for transvaginal repair of POP, in part because you contend that

they offer no clinically significant benefits compared to repairs of POP without surgical mesh and that the use of surgical mesh for transvaginal POP repair “commonly causes serious complications.” See Petition at 16.

FDA reviewed the studies you provided and agrees that the adverse events associated with the use of surgical mesh for transvaginal POP repair include post-operative complications such as mesh exposure; mesh extrusions; vaginal scarring, shrinkage, and tightening; pelvic pain; infection; *de novo* dyspareunia; *de novo* voiding dysfunction (e.g., incontinence); neuro-muscular problems (including groin and leg pain); recurrent prolapse; and re-surgery. As discussed below in Section IV of this letter, FDA has published a proposed order in the **Federal Register** of May 1, 2014 (79 FR 24634) under section 513(e) of the FD&C Act (513(e) Proposed Order) to reclassify surgical mesh for transvaginal POP repair from class II to class III (PMA).

Specifically, Section VII of the 513(e) Proposed Order provides detailed explanation, including review of relevant scientific literature, on the safety and effectiveness of these devices. As discussed in Section IX of the 513(e) Proposed Order, FDA has tentatively determined that the safety and effectiveness of this device type have not been established and that the collection of additional clinical evidence on these devices is needed. Such additional evidence may provide information to mitigate the risks and more clearly characterize the benefits of these devices. In addition, based on our assessment of the published literature, input from clinical organizations, and the Panel’s recommendations, we believe there are potential benefits from surgical mesh used for transvaginal repair of POP.

As discussed in Section IV below, FDA has also issued a proposed order in the **Federal Register** of May 1, 2014 (79 FR 24642) under section 515(b) of the FD&C Act (515(b) Proposed Order) to require the filing of premarket approval applications for these devices following reclassification. If finalized, this order 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, FDA recognizes 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 non-surgical options, so patients understand long term safety and effectiveness outcomes. In the 515(b) Proposed Order, FDA tentatively asserts 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.

In sum, FDA believes that the appropriate approach at this time is to propose to upclassify the device and require the filing of premarket approval applications. The agency does not believe that a ban is warranted at this time. However, FDA may consider future action against individual products or this product type as appropriate.

### **III. Recall of Non-Absorbable Surgical Mesh for Transvaginal Repair of POP**

Under section 518(e) of the FD&C Act “(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)— (A) to immediately cease distribution of such device, and (B) 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.”

Based on the information available to the agency at this time, FDA does not believe mandatory recall of all currently marketed non-absorbable surgical mesh products for transvaginal repair of POP is warranted. There is not sufficient evidence at this time to support a finding that there is a reasonable probability that all non-absorbable surgical mesh products specifically designed and labeled for transvaginal repair of POP would cause serious, adverse health consequences or death. FDA’s assessment of the currently available scientific evidence is presented in the 513(e) Proposed Order.

The issuance of post-market surveillance orders to manufacturers will allow FDA to continue to evaluate the benefit-risk profile of the device. Further, reclassifying these devices to class III and requiring PMA approval would ensure that the devices independently demonstrate a reasonable assurance of safety and effectiveness in order to remain on the market in the U.S. In addition, FDA may consider future action against individual products for which regulatory action is indicated.

#### **IV. Reclassification for Non-Absorbable Mesh for Transvaginal Repair of POP to Class III with PMA**

The agency reviews requests for reclassifications of devices under 21 C.F.R. Part 860, Medical Device Classification Procedures. The requirements for a reclassification petition under Part 860 are different from those for a citizen petition. In particular, section 860.123 dictates the form for reclassification petitions as well as the information a device reclassification petition must include. Your request does not meet the content and form requirements of that regulation. Therefore, the agency is unable to grant this request.

FDA has evaluated the risks to health associated with use of surgical mesh indicated for transvaginal POP repair by analyzing information from the Panel’s recommendations and scientific evidence in published literature to reach a tentative determination that the device should be reclassified from class II to class III. As a result, FDA has published in the **Federal Register** of May 1, 2014 two separate proposed orders: one proposing to reclassify surgical mesh for transvaginal POP repair to class III (79 FR 24634) and one proposing to call for premarket approval (PMA) of the device (79 FR 24642). FDA’s proposed change in classification of surgical mesh for POP devices from class II to class III is based on the agency’s tentative determination that general controls and special controls together are not sufficient to provide reasonable assurance of safety and effectiveness for devices within this type.

FDA also tentatively concludes that PMA approval will provide a reasonable assurance of safety and effectiveness for surgical mesh for transvaginal POP repair. If these orders are finalized, all manufacturers will be subject to the requirement of submission of a PMA, to provide an independent demonstration of safety and effectiveness for their devices; devices for which no

such showing is made will be considered adulterated and misbranded and prohibited from marketing.

Therefore, while FDA cannot grant your third request at this time, FDA has initiated the process that could ultimately result in the action you seek.

#### **V. Actions Taken by FDA in Response to Adverse Effects of Non-Absorbable Mesh for Transvaginal Repair of POP**

FDA has taken several actions to address concerns about currently marketed surgical mesh for transvaginal repair of POP, including, but not limited to:

- Publishing “Urogynecologic Surgical Mesh: Updated on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse” in July 2011 summarizing published literature and adverse event information about urogynecologic surgical mesh to advise the public and the medical community of complications related to transvaginal POP repair with mesh;
- Issuing a safety communication in 2008 and updating the safety information in 2011;
- Holding an advisory committee meeting on the upclassification of surgical mesh for transvaginal POP repair; and
- Issuing post-market surveillance orders for all devices of this type. The required 522 orders will have a 3 year follow-up with manufacturers submitting progress reports to ensure the safety and effectiveness of their device.

Also as stated above, FDA has published a proposed order to reclassify the device from class II to class III under section 513(e) of the FD&C Act and published a proposed order to require the filing of premarket approval applications for these devices following reclassification under section 515(b) of the FD&C Act. FDA tentatively concludes that general and special controls together are not sufficient to provide reasonable assurance of the safety and effectiveness of surgical mesh indicated for transvaginal repair of POP.

#### **VI. Conclusion**

For the reasons discussed above, FDA is denying your petition. Based on the information available, FDA does not believe a ban or recall on surgical mesh for transvaginal POP repair is warranted at this time. FDA does tentatively agree that reclassification of the device from class II to class III (PMA) is warranted to mitigate the risks to health associated with use of surgical mesh indicated for transvaginal POP repair and has proposed these changes in the proposed orders that were published in the **Federal Register** of May 1, 2014. We encourage you to submit comments to the proposed orders to the relevant public dockets [FDA-2014-N-0297 and FDA-2014-N-0298] and FDA will consider all comments regarding the reclassification of this device.

If you have any questions about this response, please contact Erica Blake of our Regulation Staff at (301) 796-3999. For scientific questions, please contact Sharon Andrews (301) 796-6529.

Sincerely,



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