Contains Nonbinding Recommendations

Draft – Not for Implementation

Product Labeling for Laparoscopic Power Morcellators

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on February 26, 2020.

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draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

For questions about this document, contact OHT3: Office of Gastro-Renal, ObGyn, General Hospital, and Urology Devices/DHT3B: Division of Reproductive, Gynecology, and Urology Devices for gynecologic indications at (301)-796-7030 or OHT4: Office of Surgical and Infection Control Devices/DHT4A: Division of General Surgery Devices for general surgical indications at (301)-796-6970.

When final, this guidance will supersede "Immediately in Effect Guidance Document: Product Labeling for Laparoscopic Power Morcellators," issued on November 25, 2014.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number 1400052 and complete title of the guidance in the request.

Product Labeling for Laparoscopic Power Morcellators

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This draft guidance contains recommendations concerning the content and format for certain labeling information for laparoscopic power morcellators (LPMs). The recommendations in this draft guidance reflect the state of the science and available technology regarding use of LPMs and are 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 is also recommending that manufacturers incorporate into the labeling for these devices information providing greater specificity regarding the risk of use as it relates to age, information regarding the risk of spreading malignant and benign uterine tissue, and information regarding the use of laparoscopic power morcellation containment systems. FDA believes this effort will promote the safe and effective use of LPMs when used for gynecologic surgeries.

FDA's guidance documents, including this draft 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 requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Background

[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.

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. 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, and FDA has received Medical Device Reports (MDRs) 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, 3, 4] In 2014, FDA presented an analysis of available information suggesting 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, 5, 6, 7, 8, 9, 10, 11, 12, 13] FDA's analysis also suggested that patient outcomes, including survival, may be significantly adversely impacted from this upstaging of disease.[2, 4, 14, 15, 16, 17]

[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;132(2):360-365.

[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: https://wayback.archive-it.org/7993/20170405192706/https://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):481-484.

[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):414-418.

[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):193-196.

[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):651-653.

[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.

[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.

[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. Gynecol Oncol. 2011;122(2):255-259.

[16] Park JY, Kim D, Km 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;120(20):3154-3158.

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 older women when compared to younger women.[18, 19] Also, the surgical technique of *en bloc* tissue removal eliminates the need to perform morcellation, thereby reducing the risk of iatrogenic dissemination and upstaging of an occult sarcoma. Importantly, no screening procedure that can reliably detect sarcoma preoperatively has been identified.

FDA considered the 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[20] and the convening of the FDA's Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee[21] on July 10-11, 2014[22] to further discuss the use and labeling of LPMs during gynecologic surgeries. FDA issued an immediately in effect guidance document after considering the input of the Panel and other stakeholders, including comments made during the Open Public Hearing portion of the Panel meeting.

Following issuance of the 2014 guidance document, FDA continued to consider new scientific information and the input of stakeholders. FDA provided an updated analysis in 2017[23] considering new information that became available since the first analysis was performed. The publications referenced in the updated analysis continue to provide evidence for differences in patient outcomes between groups, including among groups exposed to power morcellation, non-powered morcellation or no morcellation. Further, additional scientific information is available that stratifies the risks of an undetected uterine cancer in women with presumed fibroids based on age.[24, 25, 26, 27, 28]

---

[18] Wright JD, Tergas AI, Burke WM et al. Uterine pathology in women undergoing minimally invasive hysterectomy using morcellation. JAMA 2014; 312(12): 1253-1255 (and Supplementary Online Content).

[19] 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: https://wayback.archive-it.org/7993/20170405192706/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm404143.htm.

[20] http://wayback.archive-it.org/7993/20170722043342/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm393576.htm. This Safety Communication was updated on November 24, 2014 (https://wayback.archive-it.org/7993/20170404182209/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm424443.htm).

[21] https://www.fda.gov/advisory-committees/medical-devices-advisory-committee/obstetrics-and-gynecology-devices-panel.

[22] The materials from this meeting are available at: https://wayback.archive-it.org/7993/20170405192706/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/ObstetricsandGynecologyDevices/ucm404143.htm.

[23] "FDA Updated Assessment of The Use of Laparoscopic Power Morcellators to Treat Uterine Fibroids," available at: https://www.fda.gov/media/109018/download.

[24] Raine-Bennett T, Tucker L, Zaritsky E et al. Occult uterine sarcoma and leiomyosarcoma. Incidence of and survival associated with morcellation. Obstet Gynecol. 2016; 127(1):29-39.

[25] Mahnert N, Morgan D, Campbell D et al. Unexpected gynecologic malignancy diagnosed after hysterectomy performed for benign indications. Obstet Gynecol 2015; 135 (2):397-405.

[26] Zhang J, Li, T, Zhang J et al. Clinical characteristics and prognosis of unexpected uterine sarcoma after hysterectomy for presumed myoma with and without transvaginal scalpel morcellation. Int J Gyn Cancer, 2016; 26(3):456-463.

[27] Mao, J, Pfeifer, S, Zheng, X et al. Population-based estimates of the prevalence of uterine sarcoma among patients with leiomyomata undergoing surgical treatment. JAMA Surgery, 2015; 150(4): 368-370.

[28] Rodriguez, A, Asogly M, Sak M, et al. Incidence of occult leiomyosarcoma in presumed morcellation cases: a database study. European J Obstet & Gyn and Reprod Biology, 2016; 197:31-35.

FDA also considered scientific information pertaining to the risk of spreading benign uterine tissue beyond the uterus during gynecologic surgeries when LPMs are used.[29, 30, 31] Parasitic myomas and disseminated peritoneal leiomyomatosis, while benign, have been associated with the need for additional surgery due to symptoms such as abdominal pain and distension.

Finally, FDA considered additional available mitigations for the spread of uterine tissue. Since 2014, FDA has provided marketing authorization for laparoscopic power morcellation containment systems intended to isolate and contain tissue that is considered benign. These products have been shown, through bench testing and simulated use testing, to contain such tissue during morcellation.[32]

For these reasons, FDA is proposing in this draft guidance to update its recommendations, as originally described in the 2014 guidance document, concerning the content and format of certain labeling information for LPMs. Specifically, FDA is recommending that manufacturers incorporate into the labeling for these devices information providing greater specificity regarding the risk of use as it relates to age, information regarding the risk of spreading benign uterine tissue, and information regarding the use of laparoscopic power morcellation containment systems.

III. Scope

This draft guidance provides recommendations concerning the content and format of certain labeling information for LPMs used for gynecologic surgeries. LPMs may include general indications for use (e.g., laparoscopic procedures) or specific indications for use (e.g., 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 addressed in this guidance because any sarcomatous tissue present does not enter the peritoneal cavity.

This draft guidance is not intended to include a complete listing of all labeling components for LPMs used for gynecologic surgery. Rather, this draft guidance contains recommendations

[29] Lete I, Gonzalez J, Ugarte L, Barbadillo N, Lapuente O, & Alvarez-Sala J. Parasitic leiomyomas: a systematic review. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2016;203:250-259.
[30] Tan-Kim J, Hartzell KA, Reinsch CS, et al. Uterine sarcomas and parasitic myomas after laparoscopic hysterectomy with power morcellation. Am J Obstet Gynecol. 2015;212:594.e1-10.
[31] Van der Meulen JF, Pijnenborg JMA, Boonuma CM, Verberg MFG, Geomini PMAJ, Bongers MY. Parasitic myoma after laparoscopic morcellation: a systematic review of the literature. BJOG. 2016;123:69-75.
[32] These devices are classified under 21 CFR 884.4050 (Gynecologic laparoscopic power morcellation containment system).

regarding the inclusion of certain information in LPM labeling that FDA believes is important to the safe and effective use of LPMs in gynecologic surgery. Accurate product labeling for LPMs and effective communication of that labeling are important to help ensure that physicians and patients are aware of the risks associated with the use of LPMs in gynecologic surgery, including the dissemination of malignant tissue and potential clinical outcomes associated with the laparoscopic morcellation of occult uterine malignancy. FDA believes that the physician and patient information discussed in this draft guidance should be included in labeling under sections 501(a), 201(n), and 502(f)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). When this guidance is finalized, FDA recommends that manufacturers implement the labeling recommendations discussed herein[33] and follow them in labeling submitted with future 510(k) submissions.

IV. Labeling Components

FDA recommends that the labeling of LPMs with a general indication or a specific gynecologic indication include a boxed warning, contraindications, and warnings regarding the risk of use as it relates to age, spreading malignant and benign uterine tissue, and the use of laparoscopic power morcellation containment systems. This section contains FDA's format and content recommendations for these components, and to help illustrate, FDA has provided examples in each subsection.

A. Boxed Warning

FDA believes that a boxed warning should be part of the labeling materials for LPMs. In general, boxed warnings are noticeable and easy to read and understand, and FDA believes a boxed warning here would be particularly useful in communicating certain risks that have been identified in the scientific information discussed above. FDA therefore recommends that a boxed warning generally inform physicians, and recommend that physicians share with patients, that:

- Uterine tissue may contain unsuspected cancer; and
- The use of laparoscopic power morcellators during fibroid surgery may spread cancer and decrease the long-term survival rate of patients.

An example of a boxed warning that follows this recommendation is below.

> ***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.**

[33] A manufacturer with an existing 510(k) clearance should: 1) add the information to their labeling; 2) submit both the current labeling and revised labeling to CDRH; and 3) provide updated labeling to purchasers for LPMs that have already been distributed. In addition, 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).

B. Contraindications and Other Warnings

In addition to the boxed warning, FDA also believes that the labeling of LPMs should include contraindications and warnings highlighting certain key information regarding the risks of use of LPMs in gynecologic surgeries. We recommend the labeling for LPMs generally inform physicians, and recommend that physicians share with patients, that:

- Laparoscopic power morcellators are contraindicated in gynecologic surgery in which the tissue to be morcellated is known or suspected to contain malignancy;
- Laparoscopic power morcellators are contraindicated for removal of uterine tissue containing suspected fibroids in patients who are post-menopausal or over 50 years of age, or candidates for *en bloc* tissue removal through the vagina or via a mini-laparotomy incision;
- The risk of occult cancer, including uterine sarcoma, increases with age, particularly in women over 50 years of age;
- Uncontained power morcellation has been associated with the spread of benign uterine tissue, *i.e.*, parasitic myomas and disseminated peritoneal leiomyomatosis; and
- Laparoscopic power morcellators should only be used with a containment system. The containment system should be compatible with the laparoscopic power morcellator.

Examples of labeling statements that follow these recommendations are below.

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:

- ***post-menopausal or over 50 years of age, or***
- ***candidates for en bloc tissue removal through the vagina or via a mini-laparotomy incision.***

WARNING: The risk of occult cancer, including uterine sarcoma, increases with age, particularly in women over 50 years of age. This information should be shared with patients when considering surgery with the use of these devices.

WARNING: Uncontained power morcellation has been associated with the spread of benign uterine tissue, i.e., parasitic myomas and disseminated peritoneal leiomyomatosis.

WARNING: Laparoscopic power morcellators should only be used with a containment system. The containment system should be compatible with the laparoscopic power morcellator.