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Non-Clinical Performance Assessment of Tissue Containment Systems Used During Power Morcellation Procedures

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Document issued on June 21, 2022.

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

Preface

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Non-Clinical Performance Assessment of Tissue Containment Systems Used During Power Morcellation Procedures

Draft Guidance for Industry and Food and Drug Administration Staff

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I. Introduction

This draft guidance document provides recommendations that may help manufacturers comply with the special controls related to non-clinical performance data for gynecologic and general laparoscopic power morcellation containment systems ("tissue containment systems"). Tissue containment systems are used to enable isolation and containment of tissue during a power morcellation procedure performed following a laparoscopic procedure for the excision of benign tissue that is not suspected to contain malignancy. These devices are class II (special controls) and subject to premarket notification (510(k)) requirements. Throughout this guidance, the terms "FDA," "the Agency," "we," and "us" refer to the Food and Drug Administration and the terms "you" and "yours" refer to medical device manufacturers.

For the current edition of the FDA-recognized consensus standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[1] For more information regarding use of consensus standards in regulatory submissions, please refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."[2]

[1] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

[2] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.

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II. Background

Laparoscopic power morcellators (LPMs)[3] have been associated with the spread of tissue. There is a risk of spreading unsuspected cancerous tissue beyond the uterus when LPMs are used during gynecologic surgeries intended to treat benign fibroids. Unsuspected cancerous tissue may also be spread in the abdomen during use of a LPM during general surgical procedures. This may have a negative impact on survival.[4] In addition, there is a risk of spreading benign uterine tissue beyond the uterus that may result in additional surgery due to symptoms such as abdominal pain and distension which are related to adhesions resulting in response to the devitalized tissue.[5,6,7] Benign tissue may also be spread in the abdomen during use of a LPM during surgical procedures, which can lead to abscess or infection. Tissue containment systems used during laparoscopic power morcellation are intended to isolate and contain tissue that is considered benign, which may prevent the peritoneal spread of cancerous tissue in cases of an occult cancer. While a tissue containment system cannot prevent all cases of tissue spread, as some cases may occur without morcellation or due to manipulation of the tissue before it is placed into the tissue containment system, it can provide an important mitigation for this risk. Tissue containment systems should only be used with compatible LPMs that have received FDA marketing authorization. For more information, refer to the FDA guidance document "Product Labeling for Laparoscopic Power Morcellators."[8]

[3] This guidance uses the term "laparoscopic power morcellators" or "LPMs" in lieu of laparoscopic electromechanical morcellators. FDA believes this terminology is understood and recognized both by clinicians and non-clinicians (e.g., American College of Obstetricians and Gynecologists Special Report: Power Morcellation and Occult Malignancy in Gynecologic Surgery May 2014, available at: https://www.sgo.org/wp-content/uploads/2014/04/ACOG_Statement.pdf and Society of Gynecologic Oncology Position Statement: Morcellation December 2013, available at: https://www.sgo.org/resources/morcellation/).

[4] https://wayback.archive-it.org/7993/20170404182209/https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm424443.htm.

[5] Tan-Kim J, Hartzell KA, Reinsch CS, O'Day CH, Kennedy JS, Menefee SA, and Harrison TA. Uterine sarcomas and parasitic myomas after laparoscopic hysterectomy with power morcellation. *Am J Obstet Gynecol*. 2015; 212:594.e1-10.

[6] Van der Meulen JF, Pijnenborg JMA, Boonuma CM, Verberg MFG, Geomini PMAJ, and Bongers MY. Parasitic myoma after laparoscopic morcellation: a systematic review of the literature. *BJOG*. 2016; 123:69-75.

[7] Lete I, Gonzalez J, Ugarte L, Barbadillo N, Lapuente O, and Alvarez-Sala J. Parasitic leiomyomas: a systematic review. *Eur J Obstet Gynecol Repro Biol*. 2016; 203:250-259.

[8] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-labeling-laparoscopic-power-morcellators. The FDA guidance document "Product Labeling for Laparoscopic Power Morcellators" applies to LPMs with either a general indication or a specific gynecologic indication but not LPMs specifically indicated only for non-gynecologic surgery.

A laparoscopic power morcellation containment system, for gynecologic or general use, is a prescription device consisting of an instrument port and tissue containment method that creates a working space allowing for direct visualization during a power morcellation procedure following a laparoscopic procedure for the excision of benign tissue that is not suspected to contain malignancy. FDA classified both laparoscopic power morcellation containment systems for gynecologic and general uses into class II (special controls), subject to 510(k) requirements, under section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Through this De Novo classification process, FDA determined the special controls that are necessary, in conjunction with the general controls of the FD&C Act, to provide reasonable assurance of safety and effectiveness for these devices. The special controls for laparoscopic power morcellation containment systems for gynecologic and general use are codified in 21 CFR 884.4050(b) and 21 CFR 878.4825(b), respectively.

This draft guidance recommends non-clinical test methods that may help manufacturers meet the non-clinical performance data requirements identified in the special controls codified in 21 CFR 884.4050(b)(4) (for gynecologic use) and 21 CFR 878.4825(b)(4) (for general use), as well as other non-clinical testing recommendations to support a 510(k) submission. The recommendations in this guidance are based on FDA's experience evaluating the safety and effectiveness of LPMs. However, manufacturers may use alternative approaches and provide different documentation so long as their approach and documentation satisfy premarket submission requirements in applicable statutory provisions and regulations.

For more information about the specific content requirements of and recommendations for a 510(k) submission, refer to 21 CFR 807.87 and FDA's guidance document, "Format for Traditional and Abbreviated 510(k)s."[9]

III. Scope

The scope of this guidance document is limited to the tissue containment systems used during a power morcellation procedure for gynecologic use (product code PMU) classified under 21 CFR 884.4050 and for general use (product code PZQ) classified under 21 CFR 878.4825.

The guidance document provides recommendations on (1) test methods, (2) test parameters, and (3) test acceptance criteria to support a 510(k) submission and demonstrate compliance with the special controls requiring non-clinical performance data identified in 21 CFR 884.4050(b)(4) and 21 CFR 878.4825(b)(4):

> 21 CFR 884.4050(b)(4) states (for gynecologic use):
>
> *Non-clinical performance data must demonstrate that the device meets all design specifications and performance requirements. The following performance characteristics must be tested:*

[9] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/format-traditional-and-abbreviated-510ks.

(i) Demonstration of the device impermeability to tissue, cells, and fluids;

(ii) Demonstration that the device allows for the insertion and withdrawal of laparoscopic instruments while maintaining pneumoperitoneum;

(iii) Demonstration that the containment system provides adequate space to perform morcellation and adequate visualization of the laparoscopic instruments and tissue specimen relative to the external viscera;

(iv) Demonstration that intended laparoscopic instruments and morcellators do not compromise the integrity of the containment system; and

(v) Demonstration that intended users can adequately deploy the device, morcellate a specimen without compromising the integrity of the device, and remove the device without spillage of contents.

21 CFR 878.4825(b)(4) states (for general use):

Non-clinical performance data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:

(i) Demonstration of the device impermeability to tissue, cells, and fluids;

(ii) Demonstration that the device allows for the insertion/withdrawal of laparoscopic instruments while maintaining pneumoperitoneum;

(iii) Demonstration that the containment system provides adequate space to perform morcellation and adequate visualization of the laparoscopic instruments and tissue specimen relative to the external viscera;

(iv) Demonstration that compatible laparoscopic instruments and morcellators do not compromise the integrity of the containment system; and

(v) Demonstration that users can adequately deploy the device, morcellate a specimen without compromising the integrity of the device, and remove the device without spillage of contents.

This guidance document is focused on non-clinical performance testing. Note that additional information, such as clinical data, may be needed to demonstrate substantial equivalence.

IV. 510(k) Submission Recommendations

The sections below provide recommendations on how to comply with the special controls requiring non-clinical performance data codified in 21 CFR 884.4050(b)(4) and 21 CFR

878.4825(b)(4), and describe what information is recommended for submission to FDA in a 510(k) to demonstrate that the special controls have been met. In addition to compliance with special controls requiring non-clinical performance data, manufacturers must comply with all of the other special controls identified in 21 CFR 884.4050(b) and 21 CFR 878.4825(b) and include information to demonstrate that these special controls have been met in a 510(k) submission for a tissue containment system. The other special controls include biocompatibility, sterility, shelf life, training, and labeling, which includes a boxed warning. Manufacturers are also expected to meet other applicable 510(k) requirements.[10] The sections below also provide recommendations for other non-clinical testing to support a 510(k) submission. Please note that where the guidance references final, finished device testing, this testing should be conducted on the tissue containment system that includes all manufacturing processes for the "to-be-marketed" tissue containment system including sterilization.

A. Device Description and Predicate Comparison

The 510(k) submission should include a device description that includes a labeled diagram for each model included in the submission. The device description should include:

- A description of the overall device system including accessories, pictures, samples (if practical), and engineering diagrams;
- A description of the principle of operation accompanied by labeled diagrams, as applicable, to show the insertion, deployment and removal steps;
- Specifications for the system overall as well as individual components; and
- A description of the compatible LPMs.

The 510(k) should include a comparison of the new device to a legally marketed device, commonly referred to as the "predicate" device. FDA recommends that all comparisons be provided in a manner that is clear and comprehensible, such as in tabular form that lists the similarities and differences between the new and predicate device. For more information, refer to the FDA guidance "Format for Traditional and Abbreviated 510(k)s: Guidance for Industry and FDA Staff."[11]

In addition to the non-clinical performance testing required by the special controls, differences in technological characteristics between the new and predicate devices may necessitate additional testing to demonstrate substantial equivalence. For input on additional testing to support a 510(k), we recommend that you seek FDA's feedback through the Q-Submission process. For more information, see the FDA guidance document "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[12]

[10] 21 CFR 807.87.

[11] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/format-traditional-and-abbreviated-510ks).

[12] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

B. Non-Clinical Performance Testing

The following sections provide non-clinical performance testing recommendations. Section B(1) provides recommendations on testing to comply with the special controls requiring non-clinical performance data (see 21 CFR 884.4050(b)(4) and 21 CFR 878.4825(b)(4)). Section B(2) provides additional testing recommendations for the 510(k) submission that are not associated with the special controls.

For information on the recommended content and format of test reports for the testing described in this section, refer to FDA's guidance document, "Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions."[13]

(1) Testing to Demonstrate Compliance with Special Controls

In order to demonstrate that the device meets the non-clinical performance characteristics identified in 21 CFR 884.4050(b)(4) and 878.4825(b)(4), as applicable, non-clinical performance testing information should be provided in the 510(k) submission. FDA's recommendations on the non-clinical test methods to help comply with each special control are identified in Table 1.

[13] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-content-and-format-non-clinical-bench-performance-testing-information-premarket.

273 Table 1: Special Controls and Recommended Test Methods.
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Special Control	Recommended Test Methods
21 CFR 884.4050(b)(4)(i) 21 CFR 878.4825(b)(4)(i)	• Material permeability testing (*see Section IV.B(1)(a)*) • Final Finished Tissue Containment System integrity testing (*see Section IV.B(1)(b)(i)*)
21 CFR 884.4050(b)(4)(ii) 21 CFR 878.4825(b)(4)(ii)	• Insufflation pressure control testing (*see Section IV.B(1)(b)(iii)*) • Clinical simulation study (*see Section IV.B(1)(b)(iv)*)
21 CFR 884.4050(b)(4)(iii) 21 CFR 878.4825(b)(4)(iii)	• Clinical simulation study (*see Section IV.B(1)(b)(iv)*)
21 CFR 884.4050(b)(4)(iv) 21 CFR 878.4825(b)(4)(iv)	• Clinical simulation study (*see Section IV.B(1)(b)(iv)*) • Material permeability testing (*see Section IV.B(1)(a)*) • Final Finished Tissue Containment System testing (*see Section IV.B(1)(b)*)
21 CFR 884.4050(b)(4)(v) 21 CFR 878.4825(b)(4)(v)	• Clinical simulation study (*see Section IV. B(1)(b)(iv)*) • Material permeability testing (*see Section IV.B(1)(a)*) • Final Finished Tissue Containment System testing (*see Section IV.B(1)(b)*)

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a. Material Permeability Testing

The test methods recommended in this section are intended to help demonstrate impermeability to tissue, cells, and fluids of the tissue containment system *material* and does not address the final finished device testing. You should refer to Section IV.B(1)(b) below for FDA's recommendations on the final finished device's permeability and mechanical strength testing.

Significance: If the device material, following manufacturing and additional processing, including sterilization, is not adequately robust to ensure that the tissue containment system is impermeable to tissues, cells, and fluids, cancerous and non-cancerous blood cells, tissue cells, and fluids can leak from the tissue containment system into the abdomen.

Recommendations: We recommend conducting material permeability testing that incorporates the following:

- Use an appropriate marker for material permeability testing (e.g., viral or bacteriophage marker) and provide a detailed methodology for the testing similar to the American Society of Testing and Materials (ASTM) F1671/F1671M-13 standard.[14] You should consider the worst-case scenario for the surrogate marker by using a marker size less than or equal to the size of cancer cells.
- If you are considering an alternative to the microbial leak testing methodology described in ASTM F1671/F1671M-13, you should provide validation of the detection limit of your assay and the justification as to how it is sufficiently sensitive to detect the passage of a single cancer cell. The method of leakage detection should be sensitive enough to detect the tissue containment system without and with defects (e.g., defects could be holes that are smaller than cancer cells). In addition to leakage testing of the tissue containment system under consideration, you should include positive and negative controls for leakage tests to verify the sensitivity of the test protocol.
- If you are conducting microbial leakage testing, you should provide evidence that the method is sensitive enough to identify holes smaller than cancer cells.
- While performing any type of leakage testing, challenge the tissue containment system to pressures that are clinically relevant as these devices are subjected to insufflation and additional localized pressures during the power morcellation procedure.[15] You should test the device to a pressure above the insufflation pressure using a safety factor,[16] and provide a detailed scientific rationale for the designated safety factor.
- It is important to evaluate the permeability of critical sections of the tissue containment system such as straps, tethers, and opening rings that are bonded/attached. You should

[14] ASTM F1671/F1671M-13: *Standard Test Method For Resistance of Materials Used in Protective Clothing To Penetration by Blood-Borne Pathogens Using Phi-X174 Bacteriophage Penetration as a Test System*.

[15] Herman A, Duraiswamy N, Nandy P, Myers MR, Price V, Gibeily G, and Hariharan P. In Vitro Leakage Testing of Tissue Containment Bags When Subjected to Power Morcellation Forces. *J Minim Invasive Gynecol*, Mar-Apr 2020;27(3):655-664.

[16] Herman A, Duraiswamy N, Nandy P, Myers MR, Price V, Gibeily G, and Hariharan P. In Vitro Leakage Testing of Tissue Containment Bags When Subjected to Power Morcellation Forces. *J Minim Invasive Gynecol*, Mar-Apr 2020;27(3):655-664.

provide a detailed justification for the selection of both tested and untested sections of the device.

b. Final Finished Tissue Containment System Testing

This section provides recommendations on test methods for evaluating the mechanical strength and integrity of the final finished tissue containment system. For the purposes of this testing, we recommend the use of samples at the end of their proposed shelf life as this is the least burdensome approach to addressing the requirements identified in 21 CFR 884.4050(b)(4) and 21 CFR 878.4825(b)(4) as well as the requirements identified in 21 CFR 884.4050(b)(3) and 21 CFR 878.4825(b)(3) for demonstrating device functionality over the intended shelf life. If there are multiple device sizes, you should incorporate test samples that are representative of all sizes. In addition, each test should include a statistically significant sample size to provide confidence that the results are representative of the final finished device.

i. Final Finished Tissue Containment System Integrity Testing

Significance: During the surgical procedure, the integrity of the tissue containment system could be compromised due to contact with surgical instruments, including the power morcellator, and/or due to use issues. The tissue containment system could also be leak prone without any direct contact with instruments for reasons such as design and manufacturing issues. An evaluation of the integrity of the tissue containment system following power morcellation with a leakage test is recommended to demonstrate the robustness of the device to withstand the intended clinical use. Therefore, it is important to demonstrate device system integrity post-morcellation.

Recommendations: We recommend conducting microbial leakage testing that incorporates the following:

- Samples should include the final finished tissue containment system post-clinical simulation study. (See Section IV.B(1)(b)(iv) below.)
- Use the entire device (including seams) to demonstrate that the device is capable of retaining all of the patient's cells/fluids during the morcellation procedure.
- If there are multiple device models made of the same material and you are using the same sealing method (if applicable), in lieu of testing each device model, you should conduct testing on a worst-case sample (e.g., the bag with the largest surface area). You should provide adequate justification for the worst-case sample in your submission.
- Use a quantitative method to test for the presence of leaks and/or the size of the leaks. Leakage testing with dye can be conducted prior to the quantitative test, however, a visually-inspected dye test should not be used as an endpoint to evaluate device performance.
- Ensure the device is subjected to worst-case quantitative testing during leakage testing. You should consider the worst-case conditions for duration of testing consistent with the device labeling, temperature, and appropriate pressure.

- Ensure that during the leakage testing, the bag is sufficiently filled to adequately distend the bag and prevent any folds or creases from forming in the bag, which in turn may prevent a hole in the bag from being detected.
- Provide validation of the detection limit of your assay and justification as to how it is sufficiently sensitive to detect the passage of a single cancer cell. You should ensure that the acceptance criteria of the assay are sufficiently sensitive to detect a single cancer cell crossing the device barrier.
- Provide validation data that evaluates the ability of your test method to detect leaks using tissue containment systems with known hole sizes in a volume similar to the tissue containment system test volume. You should use positive and negative controls for leakage tests to help verify the sensitivity of the test protocol.
- While performing leakage testing, pressurize the inside of the bag with the worst-case pressure expected during the surgical procedure for the following scenarios, including a safety factor, and include an adequate description for:
    - When the hole size is greater than the size of cancer cells and the ability of the cancer cells to permeate through the holes depends on the pressure differential across the barrier. Under clinically relevant pressures, the contents (i.e., tissue, cells, including blood and cancer cells, and fluids) could leak outside the tissue containment system.
    - When the surgical instruments, while damaging the tissue containment system, may create a flap instead of a complete opening. Under clinically relevant pressures, the flap might open and leak the contents outside the tissue containment system. Consequently, if the pressure applied during the leakage testing is lower than the clinically relevant pressure levels, the tissue containment system might "pass" the leakage test (because the differential pressure is low or the flap is closed without tissue containment system pressure) even though cancer cells would have leaked out of the tissue containment system under appropriate pressure conditions. Consider any transient forces that can act on the bag, such as instrument and morcellation forces, in determining the worst-case pressures, including a safety factor, for application in leakage testing.
- After the clinical simulation study, but prior to conducting the microbial leakage testing, the test samples should be subjected to cleaning and/or sterilization. You should describe and justify these processes and ensure that any residuals from cleaning and sterilization processes are effectively removed or neutralized. You should validate the neutralization step to demonstrate that the results have not been confounded by cleaning and/or sterilization residuals. As part of the consideration of worst-case conditions, you should choose a microbial species size that is significantly smaller than cancer cells (e.g., *Brevundimonas diminuta*) and a large microbial concentration (i.e., $>10^6$-10^7 CFU/mL) and you should immerse the entire device in the growth media.
- To ensure that the acceptance criteria of the assay is sufficiently sensitive to detect a single cancer cell crossing the device barrier, you should perform filtration of the entire volume of fluid.
- If you choose to conduct an alternate test to the microbial method, you should evaluate the entire bag surface for leaks and provide validation of the detection limit of your assay.

If applicable, provide a justification/rationale for not testing leaks on certain areas of the tissue containment system.

ii. Final Finished Tissue Containment System Strength Testing

(a) Tissue Containment System Pull Force Test

Significance: Tissue containment devices are generally subjected to tensile loads during laparoscopic surgery (e.g., during insertion and removal of the tissue containment system). An evaluation of the tensile strength of the tissue containment system as a final finished device is important to ensure that when used as intended, the device can withstand clinical forces during insertion and removal and not fail.

Recommendations: We recommend you conduct a pull force test on the tissue containment system that incorporates the following:

- Samples of final finished tissue containment system at the end of their proposed shelf life should be used for testing. The test samples do not need to be preconditioned (i.e., subjected to clinical simulation) before testing.
- Perform the pull test in a test fixture that mimics the clinical use conditions. The following are general considerations for the test fixture:
    - Ensure that the spatial and physical properties of the test fixture mimic the abdominal wall.
    - Create the smallest possible incision (or cavity) as per the instructions for use for your device. You should include a specific wound retractor or other accessories intended to be used with the tissue containment system in the test setup.
    - Include a tissue specimen that represents the worst-case scenario with respect to shape, size, and weight of tissue relative to the incision size. See also Section IV.B(1)(b)(iv) for additional considerations for the tissue specimen.
- To measure the applied force, use either a hand-held force gauge or a tensile testing machine attached to the part(s) of the tissue containment system that is intended to help pull the tissue containment system out of the abdominal cavity.
- For a tissue containment system with multiple openings, pull and measure the forces for all the openings.
- Compare the measured forces to the pre-defined acceptance criteria.

(b) Tissue Containment System Burst Strength Test

Significance: It is important to evaluate the burst strength of the tissue containment system as a final finished device, since the tissue containment system may be made of various components such as straps, tethers, and opening rings attached to the tissue containment system. An evaluation of the burst strength of the tissue containment system as a final finished device is important to ensure that when used as intended, the device can withstand clinical forces during use and not fail.

Recommendations: We recommend you conduct a burst strength test that incorporates the following:

- Samples of final finished tissue containment system at the end of their proposed shelf life should be used for testing. The test samples do not need to be preconditioned (i.e., subjected to clinical simulation) before testing.
- Test the device specimens to failure. Compare the measured pressure-to-failure to the pre-defined acceptance criteria.
- Provide the following results and analyses from the burst testing[17] in your submission:
    - Pressure-time curve;
    - Burst pressure (i.e., the maximum pressure prior to failure);
    - Factor of safety, which compares the burst pressure to radial forces imparted on the device during the surgical procedure (e.g., insufflation pressure, external pressure of the tissue from the abdomen); and
    - Failure locations, if any, based on the tissue containment system design and composition.

iii. Insufflation Pressure Control Testing

Significance: Insertion and withdrawal of laparoscopic instruments into the tissue containment system should not significantly impact the ability to maintain insufflation within the tissue containment system. Inability to maintain the insufflation pressure could cause the power morcellator and/or other surgical instruments to contact and damage the tissue containment system. Any damage to the tissue containment system may cause leakage of its contents.

Recommendations: We recommend you conduct insufflation pressure control testing that incorporates the following:

- Samples of final finished tissue containment system at the end of their proposed shelf life should be used for testing. The test samples do not need to be preconditioned (i.e., subjected to clinical simulation) before testing.
- In order to ensure adequate distension within the tissue containment system, you should perform tests to examine the limits of insufflation pressure losses during laparoscopic instrument insertion/removal that would still ensure that there is adequate space within the tissue containment system for surgical instruments. Test devices to ensure that they are within the acceptance criteria.
- For devices that include valves as part of the design, conduct testing on the component that includes the valve(s). For devices that rely on passage through an accessory that includes the valve(s), you should conduct testing on the complete device usage set-up.

[17] Herman A, Duraiswamy N, Nandy P, Myers MR, Price V, Gibeily G, and Hariharan P. In Vitro Leakage Testing of Tissue Containment Bags When Subjected to Power Morcellation Forces. *J Minim Invasive Gynecol*, Mar-Apr 2020;27(3):655-664.

iv. Clinical Simulation Study

Significance: The clinical simulation study is important to evaluate the ability of the tissue containment system to maintain its structural integrity and impermeability when users perform power morcellation of resected tissue. Inability to use the tissue containment system appropriately could cause damage to the tissue containment system while operating the power morcellator and other surgical instruments. Any damage to the tissue containment system may cause leakage of bag contents.

Recommendations: We recommend you conduct a clinical simulation study that incorporates the following:

Study Design Recommendations

- Describe the scope of the study and the list of pass/fail criteria.
- While choosing the people who will use the device during the study, consider the clinical specialties associated with the intended use of the device and select people with varying levels of surgical experience with different surgical specialties and clinical settings.
- Ensure that the test setup reflects the clinical settings where the device may be used and the intended users, including the surgical team.
- Ensure that the simulation study design closely mimics clinical use, which may include a bench model, animal model or cadaver, with an appropriate rationale. For the chosen model, the test setup should have the following features that are important to simulate clinical use:
    - Mimics the spatial and physical properties of the abdominal wall.
    - Simulates the presence of other organs in the abdomen and their relationship with the morcellator and the tissue containment system.
    - Distends the bag to the same level and volume as expected during clinical use.
    - Provides comparable visibility inside the bag.
        - Use blood or blood analog fluid inside the tissue containment system to mimic the same level of visibility as expected clinically.
    - Replicates forces encountered by the clinician while inserting the bag, insufflating the bag, and inserting the instruments into the laparoscopic environment and while performing the surgery.
    - Includes a tissue surrogate that can mimic the weight, dimensions, rigidity, elasticity, volume, density, and other relevant physical properties of human tissue that will be subjected to power morcellation. If *ex vivo* tissue is selected for simulation, it should mimic the true compliance of the tissue *in vivo*.
    - If your device is intended to also be used for human tissue that may contain stones (e.g., kidney stones), you should use tissue or tissue surrogate containing stones.
- As part of this simulation, we recommend that you only consider the surgical steps related to the contained power morcellation and tissue extraction. The initial surgical steps for organ excision (e.g., hysterectomy, myomectomy, splenectomy, partial hepatectomy, nephrectomy) can be omitted from the study. As mentioned above, the

surrogate tissue can be placed in the abdomen and used for the simulation in lieu of *ex vivo* organs/tissue.

Simulation Procedure Recommendations

- Select the morcellators for testing based on the proposed indications for use.
- Use all the laparoscopic instruments (e.g., trocars, graspers, tenaculum, insufflator, laparoscope) intended for use with the tissue containment system.
- Before morcellating the tissue specimen, observe and describe if the viscera and bowel are retracted sufficiently to allow for safe morcellation of the tissue in the tissue containment system.
- Track and describe the rate of leakage of CO_2 from the tissue containment system and/or the change in pressure in the device while performing the surgery (see Section IV.B(1)(b)(iii)). This information is relevant for assessing the ability of the tissue containment system to maintain a distended state during the procedure and prevent aerosol spread of cancer cells at tissue extraction sites and within the abdomen. In the event of loss of working space within the tissue containment system, assess the ability and ease of re-insufflation of the tissue containment system to regain working space.
- After the procedure:
    - Perform a visual assessment of the tissue containment system for tears and perforations.
    - Perform a qualitative leak test, which may include the use of dye to identify leaks.
    - Conduct quantitative final finished tissue containment system integrity testing (see Section IV.B(1)(b)(i)).
- Include the following information in the test report:
        - Morcellator details;
        - Incision size;
        - Tissue specimen type, size and weight;
        - Surgical instruments used;
        - Ability of the user to develop and maintain distension of the tissue containment system;
        - Ability of the user to insert and remove surgical instruments;
        - Ability of the user to introduce the tissue containment system correctly;
        - Ability of the user to place the specimen in the tissue containment system correctly;
        - Ability of the user to morcellate the tissue and maintain visual contact with the tissue and morcellator;
        - Ability of the user to remove the tissue containment system following morcellation;
        - Any additional input received from the users;
        - Documentation that the study met all pre-defined acceptance criteria; and
        - Detailed description of any protocol deviations and why they are not expected to impact the outcome of the study.

For additional information on conducting this clinical simulation study, refer to the FDA guidance document titled "Applying Human Factors and Usability Engineering to Medical Devices."[18]

(2) Additional Testing Recommendations

While not required in the special controls in 21 CFR 884.4050(b)(4) and 878.4825(b)(4), we recommend that you conduct the following additional tests to aid in demonstrating substantial equivalence of the new tissue containment system. We recommend that you provide the results from testing that demonstrate that the device specifications have been met. We recommend that you consider evaluating the design specifications for both individual device components and the final finished device.

For each test method, we recommend that you conduct comparative testing using a predicate device with similarities in device design and material composition (e.g., homogeneous versus composite materials) to your device.

a. Thickness/Material Composition

Significance: Thickness and material composition are important design parameters as they impact the physical strength and impermeability of the device. Tests that evaluate thickness and material composition generally help to ensure that the tissue containment system meets the design specifications set forth by the manufacturer and that any local defects and irregularities in the material that may cause decreased strength or increased permeability are identified.

Recommendations: We recommend you conduct testing that evaluates the thickness and material composition that incorporates the following:

- Provide complete information on the methodology used to measure thickness and identify the total thickness of the tissue containment system material. If the tissue containment system under consideration is a composite material with multiple layers (e.g., polymer and fabric material), you should describe the process used to manufacture the layered-composite.
- Include measurements of thickness for the different layers (e.g., as averages with standard deviations), and if applicable, for the entire system.
- Provide details about the material homogeneity of the system. You should observe and describe the presence of voids or defects in the polymer layer and at the intersection of polymer and fabric layers for a composite tissue containment system. The resolution of the measurement technique should be fine enough to delineate the presence of manufacturing defects such as voids that may be on the order of the size of cancer cells or

[18] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices.

smaller. We recommend using imaging techniques such as high resolution optical or electron microscopy.[19]

- For homogeneity and void testing, you should consider evaluating material specimens from multiple locations, including weak spots such as seams and straps.

b. Mechanical Strength

The tests recommended in this section are intended to evaluate the mechanical strength of the tissue containment system material. They do not address the final finished device testing. Manufacturers should refer to Section IV.B(1)(b)(ii) above for FDA's recommendations on mechanical strength testing of the final finished device.

It is important to evaluate the mechanical strength of critical sections of the tissue containment system such as straps, tethers, and opening rings that are bonded/attached. You should provide a detailed justification for the selection of both tested and untested sections of the device.

The following are general recommendations for mechanical strength characterization testing:

- When establishing the acceptance criteria, you should consider the forces applied to the tissue containment system during clinical use and include a safety factor by comparing the clinical forces to force-to-failure. We recommend that you provide a rationale for each acceptance criterion.
- We recommend that you test the specimens to failure or provide a justification for the test endpoint (e.g., choosing the maximum test withstand pressure/force in a pull test).

i. Tensile Strength Testing

Significance: Similar to the concerns associated with evaluating the tensile strength of the final, finished tissue containment system, as described in Section IV.B(1)(b)(ii)(a), if the device material does not have enough mechanical strength to withstand these loads, the device may fail and result in leakage of the device contents.

Recommendations: We recommend you conduct tensile testing and describe the results and analyses from the tensile testing by including the following information:

- Stress-strain curve;
- Ultimate tensile strength (UTS) and its comparison to the tensile forces imparted on the device during a worst-case surgical scenario;
- Elongation or strain at break;
- Toughness; and
- Failure locations, if any, based on device design and composition.

[19] Herman A, Duraiswamy N, Nandy P, Myers MR, Price V, Gibeily G, and Hariharan P. In Vitro Leakage Testing of Tissue Containment Bags When Subjected to Power Morcellation Forces. *J Minim Invasive Gynecol*, Mar-Apr 2020;27(3):655-664.

ii. Puncture Testing

Significance: The tissue containment system may be subjected to puncture forces from surgical instruments (e.g., graspers). It is critical for the device material to be able to withstand these forces without resulting in leakage.

Recommendations: We recommend you conduct puncture testing that incorporates the following:

- Use surgical instruments (e.g., graspers and trocars) that are typically used in the clinical procedure. You should test worst-case scenario(s) in terms of instrument sharpness and contact area.
- Apply the load to the side of the device that is in contact with the instrument. For composite tissue containment system with multiple layers, the force at which the tip of the instrument pierces all the layers is considered the puncture force.
- Provide the following results and analyses from puncture testing:
    - Instrument force-displacement curve;
    - Puncture force; and
    - Safety factor analysis, comparing the measured puncture force to forces imparted on the device during the surgical procedure.

iii. Partial Puncture Followed by Material Permeability Testing

Significance: For a composite tissue containment system, surgical instruments could damage one of the layers while leaving the other layers intact. For example, the layer that offers leak resistance could be damaged while the other layers remain intact.[20] The force at which a layer of the tissue containment system is damaged and causes leakage of the contents from inside is referred to as the partial puncture force. A combination of instrument puncture testing followed by leakage testing helps estimate the partial puncture force.

Recommendations: The test methodology for this test is similar to puncture testing and material permeability testing discussed in Sections IV.B(2)(b)(ii) and IV.B(1)(a) above, respectively. We recommend you conduct insufflation pressure control testing that incorporates the following:

- You should use information from the puncture testing (in Section IV.B(2)(b)(ii) above) to determine the range of applied forces for partial puncture. For a composite tissue containment system, the puncture forces used to partially puncture the device and to cause leakage can be much lower than the complete puncture forces.
- Apply force the same way as for puncture testing (with the applied force less than puncture force) followed by leakage testing with dye for detection. Alternatively, a microbial leakage test may also be used for confidence and robustness in the leakage detection study. After partial puncture testing, you should perform material permeability

[20] Herman A, Duraiswamy N, Nandy P, Myers MR, Price V, Gibeily G, and Hariharan P. In Vitro Leakage Testing of Tissue Containment Bags When Subjected to Power Morcellation Forces. *J Minim Invasive Gynecol*, Mar-Apr 2020;27(3):655-664.

testing (similar to Section IV.B(1)(a) above) with a predetermined pressure of 2 psi.[21] Alternatively, you should provide a justification for using a different pressure for leakage testing.

- Use surgical instruments that are typically used in the clinical procedure. You should consider testing a worst-case scenario in terms of instrument sharpness, contact area, and probability of contact with the tissue containment system during use.
- Apply the partial load to the side of the tissue containment system that is in contact with the instrument. Information from the puncture testing can be used to determine the range of partial loads that can be imparted on the device and you should include this information in your submission.
- Provide the following results from the partial puncture and leakage testing:
    - Partial puncture force-displacement curve;
    - Partial puncture force that created enough damage to the device to cause leakage during leakage testing; and
    - Failure locations with respect to puncture and leakage, if any, based on device design and composition.

[21] Herman A, Duraiswamy N, Nandy P, Myers MR, Price V, Gibeily G, and Hariharan P. In Vitro Leakage Testing of Tissue Containment Bags When Subjected to Power Morcellation Forces. *J Minim Invasive Gynecol*, Mar-Apr 2020;27(3):655-664.