Immediately in Effect Guidance Document: Product Labeling for Laparoscopic Power Morcellators

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Guidance for Industry and Food and Drug Administration Staff

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CDRH has reviewed all comments received regarding this guidance document as of January 27, 2015 and has determined that no revisions to the guidance should be made at this time.

For questions about this document, contact the Obstetrics-Gynecology Devices Branch, 301-796-7030 and Elaine Blyskun, 301-796-6533, elaine.blyskun@fda.hhs.gov for gynecologic indications or the General Surgery Devices Branch 2, 301-796-6970 and Joshua Nipper, 301-796-6524, joshua.nipper@fda.hhs.gov for general surgical indications.

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Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Division of Reproductive, Gastro-Renal, and Urological Devices
Division of Surgical Devices

Preface

Public Comment

You may submit comments and suggestions regarding this document within 60 days of publication in the Federal Register of the notice announcing the availability of the guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

The Food and Drug Administration (FDA) is issuing this guidance to recommend the addition of specific safety statements to the product labeling for laparoscopic power morcellators (LPMs). This recommendation is being made in light of scientific information that suggests that the use of these devices contributes to the dissemination and upstaging[1] of an occult uterine malignancy in women undergoing laparoscopic gynecologic surgery for presumed fibroids. FDA believes this effort will promote the safe and effective use of LPMs when used for gynecologic surgeries.

This guidance is being implemented without prior public comment because the agency has determined that prior public participation is not feasible or appropriate (21 CFR 10.115(g)(2)). FDA believes that immediate implementation of the guidance is needed to assist in addressing a significant public health issue. Although this guidance is immediately in effect, FDA will consider all comments received and revise the guidance document as appropriate.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory

[1] A cancer's stage is a reflection of the extent and/or severity of the disease and helps in determining the prognosis and appropriate treatment options. "Upstaging" refers to an increase in the extent or severity of the disease in a given patient, in this case due to the iatrogenic spread and growth of tumor within the peritoneal cavity.

requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

As the number of laparoscopic and minimally invasive procedures has increased with the introduction of new surgical technologies and techniques, additional safety information has become available regarding the use of LPMs. Recent discussions within the patient and clinical communities, as well as the peer-reviewed medical literature, have raised awareness of the risk of spreading unsuspected cancerous tissue beyond the uterus when LPMs are used during gynecologic surgeries intended to treat benign fibroids. Numerous case reports and case series have been published that describe the iatrogenic dissemination, implantation, and subsequent growth of unsuspected neoplastic tissue within the peritoneal cavity following laparoscopic morcellation of uterine tissue believed to contain fibroids based on pre-operative diagnosis.[2-4] FDA's recent analysis of available information suggested that the risk of an occult uterine sarcoma in a woman undergoing surgical intervention for presumed fibroids is substantially higher than had previously been assumed or reported.[4-13] FDA's analysis also suggested that patient outcomes, including survival, may be significantly adversely impacted from this upstaging of disease.[2,4,14-17]

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[2] Oduyebo T, Rauh-Hain A, Meserve E, Seidmen M, Hinchcliff E, George S, Quade B, Nucci M, Del Carmen M, Muto M. The value of re-exploration in patients with inadvertently morcellated uterine sarcoma. Gynecol Oncol. 2014 Feb;132(2):360-5. doi: 10.1016/j.ygyno.2013.11.024. Epub 2013 Dec 1

[3] Einstein M, Barakat R, Chi D, Sonoda Y, Alektiar K, Hensley M, Abu-Rustum N. Management of uterine malignancy found incidentally after supracervical hysterectomy or uterine morcellation for presumed benign disease. Int J Gyn Cancer 2008; 18:1065-1070.

[4] Seidman MA, Oduyebo T, Muto MG, et al. Peritoneal dissemination complicating morcellation of uterine mesenchymal neoplasms. PLoS One. 2012;7(11):e50058.

[5] For a summary of FDA's analysis, see pg. 18-24 of the FDA Executive Summary from the July 10-11, 2014 Meeting of FDA's Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/UCM404148.pdf

[6] Leibsohn S, d'Ablaing G, Mishell DR, Schlaerth JB. Leiomyosarcoma in a series of hysterectomies performed for presumed uterine leiomyomas. Am J Obstet Gynecol. 1990;162(4):968-974.

[7] Reiter RC, Wagner PL, Gambone JC. Routine hysterectomy for larger asymptomatic uterine leiomyomata – a reappraisal. Obstet Gynecol. 1992;79(4):481-4.

[8] Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol. 1994;83(3):414-8.

[9] Takamizawa S, Minakami H, Usui R, Noguchi S, Ohwada M, Suzuki M, et al. Risk of complications and uterine malignancies in women undergoing hysterectomy for presumed benign leiomyomas. GynecolObstetInvest. 1999;48(3):193-6.

[10] Sinha R. Hegde A, Mahajan C, et al. Laparoscopic myomectomy: do size, number, and location of the myomas form limiting factors for laparoscopic myomectomy? J Minim Invasive Gynecol. 2008;15(3):292-300.

[11] Kamikabeya TS, Etchebehere RM, Nomelini RS, Murta EF. Gynecological malignant neoplasias diagnosed after hysterectomy performed for leiomyoma in a university hospital. European journal of gynaecological oncology. 2010;31(6):651-3.

[12] Rowland M, Lesnock J, Edwards R, Richard S, Zorn K, Sukumvanich P, et al. Occult uterine cancer in patients undergoing laparoscopic hysterectomy with morcellation. Gynecol Oncol. 2012;127(1):S29-S.

[13] Leung F, Terzibackian JJ. "The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma." Gynecol Oncol. 2012;124(1):172-173.

[14] Morice P, Rodriguez A, Rey A, Pautier P, Atallah D, Genestie C, Pomel C, Lhommé C, Haie-Meder C, Duvillard P, Castaigne D. Prognostic value of initial surgical procedure for patients with uterine sarcoma: Analysis of 123 patients. Euro Journal of Gynaecological Oncology 2003 24:3-4 (237-240).

Patient selection and choice of surgical technique can reduce the risk of spreading cancer. Specifically, the prevalence of unsuspected cancer in women undergoing hysterectomy for fibroids increases with age such that the benefit/risk profile of using LPMs is worse in peri-[18] and post-menopausal women compared to pre-menopausal women.[19,20] Also, the surgical technique of *en bloc* tissue removal eliminates the need to perform morcellation, thereby reducing the risk of iatrogenic dissemination and upstaging an occult sarcoma. Importantly, no screening procedure that can reliably detect sarcoma preoperatively has been identified.

FDA considers the new scientific information outlined above to represent a significant change to the benefit/risk profile for these devices, prompting the issuance of a Safety Communication on April 17, 2014 (http://www.fda.gov/medicaldevices/safety/alertsandnotices/ucm393576.htm) and the convening of the FDA's Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee on July 10-11, 2014 (http://www.fda.gov/advisorycommittees/calendar/ucm400221.htm) to further discuss the use and labeling of LPMs during gynecologic surgeries. FDA is issuing this document after considering the input of the panel and other stakeholders, including comments made during the Open Public Hearing portion of the Panel meeting.

III. Scope

LPMs may include general indications for use (i.e., laparoscopic procedures) or specific indications for use (i.e., laparoscopic gynecologic procedures). This guidance applies to LPMs with either a general indication or a specific gynecologic indication as either may be used in gynecologic laparoscopic procedures. This guidance applies to LPMs regardless of morcellation mechanism (e.g., electromechanical, radiofrequency).

This guidance does not apply to LPMs specifically indicated only for non-gynecologic surgery. It also does not apply to hysteroscopic morcellators, which have a different principle of operation. FDA believes that, when used in accordance with current indications and instructions for use, hysteroscopic morcellators do not pose the same risk as the devices

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[15] Park J, Park S, Kim D, Kim J, Kim Y, Kim Y, Nam J. The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma. Gyn Onc 2011; 255-259.

[16] Park JY, Kim D, Kim J, Kim Y, Kim J, Nam J. The impact of tumor morcellation during surgery on the outcomes of patients with apparently early low grade endometrial stromal sarcoma. Ann Surg Oncol. 2011;18(12):3453-3461.

[17] George S, Barysauskas C, Serrano C. Retrospective cohort study evaluating the impact of intraperitoneal morcellation on outcomes of localized uterine leiomyosarcoma. Cancer. 2014 Jun 12. doi: 10.1002/cncr.28844. [Epub ahead of print]

[18] Perimenopause has been defined as "a period of changing ovarian function preceding the final menses by between 2 and 8 years" (Ref: Greendale GA, Lee NP, Arriola ER. The menopause. The Lancet 1999; 353: 571-580). Signs and symptoms of perimenopause include missed menstrual cycles and hot flashes.

[19] Wright JD, Tergas AI, Burke WM, et al. Uterine pathology in women undergoing minimally invasive hysterectomy using morcellation. JAMA 2014; 312(12): 1253-5 (and Supplementary Online Content).

[20] See the Panel Transcripts from the July 10-11, 2014 Meeting of FDA's Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm404143.htm.

addressed in this guidance because any sarcomatous tissue present does not enter the peritoneal cavity.

IV. Recommended Labeling Statements

As a result of the new information and discussions during the public Advisory Committee meeting, FDA recommends that manufacturers of LPMs with a general indication or a specific gynecologic indication prominently include the following Contraindications and Boxed Warning in their product labeling:

> ***CONTRAINDICATION: Laparoscopic power morcellators are contraindicated in gynecologic surgery in which the tissue to be morcellated is known or suspected to contain malignancy.***
>
> ***CONTRAINDICATION: Laparoscopic power morcellators are contraindicated for removal of uterine tissue containing suspected fibroids in patients who are:***
>
> - ***peri- or post-menopausal, or***
> - ***candidates for* en bloc *tissue removal, for example, through the vagina or via a mini-laparotomy incision.***
>
> ***WARNING*: Uterine tissue may contain unsuspected cancer. The use of laparoscopic power morcellators during fibroid surgery may spread cancer, and decrease the long-term survival of patients. This information should be shared with patients when considering surgery with the use of these devices.**

FDA believes accurate product labeling is important to make device users and patients aware of the risk of dissemination of malignant tissue and potential clinical outcomes associated with the laparoscopic morcellation of occult uterine malignancy. We have determined that the Contraindications and Boxed Warning are important to the safe use of LPMs. As such, FDA believes that this may be information that manufacturers should disclose to users under sections 502(a), 201(n), and 502(f)(2) of the Federal Food, Drug, and Cosmetic Act. Manufacturers should implement these labeling recommendations and include them in labeling submitted with future 510(k) submissions. Within 120 days of the publication of this guidance, a manufacturer with an existing 510(k) clearance should: 1) add the Contraindications and Boxed Warning to their labeling; 2) submit both the current labeling and revised labeling to CDRH[21]; and 3) provide updated labeling to purchasers for LPMs that have already been distributed.

[21] If a manufacturer with an existing 510(k) clearance adds the Contraindications and Boxed Warning listed above, FDA does not intend to object if such labeling changes are submitted as an "add-to-file" to the existing 510(k) rather than as a new 510(k).