Thermal Endometrial Ablation Devices

SUBMISSION GUIDANCE FOR AN IDE

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I. Introduction

This guidance is intended to identify the elements that the Office of Device Evaluation (ODE) would expect to see in an Investigational Devices Exemptions (IDE) application for a Thermal Endometrial Ablation Device. This group of devices includes new types of devices that are intended to ablate the endometrium using conductive heating, RF energy, microwave energy, cryosurgery, etc., and where the user has no direct control over the course of the procedure once it has begun (i.e., no feedback). It is important to understand that certain technologies may not require all of the information contained herein, whereas other technologies may require additional studies beyond the scope of this guidance document.

For general information about how to submit an IDE application, contact the Center for Devices and Radiological Health's (CDRH) Division of Small Manufacturers Assistance (DSMA) at (800) 638-2041 or (301) 443-6597. FDA welcomes comments on this draft guidance document and will consider all scientifically valid alternatives to the preclinical and clinical requirements stated within. ***It is also highly recommended that the sponsor of a new investigation contact the Obstetrics and Gynecology Devices Branch (OGDB) within the Office of Device Evaluation (ODE) prior to submission of an original IDE application, at (301) 594-1180.***

II. Device Design and Description

A. Device Description

A thorough understanding of device design is essential not only in evaluating the functional characteristics of the device but also in evaluating the clinical application of the device. Provide a brief overview of the principles of operation of the device. This should include:

1. **fully dimensioned engineering drawings**
2. **description of all user-accessible controls, including:**
   a. **range of control settings**
   b. **defaults (if any)**
3. **block diagram (including all temperature monitoring and feedback circuitry)**
4. **complete characterization of all components (e.g., for thermocouples provide operating range and sensitivity)**
5. **samples (where feasible) or a videotape showing the device in operation are helpful**

B. Materials

Provide a complete list of all patient-contacting materials, and where relevant, provide a discussion as to why a given material was chosen for a particular function. If any patient-contacting material contains a color pigment, please provide the following information: chemical composition, color index number, and color additive listing (from 21 CFR 73).

C. Biocompatibility Testing (for patient-contacting devices)

Provide either biocompatibility testing (performed on the finished device), or certification that identical materials are used in a legally marketed device with a similar intended use. Samples for biocompatibility testing should be prepared in such a way so as to reflect the actual conditions of use (e.g., if the material will be heated to 90°C during use, it should be heated to this temperature prior to testing). Tests should be conducted in conformance with Good Laboratory Practices (GLP) in accordance with 21 CFR 58.

For additional information on biocompatibility, please refer to the Blue Book Memorandum "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing'", available from DSMA.

D. Software

Please provide documentation describing the software development lifecycle and risk management activities. This should include:

1. **A description of the software development activities and software quality assurance procedures over the software life cycle.**

2. **System and software requirements and design. This should include: hardware requirements, programming language and program size, and software functional requirements. Traceability between safety requirements and hazards should be clearly indicated.**

3. **A structure chart depicting the partition of the system into functional units.**

4. **A description of the verification and validation activities at unit, integration, and system level, including pass/fail criteria, and the system level functional test plan. Traceability between hazards, safety functions, and testing should be demonstrated.**

5. **A summary of the verification and validation test results *in sufficient detail to demonstrate that software requirements were met* at various levels of testing, and the results of system level testing.**

6. **Current software version number and date, as well as a list of any remaining bugs or errors.**

Additional guidance on software documentation can be found in "Reviewer

Guidance for Computer Controlled Medical Devices Undergoing 510(k) Review", available from DSMA.

III. Device Performance

A. Design Specifications

1. Provide a rationale for all important specifications. For example, if it is specified that the catheter must be able to withstand a tensile force of 5 lbf, please provide a justification for why 5 lbf is appropriate.

2. System-level hazard analysis . Identify each potential hazardous event, the level of concern, the method of control for this event, the corrective measures taken, and the testing and evaluation done to show that the corrective measures are effective.

B. Electrical Safety
Provide either:

1. Certification that the device complies with applicable electrical safety standards (e.g., IEC 601-1, UL 544, UL 2601); or
2. Test results which guarantee a similar level of protection.

C. Electromagnetic Compatibility (EMC)
Provide either:

1. Certification that the device complies with applicable EMC standards (e.g., IEC 601-1-2, IEC 801-2,3,4,5, CISPR 11); or
2. Test results which guarantee a similar level of protection; or
3. Justification for why this information is unnecessary (e.g., due to device design or working conditions).

D. System-level Testing
Provide system-level testing demonstrating that the device performs as designed (e.g., it heats to the desired temperature, thermocouples accurately record temperature, etc.). Include:

1. test protocol and methods
2. results (including samples of raw data)
3. conclusions

IV. Labeling

Provide samples of all device labeling. The labeling must include the following

information (21 CFR 812.5):

A. name and place of business of the manufacturer, packer, or distributor
B. quantity of contents (if appropriate)
C. directions for use
D. reprocessing instructions (see Section VI).
E. description of all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions
F. the statement: "CAUTION - Investigational Device, Limited by Federal law to investigational use."

Note: 21 CFR 812.5 (b) stipulates that the labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.

V. Manufacturing

Provide a description of the methods, facilities, and controls used for the manufacture, processing, packaging, and storage of the device, in sufficient detail so that a person generally familiar with Good Manufacturing Practices can make a knowledgeable judgement about the quality control used in the manufacture of the device.

VI. Sterilization

Devices that are intended to contact or enter sterile tissue or a normally sterile body cavity, such as the uterus, require sterilization before use.

A. Reusable components

Provide detailed instructions for reprocessing (cleaning and sterilizing) the device, including instructions necessary for any assembly/disassembly. Also, include a warning that the device should be thoroughly cleaned and sterilized according to validated infection control procedures before use/reuse.

1. The cleaning instructions should describe careful, manual cleaning and rinsing of both the device's exterior surface and any interior channels using a brush and detergent/ enzymatic solution to dissolve and loosen proteinaceous materials immediately after use. The cleaning instructions should identify compatible cleaning solutions by generic names (e.g., enzymatic cleaning solutions, protein binding agents, etc.) and any areas of the device that are particularly difficult to clean, as well as any specified methods and necessary accessories (e.g., brushes).

2. The rinsing instructions should include purging of all internal channels (if

applicable) alternately with air and water.

3. Any liquid sterilants used must be identified and cleared by FDA. General reference to a class of germicides, e.g., 2% glutaraldehyde, is currently acceptable. Instructions should recommend that the entire device be exposed to the liquid chemical germicide according to the labeling of the germicide (appropriate time and temperature). Liquid sterilization may be manual or automated, and, if automated, instructions must identify suitable adapters for all interior channels.

4. Thorough post process drying instructions should be recommended, as needed, in order to reduce recontamination before reuse. Instructions should include a step where air is forced through all channels following either manual or automated reprocessing to remove residual rinse water.

5. Specify at least one validated method for sterilization and identify the specific parameters (e.g., cycle parameters, aeration, specific liquid chemical germicide, loading of sterilizer, etc.) which should be used. If the labeling lists a generic type of sterilization process with no specifics on cycle parameters, then the applicant must validate all forms of the listed generic process, e.g., "steam sterilization."

6. Provide information to help the user identify any circumstances or conditions when the device may be adversely affected by reprocessing. This information should address the material compatibility with the immersion fluid.

7. Provide a certification regarding validation of the reprocessing instructions signed by the applicant, its agent, or other legally responsible individual.

For important additional information on reprocessing, please refer to the draft "Labeling Reusable Medical Devices Reprocessing in Health Care Facilities: FDA Reviewer Guidance" (March 1995). A copy of this guidance may be obtained from DSMA.

B. Single-use components

1. Provide the method of sterilization, and the sterility assurance level.
2. Identify the method used to validate the sterilization procedures. If the method is a standard, well-recognized method, simply provide the name. If not, please provide a copy of the protocol itself.
3. Describe the packaging system that will maintain sterility.
4. If the device is sterilized using ethylene oxide, identify the maximum levels of residues of ethylene oxide, ethylene chlorohydrin and ethylene glycol. If

the device is radiation sterilized, identify the radiation dose.

VII. Other required information (812.20)

A. Commercialization.
Specify whether or not the device is to be sold to the patient during the clinical study. If so, explain why this does not constitute commercialization.

B. Environmental Impact.
Provide either:

1. An environmental impact assessment describing the potential environmental impact of manufacturing and investigating the device, OR
2. A claim for categorical exclusion from the requirement, in accordance with 21 CFR 25.24.

VIII. Summary of all prior investigations

A. In vitro and animal testing
Provide a complete description of all in vitro (e.g., extirpated uteri) and animal testing. This should include:

1. justification for choice of model
2. comparison of the treatment parameters used in the study to those proposed to be used in humans
3. test protocols and methods
4. results (including samples of raw data)
5. conclusions

Note: Adequate data from in vitro and animal testing, demonstrating that the device is relatively safe and that it functions as intended, must be submitted before approval for clinical studies in humans will be granted.

B. Clinical Testing
Provide the following information about all prior clinical investigations involving the device:

1. complete bibliography, including copies of important references
2. summary of unpublished data
3. complete discussion of all known adverse events or device failures

IX. Feasibility Study - Safety(Pre-hysterectomy patients)

A. Objectives

The purpose of the Feasibility Safety Study is to demonstrate the safety of the device in a limited number of women already scheduled for a hysterectomy. This involves monitoring temperatures within the uterine wall and on the serosal surface during the ablation procedure, and conducting a histological examination of the uterus once it is removed.

Significant changes to the temperature/time parameters or to the system design may require revalidation via an additional feasibility study.

B. Description of patient population

1. Inclusion criteria
   a. patients diagnosed as suitable candidates for a hysterectomy
   b. uterine sound measurement $\leq$ 8 cm
   c. other device specific criteria

Note: If the safety and effectiveness study will include women who have had previous uterine surgery (e.g., caesarean section, myomectomy), then the safety study should include sufficient numbers of both women who have had pervious uterine surgery and those who have not.

2. Exclusion criteria
   a. active pelvic inflammatory disease
   b. abnormal psp smear, unless appropriately evaluated
   c. history of gynecologic malignancy within the past 5 years
   d. submucous myomas and polyps
   e. septate uterus
   f. previous endometrial ablation procedure
   g. pregnancy
   h. other device specific criteria

C. Investigational Plan

1. Study Design
   This is a single-arm study with 5-10 patients.

2. Protocol
   a. Pre-procedure evaluation should include:
      (1) pelvic examination
      (2) Pap smear

(3) pregnancy test
(4) endometrial biopsy

b. Endometrial preparation
All patients should receive either hormonal pre-treatment to thin the endometrium, or an immediate pre-procedure D&C. All subjects should receive the same pre-treatment regimen.

c. Endometrial ablation protocol
(1) Provide the procedures used for the ablation procedure. Ablation parameters should be exactly the same as those to be used in the safety and effectiveness study. If they are not, provide a detailed discussion of why results from the feasibility study will still be relevant.

(2) The following data should be collected:
(a) temperature measurements during the ablation procedure, including the location of the thermocouples or other temperature measuring devices.
(b) histology, including both gross and microscopic.
(c) depth of penetration of thermal injury.

(3) Provide a complete discussion of any adverse events.

3. Follow-up
Patients should be followed-up according to the standard of care for hysterectomy.

D. Risk Analysis
Provide a complete description of all potential risks to the patient.

E. Informed Consent
Provide copies of the informed consent forms that will be used during the study. You may wish to consult the "Investigational Device Exemption Manual", available from DSMA, for additional guidance on informed consent.

X. Feasibility Study - Effectiveness

A. Objectives
The purpose of this study is to establish tentative effectiveness rates for use in sample size calculations, and to support beginning a full-scale safety and effectiveness study. This is a single arm feasibility study in at least 20 women who

are candidates for endometrial ablation.

Note: Previously collected data from studies conducted at foreign sites may be accepted in lieu of this study. In this case, the following information should be provided:

1. Summary of study design
    a. inclusion/exclusion criteria
    b. detailed description of procedure - should be exactly the same as what will be proposed in proposed pivotal study (Section XI)
    c. follow-up procedures

2. Summary of safety and effectiveness data
    a. sufficient number of patients
    b. low adverse event rate
    c. reasonable effectiveness rate

B. Description of patient population

1. Inclusion criteria
    a. uterine bleeding resulting from a benign condition that meets the study entrance requirements for excessive uterine bleeding. (Note: the study sponsor is responsible for determining and justifying what constitutes excessive uterine bleeding).
    b. uterine sound measurements $\leq$ 12 cm
    c. other device-specific criteria

2. Exclusion criteria
    a. active pelvic inflammatory disease
    b. clotting defects or bleeding disorders
    c. abnormal Pap smear, unless appropriately evaluated
    d. malignant pathology, as documented by endometrial biopsy
    e. history of gynecologic malignancy within the past 5 years
    f. submucous myomas and polyps
    g. septate uterus
    h. previous endometrial ablation procedure
    i. previous uterine surgeries, unless these patients have previously been included in the safety study
    j. pregnancy
    k. desire for future fertility
    l. other device-specific criteria

C. Investigational Plan
1. Study Design
    a. Hypothesis

The study sponsor must determine the appropriate hypothesis and study endpoints. Primary study endpoints should be quantitative in nature (e.g., reduction in uterine bleeding, elimination of uterine bleeding (amenorrhea), increase in hematocrit). However, studies should also include a secondary quality-of-life endpoint.

b. Follow-up
Six months of follow-up data from this "Feasibility - Effectiveness" study should be provided to FDA prior to submission of an IDE for the safety and efficacy study. *In addition, all patients should be followed for a total of 2 years (i.e., 6 months pre-submission plus 18 months post-submission). Once all data are collected, a final report should be submitted to FDA.*

2. Protocol
   a. Pre-procedure examination
      (a) pelvic examination
      (b) Pap smear
      (c) pregnancy test
      (d) hematocrit
      (e) diagnostic hysteroscopy with endometrial biopsy

   b. Collection of baseline data
   If patient blood loss is to be used as a study endpoint, baseline data should be collected for three months prior to the ablation procedure.

   c. Endometrial preparation
   Patients should receive either hormonal pre-treatment to thin the endometrium, or an immediate pre-procedure D&C. All subjects should receive the same pre-treatment regimen.

   d. Endometrial ablation
   Provide the following information for each patient:

      (1) The procedures used for the ablation procedure. Ablation parameters should be exactly the same as those to be used in the safety and effectiveness study. If they are not, provide a detailed discussion of why the results will still be relevant.
      (2) Adverse events

3. Follow-up
   Patients should receive follow-up examinations at the following intervals: 2 weeks, 3 months, and 6 months. The study sponsor should account for

all patients lost to follow-up.

D. Risk Analysis
Provide a complete description of all risks to the patient.

E. Informed Consent
Provide copies of the informed consent forms that will be used during the study. You may wish to consult the "Investigational Device Exemption Manual", available from DSMA, for additional guidance on informed consent.

XI. Safety and Effectiveness Study

A. Objectives
The purpose of this study is to obtain the safety and effectiveness data necessary to support a PMA.

B. Description of patient population

1. Inclusion criteria
   a. uterine bleeding resulting from a benign condition that meets the study entrance requirements for excessive uterine bleeding, and which continues for multiple cycles. (Note: the study sponsor is responsible for determining and justifying what constitutes excessive uterine bleeding. The ACOG guidelines for endometrial ablation offer one possible alternative.)

   b. previously failed medical therapy with either oral contraceptives or cyclic progestins. Patients who were previously unsuccessfully treated with medical therapy must provide records documenting the previous treatment.
   Note: *This inclusion criterion is intended to exclude anovulatory patients from the study, so as to produce a "cleaner" study. It is not intended to reflect the ultimate use of the device once it has been cleared by FDA.*

   c. uterine sound measurements $\leq$ 12 cm
   d. other device specific criteria

2. Exclusion criteria
   a. active pelvic inflammatory disease
   b. clotting defects or bleeding disorders
   c. abnormal Pap smear, unless appropriately evaluated
   d. malignant pathology, as documented by endometrial biopsy

e. history of gynecologic malignancy within the past 5 years
f. submucous myomas and polyps
g. intramural fibroids
h. septate uterus
i. previous endometrial ablation procedure
j. previous uterine surgeries, unless these patients have previously been included in the safety study
k. pregnancy
l. desire for future fertility
m. other device-specific criteria

C. Investigational Plan

1. Study Design

a. Prospective, Randomized, Controlled

(1) The study should compare the investigational device to a legally marketed device intended for endometrial ablation (e.g., electrosurgical resection, rollerball ablation, or laser ablation). Control arms such as sham or D&C are not acceptable.

(2) Describe the methods used to ensure uniformity of the control procedure from investigator to investigator. A single control procedure should be chosen, and investigators must be of recognized competence in performing the procedure.

(3) Multi-Center
The study should be conducted at several centers, with at least 10 patients from each procedure at each center.

(4) Describe the methods that will be used to minimize bias, including:
(a) randomization of patient selection process
(b) procedures intended to prevent "shopping" for treatment

b. Hypothesis
The study sponsor must determine the appropriate hypothesis and study endpoints. Primary study endpoints should be quantitative in nature (e.g., reduction in uterine bleeding, elimination of uterine bleeding (amenorrhea), increase in hematocrit). However, studies

should also include a secondary quality-of-life endpoint, based on a scaled questionnaire. In addition, the sponsor should also collect data on the amenorrhea rate and the need for future surgical interventions.

c. Number of study subjects
   (1) provide appropriate statistical justification
   (2) adequate numbers at each site - see C.1.a (2) above.

d. Follow-up
   12 months of follow-up data will be required prior to PMA approval. However, the PMA may be submitted once 6 months of data has been obtained for all subjects. *In addition, all patients should be followed for a total of 3 years (i.e., 1 year pre-approval plus 2 years in a post-market setting). Data collection in the post-approval setting should focus on the need for repeat ablations or hysterectomy - qualitative blood loss data need not be collected. Once all data are collected, a final report should be submitted to FDA as a PMA supplement.*

2. Protocol

   a. Pre-procedure examination should include:
      (1) pelvic examination
      (2) pap smear
      (3) pregnancy test
      (4) hematocrit
      (5) endometrial biopsy
      (6) uterine evaluation by one of the following: diagnostic hysteroscopy, transvaginal ultrasound, or hysterosalpingogram (HSG)

   b. Collection of baseline data
      If patient blood loss is to be used as a study endpoint, baseline data should be collected for three months prior to the ablation procedure.

   c. Endometrial preparation
      Patients in both study arms should receive either hormonal pre-treatment to thin the endometrium, or an immediate pre-procedure D&C. All subjects should receive the same pre-treatment regimen.

3. Follow-up
   Patients should receive follow-up examinations at the following intervals:

a. 2 weeks
   (1) pelvic exam
   (2) adverse event report

b. 3 months
   (1) pelvic exam
   (2) adverse event report
   (3) hematocrit
   (4) evaluation of diaries and Quality of Life

c. 6 months
   (1) pelvic exam
   (2) adverse event report
   (3) hematocrit
   (4) evaluation of diaries and Quality of Life

d. 12 months
   (1) adverse event report
   (2) evaluation of diaries and Quality of Life

D. Risk Analysis
Provide a complete description of all risks to the patient.

E. Informed Consent
Provide copies of the informed consent forms that will be used during the study. You may wish to consult the "Investigational Device Exemption Manual", available from DSMA, for additional guidance on informed consent.

F. Data Analysis
The following analyses should be included as part of the PMA.

1. Patient tree showing the number of patients enrolled, the number of patients treated in each study arm, and the number of patients evaluated at each of the specified follow-up intervals.

2. Data table for each treated subject. Both a paper copy and a PC-formatted computer disk (Excel, Quattro Pro or Lotus 1-2-3) should be provided. The following information should be included in the table:
   a. patient identifier
   b. age
   c. treatment site
   d. control or test
   e. treatment date

f. deviations from protocol? If so, describe elsewhere.
g. adverse events? If so, describe elsewhere.
h. pre-treatment blood loss value (or other primary endpoint)
i. 6-month blood loss value (or other primary endpoint)
j. 12-month blood loss value (or other primary endpoint)
k. pre-treatment quality of life
l. quality of life at 6 months
m. quality of life at 12 months
n. pre-treatment hematocrit
o. 6-month hematocrit
p. 12-month hematocrit
q. additional surgical intervention required?
r. treatment considered success at 6 months? (Y/N)
s. treatment considered success at 12 months? (Y/N)

3. Sample raw data (e.g., menstrual diaries)

4. Statistical analyses (as appropriate)

Related FDA DocumentsRelated FDA Documents

The following related documents are available from the Center for Devices and Radiological Health's (CDRH) Division of Small Manufacturers Assistance (DSMA) at (800) 638-2041 or (301) 443-6597.

Blue Book Memorandum “Use of International Standard ISO-10993, ‘Biological Evaluation of Medical Devices Part 1: Evaluation and Testing’”

Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(k) Review

Labeling Reusable Medical Devices Reprocessing in Health Care Facilities: FDA Reviewer Guidance (March 1995)

Investigational Device Exemption Manual

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