

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 FOR EVALUATION OF NON-DRUG IUDS

Adopted by the OB/GYN Classification Panel

September 26, 1976

Prepared by the Conception Control Device Subcommittee

Subcommittee Members

Richard P. Dickey, M.D., Ph.D. (Subcommittee Chairman)
Lyra Gillette, M.D.
Charlotte Kerr, M.D.

Consultants

Melvin Sikov, Ph.D.
Louise Tyrer, M.D. (Liaison with OB/Gyn Drug Panel)

CONTENTS

	<u>Page</u>
1. Introduction	1
2. Objective	1
3. Preclinical Guidelines (Phase I)	1
4. Clinical Guidelines	5
5. Investigational Clinical Study (Phase II)	5
6. Comparative Clinical Study (Phase III)	8
7. Post-Marketing Surveillance (Phase IV)	9

Guidelines for Evaluation of Non-Drug New IUDs

INTRODUCTION

These general guidelines for a product development protocol for non-drug new IUDs have been prepared by the Conception Control Subcommittee of the Panel on Review of Obstetrical and Gynecological Devices, Bureau of Medical Devices and Diagnostic Products, Food and Drug Administration, March 15 and 16, 1976. The subcommittee members are: Richard P. Dickey, M.D., Ph.D. (Subcommittee Chairman), Lyra Gillette, M.D., M.P.H., Charlotte Kerr, M.D. and Louis Tyrer, M.D. (liaison with OB/GYN Drug Panel).

The guidelines are intended as overall guides to the investigation of non-drug IUDs and as such must be concerned primarily with generalities. The place for specifics is in the individual product development protocols. Specific protocols will be evaluated and approved of their own merits. The submitted protocol is to be specific about the relationship of the preclinical and clinical data available on the new IUD at the time of the proposed investigation as well as an outline of the protocol to be followed.

OBJECTIVE

The objective of preclinical and clinical investigation is to assess the relative safety of the new IUD, its effectiveness in preventing pregnancy, its risks or undesirable effects and the relative relationship of these assessments.

I. Preclinical guidelines (Phase I)

A. Description (Design) of Device

The applicant should provide detailed drawings and descriptions of the device and ancillary devices, e.g., inserters. Samples or prototypes should be available for examination. The physical characteristics of the device should be indicated, and the rationale for the design should be stated in the light of the relevant literature.

Design characteristics to be indicated:

1. Shape and dimensions, including surface areas
2. Presence of projections, sharp edges

3. Radio-opacity (or other means of localization)
4. String (or other means of removal)
5. Inserter design (should include physical characteristics, insertion procedures and anticipated difficulties)
6. Removal procedures and anticipated difficulties.

B. Physical Properties (Test the material prior to 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. Mechanical and Chemical Properties

- a. The details of mixing, forming, curing, including the materials and sources employed and their percentage composition must be stated.
- b. The uniformity of the V in the completed devices and the procedures for quality control should be indicated.
- c. The uniformity and texture of the surface should be established by microscopy or other appropriate methods.
- d. The tensile strength, elasticity and viscoelastic memory of the insertion device should be measured and related to the various forces anticipated in this proposed utilization. The completed device should be subjected to stress testing such as bending or compressing the device in various manners for a stated numbers of times to simulate the effect of sustained uterine contractions on the device, to establish its longevity. Generally accepted procedures for this have not been established although an intrauterine device should be able to withstand the biological and longitudinal contractions of the uterus for a period longer than the anticipated life of use.
- e. When a "string" is used as an intrinsic component of an intracavitary device, its tensile strength should be measured. The force (mean and range) required to dislodge the string from its attachment to the device

(i.e., break bond; cut-through) should be determined. These parameters should be related to the calculated forces necessary to remove the device. The type of material, its composition, and its structure must be stated. The string must be mono-filament.

2. Stability in Biological Environment

- a. It is important that the physical properties of intracavitary or implanted devices not be degraded by prolonged exposure to the biological environment or by procedures of sterilization. When materials are proposed for use in a device, which has not previously been used in an implant, their response to body fluids should be examined. The peritoneal cavity of the laboratory animals appears to be suitable for such exposure. To detect changes, 15 devices (one per animal) should be exposed for three months and 15 for one year, removed, and tested for the same physical properties as the unexposed devices.

3. Biological Test for Toxicity Testing for New Materials

Proper toxicology studies should be done.

C. Packaging

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

D. Sterilization Process

Assurance of adequacy of sterilization process by the manufacturer.

1. Steam Sterilization (saturated steam under pressure).
 - a. Determination of D-values for natural contaminants on nonsterile devices by means of subprocess treatments.
 - b. Calculation of process time to show that probability of a survivor is less than 10^{-6} for the steam sterilization cycle.

- c. Inoculated product biological indicator (BI) samples.

2. Dry Heat Sterilization

- a. Determination of D-values for natural contaminants on nonsterile devices by means of sub-process treatments at the processing sterilization temperature.
- b. Calculation of process time to show that the probability of a survivor is less than 10^{-6} for the dry heat sterilization cycle.
- c. Inoculated product BI samples.

3. Radiation Sterilization

- a. Determination of D-values for natural contaminants on sterile devices by means of sub-process radiation dose exposures.
- b. Calculation of total radiation dose needed to show that probability of a survivor is less than 10^{-6} .
- c. Inoculated product BI samples.

4. Ethylene Oxide (ETO) Gaseous Sterilization

- a. Determination of D-values for natural contaminants on nonsterile devices by means of subprocess time exposures to the ETO cycle.
- b. Calculation of process time needed to show that probability of a survivor is less than 10^{-6} fir the ETO sterilization cycle.
- c. Inoculated product BI samples.
- d. Residue determinations.

5. Liquid Chemical Sterilants

- a. Determination of D-values for natural contaminants on nonsterile devices by means of sub-process time exposure to the chemical sterilant.
- b. Calculation of process time needed to show that probability of a survivor is less than 10^{-6} for liquid chemical sterilizing cycle.
- c. Inoculated product BI samples.

- d. Neutralizers.
- e. Residue determinations.

6. Sterile Assembly or Aseptic Processing Techniques

CLINICAL GUIDELINES

Prior to clinical testing, it must be documented that toxicology appropriate for the proposed clinical trial has been carried out. Animal findings relevant or potentially relevant to the safety of IUDs should 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. The patients must be fully aware of:

1. The benefits and risks of other available contraceptive methods.
2. The risks as well as benefits of IUDs in general any special risk of the IUD being investigated.
3. An experimental device is to be fitted in the patient and the possibility of pregnancy as well as the potential hazards of pregnancy or abortion.
4. The patient should also be advised that she must agree to have her device removed if she intends to leave the area or at the end of the Phase II study if necessary or sooner if experience indicates the necessity to terminate the study.

II. Investigational Clinical Study - Phase II

Investigational clinical study is intended to include the initial introduction of an IUD woman.

This clinical investigation is intended to include an early controlled clinical trial designed to demonstrate relative safety, efficacy and ease of insertion and removal. The number of subjects and patients in Phase II should not be less than 200 nor more than

300 to be able to proceed to Phase III. These trials are performed on closely monitored patients with 100 percent follow-up or with detailed explanation required for any lost to follow-up. They should be contacted by several investigators, experience in the use of IUDs. The study will not be less than six months with monthly reporting of events by the sponsor. The status of each patient must be determined monthly.

A. Criteria for Selecting Patients

1. Subjects must be of legal age or older and not more than 45 years old.
2. They must be currently cohabiting and exposed to the risk of an pregnancy.
3. Women who have been using oral contraceptive pills must have had at least one normal menstrual cycle after discontinuing.
4. Women who have been pregnant must have had at least one normal menstrual period subsequent to delivery or abortion, and not less than two months following the termination of a pregnancy.
5. Women who discontinued use of other IUDs because of side effects are to be excluded.
6. Women must not have a history or findings of any of the disorders listed under contraindications:
 - a. pregnancy or suspected pregnancy;
 - b. uterine fibroids;
 - c. bicornuate uterus;
 - d. any other abnormalities of the uterus which distort the intrauterine cavity;
 - e. intramenstrual bleeding;
 - f. positive culture of gonorrhea unless followed by a normal pregnancy;
 - g. postpartum endometritis or infected abortion;
 - h. PID in the past three months or history of repeated PID;
 - i. endometrial disease such as hyperplasia, polyps or suspected uterine malignancy;
 - j. suspicious PAP smear; and
 - k. a history of ectopic pregnancy.

The data on women fitted with an investigational IUD and later found to have one of these conditions must be analyzed and reported. However, they will not count towards the required (minimum) total of 200 patients with 100 percent follow-up.

7. They must not use additional forms of contraception.
8. They must be accepting of the potential risk of pregnancy.

B. Patient Information and Consents, (HEW guidelines on Protection of Human Subjects - F.R. Vol. 40, #50, Page 11854-11858)

The patient must be advised that the device is an investigational device. An 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. The individual protocol must identify the mechanism for reimbursement, if any, to the patient for care resulting from pregnancy whether the patient elects to continue pregnancy or terminate.

C. Criteria for Selecting Investigators

The investigators shall each include enough patients to comprise a statistically valid sample. The number of investigators required shall be no less than five. An investigator must be generally knowledgeable about IUDs and experienced in the technique of inserting different IUDs.

D. Statistical Evaluation

The analysis of the study should be done by the life table method. Each patient who has not terminated use or who has not been lost to follow-up should have six full months of observed use of the device prior to completion of the analysis. Both net and gross life table rates should be presented. In the case of the net rates of six months when there is no lost to follow-up, the net rates should simply represent the number of terminations for the specific reason in the first six months divided by the number of patients in the study. Data needed to record and analyze of evaluation of safety and effectiveness:

1. difficulty of insertion and removal;
2. all usual and unusual hazards and adverse effects;

3. the pregnancy rate (estimated to be 2-4 percent for marketed non-drug IUDs);
4. the infection rate (estimated to be 2.5-5 percent for marketed non-drug IUDs);
5. perforation rate (estimated to be 0.3-1.8 percent for marketed non-drug IUDs);
6. expulsion rate (estimated to be 7-14 percent for marketed non-drug IUDs)
7. bleeding and pain;
8. removal rate, personal reasons (specify);
9. removal rate, medical reasons (specify);
10. incidence of syncope or seizures with insertion;
11. pregnancy complications:
 - a. abortion rate
 - b. sepsis
 - c. ectopic rate
 - d. other
12. Outcome of patient for at least two months post abortion or postpartum and outcome of the child for one year, whether or not the IUD is removed.
13. Aerobic and anaerobic culture of IUD at the time of medical removal for infection or in conjunction with a pregnancy should be carried out.

At the conclusion of investigational clinical studies, IUDs may be left in situ if there are no contraindications to further device use. For progression to comparative clinical studies, the new device should initially appear to be at least as safe and effective (in other words, not to incur more risks) as the non-drug devices currently on the market. If the device exhibits an important advantage over other marketed devices, consideration may be given to progression to Phase III even in the event of less effectiveness.

III. Comparative Clinical Study - (Phase III)

The new device must be compared in patients of equal age, parity, and marital status in randomized studies to a non-drug IUD that is currently available on the market,

appropriate to the type of patient for whom the new IUD is intended (e.g., nulligravida or multipara).

The comparative clinical study, (Phase III) should follow the guidelines in the investigational clinical studies (Phase II) for the following:

1. criteria for selecting patients;
2. patient information and consent;
3. criteria for selecting investigators;
4. statistical evaluation; and
5. data needed to record for evaluation of safety and effectiveness.

The number of patients should be done by the life table method with a minimal number of patients lost to follow-up not to exceed approximately 10 percent.

In a subgroup of the patients, additional data may be necessary to collect, for example the hemoglobin or hematocrit product development protocol.

The patients with the new device from this clinical phase who desire to continue their IUD use may be continued in the post-marketing surveillance.

IV. Post Marketing Surveillance (Phase IV)

Post marketing surveillance is needed for a newly marketed IUD for the for the following reasons:

- A. The need to locate women wearing IUDs in the event that unforeseen problems arise which necessitate recall.
- B. The need to know numerator and denominator use data on all marketed IUDs.
- C. The need to survey the following:
 1. infection;
 2. pregnancy complications including the incidence of ectopic pregnancy;
 3. outcome of pregnancy;
 4. follow-up on children (minimum one year) conceived while wearing an IUD and within three months following removal;

5. perforation rates;
 6. rare adverse effects; and
 7. incidence of hospitalization.
- D. The required post marketing surveillance:
1. The patients with the new marketed device inserted on clinical Phase II or III be followed for an additional three years or until the device is removed for any reason.
 2. In order to locate the patient without jeopardizing the patient's right to confidentiality, the manufacturer should include a card for identification of the physician or professional who performed the insertion, the date of insertions, and the age and parity of the patient in each package of IUD. The physician or professional after inserting the device the patient, should complete the card with his or her name and date of insertion. Note the patient's name is not to be indicated. The card should be sent to the manufacturer for record. In the event of recall, the manufacturer is responsible to contact all the physicians and clinics who send in the cards. A physician or clinic should have some means of identifying the patient when the device is inserted. Manufacturer will provide total numbers inserted to FDA quarterly or as necessary in the event of recall or the need to survey any adverse reaction.
 3. The manufacturer shall conduct an adverse reaction reporting system in order to actively solicit adverse reactions from physicians and clinics for three years from the date of marketing a new IUD and from January 1, 1977, or before for currently marketed non-drug devices.
 4. In order to locate all IUDs, including those inserted, the manufacturer is to keep records of regional distribution and final distribution (e.g., individual physician or clinics). In the event of recall or the need to survey the incidence of adverse reactions, manufacturer will provide this information to the FDA. In addition, manufacturer will provide total numbers distributed quarterly.