This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

# GUIDELINES OF EVALUATION OF HYSTEROSCOPIC STERILIZATION DEVICES

Adopted by the OB/GYN Device Classification Panel

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Prepared by the Endoscopic and Electrosurgical Subcommittee
of the
Obstetrical and Gynecological Device Classification Panel

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Invited Guests

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Robert S. Neuwirth, M.D.

# GUIDELINES FOR EVALUATION OF HYSTEROSCOPIC STERILIZATION DEVICES

## INTRODUCTION

These general guidelines for a product development protocol for hysteroscopic sterilization devices have been prepared by the Endoscopic and Electrosurgical Subcommittee of the OB/GYN Devices Classification Panel, Bureau of Medical Devices and Diagnostic Products, Food and Drug Administration. The Subcommittee members are:

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The guidelines are intended as overall guides to the investigation of hysteroscopic sterilization device. This would cover different modalities of devices and techniques, including tubal blockage, implants, chemical injury techniques, and physical injury techniques. The place for specifics is in the individual product development protocols. Specific protocols will be evaluated on their own merits.

## OBJECTIVE

The objective of preclinical and clinical investigations is to assess the relative safety of a hysteroscopic sterilization device, its effectiveness in preventing pregnancy, its risks or undesirable effects and the relative relationship of these assessments.

## I. Preclinical Guidelines (Phase I)

### A. Description of Device and Technique

The applicant should provide detailed diagrams and descriptions of the device and its applicator. Where appropriate, samples of the devices should be available for examination. The physical characteristics of the device should be indicated and the rationale for the design should be stated in light of the relevant literature.

Design characteristics to be indicated:

1. Description and data on equipment and method proposed for the procedure.

2. Dimensions (where appropriate)

3. Radiopacity (where appropriate)

4. Details of the specific materials in all equipment.

5. Applicator Design

    a. Details of the hysteroscopic system used in sterilization

    b. The compatibility of the applicator and device as a system.

    c. How to clean and maintain the hysteroscope in the normal hospital environment.

**B. Physical Properties (material, where appropriate, to be tested before and after sterilization process)**

As appropriate, engineering tests should be performed and the results considered relative to physical properties as well as design and rationale.

1. Electrical, Mechanical, and Chemical Properties

    a. For physical injury systems: details of the range of energy, reproducibility, accuracy of delivery, and precision of technique, etc.

    b. For tubal plug systems: details of plug sizes, composition, tensile strength, viscoelasticity, etc. Parameters, should be measured and related to the proposed applicator.

    c. For chemical injury system: details relating to drug evaluation or suture evaluation, duration of use, accuracy of delivery, etc. as appropriate.

2. Stability in Biological Environment

    For any proposed systems, data is necessary on hysteroscopic applications of the system to extirpated human uteri specimens. The study should determine the effects on adjacent tissues if the application is misplace or migration occurs.

a. For physical injury systems: data on the stability of physical delivery in in vivo animal studies.

b. For tubal plug systems: data that the physical properties of implanted devices are not degraded by prolonged exposure to the biological environment or by procedures of sterilization. When materials are proposed for use in a device which as not be previously been used in an implant, their response to body fluids must be examined and their stability and reactivity documented. Data on local reactions of materials with tissues are necessary.

c. For chemical injury systems: There must be an evaluation of local effects particularly as they relate to pharmacokinetics.

3. Biological Tests for Toxicity Testing for New Materials

a. Proper toxicity studies should be done.

**C. Packaging (as appropriate)**

The method of packaging should allow easy removal of the device and preparation for use with the hysteroscope without contamination.

**D. Sterilization Process**

Assurance od adequacy of sterilization process(es) by manufacturer.

**E. Animal Study**

The data gathered from a study using suitable animal models should deal with local reactions:

1. Tissue fibrosis

2. Local leeching of chemicals

3. Migration

4. Effects of the proposed delivery system on myometrial tissue.

5. Menstrual history studies are of significance as well.

Animal data on the plug chemical or other type injury induced to the tube at the site proposed for human delivery.

1. Use of monkeys (baboons are recommended for tubal plug systems).

2. x-ray studies

3. Pathological studies

## II. Clinical Guidelines

Prior to clinical testing, it must be documented that appropriate toxicology and animal studies for the proposed clinical trial have been done. Animal findings relevant to the safety of hysteroscopic sterilization devices will be completed prior to initiation of phase II clinical studies.

Investigations of this nature are to be conducted in such a way that the participating subjects or patients are exposed to the least possible risk consistent with the anticipated benefit. Informed consent of the patient will be obtained and there are already several documented informed consent procedures (Guidelines on Protection of Human subjects - **FEDERAL REGISTER** Vol.40, No. 50 pp. 11854-11858.

The patient must be fully informed of:

1. The benefits and risks of other sterilization methods.

2. The risk as well as benefits of hysteroscopic sterilization in general and any specific risks of the procedure or device being investigated.

3. An experimental procedure is to be used on the patient for sterilization and the possibility of pregnancy as well as potential hazards of pregnancy.

4. The possibility that it may be necessary to subsequently remove the device and/or utilize other methods to ensure sterilization .

5. The patient should also be advised that she must agree to remain in communication with the investigator or the manufacturer with no time limit in order that the long term consequences may be determined.

### Investigational Clinical Study (Phase II)

Investigational clinical studies are intended to include the initial use of the hysteroscopic sterilization device as s system for women. This clinical investigation is an early

controlled clinical trial designed to demonstrate relative safety, efficacy, and ease of application.

Patients must be advised that an investigational device is being used and informed consent must be executed by the patient with the understanding that pregnancy referral for prenatal care or referral for termination will be made available as backup. if necessary and desired.

This is a two step study, with the second step contingent upon approval of the first.

**A. Hysteroscopic Application of the System in Patients Undergoing Hysterectomy or Laparoscopic Tubal Sterilization**.

This study intends to determine the mechanical feasibility of the technique in the human patient. It is designed to give relatively instantaneous information with regard to the testing of the hysteroscopic sterilization system such that there can be intervention or termination of the procedure, if necessary.

1. This study is to be done by one or two investigators on a minimum of five patient (the actual number determined in the specific protocol) undergoing hysterectomy with an open abdomen. Then sequential hysterectomy data would be accumulated, when applicable, from one day to six months. This study could also be done as part of a laparoscopic sterilization, simultaneously using hysteroscopy to apply the investigated technique and then remove it later.

2. A dye of x-ray technique can be used to determine tubal occlusion.

**B. Preliminary Feasibility Trial**

This would consist of a maximum of five investigators and a minimum of 50 cases, with an emphasis on a well-controlled technique. Important parameters are:

1. Patient selection

2. Procedures

3. Appropriate clinical criteria

The patients would undergo a hysterosalpingogram after three months to determine tubal occlusion. The WHO standard for hysterosalpingograms would be applicable to these studies. A pressure of 150 mm Hz held for one minute will be the standard to determine tubal occlusion. Safety of the technique is the other important issue to deal with at the three month check. During this three month

period, the patient will be on an alternative contraceptive. Additional variables will be followed as well, (1) menstrual pattern), (2) dysmenorrhea, (3) vaginal bleeding, (4) perforation, and (5) infection. These fifty or more cases will be followed for a minimum of one year and will continue afterward to be the leading study of the procedure and device, but if there are no adverse reports after the three month check-up, the investigator can move to phase III. For each subject lost to follow-up in the study, an additional study subject must be done again from day one if the number of patients drops below the minimum or 50 cases.

## III. Clinical Study (Phase III)

The clinical study (Phase III) should follow the guidelines regulatory established for:

1. Patient informed consent

2. Criteria for selecting investigators

3. Statistical evaluation based on life tables.

4. Data acceptable for evaluation of safety and effectiveness (Standard forms of this nature have been drawn up by several organization, e.g., IFRP, PARFAR, WHO).

## IV. Post Marketing Surveillance (Phase IV)

The last part of these guidelines deals with long term pathological and efficacy data to be collected continuously. It is the manufacturer's responsibility, in the form of market surveillance, to keep records of adverse reports.

The subsequent expanded trial would include an additional 2000 cases to be followed for a minimum of five years, a continuation of the clinical study in several medical centers with reports of failures, problems, and complications (i.e., ectopic pregnancies, recannulization, menstrual dysfunction, etc.) over the five years with hysterosalpingograms.

### A. Post marketing surveillance is needed for hysteroscopic sterilization devices for the following reasons:

1. The possibility of increased pregnancy rates occurring more than two years after application due to recannulization or fistula formation.

2. The possibility of defects in the manufacture of a particular "run" or lot of devices, when it is necessary to have a method of locating patients.

3. The need to warn patients to take additional preventative measures in the event that a greater pregnancy rate than originally reported is found as a result of extended studies.

4. The possibility that hazards during extended use are discovered later.

**B. The required post marketing surveillance:**

1. The subjects participating in clinical Phase II or III studies will be followed for an extended period of time. The patients are urged to remain in communication with the investigator of the manufacturer for no time limit.

2. The hospital or medical facility where the procedure was performed should maintain records of devices purchased and the patients who receive the devices.

3. The manufacturers will keep records of regional distribution and final distribution. (e.g., individual physician or clinics or hospitals). In the event of recall or the need to survey the incidence of adverse reactions, the manufacturer will provide this information to FDA. In addition, the manufacturer will provide the FDA with total numbers distributed quarterly.

4. The manufacturer should contact an adverse reaction reporting system in order to solicit adverse reactions from physicians and other medical personnel and provide educational information for the procedure to these practitioners.