

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 TUBAL OCCLUSION DEVICES

Adopted by the OB-GYN Device Classification Panel

November 22-23, 1977

Prepared by the Conception Control Device Subcommittee

Subcommittee Members

Richard P. Dickey, M.D., Ph.D. (Subcommittee Chairman)

Lyra Gillette, M.D., M.P.H.

John Josimovich, M.D.

Charlotte Kerr, M.D.

Consultant

Jordan M. Phillips, M.D.

Guidelines for Evaluation of Tubal Occlusion Devices

Introduction

These general guidelines for a product development protocol for tubal occlusion devices have been prepared by the Conception Control Device Subcommittee of the OB-GYN Device Classification Panel, Bureau of Medical Devices and Diagnostic Products, Food and Drug Administration.

The subcommittee members are:

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

The consultant is:

Jordan Phillips, M.D.

The guidelines are intended as overall guides to the investigation of tubal occlusion devices. There are different types of tubal occlusion devices, metal clips, plastic rings, inserters, and valves. The place for specific is in the individual product development protocols. Specific protocols will be evaluated and approved on their own merits.

Objectives

The objective of preclinical and clinical investigations is to assess the relative safety of the tubal occlusion devices, 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 its applicator. Samples of the tubal occlusion 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 the light of the relevant literature.

Design characteristics to be indicated.

1. Shape and dimensions including the thickness of the ring;
2. Radiopacity (or other means of localization); and
3. Applicator design
 - a. the compatibility of the applicator and tubal occlusion devices as a system; and
 - b. how to clean and maintain the applicator in the normal hospital environment.

B. Physical Properties (test the material prior to an 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 components in the completed devices and the procedures for quality control should be indicated.
- c. The uniformity and the texture of the surface, the diameters, the thickness of the wall should be established by appropriate methods.
- d. the tensile strength, elasticity and viscoelasticity of the tubal occlusion device should be measured and related to the applicator anticipated in its proposed utilization. The device should be subject to stress testing as to the compatibility for use with the applicator.

2. Stability in Biological Environment

- a. It is important that the physical properties of 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 have not previously been used in an implant, their response to body fluids must be examined. The peritoneal cavity of the laboratory animals appears to be suitable for such exposure. To detect changes 15 devices (1 per animal) should be exposed for 3 months and 15 for one year, removed, and tested for the same physical properties as an exposed device.

3. Biological Tests 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 use with the applicator without contamination.

D. Sterilization Process

Assurance of adequacy of sterilization process by manufacturer.

1. Steam sterilization (saturated steam under pressure)
2. Dry heat sterilization
3. Radiation sterilization
4. Ethylene Oxide gaseous sterilization
5. Liquid chemical sterilants
6. Sterile assembly or aseptic processing techniques

E. Animal Study

A small study (20 animals) using suitable animal models, i.e., swine or cattle at 100% efficacy.

CLINICAL GUIDELINES

Prior to clinical testing, it must be documented that appropriate toxicology and animal study for the proposed clinical trial have been carried out. Animal findings relevant to the safety of tubal occlusion devices to be completed prior to initiation of Phase II clinical studies.

Investigation 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 informed of:

1. the benefits and risks of other sterilization methods;
2. the risks as well as benefits of tubal occlusion devices in general and any special risk of the tubal occlusion devices being investigated;
3. an experimental device is to be used in the patient for sterilization and the possibility of pregnancy as well as the 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 failure may be detected.

II. Investigation Clinical Study (Phase II)

Investigational clinical study is intended to include the initial insertion of tubal occlusion devices with the application of applicator as

a system into a woman. This clinical investigation is intended to include an early controlled clinical trial designed to demonstrate relative safety, efficacy and ease of application. The principal investigator must use the prototype device on 50 patients. A small collaborative study must follow with at least 4 additional investigators in 4 other hospitals and 200 patients. These trials should be performed on closely monitored patients with 100% follow-up. They should be conducted by investigators experienced in the procedure of using tubal occlusion devices.

- A. Patient information and consent (HEW Guidelines on Protection of Human Subjects - FEDERAL REGISTER Vol. 40, No. 50, pp. 11854-11858)

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 back-up, if necessary and desired.

- B. Criteria for selecting investigators.
- C. Statistical evaluation
- D. Data needed to record and analyze for evaluation of safety and effectiveness.
1. difficulty of the application of the device to the fallopian tubes;
 2. menstrual irregularity;
 3. abnormal bleeding;
 4. the pregnancy rate;
 5. the infection rate;
 6. pregnancy complications
 - a. ectopic pregnancy; and
 7. post operation pain.

III. Clinical Study (Phase III)

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

1. patient informed and consent;
2. criteria for selecting investigators;
3. statistical evaluation; and
4. data needed to record for evaluation of safety and effectiveness (see Phase III).

The number of patients should be instituted to determine the effectiveness of the device with 250 patients completing a two year study, 500 patients completing an 18 month study, and a total of 1000 patients completing a one year study.

The analysis of the study should be done by the life table method with a minimal number of patients lost to follow-up.

IV. Post Marketing Surveillance (Phase IV)

A. Post marketing surveillance is needed for tubal occlusion devices for the following reasons:

1. the possibility of pregnancy occurring more than 2 years after application due to recannulization or fistula formation;
2. the possibility of defects in manufacture of a particular "run" or lot of devices, in which it is necessary to have a means of locating patients;
3. the need to warn patients to take additional preventative measure 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 at some future date.

B. The required post marketing surveillance:

1. The patients with the tubal occlusion devices in Clinical Phase II or III, be followed for an extended period of time. The patients are required to remain in communication with the investigator or the manufacturer for no time limit.
2. The hospital or medical facility where surgery actually takes place should be responsible for maintaining records of devices purchased and the patients who receive the devices.
3. The individual protocol should include a system to determine the long term safety and efficacy (pregnancy rate and ectopic pregnancy rate) of the tubal occlusion devices for at least 5 years post marketing. This study is to include at least 1500 patients in addition to those in Phase II and III.
4. In order to locate all the tubal occlusion devices, including those used, the manufacturer is keep records of regional distribution and final distribution. (e.g., individual physician or clinic or hospital). In the event of recall or the

need to survey the incidence of adverse reaction, the manufacturer will provide FDA with total numbers distributed quarterly.

5. The manufacturer should conduct an adverse reaction reporting system in order to actively solicit adverse reactions from physicians and hospitals. The manufacturer should provide educational information for the use of the tubal occlusion device and its applicator to the physicians and the hospitals.